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Published in:
Psychosomatic Medicine

DOI:
10.1097/PSY.0000000000001117

Publication date:
2022

Cognitive Task Performance and Subjective Cognitive Symptoms in Individuals With Chronic Fatigue Syndrome or Fibromyalgia: A Cross-Sectional Analysis of the Lifelines Cohort Study

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ABSTRACT

Objective: This study examined cognitive task performance and self-reported cognitive functioning in individuals with chronic fatigue syndrome (CFS) and fibromyalgia (FM) in a population-based sample and investigated the role of mood and anxiety disorders as well as severity of the physical symptoms.

Methods: This study was performed in 79,966 participants (mean [standard deviation] age = 52.9 [12.6] years, 59.2% women) from the Lifelines general population. Symptoms consistent with the diagnostic criteria for CFS and FM were assessed using questionnaires. Two comparison groups were used: participants with self-reported medical disorders with well-defined pathophysiology (i.e., multiple sclerosis and rheumatic arthritis) and controls without these diseases. Objective task performance was based on the computerized CogState cognitive battery and subjective cognitive symptoms using the concentration subscale of the Checklist Individual Strength.

Results: Cognitive task performance was poorer in individuals with CFS versus controls without disease and controls with a medical disorder, although the severity of cognitive dysfunction was mild. Participants meeting the criteria for CFS (n = 2461) or FM (n = 4295) reported more subjective cognitive symptoms compared with controls without a medical disorder (d = 1.53, 95% confidence interval [CI] = 1.49–1.57 for CFS; d = 1.25, 95% CI = 1.22–1.29 for FM) and participants with a medical disease (d = 0.62, 95% CI = 0.46–0.79 for CFS; d = 0.75, 95% CI = 0.70–0.80 for FM). These differences remained essentially the same when excluding participants with comorbid mood or anxiety disorders or adjusting for physical symptom severity.

Conclusions: Subjective cognitive symptoms and, to a lesser extent, suboptimal cognitive task performance are more prevalent in individuals with CFS or FM compared with controls without these conditions.

Key words: cognition, CFS, fibromyalgia, CogState, concentration.

INTRODUCTION

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are serious disabling health conditions that are associated with a reduced quality of life and reduced social participation (1–4). Both CFS and FM are symptom-based diagnoses because they require the presence of specific clusters of somatic symptoms (5–7). The diagnostic criteria for CFS and FM include a description of the main symptom and additional symptoms. Diagnostic criteria for CFS and FM attempt to distinguish these syndromes from well-defined medical diseases that present with comparable symptoms, but they also require the absence of detectable pathological explanations for these symptoms (5,7). The main and additional symptoms in CFS and FM partly overlap; for example, both patient groups can suffer from cognitive symptoms, unrefreshing sleep, fatigue, or postexertional malaise (5–7).

Cognitive impairment is frequently reported in both CFS and FM (5–9). A previous meta-analysis found that studies examining cognitive impairments in CFS reported inconsistent results (10). The authors suggested that these inconsistencies could be explained by methodological differences because the studies used a wide variety of cognitive tasks that could not be directly compared. They also identified several limitations of the existing literature: most studies contained small samples, did not include a control group, or did not report the diagnostic algorithm that was used to select the patient group (10). Similar conclusions were drawn in a review focusing on cognitive impairments in patients with FM (11). In particular, the authors recommend a study with a large sample of participants with varying levels of mood and anxiety disorders, pain, fatigue, and sleep

CFS = chronic fatigue syndrome, **CIS** = Checklist Individual Strength, **CIS-fatigue** = fatigue subscale of the Checklist Individual Strength, **DET** = detection task, **FM** = fibromyalgia, **IDN** = identification task, **MS** = multiple sclerosis, **OBK** = one back, **OCL** = one card learning task, **RA** = rheumatoid arthritis

SDC Supplemental Digital Content

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Received for publication November 9, 2021; revision received June 26, 2022.
DOI: 10.1097/PSY.0000000000001117

disruption, which would allow for assessment of the contribution of these comorbid symptoms to cognitive impairments. Mood and anxiety disorders are more prevalent in individuals with CFS and FM (12), and both psychiatric disorders and the severity of somatic symptoms can interact with cognitive functioning (8,13). Therefore, larger studies investigating both subjective and objective cognitive impairments in CFS and FM patients and controls are needed.

In the current study, we will examine cognitive task performance and subjective cognitive symptoms in individuals with CFS and individuals with FM in a large population-based cohort study of more than 79,000 participants. First, we will examine whether participants with CFS and participants with FM differ significantly from each other and from controls or participants with a well-defined medical disease with comparable core symptoms (CFS versus multiple sclerosis [MS] and FM versus rheumatoid arthritis [RA]) on cognitive task performance and subjective cognitive symptoms. We will additionally explore whether these differences can be related to comorbid mood and anxiety disorders. Lastly, the relationship between physical symptom severity and cognitive task performance will be examined, and whether it differs between participants with CFS and those with FM.

METHODS

Sampling Frame

This study was conducted within the sampling frame of the Lifelines cohort study (14). Lifelines is a multidisciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North East part of the Netherlands. Lifelines uses a broad range of investigative procedures in assessing biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of Lifelines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents-in-law, and children to participate as well. In this way, participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language, were excluded. Parents and children were not excluded in case of the mentioned criteria, when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until 6 months after pregnancy or 3 months after breastfeeding. Second, persons who were interested to participate could register themselves via the Lifelines Web site and then participate.

All participants received written information on the purpose and methods of the study, and written informed consent was obtained after the procedure was fully explained. All data are kept confidential and are only used for medical research. Approval by the Medical Ethical Committee of the University Medical Center Groningen was obtained for the study (2007/152).

Data Collection

The first participants were included at the end of 2006, and the recruitment period was closed after reaching the target number of participants in 2013. Participants who were included in the Lifelines study will be followed for at least 30 years. At baseline, participants visited one of the Lifelines research sites for a physical examination. Before these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires were administered to all participants approximately every 18 months, and participants have been invited for a renewed physical examination at the Lifelines research site, on average, every 5 years. At the time of writing, data from baseline assessment, and first and second follow-up questionnaires, and data from the second assessment were available. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g., electrocardiogram, lung function), and lastly, the CogState computerized cognitive battery and psychiatric assessment were conducted, respectively.

CFS, FM, and Medical or Psychiatric Health Conditions

Symptoms consistent with the diagnostic criteria for CFS and FM were assessed using questionnaires. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (5), and for FM, it was the 2010 American College of Rheumatology criteria (7) (Appendix A, http://links.lww.com/PSYMED/A859: scoring algorithm).

MS and RA were assessed based on self-reported disease status derived from the questionnaire. CFS with comorbid MS ($n = 29$) and FM with comorbid RA ($n = 443$) were excluded from the analyses. Controls were defined as participants who did not fulfill the diagnostic criteria for CFS and FM and did not report MS or RA.

Psychiatric health conditions, including current mood (i.e., major depressive disorder, dysthymia) or anxiety disorders (i.e., panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, generalized anxiety disorder), were assessed with a standardized instrument, which was completed by participants at the Lifelines location. This instrument was a digitalized self-report version of the Mini International Neuropsychiatric Interview. The Mini International Neuropsychiatric Interview is a brief structured instrument for diagnosing psychiatric disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) and *International Classification of Diseases, Tenth Revision* (15).

Cognitive Task Performance

We used the CogState computerized cognitive battery because it measures multiple domains of cognitive functioning and is brief, using automated data processing and scoring. It is suitable for research among people from the general population with a wide range of ages and educational levels (16,17). Furthermore, the CogState battery has shown to have good test-retest reliability (18) and validity (19).

The CogState Brief Battery is a collection of four short card tasks. Different cognitive domains are tested: a) speed of processing (detection task [DET]; 2 minutes), visual attention/vigilance (identification task [IDN]; 2 minutes), working memory (one back [OBK]; 2 minutes), and visual learning and memory (one card learning task [OCL]; 5 minutes). During the CogState Brief Battery, a supervisor was available in case participants needed assistance.

Detection Task

The DET is a simple reaction time task involving visual signal detection and motor response, measuring basic visuomotor processing speed. In this task, the participant is instructed to attend to the center of the screen and follow the rule, "Has the card turned face up?" Participants were instructed to press the "Yes" key as soon as the card turned face up. The task ended after 35 correct trials had been recorded. The primary outcome measure was reaction time (in milliseconds), which was normalized using log10 transformation.

Identification Task

The IDN is a choice reaction task that measures visual attention. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question, "Is the card red?" Participants were instructed to press the "Yes" key if it is and the "No" key if it is not. This

task continued until 30 correct responses had been recorded. Reaction time (in milliseconds and log10 transformed) was the primary outcome measure.

One Back

The OBK is a measure of working memory maintenance. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question, "Is this card the same as that on the immediately previous trial?" If the answer was yes, participants were instructed to press the "Yes" key, and the "No" key if the answer was no. The task ends after 30 correct trials. The primary outcome measure was the proportion of correct answers, which was normalized using arcsine transformation. We also reported reaction time (in milliseconds) corrected for baseline speed, which was normalized using log10 transformation.

One Card Learning Task

The OCL is a visual learning and memory task. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question, "Have you seen this card before in this task?" If the answer was yes, participants were instructed to press the "Yes" key and the "No" key if the answer was no. The task ended after 42 trials. The primary outcome measure was the proportion of correct answers, normalized using arcsine transformation.

Subjective Cognitive Symptoms

The Checklist Individual Strength (CIS) is a 20-item self-report questionnaire that covers four domains of the subjective fatigue experience, including fatigue severity (eight items; e.g., physically I feel exhausted), concentration (five items; e.g., thinking requires effort), motivation (four items; e.g., I don't feel like doing anything), and physical activity levels (three items; e.g., I think I do very little in a day) (20). Participants were asked to indicate how they recognize themselves in the mentioned statements during the past 2 weeks on an (1) "No, that is not true" to (7) "Yes, that is true" scale. A CIS total score (ranging from 20 to 140) can be obtained by adding the individual scores on the 20 questions. Furthermore, the summary scores can be calculated for the four domains (fatigue severity range, 8–56; concentration range, 5–35; motivation range, 4–28; physical activity level range, 3–21). Higher scores indicate a higher degree of fatigue severity, more concentration problems, reduced motivation, or less physical activity. We assessed subjective cognitive symptoms using the concentrating scale of the CIS (Cronbach $\alpha = .84$).

Fatigue, Pain, and General Symptom Severity

Fatigue severity was assessed using the results of the CIS-fatigue severity subscale (20). To assess subjective pain, participants were asked to indicate in which of 19 mentioned body areas they had pain during the last week using the Widespread Pain Index (Appendix A, http://links.lww.com/PSYMED/A859) (5–7). The Widespread Pain Index score was determined by counting the number of body areas in which the participant reported pain during the last week.

To determine general symptom severity, the 12-item somatization scale of the Symptom Checklist-90 was used (21). This scale consists of 12 somatic symptoms, including the following: headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach, soreness of your muscles, numbness or tingling in your body, hot or cold spells, feeling weak in parts of your body, heavy feelings in arms or legs, a lump in your throat, and trouble getting your breath. Participants were asked to what extent they had been limited by these symptoms in the past 7 days. Items were scored on a 5-point scale ranging from (0) "Not at all" to (4) "Extremely." The outcomes of 12 items of the somatization scale of the Symptom Checklist-90 were summed (total scale ranging from 0 to 48).

Covariates

Age, sex, and educational level were included as covariates owing to their associations with CFS, FM, and cognition. Educational level was assessed using the question: "What is your highest completed education?" resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational levels.

Statistical Analyses

The characteristics of the different study groups were evaluated first. For continuous outcomes, means (standard deviations) were calculated. One-way analyses of variance were performed for continuous data, to test the differences in sample characteristics. In addition, χ^2 tests were performed for categorical data. Associations between cognitive task performance and subjective cognitive symptoms were calculated using multivariable regression analyses, adjusted for age, sex, and educational level. Cohen *d* effect sizes were calculated for the differences between study groups in cognitive task performance and subjective cognitive symptoms, based on the estimated means and standard deviations using analysis of covariance adjusted for age, sex, and educational level. To determine 95% confidence intervals for effect sizes, the following formulas were used (22,23):

$$\sigma\,(d) = \sqrt{\frac{N1+N2}{N1\times N2} + \frac{d^2}{2(N1+N2)}}$$

$$95\%\ \mathrm{CI}\ d = [d - 1.96\times\sigma(d), d + 1.96\times\sigma(d)]$$

Effect sizes of 0.2, 0.5, 0.8, and 1.3 were interpreted to reflect small, medium, large, and very large effects, respectively (22,24). If applicable, effect sizes were reversed to ensure that a positive effect reflected better cognitive function, as reflected in better performance on a cognitive task or less subjective cognitive symptoms. Lastly, to investigate whether fatigue severity, pain severity, and general symptom severity were related to cognitive task performance, multivariable linear regression analyses were performed using standardized variables, adjusted for age, sex, and educational level. Cases with missing data were deleted listwise. To investigate whether the regression coefficients differed significantly between groups (i.e., $b1 \neq b2$), a dummy variable for group and the interaction term (independent variable by dummy) were added to the regression models. Statistical significance was defined as $p < .05$. All analyses were performed using SPSS version 22.

RESULTS

Sample Characteristics

This study was performed in 79,966 participants (age = 52.9 [12.6] years, 59.2% female) of the general-population cohort Lifelines. Of the included participants, 3.1% (n = 2461) fulfilled the Centers for Disease Control and Prevention criteria for CFS, 0.2% reported MS (n = 156), 5.4% fulfilled the College of Rheumatology criteria for FM (n = 4295), 3.0% reported RA (n = 2415), and 88.7% were considered controls because they did not fulfill the diagnostic criteria for CFS or FM and did not report MS or RA (n = 70,951). Of the participants, 1.5% (n = 1217) fulfilled the diagnostic criteria for both CFS and FM. An overview of the general sample characteristics is presented in Table 1. Participants with CFS or FM reported significantly higher fatigue severity, subjective cognitive symptoms, pain complaints, and general symptom severity compared with both controls and participants with MS or RA. Participants with CFS or FM had significantly higher current comorbid mood or anxiety disorder than did the controls and participants with MS or RA. Table S1, Supplemental Digital Content (http://links.lww.com/PSYMED/A860), shows the associations between cognitive task performance and subjective cognitive symptoms.

TABLE 1. General Characteristics of the Study Groups

	Controls	CFS	MS	FM	RA
N (%)	70,951 (88.7)	2461 (3.1)	156 (0.2)	4295 (5.4)	2415 (3.0)
Female, *n* (%)	41,601 (58.6)	1823 (74.1)*	121 (77.6)	3296 (76.7)*,***,****	1568 (64.9)
Age, mean (SD)[a], y	52.7 (12.6)	54.2 (11.8)*	51.9 (9.8)	51.7 (11.4)*,***,****	61.3 (11.9)
Education, % low-middle-high[b]	2.4–65.3–30.1	4.8–72.6–19.6*,**	1.9–69.2–26.9	3.1–73.4–20.9*,***,****	5.6–70.1–21.0
CIS-fatigue, mean (SD)[a]	21.3 (10.6)	44.2 (8.0)*,**	33.2 (11.5)	40.5 (9.5)*,***,****	24.8 (11.7)
CIS-concentration, mean (SD)[a]	12.0 (6.3)	21.7 (7.4)*,**	16.2 (7.4)	20.1 (7.3)*,***,****	12.5 (6.4)
WPI, mean (SD)[a]	2.0 (2.2)	7.6 (4.1)*,**	2.9 (2.7)	8.8 (2.9)*,***,****	3.5 (3.0)
General symptom severity, mean (SD)[a]	1.3 (0.4)	2.1 (0.6)*,**	1.5 (0.4)	2.0 (0.5)*,***,****	1.5 (0.5)
DET, mean (SD)[a]	2.57 (0.18)	2.59 (0.19)*	2.61 (0.21)	2.58 (0.18)***	2.63 (0.21)
IDN, mean (SD)[a]	2.69 (0.094)	2.70 (0.096)*	2.70 (0.087)	2.69 (0.094)***	2.72 (0.11)
OBK (correct answers), mean (SD)[a]	1.29 (0.23)	1.26 (0.25)*	1.28 (0.22)	1.29 (0.23)***	1.24 (0.26)
OBK (reaction time), mean (SD)	2.91 (0.11)	2.93 (0.11)*,**	2.90 (0.10)	2.92 (0.11)*,***	2.94 (0.11)
OCL, mean (SD)[a]	0.95 (0.12)	0.93 (0.13)*	0.93 (0.12)	0.94 (0.13)*,***	0.93 (0.13)
Current mood disorder, *n* (%)[b]	1455 (2.1)	544 (22.1)*,**	3 (1.9)	633 (14.7)*,***,****	73 (3.0)
Current anxiety disorder, *n* (%)[b]	4228 (6.0)	754 (30.6)*,**	14 (9.0)	1032 (24.0)*,***	138 (5.7)

CFS = chronic fatigue syndrome; MS = multiple sclerosis; FM = fibromyalgia; RA = rheumatoid arthritis; SD = standard deviation; CIS = Checklist Individual Strength; WPI = Widespread Pain Index; DET = detection task; IDN = identification task; OBK = one back; OCL = one card learning task.

* $p < .01$ versus controls.

** $p < .05$ versus MS.

*** $p < .01$ versus RA.

**** $p < .01$ versus CFS.

[a] Using analysis of variance.

[b] Using χ^2 tests.

Cognitive Task Performance in CFS and FM as Compared With Controls, MS, and RA

In the current sample, 69.6% of the control group (n = 49,386), 65.4% of participants with CFS (n = 1609), 71.8% of participants with MS (n = 112), 69.1% of participants with FM (n = 2969), and 61.9% of participants with RA (n = 1494) completed the CogState computerized cognitive battery. Figure 1 shows the differences between groups in cognitive task performance and subjective cognitive symptoms. Participants with CFS performed significantly poorer on all tasks compared with controls with only small effect sizes, except for OBK (reaction time; Figure 1A). Participants with FM performed significantly poorer on the OCL task (visual learning/memory) compared with controls with small effect size, whereas no significant differences were found for the other tasks. Furthermore, participants with CFS or FM reported significantly more subjective concentration problems compared with controls with large to very large effect sizes.

When comparing participants with CFS or FM and participants with well-defined medical diseases (Figure 1B), no significant differences were found for all cognitive tasks between participants with CFS or FM compared with participants with MS or RA, with the exception of a significantly better performance on OBK (reaction time) in participants with FM compared with participants with RA. Participants with CFS or FM reported significantly more subjective concentration problems compared with participants with MS or RA with medium to large effect sizes.

When comparing participants with CFS versus participants with FM (Figure 1C), participants with CFS scored significantly lower on the IDN (visual attention) and OBK (attention/working memory) tasks compared with participants with FM with a small effect size. In addition, participants with CFS reported significantly more subjective concentration problems compared with FM participants with small effect sizes.

Comorbid Mood or Anxiety Disorder

Analyses were repeated excluding participants with comorbid mood or anxiety disorders. Among all comparisons, the results with regard to differences between groups in cognitive impairments remained essentially the same (Figure 2). No differences were found in the comparison of participants with CFS or FM versus controls (Figures 2A, B) or versus participants with MS or RA (Figures 2C, D). In contrast to the main analyses, the exclusion of participants with mood or anxiety disorders resulted in significantly lower scores on the DET task (speed of processing) in participants with CFS compared with FM (Figures 2E, F).

Associations Between Symptom Severity and Cognitive Task Performance

Results of the multivariable regression analyses investigating the association between fatigue, pain, or general symptom severity and cognitive task performance can be found, per group, in Table 2. In controls, severity of fatigue was significantly negatively associated with DET, but not associated with IDN, OBK, or OCL scores. General symptom severity was positively associated with IDN, OBK (correct answers), and OCL. In participants with CFS, severity of fatigue was significantly negatively associated with DET, and general symptom severity was significantly positively associated with DET, IDN, and OBK (correct answers). General symptom severity was

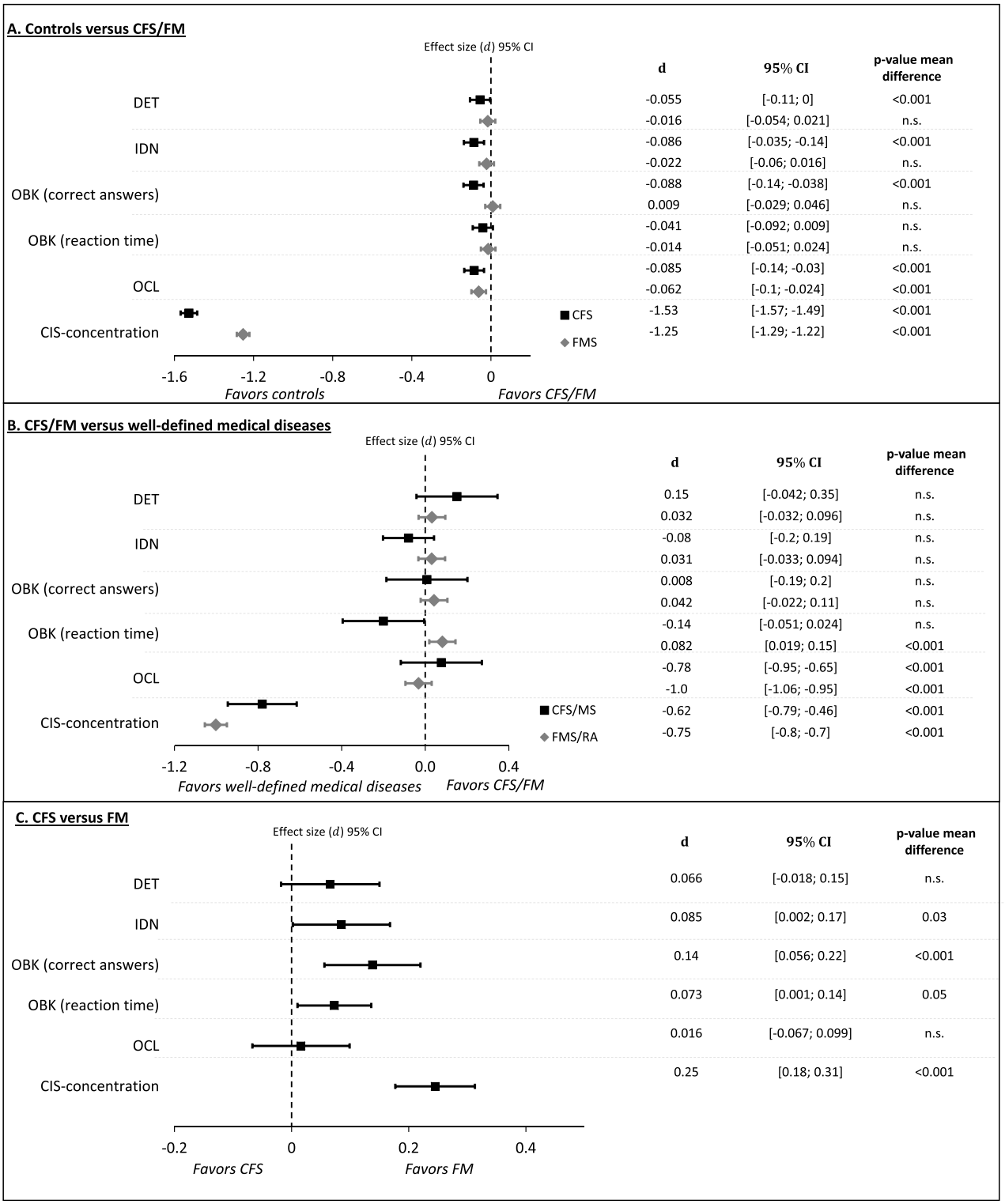

FIGURE 1. Effect sizes' objective and subjective cognitive functioning. Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms. Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level. CFS = chronic fatigue syndrome; MS = multiple sclerosis; FM = fibromyalgia; RA = rheumatoid arthritis; CI = confidence interval; DET = detection task; IDN = identification task; OBK = one back; OCL = one card learning task; CIS = Checklist Individual Strength.

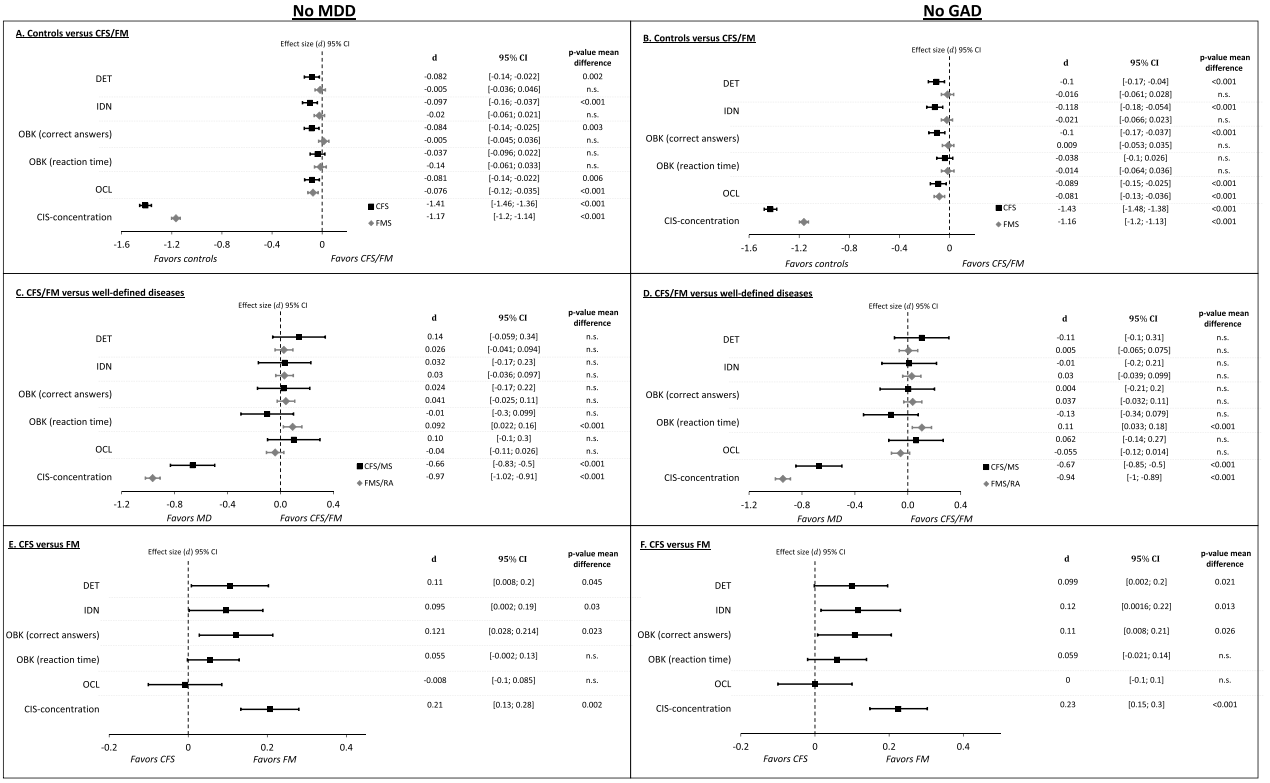

FIGURE 2. Effect sizes' objective and subjective cognitive functioning, when excluding comorbid major depressive disorder or generalized anxiety disorder. Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms. Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level. CFS = chronic fatigue syndrome; GAD = generalized anxiety disorder; MDD = major depressive disorder; MS = multiple sclerosis; FM = fibromyalgia; RA = rheumatoid arthritis; CI = confidence interval; DET = detection task; IDN = identification task; OBK = one back; OCL = one card learning task; CIS = Checklist Individual Strength.

significantly positively related to all four tasks in participants with FM, but not for OBK (reaction time), indicating that a high symptom severity was associated with reduced task performance in FM.

Statistical tests of differences in regression coefficients between groups (see note under Table 2) indicated some differences between groups. Although one association was significantly different in participants with CFS from that in controls, and two from those in participants with MS, the estimates were very small and mainly nonsignificant. In participants with FM, a few associations were significantly different from controls, and one association was significantly different from participants with RA. However, estimates were again very small and, in one case, nonsignificant within the group of FM.

Post hoc, we tested associations between cognitive task performance and subjective cognitive symptoms in each of the groups using multivariable regression analyses, adjusted for age, sex, and educational level. These associations were not significant except for the RA group in which a significant but low association was found four all four tasks.

DISCUSSION

This is the first large population-based study that assessed both objective cognitive task performance and subjective cognitive symptoms in individuals with CFS and FM compared with individuals with MS and RA and a control group, including relevant confounding variables. We found that subjective cognitive symptoms are more prevalent in individuals with CFS and FM than in controls and individuals with MS and RA, respectively. Participants with CFS had significantly more subjective cognitive symptoms and impairments in cognitive task performance compared with participants with FM, which could not be attributed to the presence of comorbid mood or anxiety disorders. In addition, associations between physical symptom severity and cognitive task performance were, in most cases, not significantly different between participants with CFS or FM and controls or participants with well-defined medical diseases. General symptom severity, but not the main symptoms fatigue or pain, was, in most cases, significantly associated with the performance on the cognitive tasks in all groups.

The main strength of the current study is that it was performed in a large population-based sample, in which data on subjective cognitive symptoms, cognitive task performance, and relevant confounding variables were collected. This enabled comparing participants with CFS or FM and participants with well-defined medical diseases in a single cohort, avoiding differences in selection procedures between cases and controls. Because we selected the groups from the general population, it was possible to examine subjective cognitive symptoms and cognitive task performance of the different study groups irrespective of help-seeking behavior, referral by clinicians, and differences in diagnostic assessment.

TABLE 2. Associations Between Symptom Severity and Objective Cognitive Functioning

	DET	IDN	OBK (Correct Answers)	OBK (Reaction Time)	OCL
Controls					
CIS-fatigue	**−0.016 (−0.025 to −0.007)**	0.001 (−0.008 to 0.011)	0.007 (−0.016 to 0.003)	0.008 (−0.001 to 0.018)	0.008 (−0.001 to 0.018)
WPI	−0.01 (−0.021 to 0.00)	−0.008 (−0.018 to 0.002)	−0.001 (−0.012 to 0.01)	−0.008 (−0.021 to 0.00)	0.002 (−0.01 to 0.010)
SCL-90 SOM	0.01 (0.00 to 0.021)	**0.017 (0.007 to 0.028)**	**0.031 (0.02 to 0.042)**	**0.004 (−0.006 to 0.016)**	**0.027 (0.016 to 0.038)**
CFS					
CIS-fatigue	**−0.093 (−0.16 to −0.025)***,**	0.004 (−0.067 to 0.074)**	−0.03 (−0.11 to 0.046)	−0.01 (−0.083 to 0.054)	−0.042 (−0.12 to 0.032)***
WPI	−0.01 (−0.042 to 0.022)	0.016 (−0.017 to 0.049)	−0.004 (−0.04 to 0.032)	−0.024 (−0.048 to 0.016)	0.019 (−0.016 to 0.054)
SCL-90 SOM	**0.038 (0.003 to 0.072)**	**0.042 (0.006 to 0.079)**	**0.048 (0.008 to 0.088)**	0.029 (−0.014 to 0.056)	0.031 (−0.007 to 0.07)
MS					
CIS-fatigue	0.15 (−0.054 to 0.35)	**0.20 (0.031 to 0.38)**	−0.12 (−0.31 to 0.07)	0.006 (−0.17 to 0.18)	0.069 (−0.12 to 0.26)
WPI	−0.048 (−0.26 to 0.16)	0.011 (−0.17 to 0.19)	−0.043 (−0.24 to 0.15)	0.022 (−0.16 to 0.20)	0.076 (−0.12 to 0.27)
SCL-90 SOM	**0.22 (0.002 to 0.43)**	0.10 (−0.082 to 0.29)	−0.052 (−0.24 to 0.13)	−0.031 (−0.20 to 0.15)	0.01 (−0.18 to 0.21)
FM					
CIS-fatigue	−0.029 (−0.071 to 0.012)	0.003 (−0.04 to 0.046)	0.004 (−0.04 to 0.048)	−0.006 (−0.046 to 0.032)	−0.034 (−0.078 to 0.010)*,****
WPI	−0.013 (−0.046 to 0.019)	0.004 (−0.029 to 0.037)	−0.002 (−0.036 to 0.032)	−0.009 (−0.038 to 0.021)	0.005 (−0.029 to 0.039)
SCL-90 SOM	**0.053 (0.025 to 0.081)***	**0.055 (0.027 to 0.084)***	**0.042 (0.013 to 0.072)**	**0.03 (−0.002 to 0.051)**	**0.051 (0.021 to 0.08)**
RA					
CIS-fatigue	0.001 (−0.055 to 0.056)	0.032 (−0.024 to 0.088)	0.056 (0 to 0.12)	0.003 (−0.048 to 0.054)	0.045 (−0.008 to 0.097)
WPI	−0.045 (−0.099 to 0.01)	0.011 (−0.045 to 0.066)	0.027 (−0.031 to 0.085)	0.007 (−0.044 to 0.058)	0.01 (−0.043 to 0.062)
SCL-90 SOM	0.003 (−0.05 to 0.055)	0.03 (−0.023 to 0.083)	**0.065 (0.009 to 0.12)**	**0.024 (−0.025 to 0.074)**	**0.06 (0.01 to 0.11)**

DET = detection task; IDN = identification task; OBK = one back; OCL = one card learning task; CIS-fatigue = fatigue subscale of the Checklist Individual Strength; WPI = Widespread Pain Index; SCL-90 SOM = 12-item somatization scale of the Symptom Checklist-90; CFS = chronic fatigue syndrome; MS = multiple sclerosis; FM = fibromyalgia; RA = rheumatoid arthritis.

Multivariable regression analyses, adjusted for age, sex, and educational level. Reported as standardized *B* (95% confidence interval). Significant associations are set in bold. A positive association indicates that the experience of more symptoms was associated with worse performance on the objective cognitive tasks.

Asterisks refer to associations that differed between groups.

* $p < .05$ versus controls.

** $p < .05$ versus MS.

*** $p < .05$ versus FM.

**** $p < .01$ versus RA.

There are also limitations of the current study. First, we used a brief battery that aims to measure the presence of cognitive problems in four cognitive domains. This brief battery only covers these domains in a relatively short time span. It follows that the scores can only be proxies for more lengthy cognitive (computer) tasks, whereas adequate cognitive functioning in daily life obviously requires much more, and more complex, processing. We deem our findings as valid, although we may have missed more subtle cognitive differences in objective cognitive functioning between individuals with CFS or FM and controls or individuals with well-defined medical diseases. From a clinical point of view, scores on the CogState brief battery should be seen as a proxy for cognitive functioning problems. If cognitive impairments are detected, more extensive (computerized) neuropsychological testing is warranted. Second, because of the sample size and wide geographical region in which the participants lived, it was not possible to perform all CogState tests on the same computer. Differences between computers might have caused differences between participants. However, we expect that such effects would be random, and therefore, we do not expect this to have influenced our results. Third, cognitive tasks assess specific cognitive functions, whereas questionnaires cover more global cognitive functions, which makes it difficult to compare results obtained by cognitive tasks and subjective cognitive symptoms. The CIS-concentration scale was used to reflect subjective cognitive symptoms, but this questionnaire is designed to measure subjective fatigue. Therefore, the concentration scale may not fully reflect subjective cognitive symptoms. However, because of the limited number of items that each research area can contribute to a multidisciplinary study such as Lifelines, it was not possible to include an additional questionnaire specifically focused on subjective cognitive symptoms. Fourth, CFS and FM diagnoses were based on the responses to a questionnaire. This questionnaire included the official positive diagnostic criteria, so we assessed the symptoms that comprise the diagnosis instead of the presence of the diagnosis itself, but without an assessment by a physician or additional blood tests. Because Lifelines is a large population cohort study that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to determine whether participants met the diagnostic criteria for CFS or FM based on clinical and physical examinations. Also, RA and MS were assessed based on self-reported disease status derived from the questionnaire; validation studies using clinical diagnosis or medical records are lacking. In addition, controls might have suffered from another condition that may have influenced their cognitive function. However, such disorders are also present in the participants fulfilling the diagnostic criteria for CFS or FMS, so it seems unlikely that this would have had a major influence on the results.

Our study supports previous findings that cognitive symptoms are more prevalent and severe in both patients with CFS and FM compared with controls (8,9). Furthermore, we found that individuals with CFS had reduced visual learning and working memory maintenance, and individuals with CFS or FM had reduced visual attention scores compared with controls. Individuals with CFS or FM did not differ from controls in visuomotor processing speed. Therefore, this very basic process cannot serve as an explanation for the differences found in visual attention, working memory, and visual learning as measured by CogState. These findings are in accordance with meta-analyses that concluded that patients with CFS and FM have primarily cognitive impairments in the domains of attention, memory, and tasks requiring working memory (10,11). In contrast to earlier research, we found only small effect sizes for the differences, and we found that the cognitive task performance of individuals with CFS and FM is comparable with those in individuals with MS and RA (25). A possible explanation for these differences might be that we have avoided some limitations of previous studies, such as the use of small samples and self-report diagnoses. In addition, previous research mostly recruited referred patients, whereas we selected individuals from the general population. Thus, the results in previous research might be influenced by help-seeking behavior, referral practices by clinicians, or differences in diagnostic assessment. That said, our cognitive task was brief and should be regarded as a proxy of more extensive (computerized) neuropsychological testing. This study may therefore not have detected all cognitive differences between the groups.

This study found that subjective cognitive symptoms were more prevalent in individuals with CFS or FM compared with control participants and individuals with well-defined medical diseases, whereas differences in cognitive task performance between the groups were rather mild. Similar findings have been reported in previous studies, investigating both healthy participants and patients with CFS or other disorders (26–28). The difference between the outcomes of subjective and objective assessments may be due to the fact that questionnaires measure different domains of cognitive function than cognitive tasks (10,28). Questionnaires cover more global and overarching cognitive functions, whereas tasks assess much smaller and specific functions. In addition, the CogState brief battery covered four cognitive domains, whereas adequate cognitive functioning in daily life requires much more, and more complex, processing. Furthermore, in accordance with previous research, the presence of comorbid mood or anxiety disorders did not explain the differences in cognitive performance between groups (29). Thus, although mood or anxiety disorders are relatively common in patients with CFS and FM (12), we found no evidence to suggest that they contribute to cognitive impairments in our study. We also found that the associations between physical symptom severity and cognitive task performance were, in most cases, not significantly different between individuals with CFS or FM and controls or individuals with well-defined medical diseases. Moreover, general symptom severity, but not the main symptoms fatigue or pain, was, in most cases, significantly associated with the performance on the cognitive tasks in all groups. The associations between the experience of somatic symptoms and the performance on the cognitive tasks were therefore not unique to individuals with CFS or FM, as shown by the results in controls or the MS/RA groups.

Lastly, we investigated differences between participants with CFS and participants with FM. We found that participants with CFS had significantly more subjective cognitive symptoms and performed significantly worse on tasks measuring speed of processing and attention/working memory, compared with participants with FM. These findings indicate that cognitive problems seem to be a more prominent symptom in individuals with CFS compared with FM.

Although our study addresses many limitations of previous research, our cross-sectional design provides only a first step. Future studies will be necessary to understand the causes of and contributors to cognitive problems in patients with CFS or FM and the

clinical relevance of these findings. Furthermore, the fluctuations that occur in symptoms in these patients (e.g., pain, fatigue) may result in variable results on objective cognitive tasks (30). We recommend the use of a more extensive cognitive battery that measures more aspects of cognitive functioning, in correctly diagnosed CFS and FM patients compared with a well-matched control group, including relevant confounding variables and taking into account the fluctuations of symptoms experienced.

The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

Source of Funding and Conflicts of Interest: This research received no specific grant from any funding agency, commercial or not-for-profit sectors. Lifelines has been funded by a number of public sources, notably the Dutch government, the Netherlands Organization of Scientific Research NWO, the Northern Netherlands Collaboration of Provinces (SNN), European fund for regional development, the Dutch Ministry of Economic Affairs, Pieken in de Delta, Provinces of Groningen and Drenthe, the Target project, BBMRI-NL, the University of Groningen, and the University Medical Center Groningen, the Netherlands. All authors declare that there are no conflicts of interest.

Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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