Similar but different

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Functional limitations in functional somatic syndromes and well-defined medical diseases. Results from the general population cohort LifeLines

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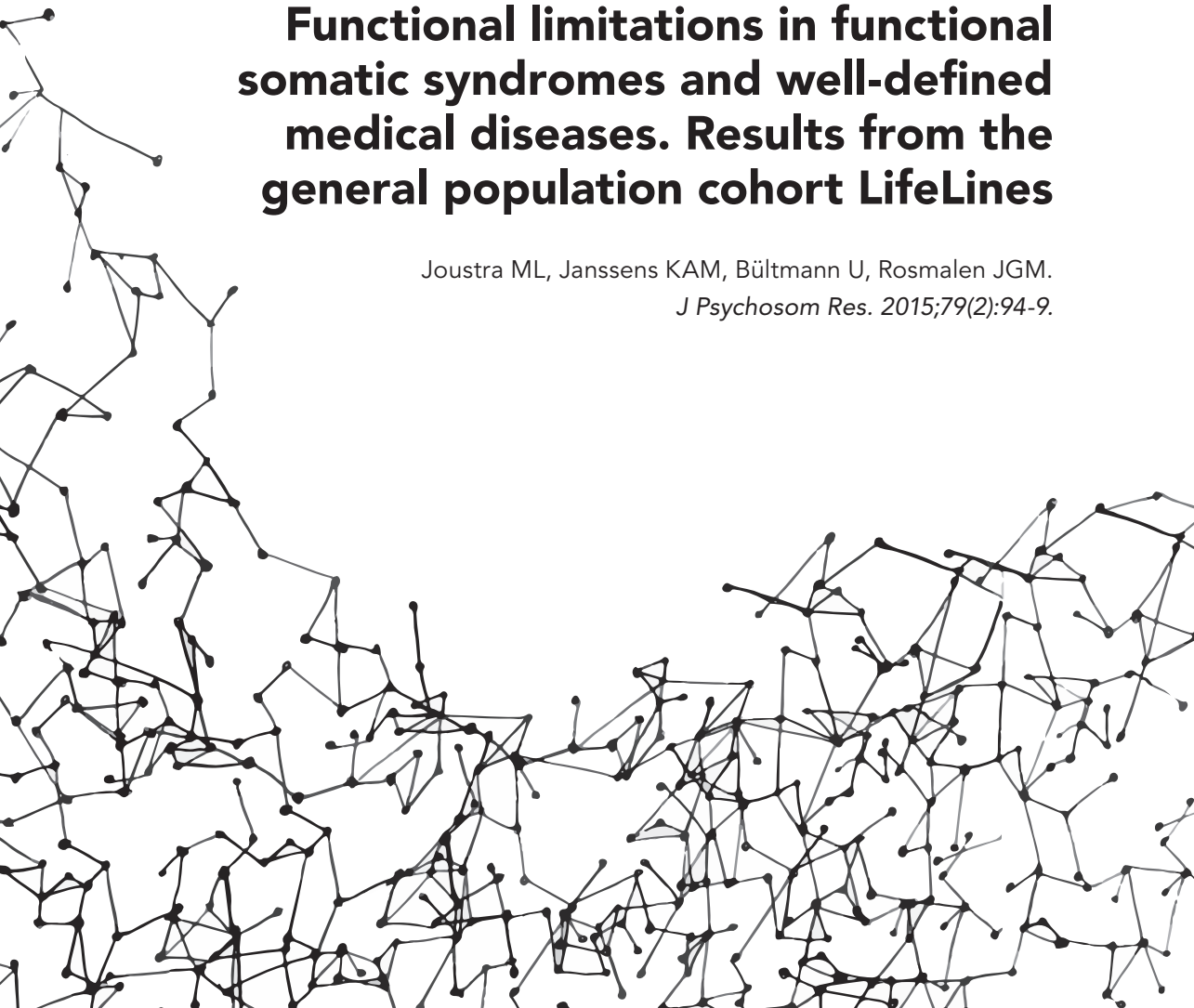

ABSTRACT

Objective: Functional somatic syndromes (FSS), defined as physical syndromes without known underlying organic pathology, are sometimes regarded as less serious conditions than well-defined medical diseases (MD). The aims of this study were to evaluate functional limitations in FSS, and to compare the results to MD patients with the same core symptoms.

Methods: This study was performed in 89,585 participants (age:44.4±12.4 years, 58.5% female) of the general-population cohort LifeLines. Quality of Life (QoL) and work participation were examined as indicators of functional limitations. QoL was assessed with two summary scales of the RAND-36: the physical component summary (PCS) and the mental component summary (MCS). Work participation was assessed with a self-reported questionnaire. QoL and work participation were compared between FSS and MD patients, using Chi-squared tests and ANCOVA-analyses, adjusted for age, sex, educational level, and mental disorders.

Results: Of the participants 11.0% (n=9,861) reported a FSS, and 2.7% (n=2,395) reported a MD. Total QoL, PCS and MCS were significantly lower in all the separate FSS and MD compared to controls ($p \leq 0.001$). Clinically relevant difference in QoL between chronic fatigue syndrome and multiple sclerosis patients, and fibromyalgia syndrome and rheumatoid arthritis patients were found. FSS and MD patients reported a comparable reduced working percentage, increased sick absence, early retirement due to health-related reasons and disability percentage, compared to controls ($p \leq 0.001$).

Conclusion: Functional limitations in FSS patients are common, and as severe as those in patients with MD when looking at QoL and work participation, indicating that FSS are serious health conditions.

INTRODUCTION

The experience of physical symptoms in the general population is common (1). When medical evaluation does not reval sufficient explanatory pathology, these symptoms are referred to as functional somatic symptoms. Functional somatic symptoms often occur together resulting in functional somatic syndromes (FSS). Chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS) are the most well-known FSS. CFS is mainly characterized by fatigue without sufficient explanatory pathology (2), FMS patients suffer from musculoskeletal pain with unknown etiology (3), and IBS patients suffer from bowel complaints with unknown underlying pathology (4). These core symptoms are typically accompanied by various additional symptoms. The etiology of all FSS is assumed to be multifactorial involving biological, psychological, and social factors (5).

Because physicians cannot find a disease-based explanation for these syndromes nor offer appropriate treatment, they find it often difficult to deal with FSS. Physicians are also often frustrated as a result of difficulties in controlling the symptoms and the patients' emotional responses to the syndromes (6). Furthermore, it is often assumed that functional limitations in FSS patients are less severe than in patients with well-defined medical diseases (MD). To date, relatively little is known about functional limitations in FSS patients compared to MD patients. FSS patients have been shown to suffer from productivity loss in daily activities, and from social isolation (7,8). Several studies suggest that Quality of Life (QoL) is impaired in FSS patients (9-11). For instance, overall QoL scores in CFS patients were significantly lower than in other chronic illness groups (12). QoL and functional disabilities among patients with FMS has been found to be similar to or worse than QoL in patients with rheumatoid arthritis (RA), Parkinson's disease, and other pain conditions (11,13-15). Also IBS patients had significantly lower QoL scores than the general population (16,17). QoL appeared to be similarly reduced in IBS and inflammatory bowel disease (IBD) (18). While previous studies only compared one FSS and MD, we aimed to compare multiple FSS and MD in one cohort, thereby avoiding differences in selection procedure or measurement.

FSS are associated with relevant indirect costs (8). A recent study showed that costs for healthcare services use and work-related costs in functional somatic

symptoms was estimated to be €6,815.91±10,923.14 per patient per year (19,20). Work-related costs are predominantly caused by productivity loss at work (56%), early retirement (29%), and sickness absence (14%) (21). Moreover, high levels of somatic symptoms are a determinant of long-term sickness absence, health-related job loss, and work disability (22). FSS patients often encounter difficulties at work, as a result of the somatic symptoms (8,23). For instance, fatigue is significantly influencing work participation in FSS patients resulting in more productivity loss at work and sickness absence (24,25). Because there are no studies that compare work participation between FSS and MD patients, it is unknown to what extent work participation is affected in FSS patients compared to MD patients.

The aim of the current study was to compare functional limitations in FSS patients, MD patients, and controls (defined by the absence of self-reported FSS or MD). We hypothesize that FSS and well-defined medical diseases are associated with equal functional limitations. This study is based on data of LifeLines, a large population-based cohort study of over 89,000 participants. To the best of our knowledge, there are no studies that evaluate functional limitations in both FSS and MD patients in one cohort. CFS patients were compared with patients who suffer from multiple sclerosis (MS), because fatigue is the most common symptom experienced by persons with MS (26). FMS patients were compared with RA patients, because they share similar symptoms including pain and sleep disorders (27). Lastly, IBS patients were compared with IBD patients, consisting of Crohn's disease and ulcerative colitis, because they share many of the clinical symptoms of IBS (28).

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study. LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of 165,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics (29).

Recruitment

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 in 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 website.

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.

Measures

Functional somatic syndromes and well-defined somatic diseases

FSS and MD were assessed by questionnaire, including a list of chronic disorders with three FSS (spastic or irritable bowel syndrome, fibromyalgia syndrome, chronic fatigue syndrome) and four MD (Crohn's disease and ulcerative colitis, multiple sclerosis and rheumatoid arthritis). Participants were asked to indicate which of these diseases they have or have had, with more than one answer allowed. IBD was defined as the presence of Crohn's disease or ulcerative colitis. Controls were defined by the absence of self-reported FSS or MD. To define a more strict diagnosis, FSS patients with a comorbid well-defined medical disease were excluded, including CFS patients who reported comorbid MS (N=6), FMS patients who reported comorbid RA (N=196), IBS patients who reported comorbid IBD (N=103), and other combinations (N=258). Furthermore, participants who

reported more than one FSS (N=1,281) (for more details, see 30) or well-defined medical disease (N=29) were excluded, so that the different groups present their own corresponding core symptom.

Functional limitations

The RAND-36 was used to evaluate health-related QoL (31). The RAND-36 consists of 36 closed-ended, structured questions that measure QoL in eight subscales (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health). The subscales were summarized in two components: the physical component summary (PCS) and mental component summary (MCS). The PCS includes physical function, role physical, bodily pain, and general health, while the MCS includes vitality, social function, role emotional, and mental health. The PCS, MCS, and total QoL score were calculated as recommended by the RAND-36 guideline (32), to generate a score from 0 to 100, with 0 being the lowest score and 100 being the best score for QoL. The outcome measures were transformed in T-scores performing a Z-score transformation ([Z * 10] + 50). The T-score with the mean of 50 and an SD of 10 is the average for the Dutch population. Thereafter, summary score coefficients of the RAND-36 were used to calculate the PCS, MCS and total QoL score correctly (32). A minimum difference of three points on any given RAND-36 scale was considered clinically relevant (31). The RAND-36 is validated in the general population and for patients suffering from several medical conditions (31).

Work participation was assessed with a self-reported questionnaire, including the following questions: "Which situation applies to you?" (answer categories: working, retired; early retired; unemployed/looking for work; disabled for work; welfare; homemaker; study), and "On average how many hours per week do you spend on paid work?". Participants who indicated they were early retired, the reason for stop working was asked (answer categories: retirement; illness/unfit for work; dismissal/unemployment; other). Participants who indicated that they were disabled for work were asked for what percentage they were disabled for work (ranging between 0- 100%). According to the definition of Statistics Netherlands, the working population was defined working ≥12 hours per week (33). Sick leave was assessed by the following questions: "In the past 3 months, how many days did you not work because of an illness or health problems?", and "In the past year, how often

did you stay home from work because of an illness or health problems?". Sick leave frequency was dichotomized (<4 and ≥4 days).

Covariates

Information on age and sex were obtained by questionnaire. Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low, middle, and high educational level. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education. Mental disorders, including current major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and generalized anxiety disorder were assessed with a standardized diagnostic interview: the Mini International Neuropsychiatric Interview (MINI) 5.0.0. The MINI is a brief structured interview for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10. A dichotomous variable for mental disorders (i.e. mood and/or anxiety disorders present or all absent) has been constructed from the MINI interview.

Statistical analyses

All analyses were performed using SPSS version 20. Analyses of covariance (ANCOVA) with Bonferroni correction were conducted to examine whether FSS, MD, and controls differed in age, QoL, working hours and days of sick leave. The percentage of participants that reported a frequency of sick leave of ≥4 times in the past year was described. Chi-squared tests were used to examine significant differences between FSS, MD and controls in sex, educational level, work participation, sick leave frequency, disability and retirement due to health-related reasons. Analyses with regard to QoL and work participation were adjusted for age, sex, and educational level. Analyses were repeated after an additional correction for mental disorders. Statistical analyses were corrected for age, sex, educational level, and mental disorders, because these factors are known to be related to FSS (2,3,30,34), MD (35-38), QoL (39,40), and work participation (25,41). Findings were considered statistically significant when $p \leq 0.05$, and clinically relevant with a minimum difference of three points on any given RAND-36 scale.

RESULTS

Demographic and work sample characteristics

Data were available for 89,585 participants, with a mean age of 44.4±12.4 years, and 58.5% female. Of these participants, 11.0% (n = 9,861) reported one FSS, 2.7% (n = 2,395) reported one of the specified MD, and 86.3% reported neither FSS nor MD (n = 77,329). An overview of prevalence rates of major medical conditions (lifetime) in the control population are presented in Table 1. Furthermore, prevalence rates of the separate FSS and MD, and their general characteristics are presented in Table 2. Lastly, prevalence rates of mental disorders in FSS and MD patients are presented in Table 3.

Table 1. Prevalence rates of major medical conditions in controls (lifetime).

	n	%
Arteriosclerosis	328	0.4
Cancer	3718	4.1
Diabetes	1621	2.1
Hypertension	15800	20.4
Stroke	475	0.6
Heart failure	517	0.7
Heart infarct	714	0.9
COPD	3545	4.6
Asthma	6162	8.0

Table 2. General characteristics of the study groups.

	n (%)	Female %	Age (years) mean (SD)	Education % Low – Middle -High
Controls	77329 (84.8)	55.6	44.2 (12.3)	28.7 39.1 30.0
Chronic fatigue syndrome	666 (0.8)	60.5[a,b]	44.8 (11.3)	30.5 40.8 24.8[a]
Multiple sclerosis	198 (0.2)	76.8[c,d]	44.9 (9.7)	30.3 42.9 25.3
Fibromyalgia syndrome	1686 (1.9)	90.4[c,e]	48.5 (10.5)[c,e]	44.0 38.3 14.5[c,e]

Table 2. Continued.

	n (%)	Female %	Age (years) mean (SD)	Education % Low – Middle -High
Rheumatoid arthritis	1572 (2.0)	60.8[c,f]	53.2 (13.2)[c,f]	44.0 31.0 21.8[c,f]
Irritable bowel syndrome	7509 (8.6)	79.2[c,g]	43.2 (12.1)[c,g]	29.1 40.1 28.4[a]
Inflammatory bowel disease	625 (0.7)	61.0[a,h]	45.9 (10.7)[c,h]	31.4 39.8 27.2

[a] p ≤ 0.05 versus controls, [b] p ≤ 0.001 versus MS patients, [c] p ≤ 0.001 versus controls, [d] p ≤ 0.001 versus CFS patients, [e] p ≤ 0.001 versus RA patients, [f] p ≤ 0.001 versus FMS patients, [g] ≤ 0.001 versus IBD patients, [h] ≤ 0.001 versus IBS patients.

Table 3. Prevalence rates of mental disorders.

	Mood disorder[1]	Anxiety disorder[2]	Mood and/or anxiety disorder
Controls	4.3	8.4	9.0
CFS	17.0	23.0	26.4
MS	6.6	9.6	11.1
CFS vs MS (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*
FMS	11.0	18.0	20.1
RA	6.0	10.3	11.3
FMS vs RA (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*
IBS	9.1	16.9	18.0
IBD	4.5	9.0	9.8
IBS vs IBD (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*

Data are presented as %
CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.
[1] Major depressive disorder, dysthymia; [2] Generalized anxiety disorder, social phobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without panic disorder.
[a]Using Chi-squared test.

Functional limitations

Health-related QoL

Total QoL, PCS and MCS were significantly lower in all the separate FSS and MD compared to controls (Figure 1; p≤0.001). In the comparisons between FSS and MD patients, only FMS patients (42.9±8.7) reported a significantly lower total QoL score than RA patients (46.3±8.5). Without adjusting for mental disorder, the total QoL score differed significantly between CFS (39.0±10.8) and MS patients (40.8±10.5; p = 0.003), and IBS (47.3±8.0) and IBD patients (48.3±8.1; p≤0.001). After adjusting for mental disorders, these differences were not statistically significant anymore. Furthermore, the PCS was found to be statistically different between CFS (40.2±10.8) and MS patients (38.3±10.9), and FMS (39.8±10.2) and RA patients (42.5±10.7), both with and without adjusting for mental disorders. Lastly, the scores for the MCS were found to be statistically different in all three comparisons, both with and without adjustment for mental disorders.

When considering clinically relevant differences, CFS patients reported a clinically relevant lower mental component score compared to MS patients (39.7±11.3 and 45.5±9.0). FMS patients reported a clinically relevant lower physical component score, mental component score, and total QoL score compared to RA patients. No clinically relevant differences between IBS and IBD patients were observed.

Work participation and sick leave

Analyses regarding work participation and sick leave were limited to the working age population (18 to 65 years). Of our participants, 84,607 (94.4%) were of working age (age: 42.8±10.8 years, 58.8% female); 56,513 (63.1%) of these participants reported to work 12 hours per week or more (age: 42.1±9.8 years, 54.8% female).

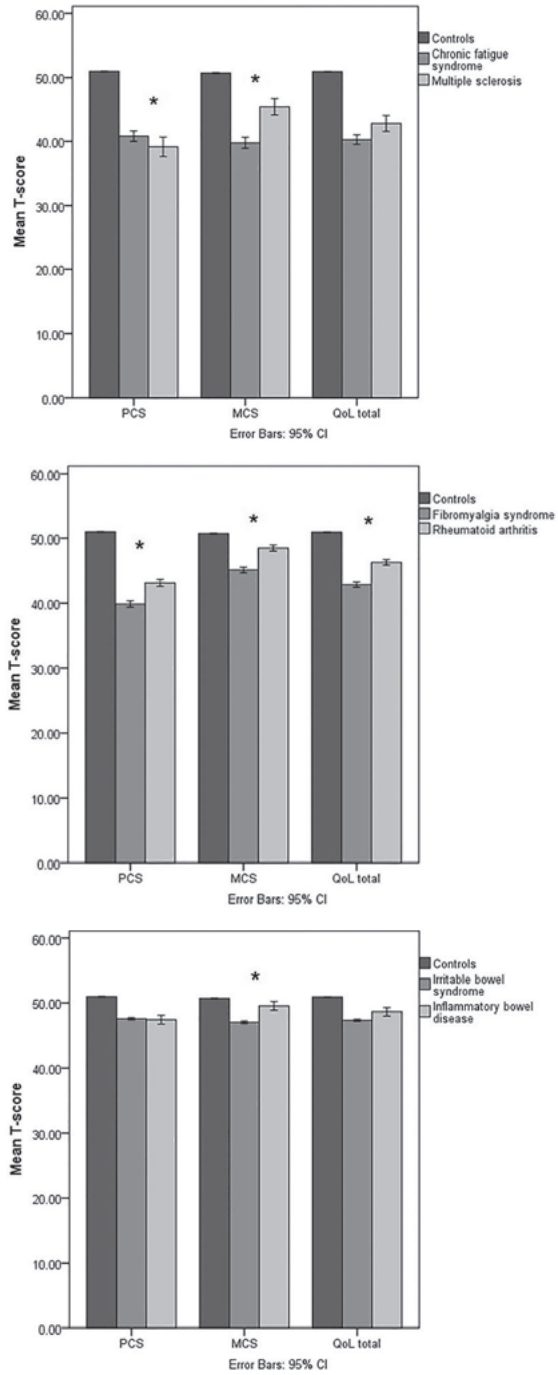

Figure 1. Differences between the groups with regard to the Quality of Life. QoL=quality of life, PCS=physical component summary, MCS=mental component summary. P ≤ .001 for all analyses that compared FSS or MD patients to controls. * P ≤ .001 for functional somatic syndrome patients versus well-defined medical disease patients.

As shown in Table 4, controls reported higher employment percentages (working ≥12 hours per week) than separate FSS and MD groups (p ranging from 0.02 to ≤0.001). When working, controls worked equally hours per week as FSS patients and MD patients, except for FMS (p=0.029), RA (p=0.046) and IBD patients (p=0.002) who worked less hours than controls. Working FSS and MD patients reported significantly more sick leave days, except for IBD patients (p=0.496), and a higher sick leave frequency than controls. When considering the separate syndrome comparisons, only statistically significant differences in work hours between IBS and IBD patients, and sick leave days between CFS and MS patients were found.

Retirement and work disability

Overall, controls retired less often due to health-related reasons, and reported a lower disability percentage than FSS and MD patients (Table 5; p≤0.001). When considering the separate syndrome comparisons, no statistically significant differences were found in early retirement due to health-related reasons, and disability percentage between FSS and MD patients.

Table 4. Work participation and sick leave among the working population (working ≥12hours/week).

	Working (%)[1,2]			Working (hours/ week) mean (SD)[3]			Sick leave (days/3 months) mean (SD)[3]	Frequent sick leave (%)[2,4]
	All	Men	Women	All	Men	Women		
Controls	67.8	73.8	63.1	33.6 (12.0)	40.5 (10.6)	27.2 (9.5)	0.8 (3.4)	3.6
CFS	50.3	59.6	44.1	33.5 (15.3)	40.6 (16.1)	27.1 (11.1)	1.5 (4.6)	13.7
MS	46.3	59.1	42.5	30.2 (12.6)	38.6 (14.0)	26.6 (10.0)	3.0 (7.8)	13.6
CFS vs MS (p-value)	*0.333[a]*			*0.593[b]*			*0.059[b]*	*0.983[a]*
				0.578[c]			*0.036[c]*	
FMS	51.9	61.3	50.9	27.2 (10.4)	40.0 (11.3)	25.6 (9.0)	1.3 (4.5)	7.6
RA	54.4	61.4	49.6	32.2 (12.3)	39.2 (11.2)	26.2 (9.7)	1.0 (3.1)	6.3
FMS vs RA (p-value)	*0.193[a]*			*0.885[b]*			*0.716[b]*	*0.296[a]*
				0.706[c]			*0.715[c]*	
IBS	64.0	70.4	62.4	30.1 (10.8)	39.9 (9.7)	27.3 (9.3)	1.1 (5.3)	6.6
IBD	63.4	70.6	58.8	31.2 (11.1)	37.5 (10.4)	26.5 (9.0)	0.8 (2.6)	7.4
IBS vs IBD (p-value)	*0.756[a]*			*0.015[b]*			*0.073[b]*	*0.532[a]*
				0.015[c]			*0.118[c]*	

CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.

[1] Percentage of all participants who are working ≥12 hours, [2] Chi-squared tests, [3] Analyses of Covariance, [4] ≥4 times of sick leave in the past year.

[a] Uncorrected using Chi-squared tests, [b]Adjusted for age, sex, and educational level, [c]Adjusted for age, sex, educational level, and mental disorders.

Table 5. Early retirement and work disability among the working age population.

	Early retirement due to health-related reasons (%)[1]	Disability % Mean (SD)[2]
Controls	2.0	53.5 (41.6)
CFS	15.4	75.8 (31.9)
MS	20.5	80.1 (28.5)
CFS vs MS (p-value)	*0.061*[a]	*0.307*[b] *0.094*[c]
FMS	10.8	70.7 (34.6)
RA	7.8	69.4 (34.5)
FMS vs RA (p-value)	*0.033*[a]	*0.991*[b] *0.852*[c]
IBS	3.4	63.0 (38.6)
IBD	4.7	62.2 (35.5)
IBS vs IBD (p-value)	*0.184*[a]	*0.806*[b] *0.431*[c]

CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.
[1] Among the participant who indicated that they were early retired using Chi-squared tests, [2] Among the participants who indicated that they were disabled for work using Analyses of Covariance.
[a] Uncorrected using Chi-squared tests, [b]Adjusted for age, sex, and educational level, [c]Adjusted for age, sex, educational level, and mental disorders.

DISCUSSION

Our study revealed that functional limitations in FSS patients are comparable to those in patients with a MD. FSS and MD patients had a reduced QoL compared to controls. FSS patients reported a lower mental component score compared to MD patients, with relevant clinically differences between CFS and MS patients, and FMS and RA patients. Controls, FSS, and MD patients reported a comparable working percentage. But when working, FSS and MD patients worked less hours per week and reported higher sick absence compared to controls. Thus, functional

limitations in FSS patients are common, and as severe when looking at QoL and work participation, as those in MD.

The main strength of this study is the large population-based sample. This study included a sufficient number of participants with the various disorders, allowing meaningful cross-group statistical comparisons. Additionally, information about the three main FSS and related MD was available which enabled comparing these FSS and MD in one cohort, limiting differences in selection procedures or measurement. To the best of our knowledge, this is the first study that evaluates functional limitations in FSS and MD patients in one large population cohort.

There are also several limitations in our study. As a self-reported questionnaire was used for the diagnosis of FSS and MD as well as for the assessment of QoL and work participation common method variance can not be excluded. Although self-reports may underestimate the amount of persons with FSS (42), this underestimation seems unlikely in our study because the prevalence rates for CFS, FMS and IBS were comparable to those reported in previous studies (2,3,43). Another limitation is that lifetime diagnoses of FSS were available instead of current diagnoses. A previous study in a general population cohort from the same geographical area suggests that a vast majority (i.e. 75%-100%, depending on the syndrome) of the participants that reported a history of CFS, FMS or IBS, still had this syndrome at the time of reporting (44). Moreover, the majority of the patients with CFS (>95%) and FMS (>93%) in the current study recently experienced fatigue and musculoskeletal pain in the past week(s). Unfortunately, no information about bowel complaints was available. To overcome the methodical weakness of self-reported questionnaires for the diagnosis of FSS and MD in the future, it is recommended to use patients' clinical records when possible. 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 more extensively assess the prevalence of the three FSS during the baseline assessment through practical limitations. We aim to assess FSS more extensively in future assessment waves, preferably by the use of clinical records. Lastly, because of the cross-sectional design, cause-effect relationships can not be examined. Furthermore, individuals who fulfil criteria for FSS and MD, but did not seek treatment and thus never received a diagnosis might differ from those who seek medical care and receive a diagnosis. Our study design may primarily have sampled FSS and MD

patients who received a diagnosis and sought medical care, and thus have more limitations than patients who did not seek medical care, thereby overestimating functional limitations in FSS.

Our study supports previous findings that FSS are associated with impaired QoL (9,10). Also in line with earlier studies, mental component scores were significantly lower in CFS and IBS patients than in MS and IBD patients (12,18). Furthermore, overall QoL, the PCS and MCS scores in FMS patients were significantly lower than in RA patients, which is also in accordance with previous findings (11,13-15). Although several QoL scores differed statistically between patients with FSS and well-defined medical diseases, not all of these differences were clinically relevant (i.e. differences larger than three points on the QoL scale). Nevertheless, CFS patients reported a clinically relevant lower mental component score compared to MS patients, and FMS patients reported a clinically relevant lower physical component score, mental component score, and total QoL, compared to RA patients. In addition to previous studies, we found that the lower QoL of FSS patients compared to MD patients is particularly related to mental limitations. The clinically relevant lower scores in the MCS in CFS and FMS patients might due to the difficulty in dealing with their disease symptoms. For instance, FSS patients reported that they felt not be taken seriously, because the absence of detectable pathology is sometimes interpreted as evidence that their problems are mental rather than physical (45). Moreover, FSS patients felt stigmatized, since others tended to doubt the accuracy and truthfulness of patients' reported disabling symptoms (46,47).

Our findings also indicate that working FSS patients worked equal hours per week, and reported equal sick leave days and frequency compared to MD patients (21). This indicates that both FSS and MD are associated with relevant indirect costs (8). Regarding sick leave, it is likely that both FSS and MD patients often encounter difficulties at work (8,23). For example, fatigue is a significant problem in both FSS and MD patients, influencing work participation (24,25). Thus, this may suggest that FSS symptoms affect work participation just like in MD symptoms. In summary, this population-based study revealed that the functional limitations in FSS patients are common and as severe as those in patients with MD, despite the absence of underlying organic pathology. It shows that FSS have not only individual, but also societal consequences. Therefore, health care professionals

in public and occupational health, researchers and society should pay more attention to these disorders and their consequences in terms of QoL and work participation. Increased knowledge and understanding of the etiology and impact of FSS may eventually improve the treatment of a significant proportion of the population (in our cohort 11.0%) who is suffering from FSS. The study urges the need for more research on FSS, a relatively neglected research area, especially studies on a better understanding of the etiology and treatment of these disorders are needed. Specific suggestions for studies with regard to QoL and functional limitations are to examine the cause-effect relationships between FSS and QoL as well as work participation, and to gain insight in the working conditions and work accommodations of FSS patients.

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