Similar but different

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Mood and anxiety disorders in chronic fatigue syndrome,fibromyalgia, and irritable bowel syndrome. Results from the LifeLines Cohort Study.

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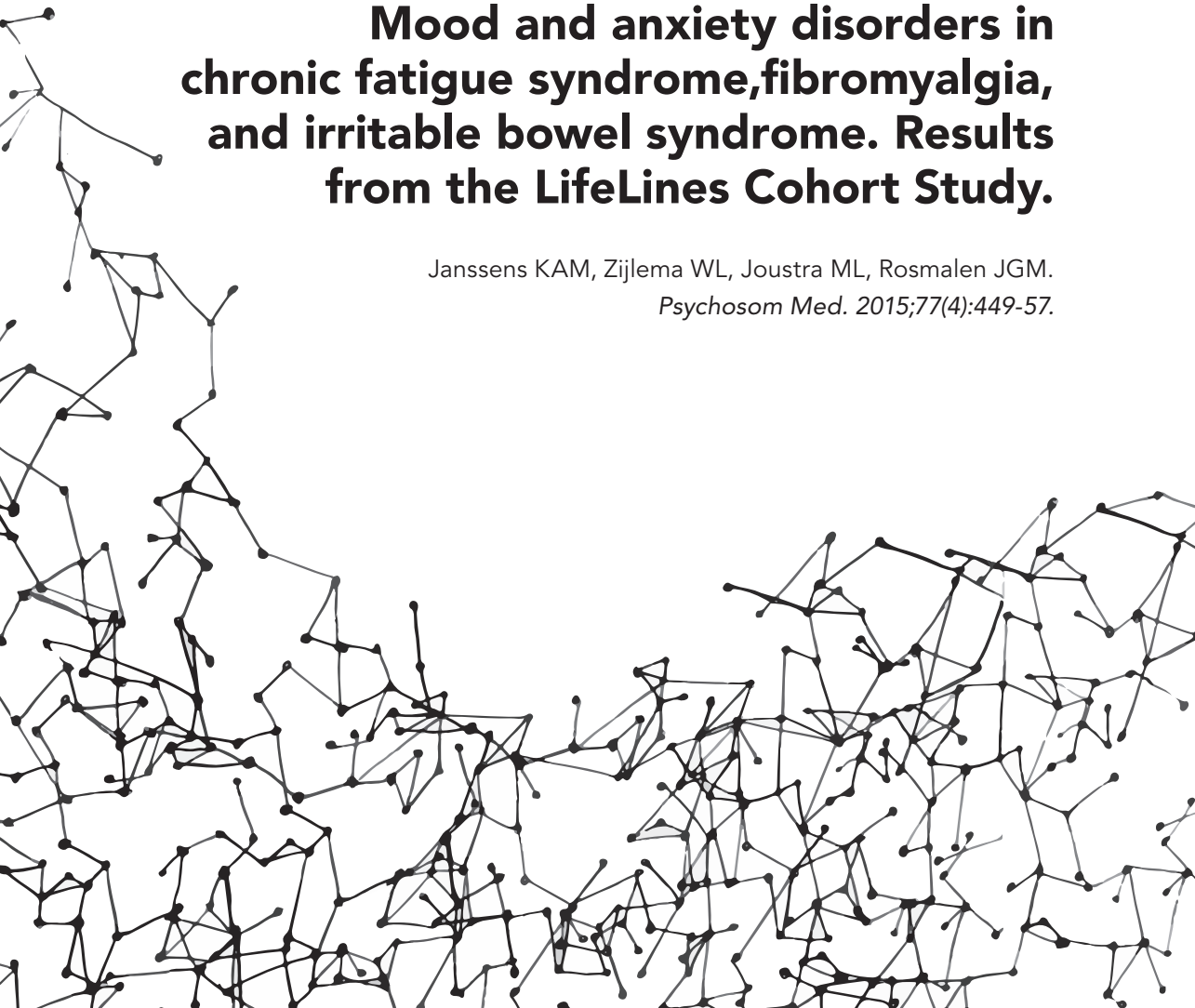

ABSTRACT

Objective: Functional somatic syndromes (FSS) have often been linked to psychopathology. The aim of the current study was to compare prevalence rates of psychiatric disorders between individuals with chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS).

Methods: This study was performed in 94,516 participants (mean age: 44.6 years, SD 12.5, 58.7 % female) of the general-population cohort LifeLines. FSS were assessed by self-reports. Mood disorders (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. generalized anxiety disorder, social phobia, panic disorder with/without agoraphobia, and agoraphobia) were assessed by means of the Mini International Neuropsychiatric Interview. Risks on psychiatric disorders were compared for individuals suffering from CFS, FMS, and IBS using logistic regression analyses adjusted for age and sex.

Results: Prevalence rates of CFS, FMS, and IBS were 1.3%, 4.0%, 9.7%, respectively. Individuals with CFS, FMS and IBS had significantly more mood (ORs 1.72 to 5.42) and anxiety disorders (ORs 1.52 to 3.96) than individuals without FSS, but prevalence rates were low (1.6 to 28.6%). Individuals with CFS had more often mood (ORs 2.00 to 4.08) and anxiety disorders (ORs 1.63 to 2.32) than individuals with FMS and IBS. Major depressive disorder was more common in FMS than IBS (OR 1.58, 95%CI=1.24-2.01) whereas these groups did not differ on dysthymia or anxiety disorders.

Conclusions: Mood and anxiety disorders are more prevalent in individuals suffering from FSS, and particularly CFS, than in individuals without FSS. However, most individuals with FSS do not suffer from mood or anxiety disorders.

INTRODUCTION

Somatic symptoms that cannot be sufficiently explained by underlying organic pathology are called functional somatic symptoms. Functional somatic symptoms tend to occur together and result in functional somatic syndromes (FSS). FSS are common, disabling and costly (1-4). Many FSS exist, and every medical specialty seems to have at least one. Chronic fatigue syndrome (CFS) is diagnosed by internists for patients suffering from unexplained fatigue; irritable bowel syndrome (IBS) is diagnosed by gastroenterologists for patients with unexplained bowel complaints; and fibromyalgia syndrome (FMS) is diagnosed by rheumatologists for patients having unexplained muscle pains.

Since several decades researchers have discussed co-morbidity of different FSS and wondered whether different FSS could result from the same underlying physiopathology (5, 6).Over 10 years ago, a landmark paper was published suggesting that the existence of different FSS is an artefact of medical specialization, and that in fact all patients with FSS (e.g. CFS, FMS, and IBS patients), suffer from the same syndrome (7). That paper has further fueled the lumper-splitter discussion that has been going on until today. "Lumpers" take the approach that all FSS result from the same etiology and thus can be studied together (7-9). "Splitters" believe that every particular FSS has its own specific background and should therefore be studied separately (10). More recent studies suggested a combination of both approaches (11-14). One argument in favor of the lumpers is that all FSS are associated with psychiatric symptoms and disorders, especially anxiety and depression.

FSS have indeed frequently been linked to psychopathology (12, 14, 15). However, these studies often relied on self-reports of anxiety and depression symptoms instead of diagnostic interviews. Therefore, information about prevalence rates of specific psychiatric disorders in FSS patients is scarce, while this information about psychiatric diagnoses is important since it might shed light on specific pathways underlying different FSS. Moreover, comparisons of psychiatric co-morbidity in different FSS within one study population are rare (16, 17), making it hard to examine whether psychiatric diagnoses are evenly prevalent in all FSS. A meta-analytic review comparing patients with FSS from different studies showed only minor differences in psychiatric co-morbidity between patients:

CFS patients were characterized by higher depression scores than IBS patients and FMS patients by lower anxiety scores than IBS patients (18). Persons with multiple FSS were not included in these studies, which hampered studying the influence of syndrome overlap. Moreover, most studies in this review concerned patients referred to tertiary care centers; these patients are more likely to resemble each other than patients that do not seek (specific) medical care. For example, help seeking behavior of FSS patients is related to higher levels of anxiety and depression (18, 19). Hence, differences in psychiatric co-morbidity between FSS might have been underestimated. Therefore, studies examining FSS patients in one population cohort are necessary.

The aim of the current study was to compare prevalence of mood and anxiety disorders in CFS, FMS and IBS patients based on diagnostic interviews in a large population-based cohort of over 90,000 adults.

METHODS

The sample

This study is based on data of LifeLines. LifeLines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the 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 (20).

Participants

Participants of LifeLines were obtained 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 probands 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. The general practitioners evaluated whether probands met the following exclusion criteria: severe psychiatric or physical illness; not being able to visit the general practitioner; not being able to fill in the questionnaires; not

being able to understand the Dutch language. Parents and children of probands were not excluded based on those criteria if a representative was willing to assist these participants in the fulfillment of the study. Inclusion of pregnant women was rescheduled until 6 months after pregnancy or 3 months after breast feeding. Second, persons who were interested to participate could register themselves via the LifeLines website. Data were collected between 8 November 2006 and 31 December 2012.

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 were 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. For this study, data of 94,516 participants were available, with an age range between 18 and 93 years, and a mean age of 44.6 (SD 12.5). The majority (58.7%) was female. More details about the sample can be found in Table 1.

Measures

Functional somatic syndromes

History of FSS was assessed by means of a questionnaire, which participants were asked to fill out at their homes. Within this questionnaire, a list of chronic disorders was presented, including CFS, FMS, and IBS. The participants were asked to indicate whether they ever suffered from each of these FSS. Although we thus asked for history of FSS within the LifeLines population, a previous study using a more extensive question in a general population cohort of 976 participants (21) suggests that a vast majority (i.e. 75-100%, depending on the syndrome) of persons indicating a history of CFS, FMS or IBS report to still being suffering from these syndromes. CFS patients also reporting multiple sclerosis (n = 6), FMS patients also reporting rheumatoid arthritis (n = 196) and IBS patients also reporting Crohn's disease or ulcerative colitis (n = 103) were excluded from our analyses, to exclude the possibility that the symptoms were caused by these underlying inflammatory diseases.

Co-morbid psychiatric disorders

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

Table 1. General description of the LifeLines cohort (n=94,516).

	Valid N	Mean (SD) or %
Age	94516	44.6 (12.5)
Sex (Male)	39007	41.3
Race (both parents born in the Netherlands)	88930	94.1
Education	28508	30.3
Low	36574	38.9
Middle	27187	28.9
High	1801	1.9
Other		
Netto income/month	3185	3.5
Lower than 750	2724	3.0
750-1000	7488	8.1
1000-1500	11531	12.5
1500-2000	12446	13.5
2000-2500	13524	14.7
2500-3000	11296	12.3
3000-3500	13950	15.2
Over 3500	15972	17.3
Unknown		
Marital status	61160	64.8
Married/Registered relationship		
Cohabiting	14906	15.8
Single	8689	9.2
Widow	1693	1.8
Divorced	3186	3.4
Partner, but non-cohabiting	3732	4.0
Other	989	1.0
Major medical conditions		
Arteriosclerosis (lifetime)	430	0.5
Cancer (lifetime)	4164	4.4
Diabetes (lifetime)	2238	2.4
Hypertension (lifetime)	19933	21.5
Stroke (lifetime)	688	0.7
Heart failure (lifetime)	668	0.7
Heart infarct (lifetime)	946	1.0
COPD	4919	5.2
Asthma	8018	8.5
Medication use (prescribed by doctor)	43081	46.9

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 (22). LifeLines participants were interviewed by trained medical professionals during their visit to the research facilities. Sections on depressive disorder, dysthymia, panic disorders, agoraphobia, social phobia, and general anxiety disorder were administered. The DSM-IV criteria were used to determine whether participants suffered from these disorders. Previous studies suggested acceptable validity and reliability of the MINI (22). Valid interview data were available for 97.5% of the participants (n = 92164).

Statistical analyses

Descriptive statistics were performed to compare prevalence rates and sex ratios between individuals with CFS, IBS, or FMS. Additionally, syndrome overlap was studied and proportions of participants suffering from CFS, IBS or FMS were plotted per age category for males and females. To examine whether individuals with FSS had higher risk on psychiatric disorders than individuals without FSS, binary logistic regression analyses were performed with separate FSS as predictors and the psychiatric disorders as outcome variables. FSS were included simultaneously to adjust for co-morbidity between syndromes. Binary logistic regression analyses were also used to test for differences in psychiatric co-morbidity *between* individuals with CFS, IBS, or FMS. Analyses were performed in the subgroup of participants that suffered from one of these disorders, with type of FSS included as a predictor. When the main effect of type of FSS was significant, different contrasts were used to test which specific FSS differed from each other. All analyses were adjusted for age and sex, since they are known to be related to both FSS (7, 23, 24) and psychiatric disorders (25, 26). All analyses were performed using SPSS version 20. Results were considered statistically significant if the 95%-confidence interval (CI) did not include 1.

RESULTS

Prevalence rates and co-morbidity

After exclusion of participants that reported both a FSS and a medical condition resembling the core symptoms of their FSS, data on FSS were available for 91,153 participants. Of these participants, 1.3 % reported CFS (n = 1,166), 3.0 % (n =

2,765) reported FMS, and 9.7 % (n = 8,858) reported IBS. Exact prevalence rates of comorbidity can be found in Figure 1. The majority (n= 10,121, 79.1 %) of the persons that reported suffering from CFS, FMS, or IBS (n=12,789) did not report a co-morbid FSS. However, this was especially true for persons suffering from IBS. About 40 % of the participants suffering from CFS or FMS reported one or two other FSS. Binary logistic regression analyses also showed higher risk on additional FSS in presence of one FSS: OR 8.57 (95%-CI 7.39-9.96) of CFS when having FMS and vice versa, OR 3.72 (95%-CI 3.27-4.23) of CFS when having IBS and vice versa, and OR 5.18 (95%-CI 4.77-5.62) of FMS when having IBS and vice versa. Moreover, the number of persons that reported all three disorders (n=106) was 37.7 times higher than could be expected based on prevalence rates of the separate syndromes.

Demographic characteristics

All disorders were much more common in females than in males. The sex difference was smallest in participants with CFS of whom 30.9 % was male, and largest in participants with FMS of whom 8.0 % was male. Furthermore, 19.0 % of participants with IBS were male. Prevalence rates of CFS, IBS, and FMS showed a small peak around the age of 60, most pronounced for FMS (Figure 2). Exception to this pattern was that IBS prevalence decreased in females after their mid-twenties.

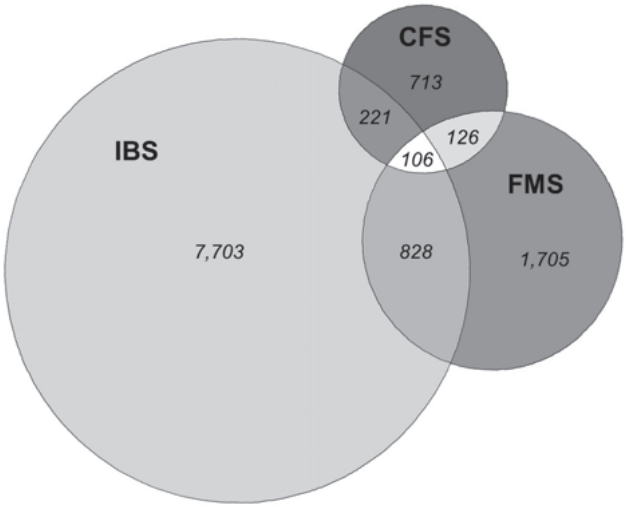

Figure 1. Overlap between chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. Depicted are the numbers of patients.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Co-morbid mood and anxiety disorders

Results with regard to psychiatric co-morbidity showed that persons with FSS had higher prevalence rates of any of the mood or anxiety disorders than persons without FSS (Table 2). Moreover, when participants had multiple FSS, their risks of having a co-morbid psychiatric disorder were higher than when they had only one FSS. However, it should be stressed that the majority of persons suffering from FSS did not fulfill the criteria of an anxiety or mood disorder.

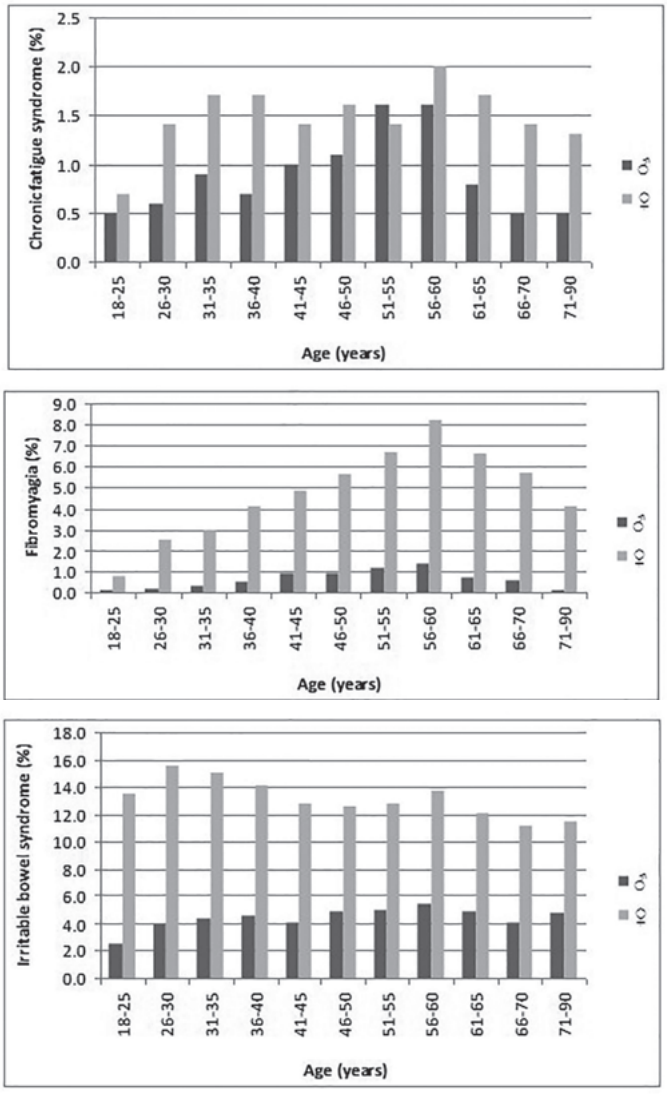

Figure 2. Prevalence rates of chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome for males and females in different age categories.

Table 2. Prevalence of psychiatric disorders in patients suffering from chronic fatigue syndrome, fibromyalgia, and/or irritable bowel syndrome.

		Major depressive disorder	Core symptoms depression	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder	Any mood disorder	Any anxiety disorder
No FSS	N	1412	1219	670	2810	599	487	1532	2231	2082	6726
	%	1.8	1.6[a]	0.9	3.6	0.8	0.6	2.0	3.0	2.7	8.4
Only CFS	N	74	59	39	86	25	13	32	61	113	171
	%	10.7	8.6[a]	6.5	12.5	3.6	1.9	4.6	8.9	17.2	24.0
Only FM	N	100	87	36	130	29	32	65	109	136	307
	%	5.9	5.2[a]	2.3	7.7	1.7	1.9	3.9	6.5	8.2	18.0
Only IBS	N	295	245	127	592	123	129	330	415	710	1305
	%	3.9	3.3[a]	1.8	7.9	1.6	1.7	4.4	5.5	5.7	16.9
2 FSS	N	124	79	46	177	37	36	75	61	170	327
	%	10.7	6.8[a]	4.5	15.3	3.2	3.1	6.5	8.9	15.4	27.8
3 FSS	N	20	14	7	30	5	6	6	15	27	43
	%	19.0	13.3[a]	8.3	28.6	4.8	5.7	5.7	14.3	29.1	40.6

FSS = functional somatic syndrome, CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; [a] When depressive disorder is defined as the two core symptoms of depression (i.e. depressed mood and anhedonia) being present.

Since the diagnostic criteria for MDD overlap with FSS, the MDD prevalence in FSS patients might have become artificially high. To control for this overlap, we examined prevalence rates of depression when defining depression as the two core symptoms of MDD (i.e. depressed mood and anhedonia, which are both cognitive) being present. Prevalence rates were indeed lower when taking this approach, particularly in participants with CFS in whom the prevalence rate was now 2.1 % lower than when the original diagnostic criteria were used (Table 2).

Logistic regression analyses showed that participants with CFS, FMS, and IBS had higher levels of mood (ORs 1.72 to 5.42) and anxiety disorders (ORs 1.52 to 3.96) than persons without FSS. Comparisons of individuals with CFS, FMS or IBS showed that participants with CFS patients had higher levels of mood (ORs 2.00 to 4.08) and anxiety disorders (ORs 1.63 to 2.32) than participants with FMS or IBS, except for panic disorders (Table 3). Individuals with FMS had higher levels of MDD (OR 1.58), but not dysthymia or anxiety disorders than individuals with IBS (Table 3).

Patients showing complaints in the past week(s)

Since lifetime diagnoses of FSS were assessed, the question remained whether patients were still suffering from the reported syndrome. Analyses were therefore repeated after exclusion of individuals with CFS who did not report fatigue in the past four weeks (n = 44), individuals with FMS that did not report muscle pain in the past week (n =148), and individuals with IBS that did not report nausea in the past week (n = 5,251). Due to the absence of assessment of gastrointestinal symptoms other than nausea, it was not possible to base this selection on bowel complaints. Fatigue was assessed using one item from the RAND-36 (27), and muscle pain and nausea were assessed by two items from the somatization scale of the Symptom Checklist-90 (28). Results are shown in Table 4. In this sample, participants with CFS did not have more anxiety disorders than participants with IBS anymore, and participants with FMS did not have more MDD than IBS patients. Results regarding the comparison between individuals with CFS and individuals with FMS in mood or anxiety disorders remained essentially the same.

Table 3. Odds ratios and 95%-CIs of psychiatric disorders in patients suffering from chronic fatigue syndrome (n= 689), fibromyalgia (n = 1683), and irritable bowel syndrome (n = 7505).

	Major depressive disorder	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder
Only CFS vs controls	**5.06 (4.20-6.10)**	**5.42 (4.12-7.12)**	**3.53 (2.99-4.17)**	**3.96 (2.92-5.39)**	**2.68 (1.86-3.85)**	**1.83 (1.40-2.40)**	**2.45 (2.00-3.01)**
Only FMS vs controls	**2.42 (2.05-2.84)**	**1.98 (1.53-2.56)**	**1.94 (1.70-2.22)**	**1.83 (1.37-2.43)**	**2.03 (1.54-2.67)**	**1.59 (1.32-1.93)**	**1.52 (1.30-1.77)**
Only IBS vs controls	**1.87 (1.67-2.10)**	**1.72 (1.44-2.04)**	**2.00 (1.84-2.18)**	**1.85 (1.54-2.22)**	**2.19 (1.82-2.63)**	**1.94 (1.72-2.17)**	**1.67 (1.51-1.85)**
CFS vs IBS	**3.16 (2.40-4.15)**	**4.08 (2.80-5.95)**	**1.77 (1.39-2.26)**	**2.32 (1.49-3.62)**	n.a.	n.a.	**1.75 (1.31-2.32)**
CFS vs FMS	**2.00 (1.45-2.76)**	**2.90 (1.80-4.67)**	**1.69 (1.26-2.27)**	**2.04 (1.17-3.56)**	n.a.	n.a.	**1.63 (1.17-2.28)**
FMS vs IBS	**1.58 (1.24-2.01)**	1.41 (0.96-2.06)	1.05 (0.86-1.28)	1.14 (0.75-1.73)	n.a.	n.a.	1.07 (0.86-1.34)

Odss ratio (95%-CI); CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; adjusted for gender and age, n.a.= not applicable, since the main effect of "type of disorder" is not significant.

Table 4. Odds ratios and 95%-CIs of psychiatric disorders in patients suffering from chronic fatigue syndrome (n = 659), fibromyalgia (n = 1578), and irritable bowel syndrome (n = 2914) who did report the core symptoms in the past weeks.

	Major depressive disorder	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder
Only CFS vs controls	**4.86 (3.98-5.93)**	**4.98 (3.69-6.72)**	**3.45 (2.89-4.13)**	**4.11 (2.98-5.67)**	**2.43 (1.65-3.58)**	**1.93 (1.45-2.56)**	**2.35 (1.88-2.94)**
Only FMS vs controls	**2.41 (2.02-2.87)**	**2.00 (1.51-2.66)**	**2.00 (1.72-2.32)**	**1.76 (1.29-2.42)**	**2.10 (1.56-2.82)**	**1.57 (1.27-1.95)**	**1.51 (1.27-1.80)**
Only IBS vs controls	**1.41 (1.28-1.57)**	**2.54 (2.05-3.16)**	**2.96 (2.66-3.30)**	**2.56 (2.04-3.22)**	**3.60 (2.90-4.47)**	**2.58 (2.23-3.00)**	**2.19 (1.91-2.51)**
CFS vs IBS	**1.72 (1.29-2.30)**	**2.54 (1.68-3.83)**	1.18 (0.91-1.53)	1.60 (0.99-2.57)	n.a.	n.a.	1.26 (0.93-1.72)
CFS vs FMS	**1.94 (1.40-2.71)**	**2.81 (1.72-4.59)**	**1.70 (1.26-2.29)**	**2.10 (1.19-3.68)**	n.a.	n.a.	**1.57 (1.11-2.22)**
FMS vs IBS	0.88 (0.68-1.14)	0.90 (0.59-1.38)	0.69 (0.56-0.87)	0.76 (0.49-1.19)	n.a.	n.a.	0.80 (0.63-1.03)

Odds ratio (95%-CI); CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; adjusted for gender and age, n.a.= not applicable, since the main effect of "type of disorder" is not significant.

DISCUSSION

Co-morbidity of CFS, FMS, and IBS in our population based-cohort study was much higher than could be expected based on the prevalence rates of 1.3 %, 3.0 % and 9.7 %, respectively. Participants that suffered from one or more of these FSS showed higher rates of mood and anxiety disorders than participants without FSS, but the majority of participants with FSS did not show a mood or anxiety disorder. Participants with CFS had higher rates of mood (MDD and dysthymia) and anxiety disorders (generalized anxiety disorder, social phobia and agoraphobia without panic disorders; but not panic disorders) than participants with IBS or FMS. Participants with FMS and participants with IBS did only differ in amount of MDD which was more prevalent in participants with FMS.

The main strength of this study is that diagnoses of psychiatric disorders were based on psychiatric interviews that in general give better estimates of psychiatric diagnoses than self-reports. Another strength is the large sample size, which enabled us to study relatively large groups of participants with FSS, hence increasing the robustness of our findings. Additionally, information about the three main FSS was available which enabled comparing these three FSS in one cohort. Comparing patients included in different cohorts is difficult, since these patients are not comparable due to different selection procedures and different measurements for psychopathology.

One limitation of this study is that diagnoses for FSS were based on self-report. An American study showed that self-reports often underestimate the amount of persons that suffer from FSS (29). This seems not likely in our study, since the prevalence rates for CFS, FMS, and IBS were comparable to previous studies (30-33), among which studies using diagnoses based on physical examination. Also demographic characteristics, like prevalence rates being highest in females and around midlife, were in line with previous studies (23, 24). Nevertheless, our choice to assess FSS using self-report was based on practical limitations associated with a cohort study of this size which aims to study a wide spectrum of mental and somatic disorders. We aim to assess FSS more extensively in future assessment waves. Another limitation is that lifetime diagnoses of FSS were available instead of current diagnoses, which might have given an overestimation of persons who are currently suffering from FSS. However, as mentioned, data of another cohort

study in the same geographical area showed that persons who reported to have experienced CFS, FMS, or IBS usually report still being suffering from the syndrome. So the overestimation of participants currently suffering from FSS is likely to be minor. Moreover, the majority (>95%) of participants reporting CFS experienced fatigue, and the majority (>93%) of participants reporting FMS experienced musculoskeletal pain in the past week(s). Thirty-nine per cent of the participants with IBS patients reported nausea. Unfortunately, no information about gastrointestinal complaints other than nausea was available for the entire sample. Further, the prevalence rates of FSS per age category also indicate that diagnoses represent current rather than lifetime diagnoses of FSS, given the absence of a linear increase during ageing. Nevertheless, as a sensitivity analysis, analyses were repeated after exclusion of patients who did not report the core symptoms in the past week(s). After exclusion of these patients, participants with CFS did not have more anxiety disorders than participants with IBS anymore, and participants with FMS did not have MDD more frequent than participants with IBS. It should be noted that IBS patients in this subsample might not be representative of average IBS patients, since only patients who reported nausea in the past week were included. Results regarding the comparison between participants with CFS and FMS in frequency of mood or anxiety disorders remained essentially the same. Finally, it is good to note that although self-reported lifetime diagnoses of FSS might have complicated the adequate characterizing of participants with FSS, the main aim of this paper was to compare psychiatric co-morbidity of the three FSS. Obtaining diagnoses for all FSS in the same way (i.e. by self-report) probably enhanced the comparability of syndromes.

To the best of our knowledge, only one previous study compared participants with chronic fatigue, widespread pain and IBS within one general-population cohort on scores of anxiety and depression (17). This previous study of 2,290 subjects did not show significant differences in anxiety and depression scores between participants with different FSS. These results might have been due to insufficient power in that study. It should be stressed that differences between FSS in frequency of mood or anxiety disorders in the current study were only small. Moreover, the previous study examined prevalence of symptoms of anxiety and depression instead of specific mood and anxiety disorders. In line with our study, (small) differences in anxiety and depression scores between CFS, FMS, and IBS patients were found in a meta-analytic review (18). This meta-analytic

review showed that CFS patients had higher depression scores than patients suffering from FMS or IBS. In contrast to that study, we found participants with FMS to have higher MDD rates than participants with IBS, while the meta-analysis found FMS patients to show lower anxiety scores than IBS patients. These differences might be due to different study characteristics or to the fact that we studied specific mood and anxiety disorders, whereas the meta-analytic review examined general mood and anxiety symptoms. An explanation for individuals with CFS reporting the highest levels of psychiatric co-morbidity might be that symptoms of psychiatric disorders, especially depressive disorder, overlap with CFS symptoms. Prevalence rates of depressive disorder in participants with CFS were indeed lower when taking the two core depression symptoms into account. Therefore, symptom overlap should be taken into account in psychiatric examination of individuals with CFS.

Because of the cross-sectional nature of our study, we could not determine whether FSS lead to mood and anxiety disorders, whether anxiety and mood disorders lead to FSS, or whether FSS and mood and anxiety disorders are manifestation of the same underlying pathology. We previously found evidence for all three hypotheses in a longitudinal population-based study of adolescents, with most pronounced evidence for depression and anxiety being risk factors of FSS (34). What can be concluded from the current study is that FSS, mood and anxiety disorders only partially overlap, and that most individuals with FSS do not suffer from mood and anxiety disorders. This finding is in line with previous studies (18, 23). Therefore, these syndromes should not be simply considered somatic expressions of anxiety and depression.

With regard to differences between CFS, FMS, and IBS, our study supports both the lumper and the splitter approach. In line with the lumper approach and previous studies (17, 35), FSS co-occurred much more often than could be expected based on separate prevalence rates, which might imply a generic etiology. Moreover, psychiatric co-morbidity, in the form of mood and anxiety disorders, was characteristic of all three FSS. In keeping with the splitter approach, mood and anxiety disorders were more common in some than in other FSS, and sex differences were more pronounced in some syndromes than in others. This finding of both specific and general characteristics of FSS is in line with factor analyses in recent population-based studies and in a twin cohort (11-13).Upcoming studies

from the LifeLines cohort will further investigate the lumper-splitter discussion, by investigating syndrome-specificity of different biological, psychological and social factors. With regard to biological factors, several potential biomarkers could be examined in the plasma, serum and urine stored for all LifeLines participants. In addition, hair and faeces have been collected providing the opportunity to study cortisol levels and alterations in microbial flora. Several other relevant data have been collected, including cardiovascular parameters (e.g. blood pressure recordings and electrocardiogram), pulmonary function as assessed by spirometry, anthropometry, muscular strength, and cognitive function as assessed by a computerised test battery. LifeLines also provides the opportunity to study lifestyle factors, including physical activity and diet.

In summary, this population-based study suggests that although individuals with CFS, FMS, and IBS suffer from mood and anxiety disorders more often than individuals without FSS, most of them do not have these psychiatric disorders. Individuals with CFS have higher rates of mood and anxiety disorders than individuals with FMS and IBS. Individuals with FMS have more MDD, but not dysthymia or anxiety disorders than individuals with IBS, but differences are small.

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