Similar but different

Joustra, Monica Laura

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Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses

Joustra ML, Bakker SJL, Gans ROB, Rosmalen JGM.

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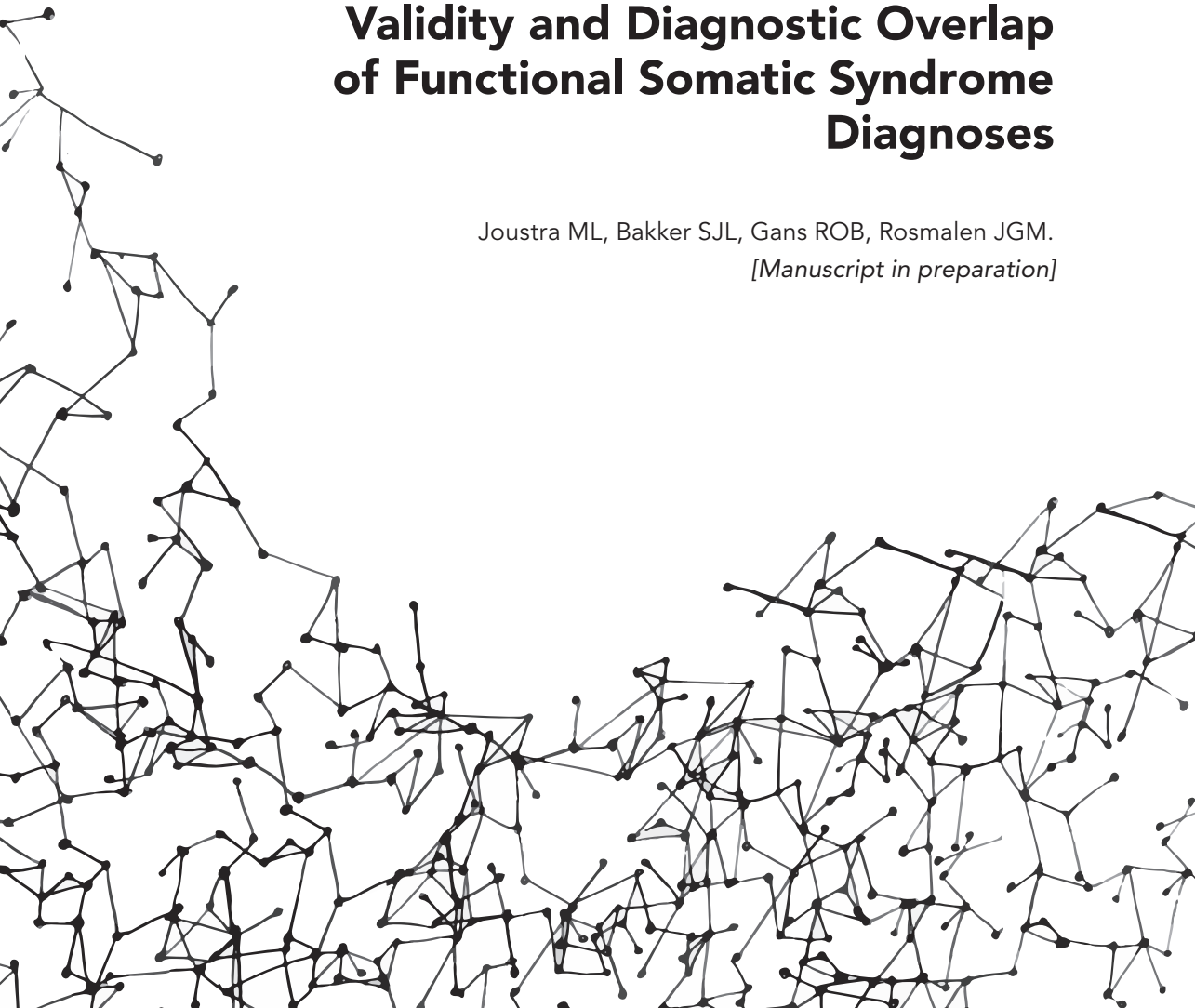

ABSTRACT

Background: Overlap between the three main functional somatic syndromes (FSS), i.e. chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS), has been suggested, but the empirical basis for the statement that they are different names for the same problem is limited. We present the first study that investigates the validity and the diagnostic overlap of the three main FSS diagnoses in the general population, irrespective of help-seeking behaviour or diagnostic biases, and irrespective or arbitrary diagnostic cut-offs with regard to chronicity or symptom interference.

Methods: This study was performed in 79,966 participants of the general-population cohort LifeLines. Diagnostic criteria for CFS (Centers for Disease Control and Prevention), FMS (American College of Rheumatology) and IBS (Rome IV) were assessed by questionnaire. Additional items were added to enable studying the effects of arbitrary cut-offs for minimum symptom chronicity (that vary from three months for FMS to six months for CFS and IBS), and symptom interference (required for CFS but not for FMS and IBS).

Findings: The diagnostic criteria were met by 3.1% for CFS, 6.4% for FMS, and 5.5% for IBS participants. The number of participants that met criteria for all three diagnoses was 48 times higher than what would have been expected based on chance. After alignment of the chronicity and symptom interference criteria to circumvent arbitrary choices in diagnostic criteria, the overlap between diagnoses increased to 153 times. Furthermore, there was a similar pattern of symptom occurrence, particularly for those fulfilling diagnostic criteria for CFS and FMS.

Interpretation: The diagnostic overlap of different FSS was much higher than would be expected by chance, and substantially increased when FSS were more chronic and serious in nature. Furthermore, FSS participants frequently reported symptoms included in the diagnostic criteria for other FSS, suggesting the existing of an underlying syndrome with different subtypes.

INTRODUCTION

In 1999, the Lancet published a landmark paper with the title: Functional somatic syndromes: one or many?[1] This paper reviewed the concept of functional somatic syndromes (FSS), which are considered specific combinations of physical symptoms that cannot be adequately explained by underlying pathology. Chronic fatigue syndrome (CFS),[2] fibromyalgia syndrome (FMS),[3] and irritable bowel syndrome (IBS)[4,5] are the three most well-known FSS. On the basis of a literature review, the authors concluded that a substantial overlap exists between these syndromes and that their similarities outweigh their differences. They suggested that the existence of different FSS is an artifact of medical specialization, and that all patients with FSS suffer from the same underlying syndrome.[1]

These conclusions were based on two main observations: first, the case definitions of FSS overlap; second, patients with one FSS frequently meet diagnostic criteria for another FSS.[6–9] Two additional arguments were presented that were less convincing. The first stated that patients with different FSS share non-symptom characteristics, such as sex, history of childhood maltreatment and abuse, emotional disorder, and difficulties in doctor-patient relationship. This argument ignored that the same characteristics are also associated with somatic diseases and/or might be consequences of a somatic disease.[6,10–12] The last argument was that all FSS respond to the same therapies: general approaches to management, antidepressants, and psychological therapies. However, various somatic diseases respond similarly to these therapies and other interventions (e.g. physiotherapy, anti-inflammatory drugs, beta-blockers), but that is no reason to consider them similar.[13–15]

The idea that FSS reflect one underlying problem is thus mainly supported by overlapping case definitions and symptom patterns. However, also these arguments can be questioned. The case definitions do indeed overlap, which implies that patients fulfilling diagnostic criteria for one syndrome automatically fulfill at least part of the diagnostic criteria for other syndromes; thus, this may artificially increase overlap. However, there also are remarkable differences that might artificially decrease presumed overlap between FSS. The diagnostic criteria are based on a main symptom, but they also include requirements for a minimum duration. These requirements vary between syndromes: the chronicity threshold

is six months for CFS or IBS, and three months for FMS. The criteria also vary with regard to whether the symptoms are required to interfere with daily life, which is a criterion for CFS but not for FMS or IBS (Table 1). Such arbitrary choices in diagnostic criteria sets reduce overlap. With regard to the other argument, the authors state that patients who meet the criteria for a specific FSS, also report symptoms other than those included in the case definition. They conclude from this that the syndromes actually reflect one underlying problem that is artificially split due to medical specialization. However, this approach ignores that such symptoms are also prevalent in chronic somatic health problems and in the general population.

The empirical basis of the statement that CFS, FMS, IBS, and other FSS, are different names for the same problem is thus very limited. In the 20 years since this landmark paper, no study has actually investigated the overlap between CFS, FMS, and IBS in a methodologically sound way based on the arguments in this paper. We will examine the validity and the diagnostic overlap of the FSS diagnoses based on the official diagnostic criteria, irrespective of help-seeking behaviour or diagnostic biases, in a large population-based cohort study of over 79,000 participants. First, to explore the observation that the case definitions of FSS overlap, we will examine whether participants with one FSS frequently meet diagnostic criteria for one of the other FSS. We will also examine the effects of arbitrary choices in case definitions on comorbidity (i.e. duration of main symptom, interference with daily life). Then, to explore the observation that patients with one FSS frequently meet diagnostic criteria for another FSS, we will examine whether participants who meet the criteria for specific FSS report symptoms formulated in the other FSS criteria. Lastly, we will examine the overlap of FSS and recognized medical or psychiatric health conditions.

Table 1. Diagnostic criteria for chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome.

	Chronic fatigue syndrome	**Fibromyalgia syndrome**	**Irritable bowel syndrome**
Main symptom	Severe chronic fatigue	Widespread pain	Recurrent abdominal pain
Chronicity	6 or more consecutive months	Present at a similar level for at least 3 months	1 day a week in last 3 months; with symptom onset at least 6 months ago
Interference	Fatigue significantly interferes with daily activities and work	-	-
Additional symptoms	>= 4 of the following: 1. Post-exertion malaise lasting more than 24 hours; 2. Unrefreshing sleep; 3. Significant impairment of short-term memory or concentration; 4. Muscle pain; 5. Pain in the joints without swelling or redness; 6. Headaches of a new type, pattern, or severity; 7. Tender lymph nodes in the neck or armpit; 8. A sore throat that is frequent or recurring.	WPI: the number of areas in which the patients had pain over the last week. Sum of the severity: 1. Fatigue; 2. Waking unrefreshed; 3. Cognitive symptoms; 4. Somatic symptoms in general.	>= 2 of the following: 1. Improvement with defecation; 2. Associated with change in frequency of stool; 3. Associated with change in form (appearance) of stool.

WPI = widespread pain index. See "Appendix A: scoring algorithm", chapter 4, for the exact questions and scoring algorithm used in this study.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study.[16] LifeLines is a multi-disciplinary, 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 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.

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 six months after pregnancy or three 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.

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. Prior to these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires will be administered to all participants every 18 months, and they will be invited for a renewed physical examination at the LifeLines research site on average every five years. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and the CogState computerized cognitive battery and the digital neuropsychiatric questionnaire were conducted respectively. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. Data of the second assessment was used in the current study, since the diagnostic algorithms for FSS were included in the second assessment.

Diagnostic criteria

The diagnostic criteria for the three FSS were criteria based on responses on the questionnaire of the most recent wave (see "Appendix A: scoring algorithm" for the exact questions and scoring algorithm, chapter 4). The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC),[2] for FMS using the 2010 American College of Rheumatology criteria (ACR),[3] and the diagnosis for IBS was assessed using the ROME III criteria.[4] However, the criteria which include occurrence of symptoms was adjusted in accordance to the ROME IV criteria,[5] namely participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (instead of 3 days per month).[4,5] To construct chronicity-aligned FSS diagnosis, the chronicity threshold was adjusted to three and six months using an additional adjusted cutoff for these corresponding questions. Furthermore, the interference-aligned FSS diagnosis was constructed by adding an identical interference with daily activities question as used with CFS, in which fatigue was replaced by musculoskeletal pain in the FMS questionnaire, and by abdominal complaints in the IBS questionnaire.

Medical and psychiatric health conditions

Psychiatric health conditions, including current major depressive disorder, dysthymia, and generalized anxiety disorder, were assessed with a standardized instrument, which was completed by participants at computer at the LifeLines location. This instrument was a digitalized self-report version of the Mini International Neuropsychiatric Interview (MINI) 5.0.0. The MINI is a brief structured instrument for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10.[17] Medical health conditions were assessed by questionnaire, including a list of chronic disorders (a.o. Crohn's disease and/or ulcerative colitis (IBD), multiple sclerosis (MS), and rheumatoid arthritis (RA)). Participants were asked to indicate which of these diseases they had or had had, with more than one answer allowed.

Statistical analyses

We performed all analyses using SPSS version 22. First, we described the characteristics of the study groups. Then, we examined the influence of the differences in diagnostic criteria between the different FSS on the diagnostic overlap, by aligning the aspects of the criteria so that they became similar for all three FSS. We examined the effect of aligning the chronicity of the symptoms (chronicity-aligned), and including or excluding an interference criteria (interference-aligned). The diagnostic overlap between the official diagnoses and the aligned diagnoses of the different FSS was summarized in area-proportional Euler diagrams, using the Package 'Eulerr' in R.[18] We made an estimate of the number of persons that fulfilled the diagnostic criteria of all three disorders based on the prevalence rates and the number of participants included in this study using the following calculation:

$$N_{estimate} = \left(\left[\frac{CFS_{\%}}{100}\right] \times \left[\frac{FMS_{\%}}{100}\right] \times \left[\frac{IBS_{\%}}{100}\right]\right) \times N_{total\ study\ population}$$

The percentages and distribution of symptoms, as reported by participants who met the official diagnostic criteria, were summarized in a radar diagram. We used Cramer's V to index the amount to which symptoms discriminated the participants who met the diagnostic criteria from the participants who did not meet the corresponding FSS diagnosis, and the participants who had a medical health condition with the same main symptoms (CFS versus MS (fatigue), FMS versus RA (locomotor system complaints), and IBS versus IBD (bowel complaints)). Cramer's V is similar to R^2 in regression models and reflects how much of the

variability in the dependent variable is explained by membership of the group. Lastly, we examined the overlap of FSS and recognized medical health conditions that should be excluded before diagnosing a FSS, and participants who had a medical health condition with the same main symptoms.[2–5] We analyzed the numbers and frequencies of participants who met the partial criteria for the different FSS (e.g. chronicity of fatigue, interference of daily activities and work, symptoms), and who met all criteria of the FSS diagnosis.

RESULTS

Prevalence rates and demographic characteristics

Data were available for 79,966 participants. Of these participants, 2,490 (3.1%) fulfilled the CDC criteria for CFS, 5,122 (6.4%) the ACR criteria for FMS, and 4,377 (5.5%) the adjusted Rome IV criteria for IBS (Table 2A). The effect of alignment in diagnostic criteria between the different FSS on the group characteristics is presented in Table 2B-E. Relatively small differences in numbers, age, and sex were found in the chronicity-aligned CFS and FMS groups. However, for IBS, an increase of participants was found (+1,928) that met the diagnostic criteria when the symptom chronicity was set to three months; age and percentage female remained comparable. When including interference in daily activities in the FMS and IBS diagnostic criteria, many participants no longer met the diagnostic criteria (-1,997 and -3,725 respectively), the age of the remaining group was slightly higher, and the percentage female became lower. An increase in participants fulfilling the criteria for CFS was found (+1,542) when the interference criterion was ignored; the age of the remaining CFS group was slightly higher and the percentage female was also higher.

Table 2. Characteristics participants fulfilling the criteria for the original diagnosis and the diagnosis with adjusted diagnostic criteria.

	CFS	FMS	IBS
(a) Original diagnosis			
n (%)	2,490 (3.1)	5,122 (6.4)	4,377 (5.5)
Age, mean (SD)	54.2 (11.8)	52.8 (11.7)	50.9 (12.9)
Female, n (%)	1,848 (74.2)	3,922 (76.6)	3,307 (75.6)
(b) Duration 3 months			
n (+/- original)	2,749 (+259)		6,305 (+1,928)
Age, mean (SD)	54.0 (11.9)		51.0 (13.2)
Female, n (%)	2,044 (74.4)		4,698 (74.5)
(c) Duration 6 months			
n (+/- original)		4,668 (-454)	
Age, mean (SD)		52.9 (11.6)	
Female, n (%)		3,586 (76.8)	
(d) Including interference			
n (+/- original)		3,125 (-1,997)	652 (-3,725)
Age, mean (SD)		54.3 (11.6)	50.7 (13.5)
Female, n (%)		2,382 (76.2)	514 (78.8)
(e) Excluding interference			
n (+/- original)	4,032 (+1,542)		
Age, mean (SD)	54.2 (11.6)		
Female, n (%)	2,913 (72.2)		

CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Do participants with one FSS frequently meet diagnostic criteria for one of the other FSS?

The diagnostic overlap between the syndromes is presented in Figure 1A. More than half of the CFS participants also met the FMS diagnostic criteria, while the smallest overlap was found between the CFS and IBS diagnostic criteria. The number of participants that reported all three disorders using the original diagnostic criteria (n=422) was 48.3 times higher than would be expected by chance, based on prevalence rates of the separate syndromes (Table 3). If chronicity thresholds were aligned, this changed to 41.4 times higher than could be expected by change for the chronicity of three months and 51.3 times higher for the chronicity of six months (Figure 1B-C). If interference thresholds were aligned, this changed to 39.3 times higher than would be expected by chance when excluding interference, and 152.5 times higher when including interference (Figure 1D-E).

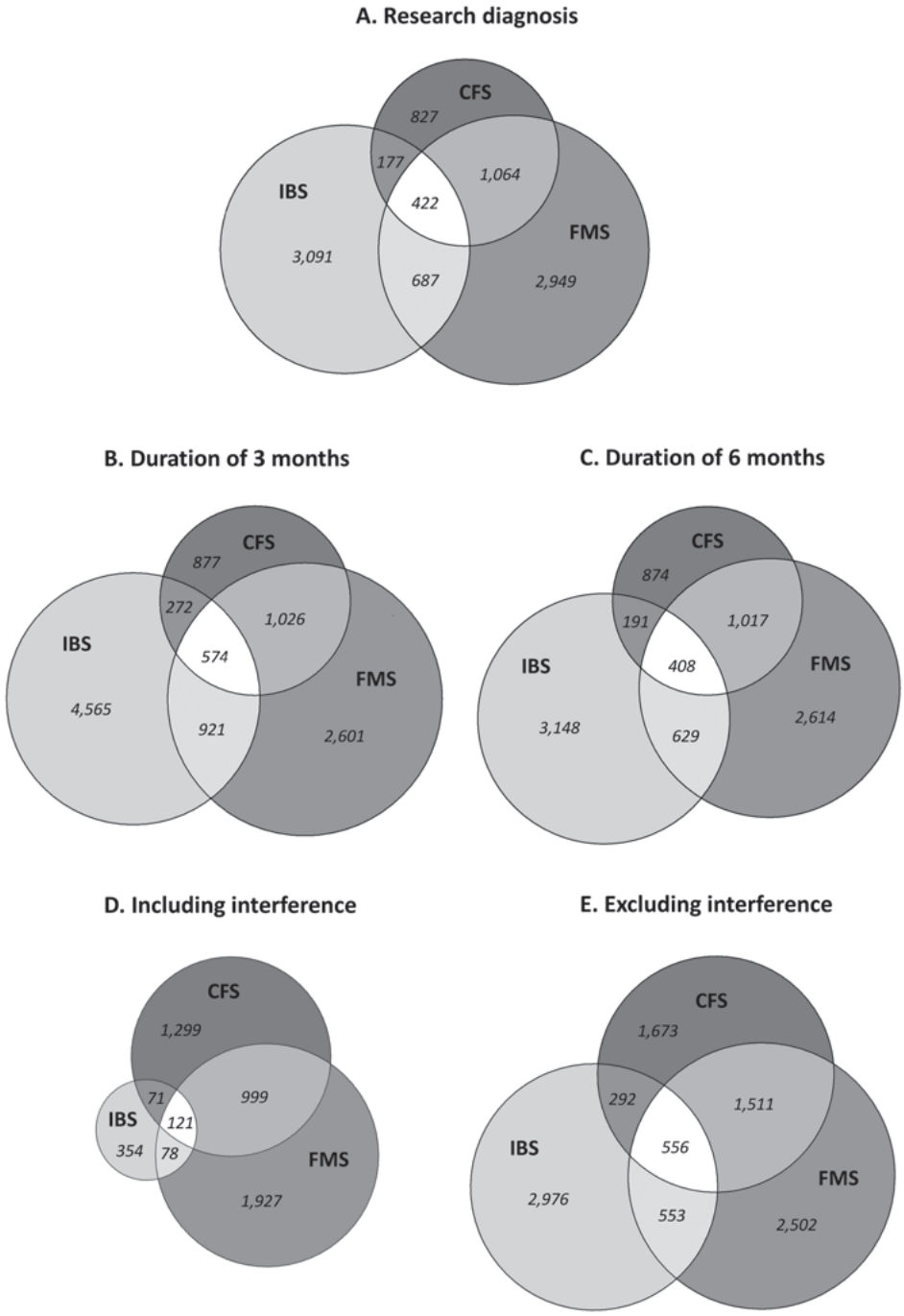

Figure 1. Diagnostic overlap presented in proportional Euler-diagrams.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Table 3. The number of participants that met two or three syndromes compared to the estimate based on prevalence rates of the separate syndromes.

	CFS & FMS	CFS & IBS	FMS & IBS	CFS & FMS & IBS
Original diagnostic criteria	9.3	4.4	4.0	48.3
Chronicity-aligned				
Duration 3 months	9.1	3.9	3.7	41.4
Duration 6 months	9.8	4.4	4.1	51.3
Interference-aligned				
Including interference	12.4	9.5	7.8	152.5
Excluding interference	8.0	3.8	4.0	39.3

CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Do participants who meet the criteria for specific FSS report diagnostic symptoms of the other FSS, and do they report these symptoms more frequently than the background population?

Figure 2 shows the proportion of participants with an FSS that reports symptoms included in the case definitions of the other syndromes. The pattern of symptom occurrence is clearly similar between CFS and FMS, with only quantitative differences in the prevalence of some symptoms. Table 4 presents the amount to which symptoms discriminated the participants who met the diagnostic criteria from those who did not, and from participants who reported a medical health condition with the same main symptoms. For CFS, post-exertional malaise discriminated the participants who met the CFS diagnostic criteria from those who did not meet the CFS diagnosis best. However, the largest contrast between CFS and MS was provided by the symptoms joint pain, unrefreshing sleep and muscle pain. For FMS, symptoms in general discriminated participants who did and did not meet FMS criteria best, while fatigue provided the best contrast between FMS and RA. For IBS, an association of recurrent abdominal pain or discomfort with change in form discriminated best between those that did and did not fulfill diagnostic criteria, and between IBS and IBD.

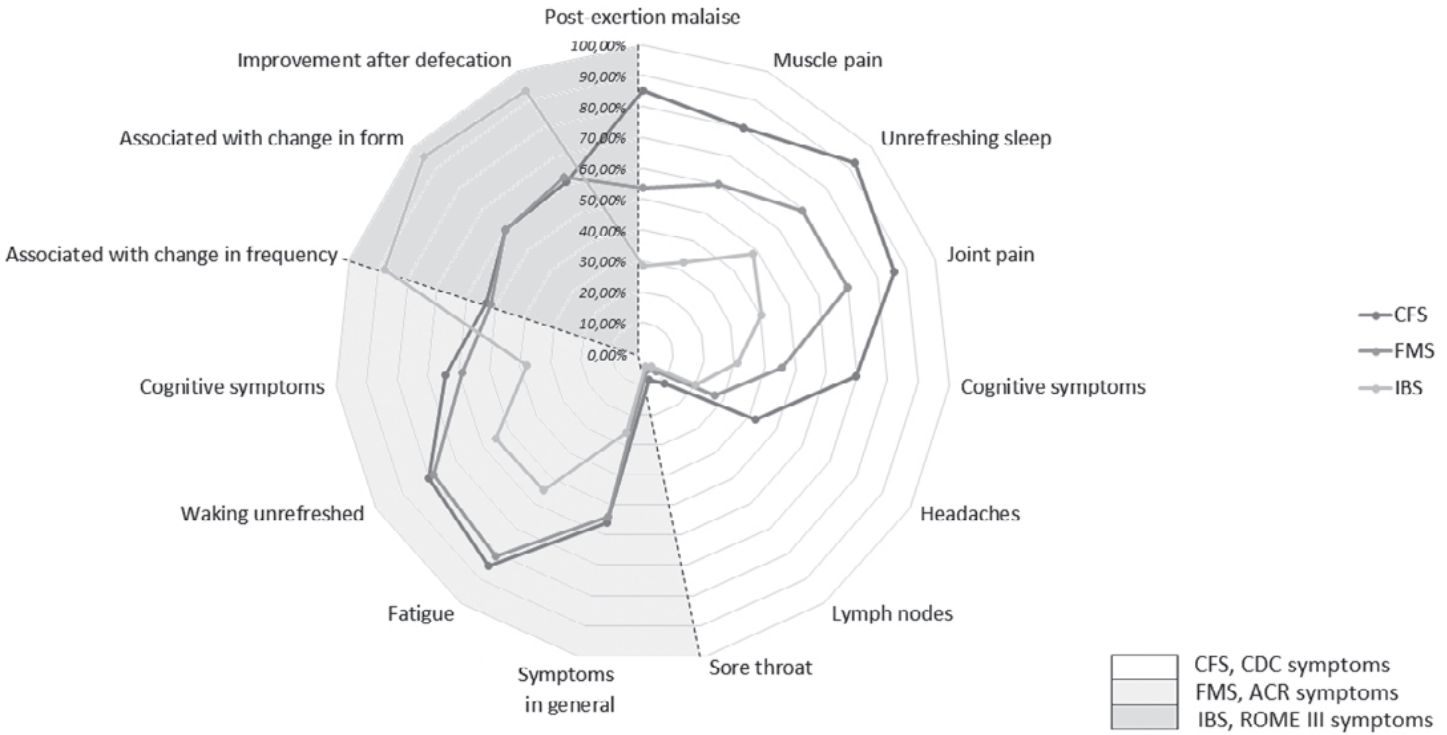

Figure 2. Percentage and distribution of symptoms mentioned in the diagnostic criteria, that participants who meet the official diagnostic criteria report.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Table 4. Distribution of symptoms mentioned in the diagnostic criteria of the separate syndromes compared with participants with somatic diseases and the general population.

CDC symptoms	**CFS** (n=2,490)	**No CFS** (n=77,289)	**Cramer's V***	**MS** (n=368)	**Cramer's V***
Post-exertion malaise	0.85 (2,123)	0.09 (7,066)	0.415	0.22 (80)	0.282
Muscle pain	0.8 (1,997)	0.13 (9,829)	0.331	0.14 (51)	0.318
Unrefreshing sleep	0.93 (2,306)	0.2 (15,197)	0.307	0.24 (96)	0.373
Joint pain	0.86 (2,142)	0.2 (15,416)	0.278	0.14 (51)	0.390
Cognitive impairments	0.7 (1,735)	0.13 (10,125)	0.277	0.19 (71)	0.172
Headaches	0.42 (1,054)	0.06 (4,851)	0.240	0.05 (19)	0.168
Lymph nodes	0.12 (295)	0.01 (783)	0.164	0.02 (6)	0.070
Sore throat	0.09 (218)	0.09 (1,064)	0.103	0.005 (2)	0.073
SS-score	**FMS** (n=5,112)	**No FMS** (n=74,842)	**Cramer's V***	**RA** (n=4,936)	**Cramer's V***
Symptoms in general	0.54 (2,772)	0.06 (4,351)	0.428	0.13 (635)	0.326
Fatigue	0.81 (4,155)	0.26 (19,635)	0.294	0.22 (1,100)	0.436
Waking unrefreshed	0.78 (4,012)	0.3 (22,388)	0.252	0.23 (1,128)	0.392
Cognitive symptoms	0.59 (3,017)	0.2 (14,960)	0.228	0.16 (771)	0.318
ROME III symptoms	**IBS** (n=4,377)	**No IBS** (n=75,587)	**Cramer's V***	**IBD** (n=1,666)	**Cramer's V***
Associated with change in frequency	0.88 (3,851)	0.22 (16,741)	0.239	0.30 (493)	0.120
Associated with change in form	0.96 (4,175)	0.27 (20,169)	0.229	0.31 (522)	0.208
Improvement after defecation	0.93 (4,085)	0.31 (23,586)	0.158	0.32 (533)	0.150

Data are presented as proportion (number) reporting symptoms. Symptoms are sorted by Cramer's V; higher values indicate symptoms that better discriminate the FSS diagnosis.
* $p < 0.001$ for all analyses.
CFS = chronic fatigue syndrome; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis; IBS = irritable bowel syndrome; IBD = inflammatory bowel disease; SS-score = symptom severity score.

Overlap medical and psychiatric health conditions.
The degree to which participants with medical and psychiatric diseases met the diagnostic criteria for the different FSS is presented in Table 5. Most participants that reported a medical health condition did not meet the diagnostic criteria for CFS, FMS or IBS. Participants who suffered from major depressive disorder, dysthymia, generalized anxiety disorder, or MS most frequently met the diagnostic criteria for CFS. For FMS, this was major depressive disorder, dysthymia, generalized anxiety disorder, or eating disorder. Lastly, for IBS this was coeliac disease, IBD, major depressive disorder, or dysthymia.

Table 5. Recognized medical health condition that meet the criteria for a functional somatic syndrome diagnosis.

	N_{total} (%)	CFS criteria 1. Duration	2. Interference	3. Symptoms	Research diagnosis	FMS criteria 1. Duration	2. Symptoms	Research diagnosis	IBS criteria 1. Duration	2. Onset	3. Symptoms	Research diagnosis
Medical health conditions with the same main symptoms												
Multiple sclerosis	185 (0.2)	140 (75.7)	95 (51.4)	36 (19.5)	29 (15.7)	105 (56.8)	42 (22.7)	33 (17.8)	35 (18.9)	43 (23.2)	77 (41.6)	12 (6.5)
Rheumatoid arthritis	2,858 (3.6)	1,339 (46.9)	707 (24.7)	572 (20)	305 (10.7)	1955 (68.4)	605 (21.2)	496 (17.4)	463 (16.2)	636 (22.3)	1,008 (35.3)	132 (4.6)
Inflammatory bowel disease	924 (1.2)	420 (45.5)	187 (20.2)	108 (11.7)	58 (6.3)	450 (48.7)	109 (11.8)	96 (10.4)	300 (32.5)	449 (48.6)	532 (57.6)	124 (13.4)
Coeliac disease	381 (0.5)	180 (47.2)	100 (26.2)	57 (15)	38 (10)	209 (54.9)	62 (16.3)	54 (14.2)	117 (30.7)	183 (48)	235 (61.7)	52 (13.6)
Medical health conditions that should be excluded before diagnosing a functional somatic syndrome												
Cancer	1,625 (2.0)	640 (39.4)	333 (20.5)	170 (10.5)	88 (5.4)	810 (49.8)	185 (11.4)	164 (10.1)	205 (12.6)	299 (18.4)	489 (30.1)	39 (2.4)
Heart failure	1,603 (2.0)	685 (42.7)	376 (23.5)	221 (13.2)	106 (6.6)	845 (52.7)	213 (13.3)	182 (11.4)	219 (13.7)	288 (18.0)	468 (29.2)	53 (3.3)
Hepatitis B	66 (0.1)	26 (39.4)	15 (22.7)	8 (12.1)	5 (7.6)	33 (50)	10 (15.2)	7 (10.6)	13 (19.7)	11 (16.7)	22 (33.3)	1 (1.5)

Table 5. Continued.

	N_{total} (%)	CFS criteria 1. Duration	2. Interference	3. Symptoms	Research diagnosis	FMS criteria 1. Duration	2. Symptoms	Research diagnosis	IBS criteria 1. Duration	2. Onset	3. Symptoms	Research diagnosis
Psychiatric health conditions that should be excluded before diagnosing a functional somatic syndrome												
Dementias	74 (0.1)	37 (50)	22 (29.7)	20 (27)	9 (12.2)	31 (41.9)	13 (17.6)	10 (13.5)	13 (17.6)	15 (20.3)	26 (35.1)	1 (1.4)
Dysthymia	781 (1.0)	559 (71.6)	360 (46.1)	222 (28.4)	164 (21)	495 (63.4)	227 (29.1)	199 (25.5)	194 (24.8)	279 (35.7)	374 (47.9)	64 (8.2)
Eating disorder	1,107 (1.4)	603 (54.5)	312 (28.2)	196 (17.7)	114 (10.3)	630 (56.9)	231 (20.9)	209 (18.9)	289 (26.1)	410 (37)	524 (47.3)	75 (6.8)
Generalized anxiety disorder	3,669 (4.6)	2,467 (67.2)	1,716 (46.8)	997 (27.2)	621 (16.9)	2,260 (61.6)	1,064 (29)	904 (24.6)	996 (27.1)	1,274 (34.7)	1,815 (49.5)	273 (7.4)
Major depressive disorder	1,593 (2.0)	1,103 (69.2)	995 (62.5)	573 (36.0)	386 (24.2)	1,023 (64.2)	650 (40.8)	536 (33.6)	519 (32.6)	589 (37)	847 (53.2)	139 (8.7)
Schizophrenia	65 (0.1)	36 (55.4)	27 (41.5)	13 (20)	10 (15.4)	28 (43.1)	8 (12.3)	4 (6.2)	12 (18.5)	12 (18.5)	21 (32.3)	2 (3.1)

Data are presented as n (%).
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

DISCUSSION

This is the first study, in the 20 years since the landmark paper, which has directly tested the ideas that started the lumper-splitter discussion in a methodologically sound way. Three key findings emerged from this study. First, the diagnostic overlap of the FSS was much higher than would be expected by chance. After alignment of the chronicity and interference criteria to circumvent arbitrary choices in diagnostic criteria, this overlap increased to 153 times what would have been expected by chance. Second, participants who met the criteria for a specific FSS frequently reported symptoms included in the diagnostic criteria for other FSS, with only quantitative differences between FSS in the prevalence of some symptoms. Lastly, most participants that reported a medical or psychiatric health condition did not meet the diagnostic criteria for CFS, FMS, or IBS.

The main strength of the current study is that the FSS were assessed using the official diagnostic criteria instead of self-reported diagnoses. The use of self-reported diagnoses might lead to an underestimation of the actual overlap due to diagnostic biases. One reason for this is that in patients who have been given an FSS diagnosis, new symptoms will be easily attributed to that FSS. Widespread pain in CFS patients might not easily lead to an FMS diagnosis, even when this person meets the FMS criteria. In addition, previous studies suggest that many of those who qualify for an FSS diagnosis never receive one.[19–21] This is partly due to the fact that the main symptoms of these syndromes, pain, fatigue, and abdominal complaints, are very common, and often do not lead to a doctor's visit. These processes decrease the overlap between syndromes as assessed using self-report diagnoses. A second important strength of our study is the large population cohort in which it was performed. The overlap reported in previous studies based on self-report diagnoses might be explained by a general tendency for help-seeking behaviour. Since we assessed the diagnostic criteria for all three FSS in a general population cohort, it was possible to examine diagnostic overlap of FSS diagnoses irrespective of help-seeking behaviour or diagnostic biases. The size of the cohort guaranteed a sufficient number of participants fulfilling the criteria for the different FSS to study their overlap. A third unique aspect of our study is the construction of chronicity-aligned and interference-aligned FSS diagnoses, which made it possible to investigate the effect of arbitrary chronicity and interference thresholds on diagnostic overlap.

Before interpreting the findings of the current study, the following limitations should be taken into account. First, the FSS diagnosis was based on the responses to a questionnaire, without an assessment by a physician. The large sample size required for the current study implied that it was not feasible to determine whether participants met the diagnostic criteria for FSS based on clinical examinations. Second, comorbid conditions that could explain the FSS symptoms were not excluded when determining the FSS diagnoses, mainly because only the CFS diagnostic criteria specifically mention recognized medical health conditions that need to be excluded before diagnosing CFS.[2] Nevertheless, we studied the extent to which participants with recognized medical health conditions fulfilled the diagnostic criteria for the different FSS, and this proportion was relatively limited. Most participants that reported a recognized medical health condition did not meet the diagnostic criteria for CFS, FMS, or IBS. Participants that were diagnosed with dysthymia, generalized anxiety disorder, or major depressive disorder most frequently and repeatedly met the diagnostic criteria for an FSS, however, most participants with an FSS did not suffer from these disorders. The additional value of defining recognized medical diseases that should be excluded before diagnosing a FSS could therefore be questioned. Third, CFS diagnoses were based on the CDC criteria, which were the most widely used criteria at the time of data collection. We do not know whether the same overlap would apply when using the CFS criteria as more recently proposed by the Institute of Medicine. We found that the diagnostic overlap of the three FSS was much higher than could be expected by chance. Our findings indicate that the diagnostic overlap substantially increased when the FSS were more chronic in nature (i.e. symptom onset at least six months ago) and interfered with daily life. In accordance with previous research, these results suggest that FSS may reflect a shared underlying syndrome.[22–24] However, the difference in clinical presentation suggests that there are different subtypes. Four subtypes introduced in the recent literature include a cardiopulmonary, gastrointestinal, musculoskeletal, and general symptom type, or a more severe multiorgan type.[23,24]

In summary, in this population-based study we examined the two main arguments described in the landmark paper published in the Lancet in 1999,[1] namely that the case definitions of FSS overlap, and that patients with one FSS frequently meet diagnostic criteria for another FSS. We revealed that the diagnostic overlap substantially increased when FSS are chronic and serious in nature, and that participants who met the criteria for a specific FSS frequently report symptoms

belonging to the diagnostic criteria of other FSS. In line with the landmark paper, this suggests that FSS may reflect the same underlying syndrome with different subtypes. This underlying syndrome should be more extensively investigated in the future to establish valid and generally accepted diagnostic criteria across medical specialties.

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