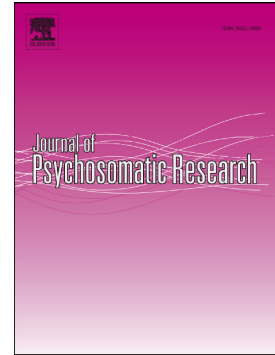


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Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses

Running title: Functional Somatic Syndrome Diagnoses

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ABSTRACT

Objective: We present the first study that investigates the validity and the diagnostic overlap of the three main functional somatic syndrome (FSS) diagnoses, i.e. chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS), irrespective of help-seeking behaviour or diagnostic habits, and irrespective of differences in diagnostic thresholds for chronicity or symptom interference.

Methods: This cross-sectional analysis was performed in 89,781 participants of the general-population cohort Lifelines. Diagnostic criteria for CFS (Centers for Disease Control and Prevention), FM (American College of Rheumatology) and IBS (Rome IV) were assessed by questionnaire. Additional items were added to enable studying the effects of differences in thresholds for minimum symptom chronicity (varying from three for FM to six months for CFS and IBS), and symptom interference (required for CFS but not for FM and IBS).

Results: The diagnostic criteria were met by 3.1% for CFS, 6.6% for FM, and 5.5% for IBS participants. The number of participants that met criteria for all three diagnoses was 45 times higher than what would have been expected based on chance. After alignment of the chronicity and symptom interference criteria to circumvent differences in diagnostic thresholds, the overlap between diagnoses increased to 152 times. Furthermore, there was a similar pattern of symptom occurrence, particularly for those fulfilling diagnostic criteria for CFS and FM.

Conclusion: 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.

Keywords: chronic fatigue syndrome, diagnoses, diagnostic overlap, fibromyalgia, irritable bowel syndrome

INTRODUCTION

Functional Somatic Syndromes (FSS) are diagnosed based on specific combinations of physical symptoms. Chronic fatigue syndrome (CFS) [1], fibromyalgia (FM) [2], and irritable bowel syndrome (IBS) [3,4] are the three most well-known FSS. There is a longstanding discussion on similarities and differences between FSS. This discussion was initiated by a review concluding that a substantial overlap exists between FSS, and that all patients with FSS might suffer from the same underlying syndrome [5].

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]. However, findings from recent research suggest that there are more differences between FSS; for example, predictors for new onset FSS are more often syndrome-specific than shared, and family genetic risk score profiles differ between FSS [10,11]. The overlap in

case definitions implies that patients fulfilling diagnostic criteria for one syndrome automatically fulfill at least part of the diagnostic criteria for other syndromes. At the same time, overlap between FSS might be artificially decreased due to remarkable differences in the chronicity thresholds, which is six months for CFS or IBS, and three months for FM [1–4]. 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 FM or IBS (Table 1). Such differences in diagnostic criteria sets reduce overlap. The other main argument to consider FSS as variants of one underlying syndrome is based on the observation that patients who meet the criteria for a specific FSS, also report symptoms other than those included in the case definition [5]. This argument ignores that such symptoms are also prevalent in other chronic health problems and in the general population.

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

| | Chronic fatigue syndrome | Fibromyalgia | Irritable bowel syndrome |
|----------------------------|--|---|--|
| <u>Main symptom</u> | Severe chronic fatigue | Widespread pain | Recurrent abdominal pain |
| <u>Chronicity</u> | 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 |
| <u>Interference</u> | Fatigue significantly interferes with daily activities and work | - | - |
| <u>Additional symptoms</u> | >= 4 of the following: <ol style="list-style-type: none"> 1. Post-exertional malaise lasting more than 24 hours; 2. Unrefreshing sleep; 3. Significant impairment of short-term memory or concentration; 4. Muscle pain; | WPI: the number of areas in which the patients had pain over the last week. Sum of the severity: <ol style="list-style-type: none"> 1. Fatigue; 2. Waking unrefreshed; 3. Cognitive symptoms; 4. Somatic symptoms in | >= 2 of the following: <ol style="list-style-type: none"> 1. Improvement with defecation; 2. Associated with change in frequency of stool; 3. Associated with change in form (appearance) of stool. |

5. Pain in the joints without swelling or redness; general.
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 = widespread pain index. See “Appendix A: scoring algorithm” for the exact questions and scoring algorithm used in this study.

The empirical basis of the statement that CFS, FM, IBS, and other FSS, are different names for the same problem is thus very limited. One study in the Danish DanFunD cohort used interviews to assess irritable bowel, chronic widespread pain and chronic fatigue in a stratified subsample of 1,590 participants from the general population. The study found that syndromes clearly overlap, but the numbers of cases per FSS (ranging from 18 for chronic widespread pain without other FSS to 228 for chronic fatigue irrespective of FSS comorbidity) limited a reliable estimation of overlap [12]. The overlap between CFS, FM, and IBS has not been studied in a large population cohort, since such cohorts typically do not include diagnostic criteria for FSS. We will examine the validity and the diagnostic overlap of the FSS diagnoses based on the self-reported diagnostic criteria, irrespective of help-seeking behaviour or diagnostic habits, in a large population-based cohort study of over 89,000 participants. First, we will examine whether participants with one FSS frequently meet diagnostic criteria for another FSS, and how this comorbidity is influenced by differences in case definitions (i.e. duration of main symptom, interference with daily life). Subsequently, 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 other somatic or psychiatric health conditions.

MATERIALS AND METHODS

Sampling frame

This study was conducted within the sampling frame of the Lifelines cohort study [13,14]. 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. Exclusion criteria for participation were terminal illness (life expectancy < 5 years), severe mental illness (i.e. not fully capable to make rational decisions), not being able to visit the general practitioner, not being able to fill in questionnaires and not being able to understand the Dutch language. 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 are administered to all participants every 18 months, and they are invited for a renewed physical examination at the Lifelines research site on average every five years. The current study used data collected between 2014 and 2017 during the second assessment, since the comprehensive questionnaire of this assessment included diagnostic criteria for FSS.

Diagnostic criteria

The diagnostic criteria for the three FSS were criteria based on responses on the questionnaire of the second assessment (see “Appendix A: scoring algorithm” for the exact questions and scoring algorithm). The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) [1], for FM using the 2010 American College of Rheumatology criteria (ACR) [2], and the diagnosis for IBS was assessed using the ROME III criteria [3]. However, the criteria which include occurrence of symptoms was adjusted in accordance to the ROME IV criteria [4], namely participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (instead of 3 days per month)

[3,4]. 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 FM questionnaire, and by abdominal complaints in the IBS questionnaire.

Somatic 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 a computer at the Lifelines location [15]. 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 [16]. Somatic 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 R version 4.2.1 [17]. 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 diagnoses according to the original

criteria 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:

$$N_{estimate} = \left(\left[\frac{CFS\%}{100} \right] \times \left[\frac{FM\%}{100} \right] \times \left[\frac{IBS\%}{100} \right] \right) \times N_{total\ study\ population}$$

The percentages and distribution of symptoms, as reported by participants who met the original diagnostic criteria, were summarized in a radar diagram. We used Cramer’s V to index to which extent symptoms discriminated the participants who met the diagnostic criteria from the participants who did not meet the corresponding FSS diagnostic criteria, and the participants who had a somatic health condition with the same main symptoms (CFS versus MS (fatigue), FM 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. For this analysis, main FSS symptoms (fatigue for CFS, pain for FM, and abdominal complaints for IBS) were excluded due to their presence in 100% of individuals affected by the respective FSS. Excluding these symptoms addressed concerns about zero counts in the contingency tables that underlie Cramer’s V, thus ensuring reliability of results. Lastly, we examined the overlap of FSS and somatic health conditions that should be excluded before diagnosing an FSS, and participants who had another somatic health condition with the same main symptoms [1–4]. 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 on at least one FSS were available for 89,781 participants. Of these participants, 2,804 (3.1%) fulfilled the CDC criteria for CFS, 5,350 (6.6%) the ACR criteria for FM, and 4,954 (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 FM groups. However, for IBS, an increase of participants was found (+2,121) that met the diagnostic criteria when the symptom chronicity was set to three months; age remained comparable and percentage female decreased slightly. When including interference in daily activities in the FM and IBS diagnostic criteria, many participants no longer met the diagnostic criteria (-2,086 and -4,253 respectively). For FM, the age of the remaining group was slightly higher, and the percentage female remained comparable. For IBS, age remained comparable and percentage female increased. An increase in participants fulfilling the criteria for CFS was found (+1,709) when the interference criterion was ignored. The age of this CFS group remained the same and percentage females decreased.

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

| | CFS | FM | IBS |
|------------------------------|--------------|--------------|----------------|
| a. Original diagnosis | | | |
| n (%) | 2,804 (3.1) | 5,350 (6.6) | 4,954 (5.5) |
| Age, mean (SD) | 51.7 (12.2) | 50.2 (11.9) | 48.3 (13.3) |
| Female, n (%) | 2,083 (74.3) | 4,102 (76.7) | 3,307 (75.5) |
| b. Duration 3 months | | | |
| n (+/- original) | 3,105 (+301) | | 7,071 (+2,117) |
| Age, mean (SD) | 51.6 (12.3) | | 48.2 (13.6) |
| Female, n (%) | 2,311 (74.4) | | 5,281 (74.7) |
| c. Duration 6 months | | | |
| n (+/- original) | | 4,876 (-474) | |
| Age, mean (SD) | | 50.3 (11.9) | |
| Female, n (%) | | 3,749 (76.9) | |

| d. Including interference in daily life | | | |
|---|----------------|----------------|--------------|
| n (+/- original) | | 3,264 (-2,086) | 701 (-4,253) |
| Age, mean (SD) | | 51.7 (11.9) | 48.0 (14.3) |
| Female, n (%) | | 2,494 (76.4) | 542 (77.3) |
| e. Excluding interference in daily life | | | |
| n (+/- original) | 4,513 (+1,709) | | |
| Age, mean (SD) | 51.7 (12.0) | | |
| Female, n (%) | 3,257 (72.2) | | |

CFS = chronic fatigue syndrome; FM = fibromyalgia; 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 FM diagnostic criteria, while the smallest overlap was found between the CFS and IBS diagnostic criteria. The number of participants that met the original diagnostic criteria for all three disorders (n=465) was 45.3 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 38.7 times higher than could be expected by change for the chronicity of three months and 49.2 times higher for the chronicity of six months (Figure 1B-C). If interference thresholds were aligned, this changed to 36.6 times higher than would be expected by chance when excluding interference, and 151.7 times higher when including interference (Figure 1D-E).

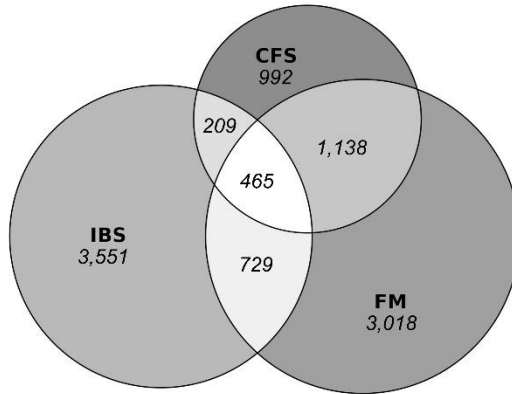
Table 3. Ratio of observed participants that met two or three syndromes to the predicted based on prevalence rates of the separate syndromes.

| | CFS & FM | CFS & IBS | FM & IBS | CFS & FM & IBS |
|------------------------------|----------|-----------|----------|----------------|
| Original diagnostic criteria | 8.6 | 4.3 | 3.7 | 45.3 |
| Chronicity-aligned | | | | |
| Duration 3 months | 8.4 | 3.9 | 3.4 | 38.7 |
| Duration 6 months | 9.4 | 4.3 | 3.8 | 49.2 |
| Interference-aligned | | | | |

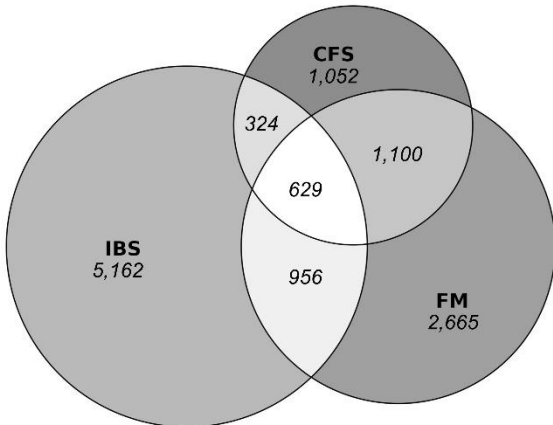
| | | | | |
|--------------------------------------|------|-----|-----|-------|
| Including interference in daily life | 12.5 | 9.1 | 7.9 | 151.7 |
| Excluding interference in daily life | 7.3 | 3.8 | 3.7 | 36.6 |

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

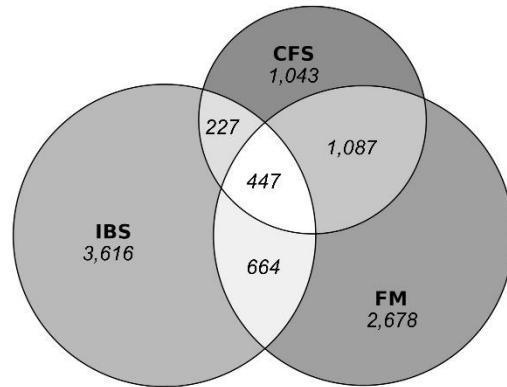
A. Research diagnosis



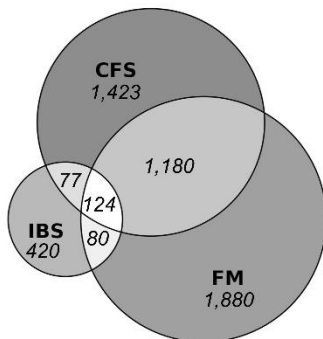
B. Duration of three months



C. Duration of six months



D. Including interference in daily life



E. Excluding interference in daily life

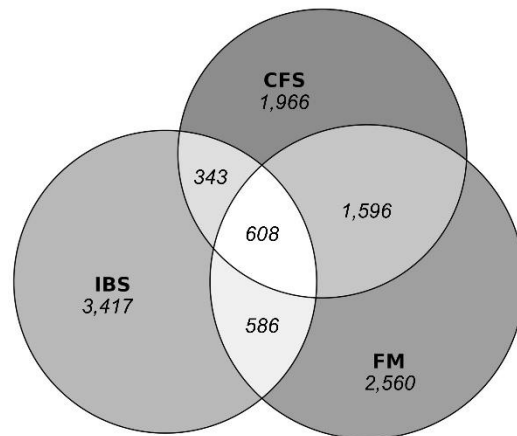


Figure 1. Diagnostic overlap presented in proportional Euler-diagrams.
 CFS = chronic fatigue syndrome; FM = fibromyalgia; IBS = irritable bowel syndrome.

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 controls?

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 FM, with only quantitative differences in the prevalence of some symptoms. Table 4 presents to which extent symptoms discriminated the participants who met the diagnostic criteria from those who did not, and from participants who reported another somatic health condition with the same main symptoms. For CFS, post-exertion 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 FM, symptoms in general discriminated participants who did and did not meet FM criteria best, while fatigue provided the best contrast between FM and RA. For IBS, an association of recurrent abdominal pain or discomfort with change in frequency discriminated best between those that did and did not fulfill diagnostic criteria. An association of recurrent abdominal pain or discomfort with change in form discriminated best between IBS and IBD.

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=2,804) | No CFS (n=86,346) | Cramer's V* | MS (n=201) | Cramer's V* |
|-----------------------|--------------------------|------------------------------|------------------------|-----------------------|------------------------|
| Post-exertion malaise | 0.85 (2,387) | 0.09 (7,530) | 0.424 | 0.42 (85) | 0.284 |
| Muscle pain | 0.81 (2,258) | 0.12 (10,704) | 0.338 | 0.26 (53) | 0.325 |
| Unrefreshing sleep | 0.93 (2,596) | 0.20 (16,911) | 0.308 | 0.46 (93) | 0.381 |
| Joint pain | 0.86 (2,402) | 0.20 (16,832) | 0.281 | 0.27 (54) | 0.384 |
| Cognitive impairments | 0.70 (1,969) | 0.13 (11,279) | 0.281 | 0.36 (73) | 0.185 |
| Headaches | 0.43 (1,193) | 0.06 (5,319) | 0.244 | 0.09 (19) | 0.171 |

| | | | | | |
|-------------------------------------|-------------------------|-----------------------------|--------------------|-------------------------|--------------------|
| Lymph nodes | 0.12 (331) | 0.01 (853) | 0.166 | 0.03 (7) | 0.067 |
| Sore throat | 0.09 (247) | 0.01 (1,160) | 0.105 | 0.01 (2) | 0.072 |
| SS-score | FM (n=5,350) | No FM (n=76,069) | Cramer's V* | RA (n=3,185) | Cramer's V* |
| Symptoms in general | 0.38 (2,025) | 0.02 (1,850) | 0.427 | 0.14 (435) | 0.269 |
| Fatigue | 0.83 (4,437) | 0.26 (19,553) | 0.311 | 0.38 (1,213) | 0.455 |
| Waking unrefreshed | 0.80 (4,281) | 0.29 (22,409) | 0.267 | 0.40 (1,262) | 0.410 |
| Cognitive symptoms | 0.63 (3,371) | 0.23 (17,630) | 0.226 | 0.31 (990) | 0.316 |
| ROME III symptoms | IBS (n=4,954) | No IBS (n=84,493) | Cramer's V* | IBD (n=1,027) | Cramer's V* |
| Associated with change in frequency | 0.88 (4,364) | 0.22 (18,618) | 0.242 | 0.54 (550) | 0.116 |
| Associated with change in form | 0.95 (4,725) | 0.27 (22,422) | 0.232 | 0.57 (585) | 0.196 |
| Improvement after defecation | 0.93 (4,628) | 0.31 (26,288) | 0.160 | 0.57 (588) | 0.157 |

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.

Main FSS symptoms (fatigue for CFS, pain for FM, abdominal complaints for IBS) were excluded from this analysis as 100% of CFS, FM and IBS cases experience the respective main symptom, which would negatively affect the reliability of Cramer's V.

CFS = chronic fatigue syndrome; MS = multiple sclerosis; FM = fibromyalgia; RA = rheumatoid arthritis; IBS = irritable bowel syndrome; IBD = inflammatory bowel disease; SS-score = symptom severity score.

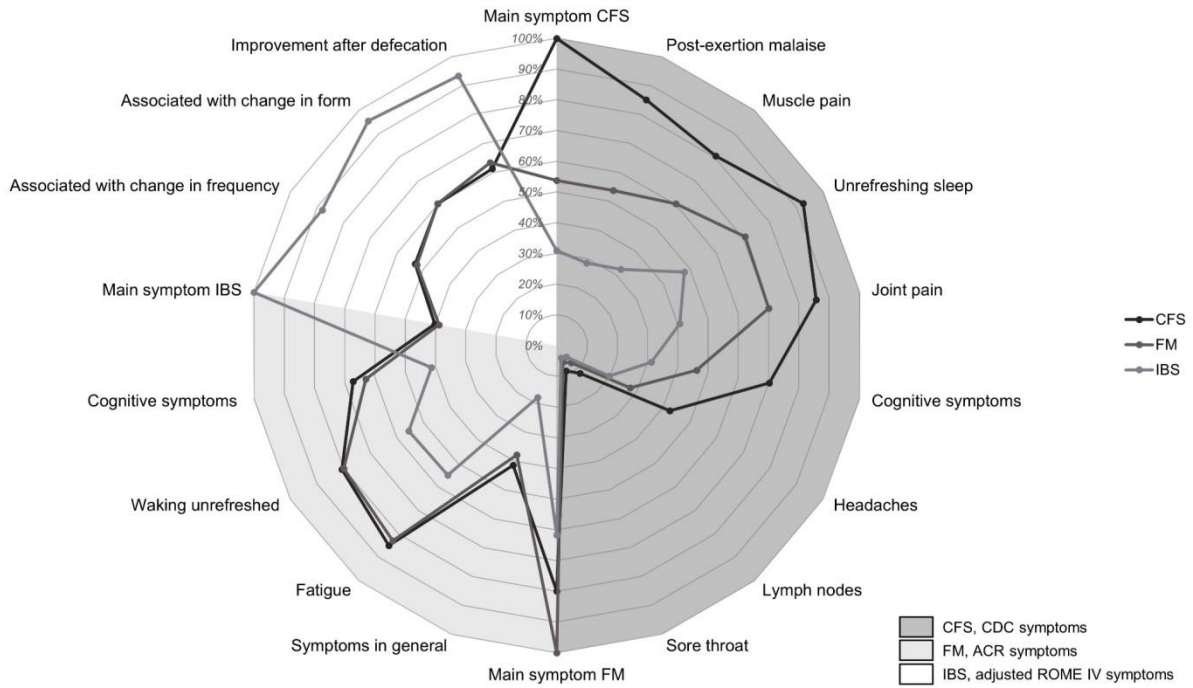


Figure 2. Percentage and distribution of symptoms mentioned in the diagnostic criteria, that participants who meet the original diagnostic criteria report.

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

Overlap somatic and psychiatric health conditions.

The degree to which participants with somatic and psychiatric diseases met the diagnostic criteria for the different FSS is presented in Table 5. Participants who suffered from major depressive disorder, dysthymia, generalized anxiety disorder, or schizophrenia most frequently met the diagnostic criteria for CFS. For FM, this was major depressive disorder, dysthymia, generalized anxiety disorder, or eating disorder. Lastly, for IBS this was IBD, coeliac disease, major depressive disorder, or dysthymia.

Table 5. Percentage of patients with various health conditions that meet the criteria for a functional somatic syndrome diagnosis.

| Somatic health conditions | N _{total} (%) | CFS criteria | | | | FM criteria | | | | IBS criteria | | | |
|---------------------------|------------------------|--------------|-------------------------------|-------------|--------------------|-------------|-------------|--------------------|---------------|--------------|-------------|--------------------|--|
| | | 1. Duration | 2. Interference in daily life | 3. Symptoms | Research diagnosis | 1. Duration | 2. Symptoms | Research diagnosis | 1. Occurrence | 2. Duration | 3. Symptoms | Research diagnosis | |
| | | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|--------------------------------------|----------------|-----------------|-----------------|-----------------|-----------------------------|-----------------|-----------------|-----------------------------|-----------------|-----------------|-----------------|-----------------------------|
| Multiple sclerosis | 201 (0.2) | 148 (73.6) | 101 (50.2) | 38 (18.9) | <u>30</u> <u>(14.9)</u> | 113 (56.2) | 44 (21.9) | <u>35</u> <u>(17.4)</u> | 36 (17.9) | 47 (23.4) | 82 (41.3) | <u>20</u> <u>(10.0)</u> |
| Rheumatoid arthritis | 3,185 (3.5) | 1,500 (47.1) | 799 (25.1) | 650 (20.4) | <u>351</u> <u>(11.0)</u> | 2,185 (68.6) | 645 (20.3) | <u>511</u> <u>(16.0)</u> | 521 (16.4) | 734 (23.0) | 1,134 (35.6) | <u>283</u> <u>(8.9)</u> |
| Inflammatory bowel disease | 1,027 (1.1) | 469 (45.7) | 209 (20.4) | 118 (11.5) | <u>64</u> <u>(6.2)</u> | 503 (49.0) | 120 (11.7) | <u>105</u> <u>(10.2)</u> | 332 (32.3) | 501 (48.8) | 591 (57.5) | <u>234</u> <u>(22.8)</u> |
| Coeliac disease | 419 (0.5) | 199 (47.5) | 105 (25.1) | 61 (14.6) | <u>41</u> <u>(9.8)</u> | 227 (54.2) | 65 (15.5) | <u>56</u> <u>(13.4)</u> | 234 (31.3) | 202 (48.2) | 255 (60.9) | <u>93</u> <u>(22.2)</u> |
| Cancer | 2,063 (2.3) | 807 (39.1) | 422 (20.5) | 211 (10.2) | <u>111</u> <u>(5.4)</u> | 1,026 (49.7) | 209 (10.1) | <u>182</u> <u>(8.8)</u> | 261 (12.7) | 381 (18.5) | 618 (30.0) | <u>116</u> <u>(5.6)</u> |
| Heart failure | 1,796 (2.0) | 771 (42.9) | 425 (23.7) | 248 (13.8) | <u>119</u> <u>(6.6)</u> | 953 (53.1) | 228 (12.7) | <u>191</u> <u>(10.6)</u> | 250 (13.9) | 330 (18.4) | 522 (29.1) | <u>124</u> <u>(6.9)</u> |
| Hepatitis B | 78 (0.1) | 33 (42.3) | 20 (25.6) | 14 (17.9) | <u>7</u> <u>(9.0)</u> | 40 (51.3) | 14 (17.9) | <u>10</u> <u>(12.8)</u> | 15 (19.2) | 13 (16.7) | 28 (35.9) | <u>8</u> <u>(10.3)</u> |
| Psychiatric health conditions | | | | | | | | | | | | |
| Dementias | 81 (0.1) | 40 (49.4) | 24 (29.6) | 21 (25.9) | <u>9</u> <u>(11.1)</u> | 35 (43.2) | 14 (17.3) | <u>11</u> <u>(13.6)</u> | 15 (18.5) | 17 (21.0) | 27 (33.3) | <u>7</u> <u>(8.6)</u> |
| Dysthymia | 882 (1.0) | 633 (71.8) | 405 (49.3) | 244 (29.7) | <u>182</u> <u>(22.1)</u> | 551 (62.5) | 249 (28.2) | <u>211</u> <u>(23.9)</u> | 232 (26.3) | 331 (37.5) | 434 (49.2) | <u>134</u> <u>(15.2)</u> |
| Eating disorder | 1,216 (1.4) | 654 (53.8) | 346 (28.5) | 209 (17.2) | <u>123</u> <u>(10.1)</u> | 690 (56.7) | 246 (20.2) | <u>218</u> <u>(17.9)</u> | 310 (25.5) | 458 (37.7) | 578 (47.5) | <u>176</u> <u>(14.5)</u> |
| Generalized anxiety disorder | 4,185 (4.7) | 2,827 (67.6) | 1,972 (47.1) | 1,145 (27.4) | <u>718</u> <u>(17.2)</u> | 2,553 (61.0) | 1,184 (28.3) | <u>984</u> <u>(23.5)</u> | 1,140 (27.2) | 1,486 (35.5) | 2,076 (49.6) | <u>595</u> <u>(14.2)</u> |
| Major depressive disorder | 2,066 (2.3) | 1,414 (68.4) | 1,251 (60.6) | 721 (34.9) | <u>476</u> <u>(23.0)</u> | 1,312 (63.5) | 801 (38.8) | <u>653</u> <u>(31.6)</u> | 678 (32.8) | 780 (37.8) | 1,096 (53.0) | <u>358</u> <u>(17.3)</u> |
| Schizophrenia | 66 (0.1) | 36 (55.5) | 27 (40.9) | 14 (21.2) | <u>11</u> <u>(16.9)</u> | 29 (43.9) | 9 (13.6) | <u>5</u> <u>(7.6)</u> | 13 (19.7) | 14 (21.2) | 21 (31.8) | <u>6</u> <u>(9.1)</u> |

Data are presented as n (%).

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

DISCUSSION

This is the first study that directly tested the ideas that started the lumpers-splitter discussion in a large general population cohort. 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 differences in diagnostic criteria, this overlap increased to 152 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 somatic or psychiatric health condition did not meet the diagnostic criteria for CFS, FM, or IBS.

The main strength of the current study is that the FSS were assessed using self-reported diagnostic symptoms instead of self-reported diagnoses. The use of self-reported diagnoses might lead to an underestimation of the actual overlap due to diagnostic habits. For example, widespread pain in CFS patients might not easily lead to an FM diagnosis, even when this person meets the FM criteria. In addition, many of those who qualify for an FSS diagnosis may 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. Our cohort enabled us to examine diagnostic overlap of FSS diagnoses irrespective of help-seeking behaviour or diagnostic habits. 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 were used to investigate the effect of chronicity and interference thresholds on diagnostic overlap. The effect of chronicity thresholds is clearly reflected in the results on the prevalence of diagnostic symptoms across diagnoses. Participants that meet the diagnostic criteria for CFS or FM score similar on the diagnostic symptoms cognitive symptoms, waking unrefreshed, fatigue as assessed using the FM items, but participants with CFS score higher than those with FM on the same symptoms as assessed using the CFS items. This might be related to the time window covered by these questionnaires, which was 2 weeks in the FM items and 6 months in the CFS items, reflecting the diagnostic criteria.

Our study also had limitations that 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. Only the CFS diagnostic criteria specifically mention somatic health conditions that need to be excluded before diagnosing CFS [1], whereas more recent FM criteria explicitly state that a diagnosis of fibromyalgia is valid irrespective of other diagnoses [25]. Nevertheless, we studied the extent to which participants with other somatic health conditions fulfilled the diagnostic criteria for the different FSS, and this proportion was relatively limited. 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. Third, CFS diagnoses were based on the CDC criteria, which were the most widely used criteria at the time of the initial data collection. Our data show that these criteria have limitations, for example, sore throat is just as prevalent in those that do or do not qualify for CFS. We do not know whether the same overlap would apply when using the CFS criteria such as those more recently proposed by the Institute of Medicine [22].

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. This could point towards shared mechanisms [6,23,24].

Alternatively, it could be interpreted as reflecting the limitations of the diagnostic criteria used in this study. This particularly applies to the CDC criteria used for CFS. The fact that

participants who met the criteria for a specific FSS frequently report symptoms belonging to the diagnostic criteria of other FSS suggests that the diagnostic criteria are not capable to sufficiently discriminate between different FSS. While this study focused on CFS, FM and IBS, several other FSS exist to which similar overlap problems might apply. It would be interesting to repeat the current study with a broader set of diagnoses.

The current diagnostic criteria should be more extensively investigated and adapted in the future to establish valid and generally accepted diagnostic criteria across medical specialties that are able to discriminate between different FSS. For future studies, it would be advisable to assess the duration of symptoms in a way that enables to include varying chronicity thresholds in data analyses. In addition, studies are advised to include the impact of symptoms on functional abilities. Such symptom interference can be assessed using existing scales that assess health-related quality of life, or simple items specifically focusing on symptom interference [26]. With the accumulation of more detailed data on the diagnostic criteria of FSD, there is potential for refining diagnoses for this large patient group.

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Competing Interest Statement

All authors have completed the Unified Competing Interest form at

http://www.icmje.org/coi_disclosure.pdf and declare that they have no competing interests to report.

Highlights

- Diagnostic overlap of functional somatic syndromes was higher than expected by chance
- Overlap increased when functional somatic syndromes were more chronic and severe
- Participants with a specific syndrome often reported symptoms of other syndromes