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DanFunD

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Published in:
Journal of Psychosomatic Research

DOI (link to publication from Publisher):
10.1016/j.jpsychores.2021.110475

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Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Petersen, M. W., Schröder, A., Eliasen, M. H., Fink, P., Dantoft, T. M., & Jørgensen, T. (2021). Three different approaches to delimitation of functional somatic disorders: DanFunD. *Journal of Psychosomatic Research*, *145*, Article 110475. https://doi.org/10.1016/j.jpsychores.2021.110475

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Journal of Psychosomatic Research 145 (2021) 110475

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Three different approaches to delimitation of functional somatic disorders: DanFunD

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ARTICLE INFO

Keywords:
Functional somatic disorders
Functional somatic syndromes
Bodily distress syndrome
Somatic symptoms
DanFunD
Epidemiology

ABSTRACT

Objective: The Danish Study of Functional Disorders (DanFunD) approaches functional somatic disorders (FSD) with three delimitations: Five functional somatic syndromes (FSS), Bodily Distress Syndrome (BDS), and eight data-driven symptom profiles (SP). This paper presents each delimitation and discusses optimal approaches for further original research into FSD epidemiology.

Methods: A total of 9656 adults from the general Danish population participated in this cross-sectional study. Case assignment of the three FSD delimitations was based on self-reported symptom questionnaires. Overlap of FSS, BDS, and SP and their association with poor self-perceived health were calculated as descriptive statistics and shown with Venn diagrams. Difference in self-perceived health between participants with severe FSD were compared with participants with no FSD and calculated as risk ratios with generalized linear models with binomial family and log link.

Results: We found pronounced overlaps between any FSS, BDS, and the SP with multiple symptoms as well as for multi-organ BDS and the SP with all symptoms. Symptoms and syndromes related to clusters of musculoskeletal and general symptoms contributed particularly to poor health as did multi-organ BDS and categories of SP with multiple symptoms.

Conclusion: Each of the three delimitations has its strengths and weaknesses, and with this study, we offer a contribution to a more valid delimitation of FSD. Future research within DanFunD and other epidemiological studies may benefit from using more than just one delimitation for capturing the diverse nature of the FSD.

1. Introduction

Functional somatic disorders (FSD) have shown to be prevalent in both medical settings and general populations [1–4]. In somatic medical practice, FSD have frequently been approached as specialty-specific, distinct diagnoses, e.g. irritable bowel (IB), fibromyalgia/chronic widespread pain (CWP), chronic fatigue syndrome/chronic fatigue (CF), whiplash associated disorders (WAD), and multiple chemical sensitivity (MCS). These diagnoses are often referred to as functional somatic syndromes (FSS). Epidemiological research has repeatedly suggested that the delimitations of the various FSS are inconsistent; several diagnostic criteria have been used for defining each of them, and most of these are consensus-based [5–7]. A considerable overlap and similarities between the various FSS have been shown [3,8,9], and individuals with more than one FSS diagnosis have markedly poorer health [3,8]. This has led some researchers to propose that FSS are manifestations of the same condition or a family of closely related conditions rather than being different entities [9,10]. In a recent general population study, we showed that the proportion of multi-syndromic individuals ranges between from 56 to 81% for each single FSS. In other words, having "pure" or mono-syndromic FSS seems to be rather uncommon when diagnostic criteria are applied consequently [8]. In the light of this new knowledge, the search for alternative, scientifically driven delimitations for the field of FSD is pertinent.

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https://doi.org/10.1016/j.jpsychores.2021.110475
Received 1 October 2020; Received in revised form 24 March 2021; Accepted 24 March 2021
Available online 27 March 2021
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More than a decade ago, the unifying diagnostic construct Bodily Distress Syndrome (BDS) [11–13] was suggested as an alternative approach to delimitate FSD. BDS is based on factor analysis for exploring the association of symptoms and on latent class analysis for the grouping of individuals based on these symptom patterns. The main aim was to construct positive diagnostic criteria for FSD. BDS takes the similarities and differences between various FSS into account, comprising four symptom clusters; cardiopulmonary (CP), gastrointestinal (GI), musculoskeletal (MS), and general symptoms type (GS) and specifies both single/oligo-organ and multi-organ types. Studies have shown that especially individuals with the multi-organ type have a poor health [3,8,13]. Moreover, the diagnostic agreement and overlap between FSS and BDS have shown to be high (>85%) in both general population samples and in clinical settings [3,8,14]. In Denmark, the BDS diagnosis has been used in a number of clinical studies and was found feasible [15–19]. Recently, the BDS concept has been tested in a number of studies in both Germany and China, and prevalence rates of BDS in both clinical and population-based settings are now available across several countries [8,20–22].

The Danish Study of Functional Disorders (DanFunD) cohort was established in 2009 in order to unravel the epidemiology of FSD [23]. In DanFunD, the FSD were approached with three different delimitations considering both the mono- and multi-systemic types of the conditions and enabling studies of risk factors and prognosis within different theoretical approaches. Moreover, the aim was to translate new findings into already existing diagnostic traditions (such as IB, CF, etc.) easing their uptake into clinical practice. Therefore, DanFunD also operates with eight data-driven symptom profiles (SP) derived from latent class analysis [24]. The eight SP were characterized by specific symptom combinations: One profile with no symptoms, three profiles with a few, specific symptoms, three profiles with multiple symptoms, and one profile with all symptoms. The last four profiles were strongly associated with poor health and had a pronounced overlap with the BDS diagnostic construct [24].

While the overlap between the FSS and BDS has been studied [8], the overlap and associations between all the three delimitations used in the DanFunD study have not yet been investigated. The aim of the current study was therefore to present and describe each of the delimitations and explore their overlap and associations in the DanFunD cohort. Furthermore, we wanted to discuss approaches for further original research in DanFunD and to suggest meaningful and scientifically sound approaches for further original research in different settings and situations.

The specific objectives were to:

1) Present and describe the three DanFunD FSD delimitations; FSS, BDS, and SP.
2) Identify the overlap between overall and severe categories of FSS, BDS, and SP.
3) Explore the distribution of FSS according to BDS.
4) Explore the distribution of FSS and BDS according to the SP.
5) Explore the impact of overlap between FSS, BDS, and the SP on their association with self-perceived health.

2. Materials and methods

2.1. Study population

Participants were invited to the study through the nationwide Danish Civil Registration System [25]. In total, the DanFunD cohort included 9656 (33.7% of invited participants) men and women aged 18–76 years, born in Denmark, and living in the Western part of greater Copenhagen. Case assignment of the three FSD delimitations was based on self-reported symptom questionnaires. Data collection is described in detail elsewhere [3,23,24].

Written informed consent was obtained from each participant before participation, and the study was approved by the Ethical Committee of Copenhagen County (Ethics Committee: KA-2006-0011; H-3-2011-081; H-3-2012-0015) and the Danish Data Protection Agency.

2.2. Measurements

Cases of the five FSS were identified with symptom lists commonly used in epidemiological research. Only bothersome symptoms were included. IB was defined according to the definition by Kay et al. [26], CWP was based on the American College of Rheumatology criteria [27] and defined according to the definition by White et al. [28], CF was defined according to the definition by Chalder et al. [29], WAD was defined according to the definition by Kasch et al. [30], and MCS was defined as an approximation of the 1999 consensus definition [31] with modifications by Lacour et al. [32].

Cases of BDS were identified with the 25-item BDS checklist using the BDS criteria from Budtz-Lilly et al. [12]. Single/oligo-organ BDS was assigned to participants with at least four symptoms within one or two of the four BDS symptom clusters. Multi-organ BDS was assigned to participants with at least four symptoms within at least three of the four BDS symptom clusters [3,11].

The SP were developed in a previous study from a list of 31 physical symptoms also required in the diagnostic criteria of the various FSS and BDS: Eight CP symptoms, nine GI symptoms, nine MS symptoms, and five GS symptoms [24]. In that study, latent class analysis was used to identify symptom profiles. The best latent class analysis model identified eight SP: One was characterized by low probability of any symptoms (“no symptoms”), three profiles were characterized by few, specific symptoms (“muscle/joint”, “lower GI”, “GS”), another three were characterized by high probability of specific combinations of multiple symptoms from different organ systems (“MS and GS”, “MS, GI and fatigue”, “GI, CP and GS”), and the last profile had high probability of all symptoms (“all symptoms”) [24].

The impact of the three FSD delimitations on self-perceived health was explored through a single item from the 12-item Short Form Health Survey (SF-12) [33]. The item assessed perceived overall health on a five-point Likert scale which was dichotomized into “poor health” (poor/fair) and “good health” (excellent//very good/good).

2.3. Statistical analyses

Data were analyzed using Stata 16.0 for Windows (StataCorp LLC, College Station, USA) [34]. Distribution of FSS according to BDS and distribution of FSS and BDS according to the SP were calculated as descriptive statistics with raw numbers and percentages.

Overlaps of FSS, BDS, and the SP were shown with Venn diagrams.

The proportion of participants with a poor self-perceived health across different combinations of FSS, BDS, and SP were calculated as descriptive statistics with percentages with exact 95% confidence intervals.

Participants fulfilling one of the severe categories of the three FSD delimitations (at least three of the five FSS, multi-organ BDS, or the SP with all symptoms) and participants fulfilling all the severe categories of the three FSD delimitations were compared with participants not fulfilling criteria for any FSD (no FSS, no BDS, and in the SP with no symptoms). Difference in self-perceived health was calculated as risk ratios with generalized linear models with binomial family and log link.

2.4. Subanalysis

A subgroup analysis was made excluding participants who reported suffering from chronic physical disease which may account for – or substantially contribute to - the obtained symptom patterns. Participants who reported suffering from at least one of two diseases shown to be associated with multiple symptoms (chronic obstructive pulmonary disease or stroke) were excluded as were participants suffering from at

least two of the following five diseases: Cancer, myocardial infarction, other heart disease, diabetes, and asthma. This approach was inspired by previous DanFunD studies [3,24].

3. Results

3.1. Characteristics of the study population

Mean age of the 9656 participants was 52.5 (SD: 13.2) and 53.9% were women. Prevalence of any FSS and BDS was 15.7% and 16.0%, respectively. In the SP construct, the three profiles characterized by a few specific symptoms had a prevalence of 36%, while 15% of the participants fell within the SP with multiple or all symptoms.

Poor health was reported by 9.2% of all participants. This constituted 30.6% of participants with FSS, 33.4% of participants with BDS, 9.4% of participants within the SP with a few symptoms, and 36.5% of participants within the SP with multiple or all symptoms.

At a glance, the three delimitations identified very similar proportions of participants as cases, and rather similar proportions of cases reported poor health.

3.2. Characteristics of the three delimitations

Table 1 gives important characteristics of each delimitation.

Fig. 1 shows the size, mean number of symptoms, and proportion of poor health for each diagnosis/profile within the three FSD delimitations. Both the delimitations of BDS and SP divided individuals into categories which could be interpreted as mild/moderate FSD and severe FSD. The delimitations of FSS could not provide such information as all categories were within the same spectrum of mild/moderate disease, meaning that both severe and moderate cases are included within each single FSS.

3.3. Overlap of overall categories of FSS, BDS, and SP

A large fraction of participants with FSS (64.4%) also fulfilled criteria for BDS or the SP with multiple or all symptoms. This was also the case for the majority of BDS cases (74.0%) (Fig. 2). Most participants (69.8%) in the SP with a few, specific symptoms neither had FSS nor BDS, while the majority of participants in the four SP with multiple or all symptoms also had BDS (74.7%) or FSS (64.5%) (Fig. 2). Nevertheless, each delimitation also defined a considerable proportion of cases that were not captured by any of the other delimitations. This proportion was particularly large (35.6%) for the FSS (which also include very mild cases together with severe cases within each FSS category), while it was rather small for the SP with multiple or all symptoms (13.1%). In combination, the three delimitations identified 2363 individuals as possible cases (24.5% of the participants) but agreed only on 678 individuals (7.0% of the participants).

3.4. Distribution of FSS according to BDS

The greatest overlap of FSS with BDS was seen for CWP where 68% also had the single-organ type of BDS, and 9% had the multi-organ type (Table 2). 6–10% within each of the five FSS also fulfilled criteria for multi-organ BDS. IB, CWP, and WAD had the greatest overlap with their corresponding BDS single-organ subtype, while individuals with CF were almost equally distributed in the MS and GS subtype. Although CF by far was the largest FSS group with 823 identified cases, the largest overlap of any FSS ("at least one FSS") was with the BDS-MS and not the GS subtype. This illustrates that the delimitations based on main or lead symptoms (as all FSS definitions do) result in other groups than delimitations using symptoms patterns (as BDS does).

Table 1
Characteristics of the three delimitations of functional somatic disorders.

	FSS	BDS	SP
Number of categories	5 (in the current study)	3	8
Number of possible combinations of categories	26 (in the current study)	0	0
Structure of delimitation	Uses main/lead symptoms and accessory symptoms	Uses characteristic symptom patterns	Uses symptom clusters
Origine	Apart from the criteria of IB which were developed from cluster analysis on gastrointestinal symptoms in an unselected general population sample, criteria are mainly based on expert consensus and selected patient samples.	Data-driven factor and latent class analysis on 81 symptoms in a sample of primary care patients and patients from neurological and internal departments.	Data-driven latent class analysis of 31 symptoms in a general population sample.
Worldwide dissemination	Most of them are well-known worldwide and used in different research settings.	Validated in another Danish primary care sample together with Danish, German, and Chinese general population samples.	Only used in the Danish Study of Functional Disorders (DanFunD).
Use in epidemiological research			
Pros	Well-known terms in specialty-specific settings. Good clinical face validity.	A unifying approach taking both oligo- and multi-systemic conditions into account. Validated in both population-based, primary care, and specialized settings. High clinical face validity. Divides cases according to illness severity. Data-driven.	A unifying approach. Includes both mono- oligo- and multi-systemic groups. Can be an indicator of illness severity. Data-driven.
Cons	Only few of them are validated in population-based samples. A splitting approach. Do not take overlapping syndromes into account. Do not divide cases according to illness severity. Multiple definitions exist for each syndrome.	Uses a rather long (25-items) checklist to assess symptoms.	No validated checklist to assess symptoms. Difficult to translate directly to other studies. Low clinical face validity.

Abbreviations: FSS = functional somatic syndromes; BDS = bodily distress syndrome; SP = symptom profile.

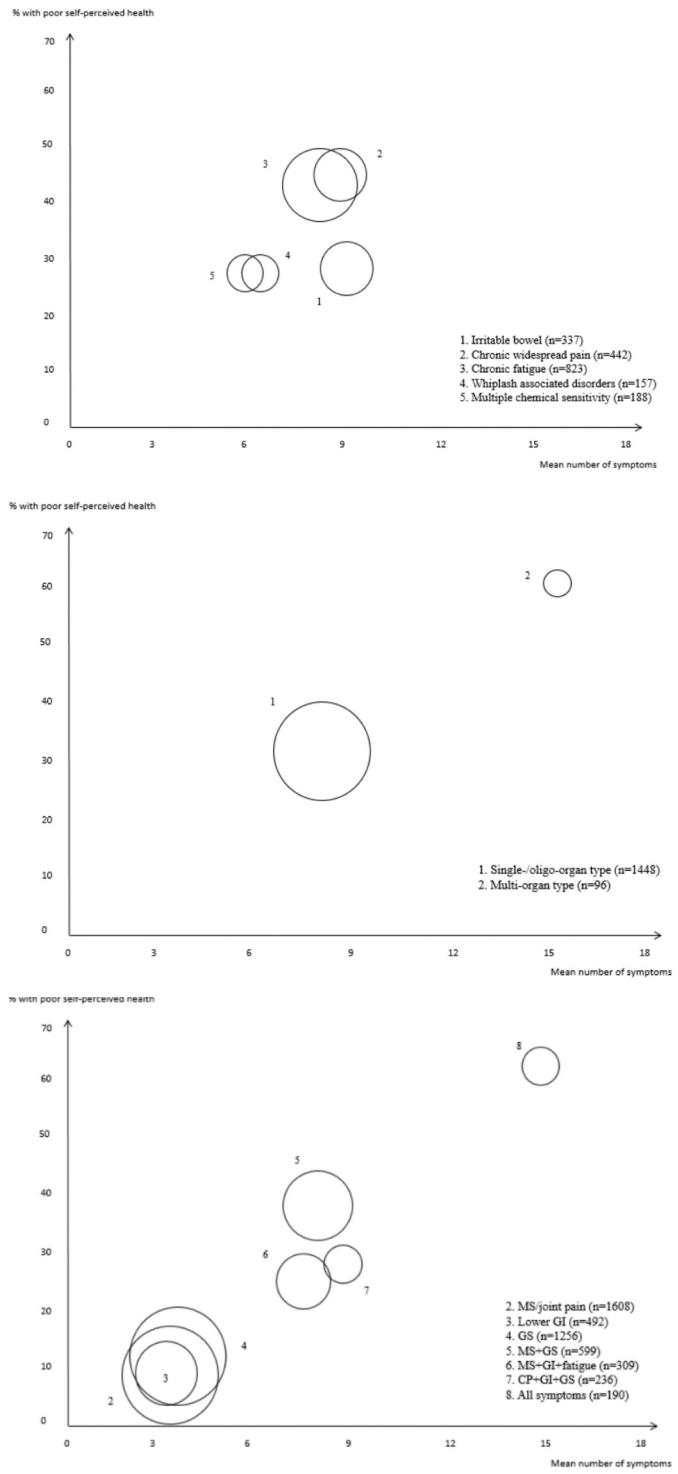

Fig. 1. Distribution of functional somatic syndromes, bodily distress syndrome, and symptom profiles according to number of symptoms and poor self-perceived health.
The size of the circles indicates the prevalence of each category of functional somatic disorder. Abbreviations: MS = musculoskeletal; GI = gastrointestinal; GS = general symptoms; CP = cardiopulmonary.

3.5. Distribution of FSS and BDS according to the SP

Except from MCS, the majority (51–100%) of those with FSS and BDS were captured in the four SP with multiple or all symptoms (Table 3). For IB, CWP, CF, BDS-GI, BDS-MS, and BDS-GS, the greatest overlap was seen with the SP with multiple symptoms corresponding to the FSS and BDS symptom characteristics. All participants with multi-organ BDS were captured by the four SP with multiple symptoms, mainly the SP with all symptoms.

A small fraction (≤3.7%) of individuals with IB, CWP, CF, BDS-GI, and BDS-MS were captured by the SP characterized by no symptoms, while the latter accounted for a larger fraction of those with WAD (11.0%) and MCS (25.0%).

For the SP with a few, specific symptoms, most FSS and all BDS subtypes overlapped with the profile with corresponding symptoms.

3.6. Overlap of severe categories of FSS, BDS, and SP

For participants with multiple FSS (at least three of the five FSS), 58.0% overlapped with the SP with all symptoms, while 29.0% overlapped with multi-organ BDS (Fig. 3). For multi-organ BDS, 87.5% overlapped with the SP with all symptoms, and 20.8% overlapped with multiple FSS. For participants in the SP with all symptoms, the largest overlap was seen with multi-organ BDS (44.2%). When combined, the three delimitations identified 227 individuals (2.4%) as severe cases but agreed only on 20 (0.2%).

3.7. Impact on self-perceived health of the delimitation overlap

Generally, the proportion of participants with poor self-perceived health increased with positive FSS status across the BDS delimitations, and likewise, the proportion of participants with poor perceived health increased with positive BDS status across all FSS (Appendix A, Table 1). Especially CWP, CF, and multi-organ BDS seemed to influence on self-perceived health.

The same tendencies were seen for the various FSS and BDS and their overlap with the SP, where also the four SP characterized by multiple or all symptoms were associated with poor self-perceived health (Appendix A, Table 2).

No differences were found regarding association with poor self-perceived health when comparing each of the three specific severe categories of FSD (multiple FSS, multi-organ BDS, all symptoms SP) with those fulfilling all severe categories of FSD (data not shown).

3.8. Subanalysis

The subanalysis excluding participants with chronic physical disease did not provide profound differences on the results on overlap and distribution compared with the main analysis (Appendix B).

4. Discussion

In the current paper, we presented the three approaches used to delimitate FSD in the DanFunD study; FSS, BDS, and SP and their overlap and association with poor self-perceived health. We found overlap between overall FSS, BDS and the multiple symptom SP as well as between multi-organ BDS and the SP with all symptoms. At the same time, the number of cases that all three delimitations agreed on was rather small, especially as regards the definitions of cases with severe illness. Symptoms and syndromes related to the MS and GS symptom clusters particularly contributed to poor self-perceived health. WAD and MCS seemed to stand out from the other FSS, and a significant proportion of these cases were captured by the SP with no symptoms. This may indicate that WAD and MCS belong to a different "family" of disease than IB, CWP, and CF.

Previous literature supports the overlap between FSS and BDS, both in clinical samples [14] and in general populations [3,8,21]. Nevertheless, this study adds to the current knowledge that different delimitations, although they report similar prevalence rates and overlaps are shown, also identify different individuals, and, for the BDS and SP definition, also similar rates of severe cases. This raises the important

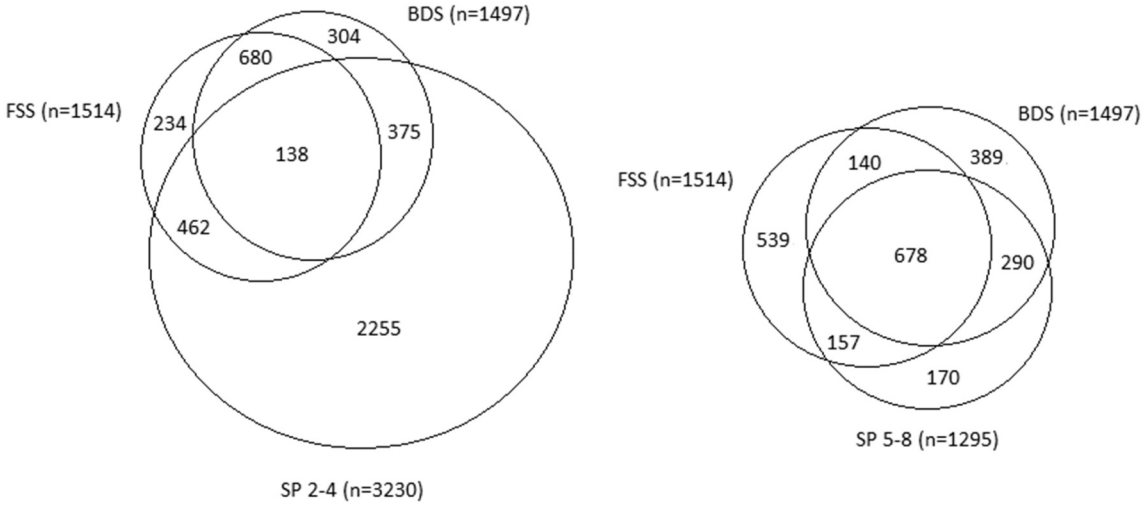

Fig. 2. Overlap of overall categories of functional somatic syndromes (FSS), bodily distress syndrome (BDS), and symptom profiles (SP).
SP 2–4: Symptom profiles with a few, specific symptoms. SP 5–8: Symptom profiles with multiple or all symptoms. SP 2–4 and SP 5–8 are mutually excluding.

Table 2
Distribution of functional somatic syndromes according to bodily distress syndrome case status and subtype.

		BDS status			BDS subtype			
		No BDS ($n = 8035$)	Single-organ ($n = 1448$)	Multi-organ ($n = 96$)	CP ($n = 137$)	GI ($n = 405$)	MS ($n = 1063$)	GS ($n = 408$)
FSS								
IB, n (%)	$n = 337$	135 (40.1)	170 (50.5)	32 (9.5)	22 (6.6)	149 (44.2)	93 (27.6)	69 (20.5)
CWP, n (%)	$n = 442$	101 (22.9)	300 (67.9)	39 (8.8)	40 (9.1)	64 (14.5)	322 (72.9)	84 (19.0)
CF, n (%)	$n = 823$	348 (42.3)	400 (48.6)	73 (8.9)	79 (9.6)	144 (17.5)	296 (36.0)	251 (30.5)
WAD, n (%)	$n = 157$	71 (45.2)	75 (47.8)	11 (7.0)	9 (5.7)	20 (12.7)	66 (42.0)	34 (21.7)
MCS, n (%)	$n = 188$	110 (58.5)	66 (35.1)	12 (6.4)	13 (6.9)	23 (12.2)	60 (31.9)	29 (15.4)
At least one FSS, n (%)	$n = 1518$	696 (45.6)	734 (48.4)	84 (5.5)	93 (6.1)	251 (16.5)	550 (36.2)	302 (19.9)

Abbreviations: FSS = functional somatic syndromes; BDS = bodily distress syndrome; GI = gastrointestinal; MS = musculoskeletal; CP = cardiopulmonary; GS = general symptoms type; IB = irritable bowel; CWP = chronic widespread pain; CF = chronic fatigue; WAD = whiplash associated disorders; MCS = multiple chemical sensitivity.

Table 3
Distribution of functional somatic syndromes and bodily distress syndrome according to symptom profiles.

Symptom profile		No symptoms	A few, specific symptoms			Multiple symptoms			
		1	2	3	4	5	6	7	8
		No symptoms	Muscle/joint pain	Lower GI	GS	MS + GS	MS + GI +Fatigue	CP + GI +GS	All
		$n = 4913$	$n = 1608$	$n = 492$	$n = 1256$	$n = 599$	$n = 309$	$n = 236$	$n = 190$
FSS									
IB, n (%)	n = 337	0 (0)	0 (0)	116 (34.4)	0 (0)	0 (0)	94 (27.9)	72 (21.4)	55 (16.3)
CWP, n (%)	n = 442	0 (0)	101 (22.9)	1 (0.23)	7 (1.6)	173 (39.1)	70 (15.8)	1 (0.2)	89 (20.1)
CF, n (%)	n = 823	16 (1.9)	25 (3.0)	23 (2.8)	248 (30.1)	194 (23.6)	61 (7.4)	115 (14.0)	141 (17.1)
WAD, n (%)	n = 157	17 (10.8)	33 (21.0)	8 (5.1)	19 (12.1)	39 (24.8)	15 (9.6)	7 (4.5)	19 (12.1)
MCS, n (%)	n = 188	47 (25.0)	27 (14.4)	8 (4.3)	23 (12.2)	39 (20.7)	16 (8.5)	8 (4.3)	20 (10.6)
At least one FSS	n = 1518	80 (5.3)	175 (11.5)	143 (9.4)	285 (18.8)	333 (21.9)	177 (11.7)	156 (10.3)	169 (11.1)
Single-organ BDS	n = 1448	16 (1.1)	322 (22.3)	73 (5.0)	135 (9.3)	460 (31.8)	187 (12.9)	152 (10.5)	103 (7.1)
CP-subtype	*n = 137*	*0 (0)*	*2 (1.5)*	*1 (0.7)*	*16 (11.7)*	*31 (22.6)*	*6 (4.4)*	*24 (17.5)*	*57 (41.6)*
GI-subtype	*n = 405*	*15 (3.7)*	*12 (3.0)*	*72 (17.8)*	*31 (7.7)*	*34 (8.4)*	*82 (20.3)*	*73 (18.0)*	*86 (21.2)*
MS-subtype	*n = 1063*	*1 (0.1)*	*312 (29.4)*	*0 (0)*	*11 (1.0)*	*417 (39.2)*	*149 (14.0)*	*8 (0.8)*	*165 (15.5)*
GS-subtype	*n = 408*	*0 (0)*	*0 (0)*	*0 (0)*	*87 (21.3)*	*85 (20.8)*	*2 (0.5)*	*100 (24.5)*	*134 (32.8)*
Multi-organ BDS	n = 96	0 (0)	0 (0)	0 (0)	0 (0)	7 (7.3)	2 (2.1)	3 (3.1)	84 (87.5)

Abbreviations: FSS = functional somatic syndrome; IB = irritable bowel syndrome; CWP = chronic widespread pain; CF = chronic fatigue; WAD = whiplash associated disorders; MCS = multiple chemical sensitivity; BDS = bodily distress syndrome; CP = cardiopulminary; GI = gastrointestinal; MS = musculoskeletal; GS = general symptoms.
The italic letters indicate that these categories (CP, GI, MS, and GS) are subtypes of the single-organ BDS.

question; which delimitation is most correct in identifying true FSD cases. Based on this study, it is not possible to answer that question. In a previous study including a stratified sample from DanFunD, the diagnoses of FSS and BDS were based on a diagnostic interview performed by trained family physicians. Hence, individuals with other physical or mental conditions that accounted for the symptom pattern were excluded. Here, we found an overall diagnostic agreement of 92% with a Kappa value of 0.78 [8]. This may indicate that the smaller overlap from

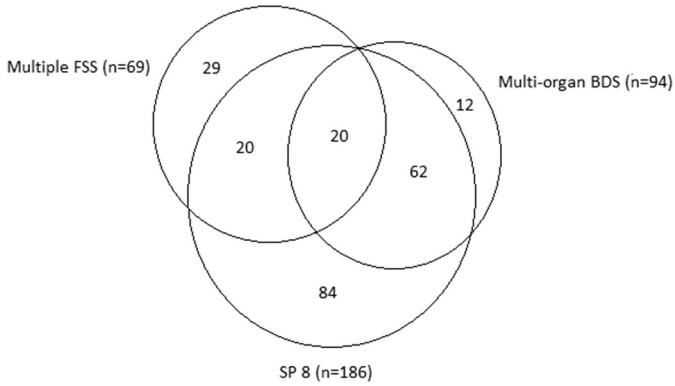

Fig. 3. Overlap of multiple (≥3) functional somatic syndromes (FSS), multi-organ bodily distress syndrome (BDS), and the symptom profile (SP) 8 with all symptoms.

the current study is caused by individuals with other physical or mental conditions that would have been excluded in a diagnostic interview.

4.1. Clinical and research implications

The FSS delimitation constitutes various syndromes defined by distinct (main) symptoms and accessory criteria but in reality with highly overlapping symptoms. Within the last decades, more studies have pointed out that the diagnostic criteria for the various FSS are mainly based on medical traditions and clinical consensus rather than research [3,4,8,9]. This may ultimately mean that the specific diagnostic label given to a patient in the specialized clinic is an artefact of medical specialization rather than a conceptualization of the patient's actual symptom pattern; a hypothesis that has been put forward decades ago but now seems to be supported by a substantial amount of research. However, the various FSS constitute well-known terms within medicine worldwide, and some are well accepted within clinical practice with high face validity and are therefore often used in both clinical and epidemiological research, thereby perpetuating the illusion of distinct syndromes. Nevertheless, the FSS may be useful for medical specialists and for researchers wanting to investigate symptom patterns from primarily one organ system or symptom patterns that are defined by a lead or main symptom. However, in summary, the huge overlap of FSS, numerous sets of different diagnostic criteria, lack of capacity to classify severely affected individuals with multiple symptoms from multiple organ systems, and less ability to provide information about illness severity constitute serious limitations when studying FSD epidemiology. It ought be a standard requirement in FSD research at least to identify – or exclude - FSS comorbidity when studying single FSS. Most original FSS studies would benefit from stratification into "pure" and multi-syndromic cases (i.e. cases that fulfill criteria for other FSS alongside the FSS under investigation).

Contrary to the FSS, the construct of BDS constitutes an approach to delimitate FSD that takes both oligo- and multi-syndromatic conditions into account. The BDS construct and the BDS checklist were initially developed and validated in a number of Danish studies [11–14,35,36], but recently a number of studies on BDS have emerged in other countries as well [20–22] increasing the worldwide dissemination of BDS research. BDS classifies individuals according to three categories of no disease, mild/moderate disease, and severe disease, and contrary to the FSS, these categories are exclusive. However, the category single/oligo-organ BDS includes individuals who present with symptoms from both one and two organ systems. Hence, BDS does not provide specific information on individuals with symptoms from only one organ system unless the four subtypes are used for further division of individuals. To our knowledge, research on whether the four symptom cluster subtypes of BDS could be used for this purpose does not yet exist. Opposite to the various measurements for FSS, the BDS symptom checklist exists in only one version, the 25-item checklist which makes it feasible to use for both clinical and research purposes [12,13,20,22,36]. However, comprising 25 symptoms, the BDS checklist is longer than most other known symptom checklists used in research such as the PHQ-15 [37], the SSS-8 [38], and the somatization subscale of the SCL-90 [39], but it also constitutes another approach: In contrast to the PHQ-15, the SSS-8 and the somatization subscale of SCL-90, which are based on symptom count, the BDS checklist was developed as a diagnostic aid for use in primary care to identify patients with FSD [12]. It is based on the identification of characteristic symptom patterns of BDS/FSD, which may exclude patients with other conditions. When using the BDS checklist in epidemiological research, you only need that one single measurement of FSD, whereas the FSS delimitation requires measurements for each specialty-specific syndrome. The BDS checklist thus avoids syndrome overlap as opposed to the FSS delimitation [13,36].

The SP were developed by latent class analysis on symptoms in the DanFunD study sample also used in the current study [24]. The difference between the BDS concept and the SP mainly lies in the statistical approach and the purpose for which they were developed: BDS was developed for clinical and research purposes, while the SP were developed for research purposes only. The great overlap between the SP and BDS in both the original and the current study implies that the SP may comprise an alternative, more detailed FSD delimitation which may be particularly beneficial in original research. While the SP and BDS captured the linear relationship between number of symptoms and poor health, this was not the case for the five FSS (unless one adds an arbitrary category of "at least three FSS"). However, even though other general population studies have shown almost similar results regarding grouping of symptoms [38,40–44], no validation studies on these specific eight SP exist. Until now, the SP are exclusively used in DanFunD without any worldwide dissemination, and they have not been tested in clinical settings. As we lack knowledge about the SP's generalizability, they cannot be used as a diagnostic framework based on diagnostic criteria as the FSS and BDS, which both resemble diagnostic labels in the Danish version of the International Classification of Diseases (ICD)-10 classification system. This means that the SP are not suitable for use in the clinic, while they may play an important role in basic FSD research: Capturing the FSD as both mono-, oligo-, and multi-systemic conditions with non-overlapping categories and acknowledging that not only multiple symptoms but also some specific symptoms (in this study MS and GS symptoms) may contribute to more impairment than others, the SP may serve as an important tool for epidemiological purposes.

4.2. Strengths and limitations

A major strength of this study is the large sample of 9656 individuals randomly sampled from the general population. The sample comprised both sexes and ranged over an age span of 50 years. Moreover, this is the first population-based study comparing three delimitations of FSD that are rooted in different research traditions and uses different methods to identify FSD cases.

Some limitations also need to be addressed: First, because of the size of the included sample, symptom registration was based on self-reported measures. Hence, obtained symptom patterns for the three FSD delimitations were not validated using medical examinations or clinical judgement.

Second, all symptoms stated to entail some degree of impairment were included, and symptom etiology was not taken into account. However, the subanalysis excluding a pre-defined list of diseases did not change the overall results. Still, this list might not be substantial, and therefore it is possible that some of the symptom patterns for the three FSD delimitations could be explained by other conditions than a FSD in both the main analysis and subanalysis. Some studies have shown that excluding cases with symptom patterns attributable to other physical and mental conditions reduces the prevalence of FSD slightly [3,45].

However, a gold standard for such exclusion using questionnaires does not exist. Recent studies have generally suggested not making this distinction on symptom etiology to avoid to distinguish between so-called medically unexplained and medically explained symptoms [46–50]. If one wanted to make such exclusion in future epidemiological research, it could for example be based on specific present conditions (self-reported or obtained from diagnosis registers) for excluding specific FSD as done in other studies [51,52]. However, making such conservative exclusion would not take into account those cases with both FSD and comorbid physical or mental conditions. Furthermore, it is unlikely that exclusion of a few cases would change the observed overlap of diagnostic categories substantially as the misclassification most probably will be the same in all delimitations [3]. False positive cases could be identified with a diagnostic assessment by a physician. However, this approach would be costly and time-demanding, and it may still not completely rule out cases with comorbid FSD.

Finally, the use of a single dichotomized item for evaluating impairment might also compose a limitation. This approach has been used in previous DanFunD studies investigating FSS, BDS, and SP [3,8,24], and we therefore chose this approach in the current study as well to obtain consistent findings and make comparison more feasible. However, other approaches to assess impairment could be applied in further research. These approaches could for example constitute use of the full 36 or 12-items Short Form Health Survey (SF-36/12) [33,53], looking into hospital admissions and treatment in primary and specialized clinical settings, and verification of symptom patterns and ailment by a trained physician.

In conclusion, each of the three delimitations may have its strengths and weaknesses, and with this study, we offer a contribution to a more valid delimitation of FSD. Although the overall numbers of FSD cases were very similar across the three delimitations, they only partly agreed on the case status of specific individuals. Future research within DanFunD and similar epidemiological studies may benefit from using more than just one delimitation for capturing the whole nature of the FSD.

Funding

This work was supported by grants from the Danish foundations The Lundbeck Foundation [grant number R155-2013-14070] and TrygFonden [grant number 7-11-0213].

Authors' contributions

MWP contributed to the conception and design of the study, performed the analyses, interpreted the data, and drafted the article. AS, ME and TJ contributed to the conception and design of the study and interpretation of the data. TMD and PF contributed to the interpretations of the data. All authors contributed to critically revising the article for important intellectual content, and all authors read and approved the final version of the article.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgements

The DanFunD steering committee consists of Professor MD DMSc Torben Jørgensen (PI), Professor MD DMSc Per Fink, Senior consultant MD PhD Lene Falgaard Eplov, MSc PhD Allan Linneberg, MSc PhD Susanne Brix Pedersen, and MD PhD Michael Eriksen Benros.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2021.110475.

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