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Similar but different

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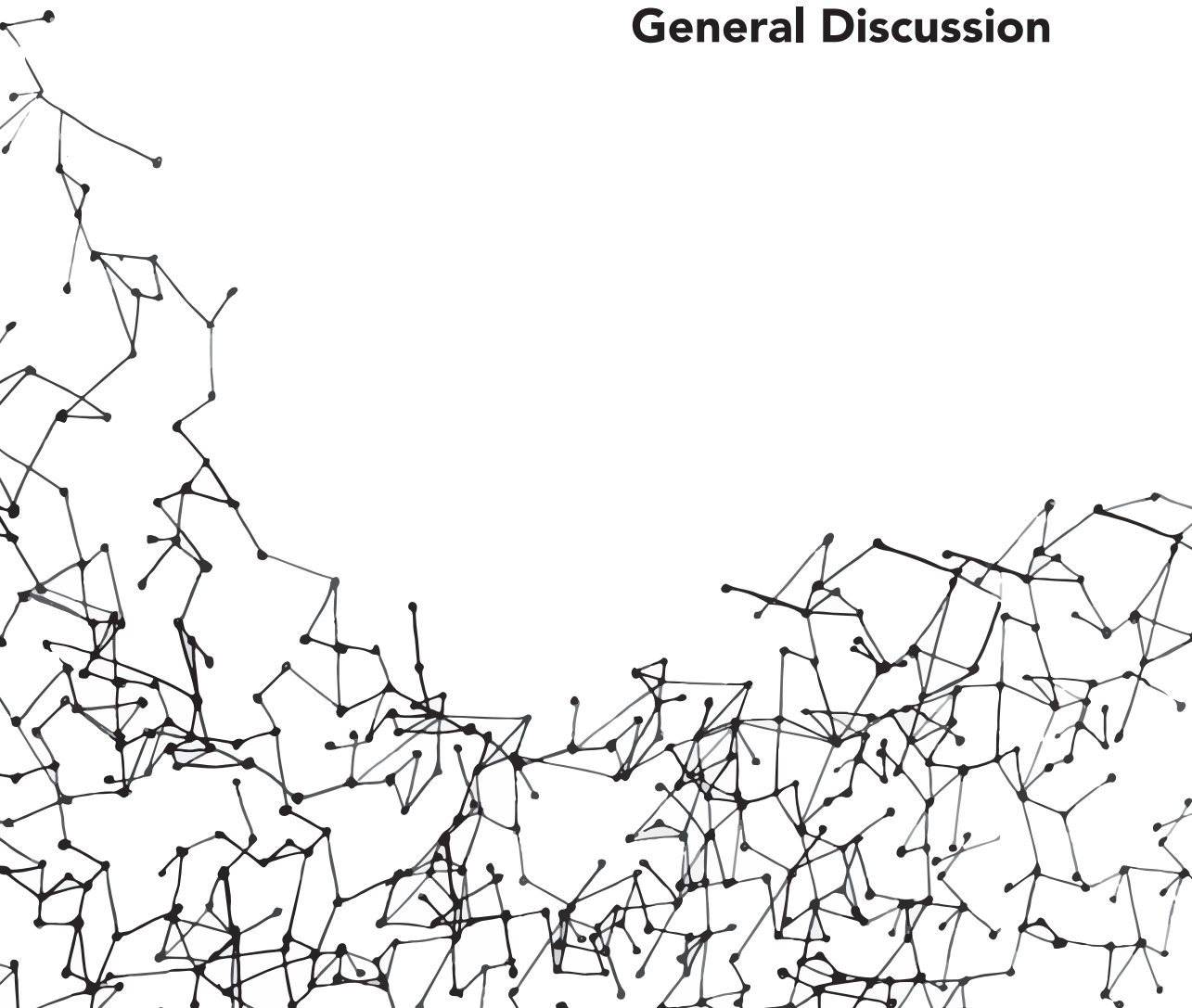
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General Discussion



The aim of this thesis was to investigate the validity of FSS diagnoses, and to examine to which degree these diagnoses are able to identify separate groups of patients in the context of the lumpers-splitter discussion. We approached this aim from different angles, taking into account the possible etiological pathways that may lead to the causation and persistence of FSS. In this chapter, I will put the main findings from this thesis into the context of the current knowledge and the lumpers-splitter discussion. I will start from the four main observations that initiated the lumpers-splitter discussion, namely that [1] the case definitions of FSS overlap; [2] patients with one FSS frequently meet diagnostic criteria for one of the other FSS; [3] patients with different FSS share non-symptom characteristics; and [4] all FSS patients respond to the same psychological and pharmacological therapies. Furthermore, I will discuss the implications of our study findings, the methodological strengths and limitations, and lastly the directions for future research.

1. The case definitions of FSS overlap

The first argument of the splitters was that the case definitions of the main three FSS overlap, namely chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). For example, both CFS and FMS diagnostic criteria describe both musculoskeletal symptoms, fatigue, cognitive symptoms, sleep disturbance or waking unrefreshed. This implies that patients fulfilling diagnostic criteria for one syndrome automatically fulfill at least part of the diagnostic criteria for other syndromes. However, besides the specific types of main and additional symptoms required, the diagnostic criteria also include other relevant aspects that have been relatively ignored: the chronicity of the main symptom, and the interference of the main symptom with daily activities and work. These requirements vary between syndromes: the chronicity threshold is six months for CFS 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 and IBS. Such arbitrary choices in diagnostic criteria may reduce overlap in an artificial way.

The overlap in case definitions of FSS does not directly imply that the different FSS reflect the same underlying construct, because the criteria are often quite non-specific. For example, the symptom of abdominal pain can be the result of inflammatory bowel disease or a urinary tract infection. However, both causes

have their own distinctive etiology and clinical presentation. Thus, the fact that fatigue, cognitive symptoms and sleep difficulties are diagnostic criteria for both CFS and FMS does not necessarily mean that these symptoms are identical across FSS. Previous studies have attempted to investigate whether FSS are distinct entities by examining the clustering of somatic symptoms in general and clinical populations (1-3). However, no previous studies had performed these analyses on the symptoms that compose the diagnostic criteria of the different FSS. We used a new approach to analyze symptom patterns, which focuses on individual symptoms and the unique patterns in which the individual symptoms co-occur with other symptoms, and to investigate networks of the diagnostic symptoms included in the criteria for the three main FSS (**chapter 4**). We found that all diagnostic symptoms of all three FSS were connected, either directly or via other symptoms. In addition, we found a non-isolated general, musculoskeletal, abdominal and other symptom cluster. We therefore concluded that these symptom networks suggest that FSS may reflect the same underlying syndrome with different subtypes based on symptoms' bodily systems rather than their current classification as criteria for CFS, FMS or IBS.

It is important to have valid and reliable diagnostic criteria for FSS in research and clinical practice. In addition, physicians, researchers, and other health care professionals must rely on patients' reports for the recognitions and evaluation of symptom burden in patients with FSS. In large cohort studies, as used in this thesis, FSS diagnoses are typically based on symptom scales that accompany the diagnostic criteria. For FMS, these are the Widespread Pain Index and the Symptom Severity Scale. While these scales cover symptoms in the last week, previous reviews showed that time frames of assessment of somatic symptom questionnaires vary considerably (4,5). We therefore examined the most clinically relevant assessment period for somatic symptom questionnaires (**chapter 2**). We found that the four-week assessment period for somatic symptoms best reflects the clinically relevant somatic symptom burden, in terms of QoL and health anxiety. Thus, we advise that future revisions of diagnostic criteria consider using a four-week assessment period to measure symptom burden.

2. Patients with one FSS frequently meet diagnostic criteria for one of the other FSS

The second argument of the lumpers is that patients with one FSS frequently meet diagnostic criteria for other FSS. As mentioned above, 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, thereby artificially increasing overlap. However, we also describe remarkable differences that might artificially decrease presumed overlap between FSS (**chapter 5**). Furthermore, in favor of the lumpers' view, it was stated that patients who meet the criteria for a specific FSS, also report symptoms other than those included in the case definition (6). Lumpers conclude from this that the syndromes actually reflect one underlying problem that is artificially split due to medical specialization. However, this approach ignores that these symptoms are also prevalent in chronic somatic health problems and in the general population.

To explore the observation that patients with one FSS frequently meet diagnostic criteria for one of the other FSS, we examined whether participants who meet the criteria for a specific FSS frequently report symptoms formulated in the other FSS criteria. We also explored the effects of arbitrary choices in case definitions on co-morbidity as described earlier (i.e., duration of main symptom, interference with daily life, **chapter 5**). Our findings indicate that the diagnostic overlap of the three FSS was much higher than could be expected by chance, and that this diagnostic overlap substantially increased when the FSS were more chronic in nature and interfered with daily life. Although patients with different FSS thus share symptoms, we did observe quantitative differences: general symptom severity and fatigue severity were higher in patients with CFS, while pain severity was higher in patients with FMS.

To further explore the existence of shared symptoms, we investigated cognitive functioning in patients with CFS and patients with FMS (**chapter 6**). We found that subjective cognitive impairments are more prevalent in both patients with CFS and patients with FMS compared to controls and patients with a well-defined medical disease (MD). However, we found that patients with CFS reported significantly more subjective cognitive impairments and performed significantly worse on the tasks measuring psychomotor functioning/speed of processing and attention/working memory, compared to patients with FMS, although effect sizes were

small. Similar results were found when aligning CFS and FMS for the duration of their main symptom and interference with daily life, limiting the possibility that the observed differences were simply the result of more strict diagnostic thresholds for CFS than for FMS.

3. Patients with different FSS share non-symptom characteristics

The third argument of the lumpers is that patients with different FSS share non-symptom characteristics. Examples of these non-symptom characteristics include being female, experiencing functional limitations and psychological distress, overlapping lifestyle factors, overlapping physiology, and difficulties in doctor-patient relationships (6). However, the validity of this argument can be questioned for all provided non-symptom characteristics.

Sex

In this thesis, we found that FSS are more common in females than in males. However, we also found that the corresponding MD with the same main symptoms (multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease) were also more prevalent in females than in males (**chapter 2, 6**). In addition, prevalence rates also varied between the different FSS groups. So, the finding that FSS are more common in females than in males is not unique to patients with FSS.

Functional limitations

Concerning functional limitations, we found that all FSS were characterized by reduced QoL and work participation, although quantitative differences were observed between FSS. However, patients with MD also reported comparable functional limitations (**chapter 3**). One difference we found was that the lower QoL of patients with FSS compared to patients with MD is particularly related to mental limitations. Although this could be regarded as a shared non-symptom characteristic specific for FSS, it is important to realize that this might be a consequence of having an FSS. The clinically relevant lower scores might be due to the difficulty in dealing with the disease symptoms related to FSS. For instance, patients with FSS reported that they felt not be taken seriously, because the absence of detectable pathology is sometimes interpreted as evidence that their problems are mental rather than physical (7). Moreover, patients with FSS felt stigmatized, since others tended to doubt the accuracy and truthfulness of patients reported disabling symptoms (8,9).

Psychological distress

This thesis revealed that patients with FSS share an increased prevalence of mood and anxiety disorders (**chapter 5**). Mood and anxiety disorders were more common in some than in other FSS. However, increased prevalence rates of psychiatric disorders were also observed in patients with MD, including multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, although the increase was lower than in patients with FSS (**chapter 3**). Furthermore, psychological distress is also prevalent in patients with other MD than investigated in this thesis, such as patients with cancer, stroke, and acute coronary syndrome (10). Thus, psychological distress can also be a reaction to experience of having a disabling and poorly understood illness (11).

Lifestyle factors

Lifestyle factors are also among the suggested shared no-symptom characteristics, particularly physical activity and sleep duration. It is assumed that both high and low levels of physical activity and sleep duration are associated with an increase in symptom severity, including pain and fatigue, in particularly in patients with CFS and FMS. Therefore, we investigated the role of physical activity and sleep in patients with CFS and FMS in this thesis (**chapter 7**). This study revealed that, on average, patients with CFS and FMS sleep longer and are less physically active than controls, and that both high and low physical activity and sleep duration are associated with higher symptom severity. The only difference we found between patients with CFS and FMS concerned sleep duration, namely that patients with CFS had a longer sleep duration compared to patients with FMS and controls. This difference might be due to the primary complaint of disabling fatigue in patients with CFS (12-14), from which patients might try to recover by extra sleep. Thus, lifestyle factors are indeed non-symptom characteristics that are shared between FSS. However, it should be emphasized that the finding that both high and low physical activity result in higher symptom severity is also observed in the general population (15). Furthermore, it is known that there is a relationship between sleep and symptom severity in the general population. For example, less than 6 or more than 9 hours of sleep may contribute to next-day pain in the general population (16). The overlap in lifestyle factors and their associations with symptom severity is thus not unique for patients with FSS, but also shared with the general population.

Physiology

As a potential shared physiology, we examined whether CFS and FMS are associated with vitamin and mineral deficiencies (17,18) by carrying out a systematic review and meta-analysis (**chapter 8**). Little evidence was found to support our hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of both CFS and FMS, or that the use of nutritional supplements is effective in these patients. The vast majority of available studies concerned patients with FMS. We only found that vitamin E levels may be lower in patients with CFS compared to controls and patients with FMS. Two previous meta-analyses have also studied the hypothesis of shared physiology between FSS. The first one studied the autonomic nervous system in patients with CFS, FMS and IBS, and this meta-analysis was not able to firmly conclude anything about differences between these syndromes (19). The second one studied the hypothalamic-pituitary-adrenal axis (HPA) and reported that a significant reduction in basal cortisol compared to healthy controls was only found in patients with CFS and in females with FMS, but not in IBS (20). Together, these findings question the idea of shared physiology between FSS.

Difficulties in doctor-patient relationships

Another argument used in favor of the lumpers is that commonalities can be observed across FSS in the interpersonal context such as difficulties in doctor-patient relationships. Difficulties in doctor-patient relationships may be affected by different factors, including the interaction between physicians, patients, situational factors or the health care system (21). Because physicians cannot find a disease-based explanation for these syndromes nor offer appropriate treatment, they find it often difficult to deal with FSS. Physicians may also be frustrated as a result of difficulties in controlling the symptoms and the patients' emotional responses to the syndromes (22). On the other hand, patients with FSS do not feel understood by physicians, since they feel that physicians do not understand or accept their symptoms. Patients with FSS also report that physicians did not perform full mental and physical examinations and did not take an adequate medical history (23-25). However, research suggests that a doctor-patient relationship which fosters mutual understanding helps patients with FSS to understand their symptoms, to maintain their QoL and to increase their ability to manage their FSS in a better manner (26). What seems overlooked is that difficulties in the doctor-patient relationship are not unique to patients with FSS. For example, patients

with multiple sclerosis or rheumatoid arthritis also often experience difficulties in the doctor-patient relationship, and the frequency of negative doctor-patient communication is also high in surgical departments (27-29).

4. FSS patients respond to the same psychological and psychopharmacological therapies

The last argument used by the lumpers was that all FSS respond to the same therapies. Examples include general approaches to management, antidepressants, and psychological therapies. Recent research focusing on the effect of different therapies on FSS concluded that results of different therapies and treatments support both the lumpers as well as the splitters approach, because some treatments seem to have effect in all FSS, while other treatments are effective in only some (30,31). Furthermore, it is important to emphasize that various somatic diseases also respond to these therapies (i.e. general approaches to management, antidepressants, and psychological therapies) and other interventions (e.g. physiotherapy, anti-inflammatory drugs, beta-blockers). For example, the synthetic glucocorticoid drug prednisone is used in a variety of diseases with distinct etiologies, including the lung diseases chronic obstructive pulmonary disease and asthma (32,33), rheumatic diseases such as rheumatoid arthritis and Sjogren's syndrome (34,35), neurological disorders such as multiple sclerosis and optic neuritis (36), kidney disorders such as nephrotic syndrome (37), and oncological disorders such as multiple myeloma (38). Thus, the finding that FSS respond to the same therapies is no reason to consider them similar (39-41).

Similar but different

In this thesis we found evidence that support both the lumpers' and splitters' perspective. The first argument in favor of the lumpers is that the case definitions of FSS overlap. In this thesis we describe the overlap in case definitions of the main three FSS, but we also describe remarkable differences. We revealed that all diagnostic symptoms are connected, either directly or via other symptoms, and that these diagnostic symptoms form non-isolated symptom clusters based on symptoms' bodily systems rather than their current classification as criteria for CFS, FMS or IBS. The second argument of the lumpers is that patients with one FSS frequently meet diagnostic criteria for the other FSS. The findings of this thesis indicate that the diagnostic overlap of the three FSS is much higher than could be expected by chance, and that the diagnostic overlap substantially

increases when the FSS are more chronic in nature and interfere with daily life. Third, lumpers state that patients with different FSS share non-symptom characteristics. In this thesis, several non-symptom characteristics have been examined. We argue that although FSS share non-symptom characteristics, such as sex, lifestyle factors, and functional limitations, these are not unique for FSS, but often shared with MD. Therefore, these shared non-symptom characteristics do not necessarily support the assumption that all FSS result from the same etiology. The last argument is that all FSS patients respond to the same psychological and psychopharmacological therapies. We emphasize that various somatic diseases also respond similarly to these therapies and other interventions, but that is no reason to assume a shared etiology.

Weighing the results of this thesis for both the splitters and lumpers views, we suggest that both sides are true and that there is commonality as well as heterogeneity between and within FSS (42). Although there is overlap in case definitions, and psychiatric co-morbidity is a characteristic of all FSS, the differences between the FSS cannot be ignored. The finding of both specific and general characteristics of FSS is in line with the results of recent analyses in recent population-based studies and in a twin cohort (1-3). For example, a latent class analysis of functional somatic symptoms in 28,531 twins aged 41-64 years revealed a five-class solution (3). The first class did not show any health problems; the following three classes tended to have abnormal tiredness, pain-related symptoms, and gastrointestinal problems, respectively. The last class included individuals that experienced multiple symptoms to a greater extent than the other three classes. All classes showed modest genetic influences and sex differences, however, the majority of influences on the class membership were the result of unique environmental factors. The authors concluded that the appropriate question about FSS is not "one or many" but "single or multiple". We state that FSS may reflect the same underlying syndrome with different subtypes based on symptoms' bodily systems rather than their current classification as criteria for CFS, FMS or IBS, because the difference in clinical presentation suggests that there are different subtypes. These subtypes may have their own unique manifestation of specific symptom patterns and share both common as well as unique factors. In this thesis, we found a general, musculoskeletal and abdominal symptom cluster in the general population, which melted to an abdominal and combined general and musculoskeletal cluster in patients with FSS. In addition, four

subtypes are introduced in the recent literature and include a cardiopulmonary, gastrointestinal, musculoskeletal, and general symptom type, or a more severe multiorgan type (43-45). This last type could explain the increase in overlap among the more chronic and serious FSS in this thesis.

Strengths and limitations

Six chapters of this thesis contained data of the LifeLines cohort study. The main strength of this cohort study is the large population-based sample. Since the LifeLines cohort study is a general population cohort, we were able to examine the validity of FSS diagnoses in the context of the lumpers-splitter discussion irrespectively of help-seeking behaviour or diagnostic biases. In addition, due to the sample size of the cohort study, we were able to include sufficient numbers of participants with FSS, MD, and a control group. Additionally, information about the three main FSS and related MD was available, which enabled comparing these FSS and MD in one cohort, allowing meaningful cross-group statistical comparisons and limiting differences in selection procedures or measurements. In three chapters of this thesis follow-up data of LifeLines were available, which allowed for basing the FSS on the official positive diagnostic criteria instead of the self-reported diagnosis. In addition, we were able to address the limitations of prior research, namely, we were able to report the diagnostic algorithm used to select the FSS patient group based on the official diagnostic criteria for each CFS, FMS and IBS. Furthermore, the inclusion of additional questions or time frames enabled us to construct chronicity-aligned and interference-aligned FSS diagnoses, which made it possible to investigate the effect of these alignments on the diagnostic overlap and non-symptom characteristics. In the last chapter, we carried out a systematic review and meta-analysis. Since we only included patients that met the official diagnostic criteria and used strict in- and exclusion criteria, we included a relatively homogeneous group of patients.

There are also several limitations associated with the studies in this thesis. Some studies used a self-reported questionnaire for the diagnosis of FSS. Although self-reports may underestimate the amount of persons with FSS (46), this underestimation seems less likely in our studies because the prevalence rates for CFS, FMS and IBS were comparable to those reported in previous studies (47-49). Another limitation related to the self-report diagnosis is that lifetime diagnoses of FSS were available instead of current diagnoses. However,

a previous study in a general population cohort from the same geographical area suggests that a vast majority (i.e. 75%-100%, depending on the syndrome) of the participants that reported a history of CFS, FMS or IBS, still had this syndrome at the time of reporting (50). The three studies that contained the FSS diagnosis that was based on the positive diagnostic criteria instead of the self-reported diagnosis, were the result of responses to a questionnaire without an assessment by a physician. Because LifeLines is a large population cohort study that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to determine whether participants meet the diagnostic criteria for FSS based on clinical examinations. In addition, co-morbid conditions that could explain the FSS symptoms were not excluded when determining the FSS diagnoses, mainly because only the CFS diagnostic criteria specifically mention well-defined medical health conditions that needs to be excluded before diagnosing CFS (12). Because of the cross-sectional design of the LifeLines study, cause-effect relationships could not be examined. For example, we could not determine whether FSS lead to mood and anxiety disorders, whether anxiety and mood disorders lead to FSS, or whether FSS and mood and anxiety disorders are manifestation of the same underlying pathology. Lastly, limitations in the systematic review and meta-analysis were due to limitations in original studies, on which the review was based since most studies were observational in nature, had a poor study quality, and had a substantial to considerable heterogeneity.

Future research

This thesis revealed that FSS have serious individual and societal consequences. Therefore, health care professionals in public and occupational health, researchers and society should pay more attention to these syndromes. The findings of this thesis urge the need for more research on FSS, especially studies on a better understanding of the classification, etiology and treatment of these syndromes. Future studies will be necessary to examine and reconsider the diagnostic criteria for FSS. The specified main or additional symptoms, the interference in daily life, but also the apparently random time frames for assessing symptoms included in the diagnostic criteria should be reconsidered. Furthermore, we found that FSS both have specific and general characteristics, which may suggest one underlying syndrome with different subtypes. It is important to study this underlying syndrome more extensively to establish valid and generally accepted diagnostic criteria with which it is possible to identify the different FSS subtypes across medical

specialties. In addition, more understanding of this concept will eventually lead to better patient care. Currently, there is a predominance of a splitting view in the current literature on FSS, since the different FSS are often researched separately. Based on the results of this thesis, we recommend a combined lumping and splitting approach for future research. Merging knowledge of the separate fields of research and using the combined approach by analyzing FSS separately but also together, may lead to more insight into the etiology and treatment options of FSS. Increased knowledge and understanding of the etiology and impact of FSS may eventually improve the treatment of a significant proportion of the population who is suffering from FSS.

There are several minor limitations of the existing literature investigating the validity of FSS diagnoses in the context of the lumpers-splitter discussion. First, current research is often based on self-reports or did not use or report the diagnostic algorithm used to select the patient group. To overcome the methodical weakness of self-reported questionnaires and the lack of diagnostic algorithms for the diagnosis of FSS in the future, it is recommended to determine whether participants meet the diagnostic criteria for FSS based on clinical examinations or on the patients' clinical records. For future research, it is also important to conduct studies that will include sufficient numbers of patients with FSS, but also include control groups of healthy participants and patients with MD. This avoids the assumption that aspects that are shared between patients with FSS indicate a shared etiology. As a result, appropriate and well-founded arguments and conclusions can be made with regard to the lumpers-splitter discussion.

Concluding remarks

This thesis provided more insight into the validity of FSS diagnoses in the context of the lumpers-splitter discussion. It revealed that, although there is overlap in case definitions, the four arguments of the lumpers-splitter discussion that suggest that all FSS result from the same etiology, are not valid. The results of this thesis support recent suggestions that FSS have both specific and general characteristics. We therefore state 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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