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General Introduction



Chapter 1

Somatic symptoms

Occurrence of somatic symptoms is very frequent in the general population: more than 90% of the general population have experienced at least one somatic symptom in the last week (1). Most somatic symptoms are benign, self-limiting, and explained by prevailing circumstances. However, some somatic symptoms persist and cause significant impairments in daily life, while no objectively underlying organic pathology can be found. These somatic symptoms are also referred to as functional somatic symptoms. Pain and fatigue are common functional somatic symptoms: one-third of the adult population reports fatigue lasting 6 months or longer (2), and more than one-third of the adult population experiences chronic musculoskeletal pain (3). Consequently, a considerable proportion of consultations in both primary and secondary care is attributable to patients experiencing somatic symptoms that cannot be explained by underlying organic pathology (4,5)

Functional somatic syndromes

If multiple persistent and disabling functional somatic symptoms occur, clusters of these symptoms can be classified as functional somatic syndromes (FSS). Many FSS exist, and almost every medical specialty has at least one. Chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS) are the three most well-known FSS. CFS is mainly characterized by disabling fatigue (6), patients with FMS suffer from musculoskeletal pain (7), and patients with IBS suffer from bowel complaints (8). A detailed description of these three main syndromes can be found below.

CFS is characterised by profound disabling fatigue, post-exertional malaise, and sleep problems (6). CFS is often accompanied by non-specific symptoms, such as cognitive symptoms, muscle pain, headaches, and tender lymph nodes. Approximately 1% of the adult population is estimated to be suffering from CFS (2). It mainly affects young adults between 20 to 40 years of age, and it has a three to four times higher prevalence in women than in men (2). CFS often begins acutely, usually in previously healthy persons. Often, the initial process resolves and the chronic symptoms develop later (9). FMS is mainly characterised by musculoskeletal pain, chronic widespread pain, joint stiffness, and systemic symptoms, including fatigue, and cognitive symptoms (10). FMS is often accompanied by non-specific symptoms, such as headache, and non-restorative sleep. Approximately 2.9% of the adult population is estimated to be suffering from FMS, and it is roughly twice as

prevalent in females as in males (7). IBS affects 5-20% of all individuals worldwide (8,11), occurring more often in women than in men and in patients younger than 50 years of age (12). The main symptoms of IBS range from diarrhoea to constipation, accompanied by abdominal pain or discomfort. The time pattern and discomfort vary considerably between patients, as well as the degree of symptoms, varying from tolerable to severe (8). Some patients report daily symptoms, while other patients report intermittent symptoms at intervals of several weeks or months.

Etiology

The exact etiology that underlies the different FSS is not fully understood, but several models in the literature have outlined possible pathways that may lead to the development of FSS. These models share common characteristics, and suggests that multiple and different pathways may lead to the development of FSS. Overall, the etiology of FSS is assumed to be multifactorial, involving biological, psychological, social, and healthcare factors (13,14). Current knowledge points to a number of etiological factors that can be divided in predisposing, precipitating, and perpetuating factors, and a set of candidate pathophysiological processes (15). Examples of the etiological factors can be found in Figure 1.

Predisposing factors are factors that make someone vulnerable for or at risk of developing FSS. Research suggests that relatives of patients with FSS have significantly higher rates of FSS compared to relatives of a control group, most likely due to familial-genetic predisposition (16-18). For instance, polymorphisms in genes of the catecholaminergic, dopaminergic, and serotonergic systems have been found to be associated with FMS (17). Furthermore, perfectionism and neuroticism may be predisposing factors for the development of FSS, since they are associated with a high prevalence of FSS (19). Precipitating factors refer to a specific trigger for the onset of a FSS. Stressful life events, stressful work conditions, and acute organic diseases are the most well-known precipitating factors for developing FSS (20,21). For example, the onset of FSS may be preceded by stressful life events that have occurred in the past year (22). Furthermore, certain viral infections such as infectious mononucleosis may trigger the onset of FSS (23,24).

FSS likely can develop when pathophysiological processes are superimposed on predisposing and precipitating factors. There are different potential

pathophysiological pathways described in the literature that may provoke the development of FSS. Examples include subtle disturbances in the neurohormonal stress system, neurotransmitter systems, the immune system, and the central pain-processing system (25-28).

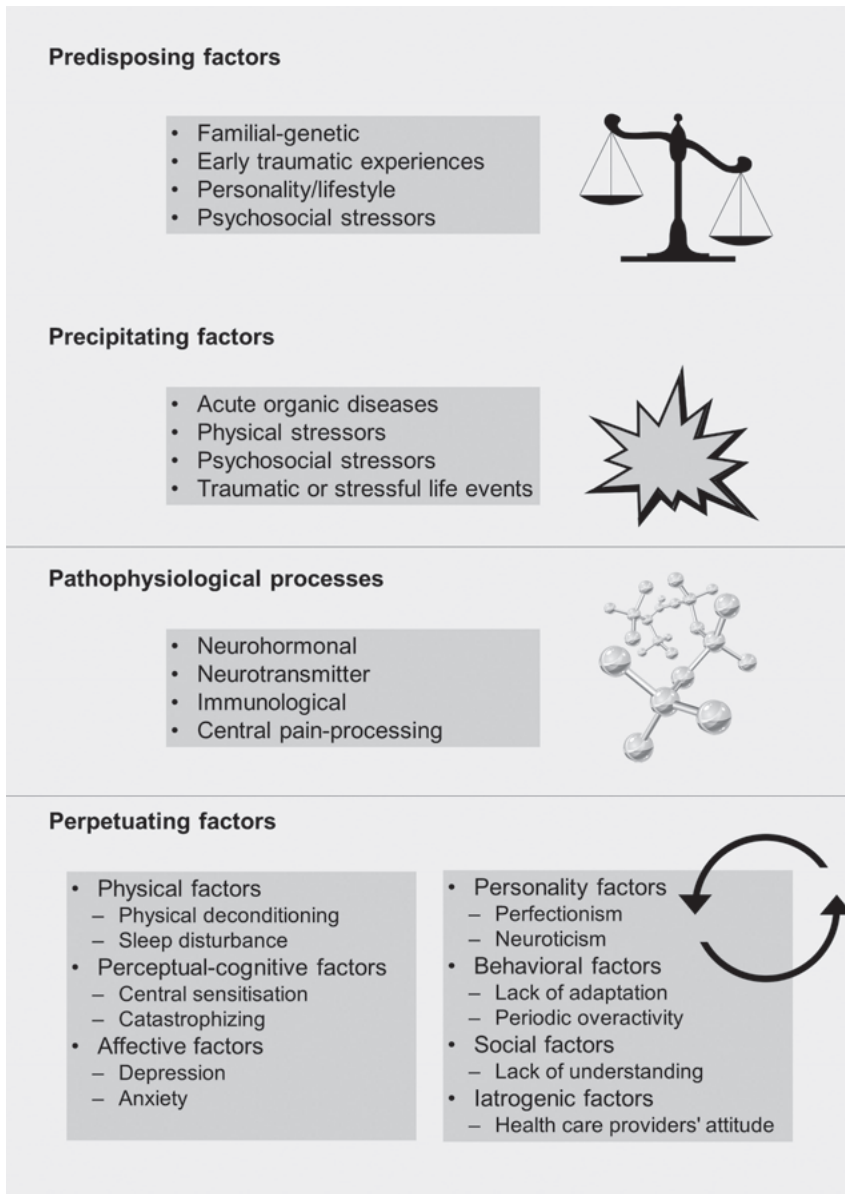


Figure 1. Examples factors along with the pathophysiological processes that may play a role in the etiology of FSS (13-15).

Lastly, once someone has developed a FSS, perpetuating factors are factors that maintain the symptoms, often via vicious circles. These factors may interact with the pathophysiological processes and may thereby aggravate disability and impede recovery (15). For example, symptoms associated with depression and anxiety may perpetuate FSS by aggravating symptoms and increasing the risk of more severe functional limitations (15,21). Furthermore, patients with FSS experience symptoms, including pain and fatigue, that may result in decreased activity, which in turn may lead to loss of muscle power and cardiopulmonary functioning, thus reinforcing and perpetuating symptoms (29).

Diagnosis

FSS are symptom-based or clinical diagnoses that cannot be confirmed by the presence of objectively measurable or distinguishable characteristics. FSS are diagnosed in clinical settings based on a two-step approach: the presence of a specific cluster of somatic symptoms (positive criteria) and the absence of detectable pathological explanations for these symptoms (negative criteria) (6,30,31). The positive criteria include a description of the main symptom with requirements for a minimum duration, and additional self-reported symptoms. An accurate assessment of the medical history of the patient, a physical and mental status examination, and laboratory tests (i.e. blood, urine) are examples of how the negative criteria can be checked. The FSS diagnoses are based on clinical criteria that attempt to distinguish them from other medical health conditions that also present with comparable symptoms (6,30,32,33).

CFS is most commonly defined by diagnostic criteria established by the United States Centers for Disease Control and Prevention and the International Chronic Fatigue Syndrome Study Group (CDC-criteria) (6). The diagnostic criteria include clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset, and four or more specifically defined additional symptoms (Table 1A). FMS is defined by the diagnostic criteria established by the American College of Rheumatology (ACR-criteria) (30). These criteria provide a scale for measuring the severity of symptoms that are characteristic of FMS, including fatigue, waking-up unrefreshed, cognitive symptoms, and pain (Table 1B). Lastly, IBS is defined by the diagnostic criteria established by Rome Foundation (ROME IV criteria) (33). The diagnostic criteria include recurrent abdominal pain at least one day per week, associated with two or more additional symptoms (Table 1C) (33).

Table 1. Positive symptom criteria for the three main functional somatic syndromes.

A. CFS CDC-criteria
<ol style="list-style-type: none"> 1. Chronic fatigue present ≥ 6 months; 2. The fatigue significantly interferes with daily activities and work; 3. Concurrently ≥ 4 of the additional symptoms: <ul style="list-style-type: none"> - Muscle pain; - Joint pain; - Headaches; - Sore throat; - Tender lymph nodes; - Cognitive dysfunction; - Sleep disturbance; - Post-exertional malaise lasting ≥ 24 hours.
B. FMS ACR-criteria
<ol style="list-style-type: none"> 1. Musculoskeletal pain symptoms present ≥ 3 months; 2. A combination of the following: Widespread pain index (WPI): the number areas in which the patient has had pain over the last week. Score will be between 0 and 19. <ul style="list-style-type: none"> - Neck - Jaw left/right - Shoulder girdle left/right - Upper arm left/right - Lower arm left/right - Chest - Abdomen - Upper/lower back - Hip left/right - Upper leg left/right - Lower leg left/right <p>Symptom severity (SS) scale score: For each of the 4 symptoms below, the level of severity over the past week is determined using the following scale: (0) no problem, (1) slight or mild problems, (2) moderate, considerable problems, (3) severe, pervasive, continuous life-disturbing problems</p> <ul style="list-style-type: none"> - Fatigue - Waking unrefreshed - Cognitive symptoms - Somatic symptoms
<p>To diagnose FMS a WPI ≥ 7 and SS scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9 is required.</p>
C. IBS ROME IV criteria
<ol style="list-style-type: none"> 1. Recurrent abdominal pain or discomfort at least 1 day per week, with a symptom onset 6 months prior 2. Associated with ≥ 2 of the additional symptoms: <ul style="list-style-type: none"> - Improvement of abdominal pain or discomfort after defecation; - Onset associated with change in frequency of stool; - Onset associated with change in form (appearance) of stool.

Lumper-splitter discussion

One important issue in diagnosing FSS is doubt about the validity of the FSS diagnoses. The diagnostic criteria for the different FSS are established via different expert committees, which have made their own agreements (6,30,32,33). This has resulted in, for example, differences in criteria for the duration of symptoms and the exact types of symptoms for each syndrome. Another issue is the question to which extent FSS identify distinct groups of patients. This is mainly because FSS are renowned for substantial clinical and diagnostic overlap. For example, up to 80% of patients with CFS report a history of clinician-diagnosed FMS (34). In contrast, only 18% of patients with FMS report co-morbid CFS (34). This phenomenon resulted in the so-called lumper-splitter discussion (35). Lumpers believe that all FSS result from the same etiology, and thus tend to emphasize the commonalities among FSS. On the other hand, splitters take the approach that every separate FSS has its own specific background. Therefore, splitters emphasize the distinctness of each syndrome.

The lumper-splitter discussion is based on four main observations (35). First, the case definitions of FSS overlap (e.g. fatigue, musculoskeletal pain, cognitive symptoms). Second, patients with one FSS frequently meet diagnostic criteria for one of the other FSS (36). Third, patients with different FSS share non-symptom characteristics (e.g. sex, physiology, a history of stressful life events). Fourth, all FSS patients respond to the same psychological and pharmacological therapies (34,36-38). Furthermore, physicians and researchers have the tendency to focus on one specific FSS pertinent to their specialty or interest (39). It has therefore been suggested that the FSS diagnoses assigned to patients depend more on the main symptom and the involved clinician than on the underlying medical condition (37,39). Splitters argue that these arguments do not apply to all patients and can thus not sufficiently explain the diversity and specificity of the syndromes.

The empirical basis of the statement that FSS are different names for the same underlying syndrome is limited. To date, no single study has been able to examine the lumper-splitter discussion in a methodologically sound way. The studies that did examine the main observations of the lumper-splitter discussion all based their analyses on self-reported FSS diagnoses (40,41). Furthermore, research also suggests that many patients who qualify for a diagnosis never receive one (41-43). This is partly because the main symptoms of these syndromes, pain, fatigue, and abdominal complaints are very common, and often do not lead to a doctor's

visit. The overlap reported in previous studies might thus be explained by a general tendency for help-seeking behaviour. Another reason for the absence of a diagnosis in individuals fulfilling the criteria is the hesitation that some physicians may have with regard to diagnosing FSS (43,44). It is therefore still unknown what the validity of FSS diagnoses is, and to which degree these diagnoses are able to identify separate groups of patients. More recently, it has been suggested that both lumpers and splitters are right and that there is commonality as well as heterogeneity between (and within) FSS in both onset-related factors and psychosocial and physiological patient characteristics (45).

Aim and outline of this thesis

The aim of this thesis is 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 lumper-splitter discussion. We will approach this aim from different angles, taking into account the possible etiological pathways that may lead to the development of FSS. The four main observations of the lumper-splitter discussion will form the basis of this thesis. Since FSS are symptom-based diagnoses, we will investigate the most relevant assessment time frame for somatic symptoms in **chapter 2**. This will be examined by relating somatic symptom burden, with varying time frames, to quality of life and health anxiety as indicators for clinical relevance of symptoms.

In **chapter 3** we will evaluate functional limitations, defined as quality of life and work participation, in the three main FSS. To examine the assumption that FSS are less serious than recognized medical health conditions, the results will be compared to patients with well-defined medical diseases with the same main symptoms and healthy controls.

In **chapter 4** we will investigate whether FSS are different names for the same problem by examining the networks of symptoms that are included in the diagnostic criteria for FSS. In the context of the lumper-splitter discussion, we will examine if there are separate clusters within the network models. We will study this in a general population cohort, and in a group fulfilling the diagnostic criteria for CFS, FMS and/or IBS.

Chapter 1

The validity and the diagnostic overlap of the three main FSS diagnoses based on the official diagnostic criteria will be examined in **chapter 5**. We will examine the effects of arbitrary choices in case definitions on overlap (i.e. duration of main symptom, interference with daily life). To explore the observation that patients with one FSS frequently meet diagnostic criteria for another FSS, we will examine whether participants who meet the criteria for specific FSS report symptoms formulated in the other FSS criteria.

To examine the association of FSS with psychiatric disorders, the role of mood and anxiety disorders in the pathophysiology of FSS will be examined in **chapter 6**. We will compare prevalence rates of these disorders between patients with CFS, FMS and IBS.

In **chapter 7**, objectively and subjectively measured cognitive functioning will be compared in CFS patients, FMS patients, patients with a well-defined medical disease with comparable main symptoms, and healthy controls. Furthermore, the effects of current mood or anxiety disorders on cognitive functioning, and the relationship between somatic symptomatology and objective cognitive functioning will be examined.

The role of physical activity and sleep in relation to CFS and FMS will be examined in **chapter 8**. We will examine whether physical activity or sleep duration are associated with the severity of the physical symptoms, and whether these associations differ between patients with CFS, patients with FMS, or controls.

Finally, we will examine whether vitamin and mineral deficiencies may play a role in CFS and FMS by carrying out a systematic review and meta-analysis in **chapter 9**. We will examine whether there is evidence for deficiencies in vitamin and mineral status in patients with CFS, patients with FMS, and healthy controls. In addition, we will examine whether vitamin and mineral status is associated with clinical parameters, and whether there is evidence for an effect of vitamin and mineral supplementation, as compared to placebo, on clinical parameters in patients with CFS and FMS.

For the first chapter, we use data of the HowNutsAreTheDutch (Dutch: HoeGekIsNL) crowdsourcing study. HowNutsAreTheDutch is a national study in the Netherlands,

examining multiple mental health dimensions in a sample from the general population of 3,477 participants. The following six chapters of this thesis are based on data of the LifeLines cohort study, 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. In the last chapter, a systematic review and meta-analysis will be presented.

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