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Similar but Different

Implications for the One versus Many Functional Somatic Syndromes Discussion

Monica L. Joustra

Similar but Different: Implications for the One versus Many Functional Somatic Syndromes Discussion
Dissertation University of Groningen, Groningen, the Netherlands

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Similar but Different

Implications for the One versus Many Functional Somatic Syndromes Discussion

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en volgens besluit van het College voor Promoties.

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Monica Laura Joustra

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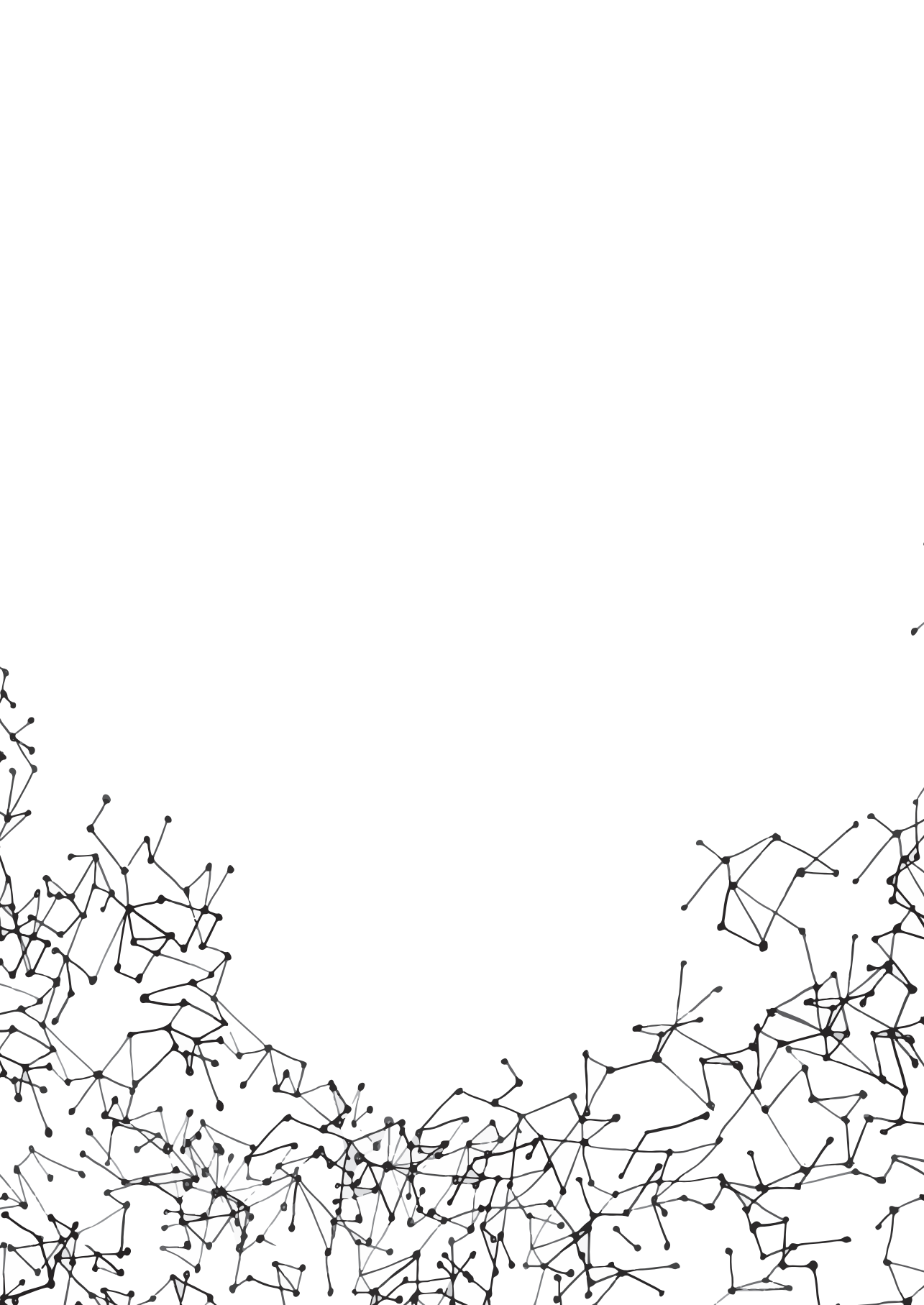

1

General Introduction

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 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).

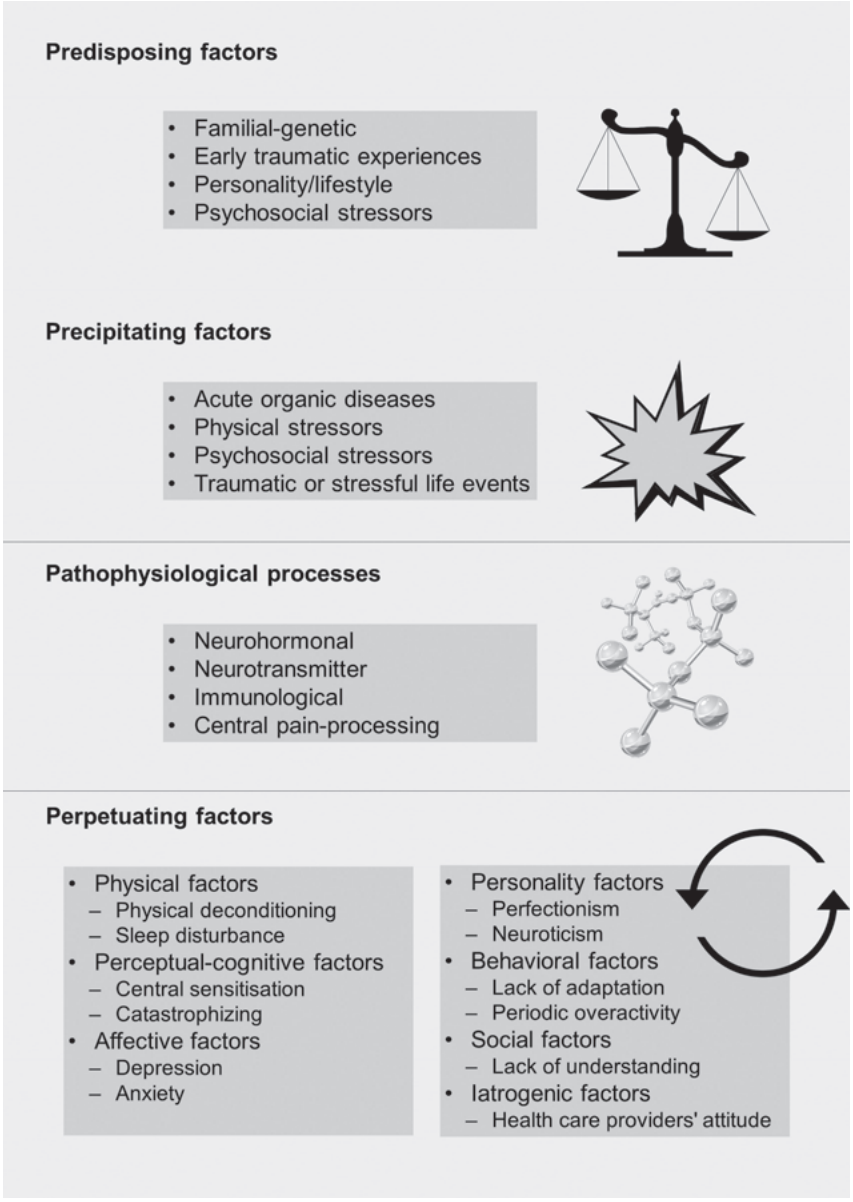

Figure 1. Examples factors along with the pathophysiological processes that may play a role in the etiology of FSS (13-15).

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

1. Chronic fatigue present ≥ 6 months;
2. The fatigue significantly interferes with daily activities and work;
3. Concurrently ≥ 4 of the additional symptoms:
   - Muscle pain;
   - Joint pain;
   - Headaches;
   - Sore throat;
   - Tender lymph nodes;
   - Cognitive dysfunction;
   - Sleep disturbance;
   - Post-exertional malaise lasting ≥ 24 hours.

B. FMS ACR-criteria

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.

- 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

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

- Fatigue
- Waking unrefreshed
- Cognitive symptoms
- Somatic symptoms

To diagnose FMS a WPI ≥7 and SS scale score ≥5 or WPI 3-6 and SS scale score ≥9 is required.

C. IBS ROME IV criteria

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:
   - 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.

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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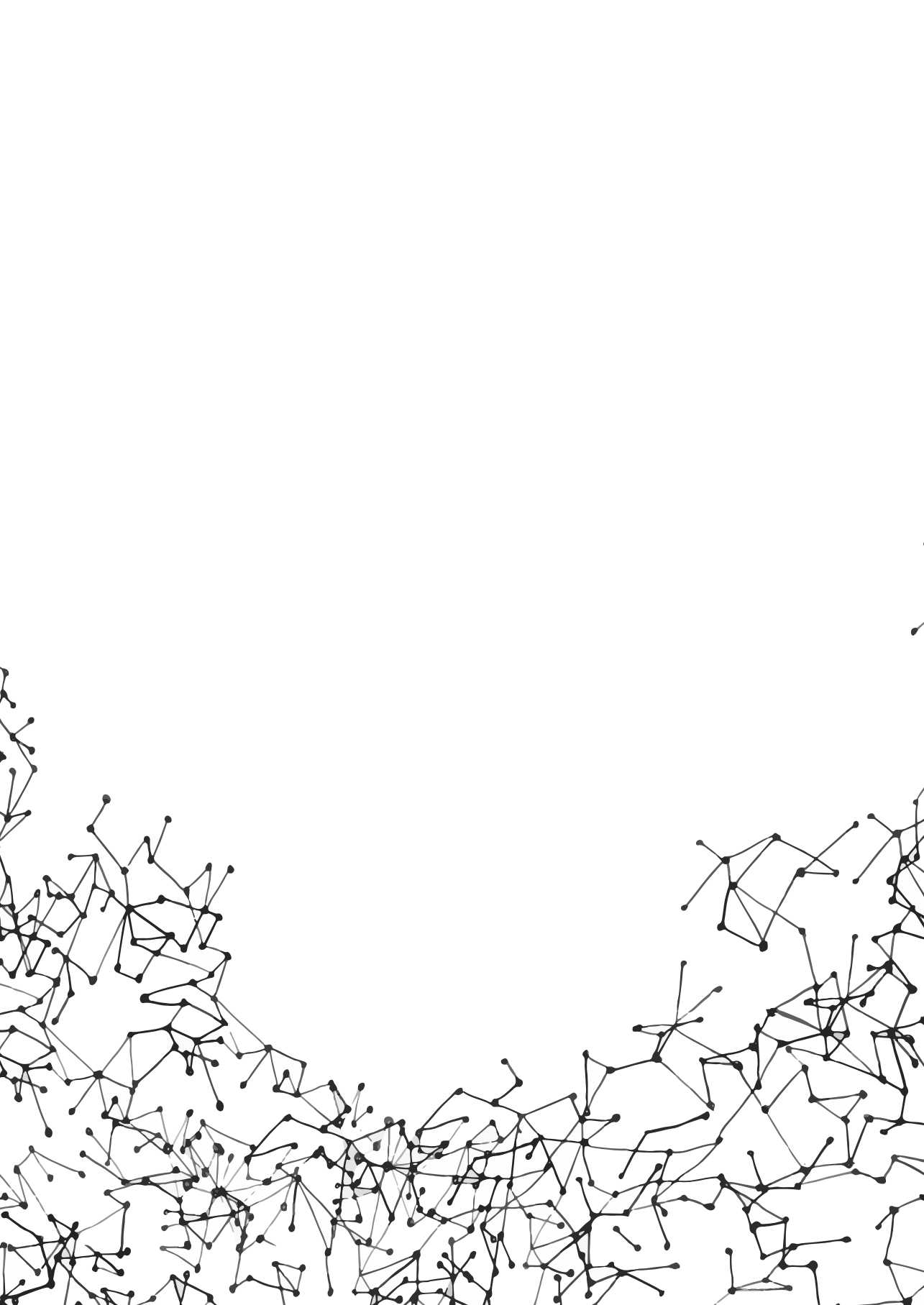
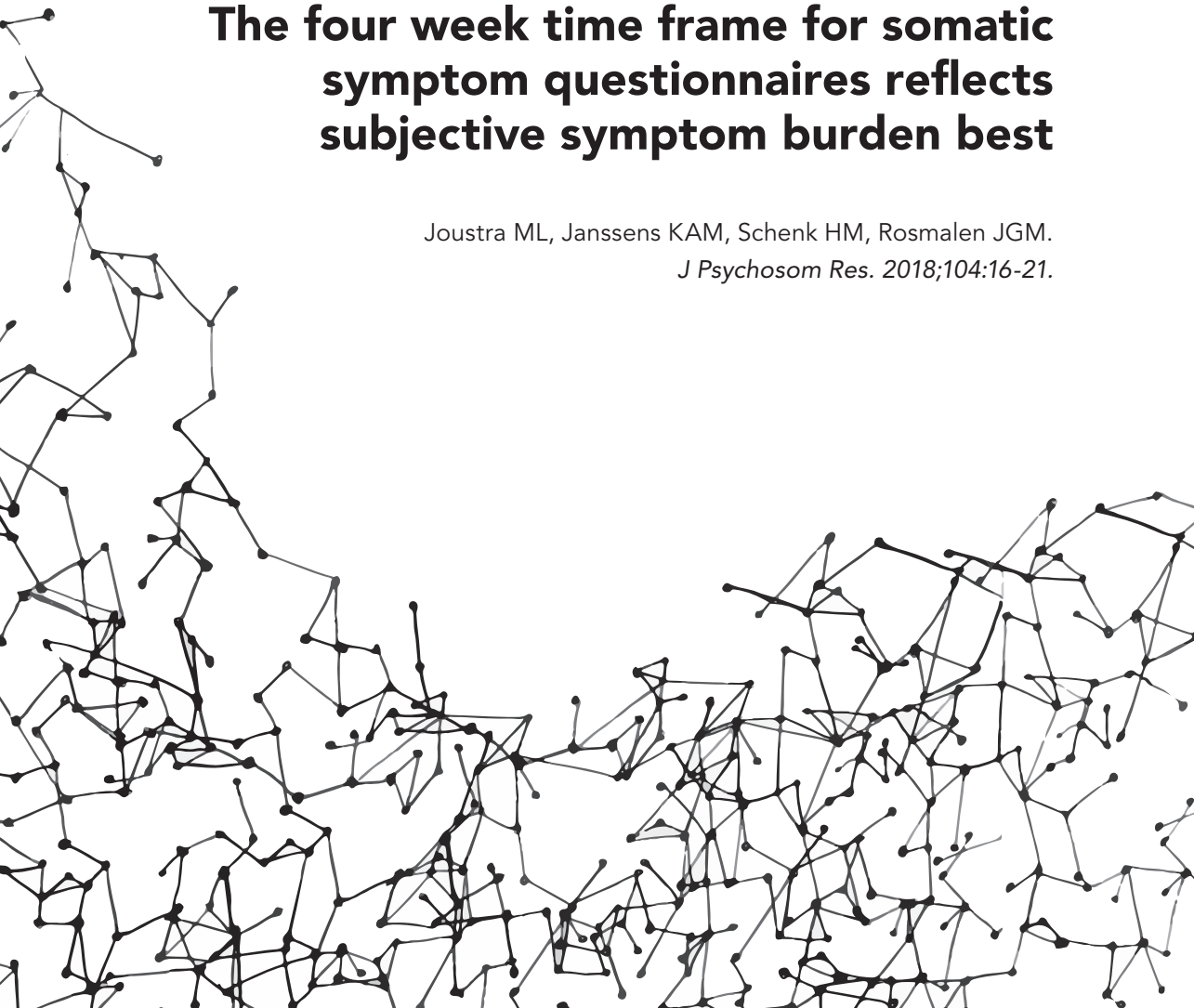


2

The four week time frame for somatic symptom questionnaires reflects subjective symptom burden best

Joustra ML, Janssens KAM, Schenk HM, Rosmalen JGM.

J Psychosom Res. 2018;104:16-21.



ABSTRACT

Objective: Various questionnaires are available to assess somatic symptom burden, however their assessment time frames vary largely. The aim of this study was to investigate the most relevant assessment time frame for somatic symptoms by relating somatic symptom burden, with varying time frames, to quality of life (QoL) and health anxiety as indicators for clinical relevance of symptoms.

Methods: This study was performed in data derived from a convenience sample of 3,477 participants (age: 48.0 (SD 14.1), 66.4% female) of the Dutch research platform HowNutsAreTheDutch. Symptom burden was assessed using all items from the Patient Health Questionnaire-15 (PHQ-15) and 6 items of the Symptom Checklist-90 SOM (SCL-90 SOM). Five versions of the questionnaire were constructed, which evaluated symptom burden during the past 24 hours, 1 week, 2 weeks, 4 weeks, and 3 months.

Results: Symptom burden significantly increased with each step increase in time frame until 4 weeks, with no further increase when comparing 4 weeks and 3 months. The time frame of 4 weeks provided the strongest associations between somatic symptom burden and health anxiety (B=1.635; 95%CI: 1.368 to 1.938;p≤.001). This was also true when analysing the association between QoL and the symptom groups of musculoskeletal (B=-1.54; 95%CI: -1.93 to -1.16;p≤.001) and gastrointestinal symptoms (B=-0.71; 95%CI: -0.96 to -0.47;p≤.001).

Conclusion: An assessment time frame of 4 weeks for somatic symptom questionnaires reflects clinically relevant somatic symptom burden in terms of QoL and health anxiety best, followed by the 3 months' time frame.

INTRODUCTION

A considerable proportion of the consultations in both primary and secondary care is due to the experience of somatic symptoms (1,2). High levels of somatic symptoms are associated with a reduced quality of life (QoL), an increase of functional limitations (3), health care service use (4), prolonged sickness absence, and health-related job loss (5). Therefore, the assessment, recognition, and evaluation of somatic symptom burden are essential in both patient care and research. Physicians, researchers, and other healthcare professionals must rely on patients' reports for the recognition and evaluation of somatic symptom burden. Self-report questionnaires are useful tools to assess symptom burden. They provide a predictor of health care use and health status over and above the effects of general medical illnesses, anxiety and depression (6).

Self-report questionnaires have been used in research for a long time, and their use in clinical practice is increasing. This is partly due to requirements of health insurance companies that want to evaluate the quality of care delivered, especially in mental health care settings. It has also been argued that the use of systematic instruments might improve clinical care for somatic symptoms, comparable to the use of biomarkers to monitor clinical outcomes of recognized diseases (7). A systematic review indicated that there are many different self-reported questionnaires available for the assessment of somatic symptoms (8,9). The use of these symptom questionnaires differs, and the content of the questionnaires varies considerably. This applies not only to characteristics of the symptoms included, but also to their answering scales and time frames of assessment (8,9). Some validated questionnaires are based on life-time symptoms, while others address time frames of a week or less. For example, the Patient-Reported Outcomes Measurement Information System (PROMIS), an initiative that established a resource for efficient and precise measurement of patient-reported symptoms, functioning, and health-related quality of life, opted for the 7-day recall period (10). They argue that the 7-day recall period provides a sufficiently long interval to capture a clinically relevant window of time and experience with minimal bias.

Both short and long recall time frames for assessing somatic symptom burden have associated problems. On the one hand, recall of life-time somatic symptoms seems unreliable and inconsistent (11). Patients frequently have forgotten previously

reported somatic symptoms, and therefore underreport (12). Recall of somatic symptoms diminishes largely over time, up to 100% over a period of 11 years (11). However, retrospective assessment of somatic symptoms over shorter time frames may also overestimate somatic symptom burden (13). At the same time, detection of daily fluctuations in somatic symptom burden by making use of a shorter time frame may not be meaningful for the evaluation of the somatic symptom burden of patients, since short recall time frames only reflect a momentary period that might not be representative for symptom burden in general (14). The balance between the risk of unreliable recall of life-time somatic symptoms and the detection of meaningful fluctuations in somatic symptoms remains to be examined.

This balance might differ between types of somatic symptoms. Somatic symptoms that are episodic in nature, such as headaches or palpitations, might require a longer time frame than symptoms typically present more or less continuously, such as fatigue or musculoskeletal pain. Somatic symptoms can be clustered into cardiopulmonary, gastrointestinal, musculoskeletal, and general symptom clusters (15,16). The most suitable time frame for specific symptom clusters may thus differ in comparison with the overall somatic symptom burden.

The question arises what the most clinically relevant time frame of assessment would be for somatic symptom questionnaires. We define clinical relevance as the time frame that reflects subjective symptom burden in daily life, in terms of QoL and health anxiety, best among participants. This is different from the time frame that gives the most realistic estimate of symptom occurrence. Both QoL and health anxiety have been shown to be associated with symptom burden in patients (3,6,17,18). To the best of our knowledge, there are no studies that examine the clinical relevance of different time frames in one large cohort. Existing studies have used symptom questionnaires that differed in time frames, but these questionnaires also differed in other aspects such as the specific somatic symptoms included (8,9). This precludes any conclusions on the assessment time frame specifically.

The aim of the current paper was to identify the time frame of assessment for somatic symptom questionnaires that reflects clinically relevant subjective somatic symptom burden best. The following research questions were examined. First, how does somatic symptom burden vary over the different time frames

used to assess symptoms? It is hypothesized that somatic symptom burden increases with longer assessments windows, until the point that the increase in captured symptoms is counterbalanced by decreases in reported symptoms due to recall bias. Second, what is the clinically most relevant time frame, as indicated by the highest association between symptom burden and QoL and health anxiety of the participants? Third, does the clinically most relevant time frame vary between different symptom clusters? To study these questions, a somatic symptom questionnaire was composed, based on all symptoms included in the two questionnaires that are most widely used and recommended: the Patient Health Questionnaire-15 (PHQ-15) (19,20), and the 12-item Symptom Checklist-90 SOM (SCL-90 SOM) (21). Five versions of this somatic symptom questionnaire were constructed, which only differed in time frame of somatic symptom assessment. These five versions were sequentially added to an online survey, together with assessments of QoL and health anxiety.

METHODS

The sample/Participants

This study is part of the HowNutsAreTheDutch (Dutch: HoeGekIsNL) crowdsourcing study (22). HowNutsAreTheDutch (henceforth HND) is a national study in the Netherlands, examining multiple mental health dimensions in a sample from the general population. An open call was launched to residents of the Netherlands to join our research, and they were invited to visit the Dutch website www.HoeGekIs.nl (also www.HowNutsAreTheDutch.com). The open call was announced on both local and national radio broadcasts, television, in newspapers, in magazines, and during local podium discussions. The news about the HND project was picked up and further disseminated via online blogs, twitter, and other social media. To join the project, participants had to register online and create an account. HND collects self-report data on mental health by making use of an internet platform. On this internet platform participants can compare themselves to other participants via cross-sectional questionnaires. The primary aim of HND is to investigate the associations and dynamic interactions between mental strengths and vulnerabilities. HND is specifically designed to reduce mental health stigma and discrete categorization of mental health. Data were available of 3,477 participants, which were included during the period 13 December 2013 until 16 June 2015, with a mean age of 48.0 (SD 14.1) years and 66.4% female.

Measures

Somatic symptoms
The somatic symptom questionnaire was based on a combination of all the 15 PHQ-15 items and 6 items from the SCL-90 SOM. The PHQ-15 is a frequently used self-reported questionnaire to assess somatic symptom burden (19,20). This questionnaire assesses the symptom burden of 15 symptoms that account for more than 90% of the somatic complaints observed in primary care. The PHQ-15 is a well validated questionnaire for monitoring symptom burden in research and clinical practice (19,20). The 12-item somatization scale (SOM) of the SCL-90 was used to investigate the presence of common somatic symptoms not covered by the PHQ-15 (21): hot or cold spells, numbness or tingling in parts of your body, a lump in your throat, feeling weak in parts of your body, heavy feelings in your arms or legs, soreness of your muscles. Participants were asked to indicate how much they have been bothered by these 21 (15 PHQ and 6 SCL) somatic complaints. The PHQ-15 is originally rated on a three-point scale, while the SCL-90 SOM is rated on a five-point scale. In order to obtain consistent results, all somatic complaints were rated on a three-point scale in the current study, i.e. (0) "not bothered at all", (1) "bothered a little" or (2) "bothered a lot". The total symptom burden, calculated as the sum of all 21 answers, thus could theoretically range between 0 and 42 points.

Five versions of the questionnaire were assessed during different time periods. We initially aimed to obtain groups of about equal sizes, replacing the questionnaire by a new variant with a different time frame after a sufficient number of respondents had completed it. However, inclusion rates were highly variable, mainly related to media attention for the HND project. Therefore, length of the time periods during which the versions were administered was also highly variable: version 1 was administered during the period 21 January until 3 April 2014 and evaluated somatic complaints during the past 4 weeks, version 2 was administered during the period 4 April until 22 April 2014 and evaluated somatic complaints during the past 24 hours, version 3 was administered during the period 22 April until 12 May 2014 and evaluated somatic complaints during the past week, version 4 was administered during the period 13 May until 18 November 2014 and evaluated somatic complaints during the past 2 weeks, and version 5 was administered during the period 19 November 2014 until 16 June 2015 and evaluated somatic complaints during the past 3 months.

The somatic symptoms assessed by the PHQ and SCL were, in line with previous studies (15,16), divided into the following symptom clusters: cardiopulmonary (chest pain; feeling your heart pound or race; shortness of breath; hot or cold spells), gastrointestinal (stomach pain; constipation, loose bowels, or diarrhoea; nausea, gas, or indigestion), musculoskeletal (back pain; pain in your arms, legs, or joints [knees, hips, etc.]); numbness or tingling in parts of your body; feeling weak in parts of your body; heavy feelings in your arms or legs; soreness of your muscles), and general symptoms (headache; dizziness; fainting spells; menstrual cramps or other problems with your periods; pain or problems during sexual intercourse; feeling tired or having low energy; trouble sleeping; a lump in your throat).

Principal component analyses of somatic symptom burden items were performed to investigate the dimensionality of the 21-item somatic symptom questionnaire for the different time frames. The analyses and corresponding scree plots for the different time frame groups revealed one main factor for all versions of the somatic symptom questionnaire (Eigenvalues: 4.92-5.93). The underlying main factor explained most variance in the 4 weeks' time frame group (28.2%) compared to the 24 hours (23.7%), 1 week (25.2%), 2 week (23.4%), and 3 months' (25.8%) time frame groups. The structure coefficient matrix shows that most items had a loading of >.4. Three items that had a loading of <.4 in the different time frames were the general symptoms: (a) fainting spells, (b) menstrual cramps or other problems with periods, and (c) pain or problems during sexual intercourse.

Quality of Life

QoL was assessed using the Manchester Short Assessment of Quality of Life (MANSA) (23). This study used the self-reported subscale of the MANSA. The self-reported subscale of the MANSA rates participants' satisfaction with 12 aspects of life without mentioning a specific time frame, namely life in general, employment, financial status, friendships, leisure activities, living conditions, personal safety, fellow residents, sex life, relationship with family, physical health, and mental health. Satisfaction was rated on a seven-point scale, ranging from (1) "could not be worse" to (7) "could not be better", with (4) as a neutral middle point. The underlying concept of the questionnaire is generic: all items allow comparison with the general population and are not specifically illness-related.

The summary score of the QoL is the mean of the self-reported 12 items with a range from 1 to 7 points, with a higher score reflecting better QoL.

Health anxiety

The Whitely Index (WI) was used to assess health anxiety (24,25). The WI consists of 14 items that assess three different dimensions of health anxiety without mentioning a specific time frame, namely disease phobia, somatic symptoms, and disease conviction. The participants were asked to indicate if each statement describes their health worries, with a dichotomised response format of (0) "no" or (1) "yes". The total scale score, calculated as the sum of all "yes" answers, ranged between 0 and 14 points. Thus, a higher WI score indicates more illness concerns in the participants.

Covariates

Information on age, sex, and educational level was obtained by questionnaire, since these variables are associated with both somatic symptoms (3,17), QoL, and health anxiety (3,17,18). Educational level was classified in low, middle, and high educational level. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education.

Statistical analyses

All analyses across the different time frames were between subjects, and were performed using SPSS version 23. Chi-squared tests were used to examine the differences between the time frame groups in sex, and educational level. Analyses of covariance (ANCOVA) with Bonferroni correction were conducted to examine whether the time frame groups differed in age, symptom burden, QoL, and health anxiety. The reliability of the 21-item somatic symptom questionnaire for the different time frames was examined by calculating the internal consistency of the items (i.e. by calculating Cronbach's alpha). Statistical tests for the comparison between two or more alpha coefficients were performed using the R package 'cocron' (online available at http://comparingcronbachalphas.org). Furthermore, multiple linear regression analyses were performed to predict QoL and health anxiety based on somatic symptom burden, and to predict QoL and health anxiety based on somatic symptom burden in the different symptom clusters. The outcomes of the regression analyses were reanalysed while excluding the

three somatic items with low factor loading. Since somatic symptom burden was not normally distributed, post-hoc bootstraps were conducted for ANCOVA and regression analyses. ANCOVA and regression analyses were adjusted for age, sex, and educational level. Findings were considered statistically significant if $p<0.05$.

RESULTS

Sample characteristics

The somatic symptom questionnaire was completed by 3,477 participants, with a mean age of 48.0 (SD 14.1) years, and 66.4% female. The numbers of participants for the different time frames, including the corresponding descriptives (sex, age, educational level, QoL, health anxiety) are shown in Table 1.

Participants who filled out the questionnaire referring to somatic symptoms in the last 24 hours and last week reported a slightly higher QoL than the participants who filled out the questionnaire referring to somatic symptoms in the last 2 weeks, 4 weeks, and 3 months. There were no significant differences in health anxiety between the participants who filled out the questionnaires with the different time frames.

Table 1. General characteristics of the study groups.

	N	Female (%)	Age (years) mean (SD)	Education (%) Low – Middle -High	MANSA (1-7) Mean (SD)1	WI (0-14) Mean (SD)1
All	3477	66.4	48.0 (14.1)	1.0 – 17.8 – 81.2	5.2 (0.7)	3.1 (2.4)
Timeframe						
24 hours	1595	64.0[a,b]	51.2 (13.1)[a,c,e,f]	0.5 – 13.7 – 85.8[a,c,e]	5.3 (0.7)[b,g]	3.1 (2.5)
1 week	797	60.9[a,c,d]	46.2 (14.0)[a]	1.4 – 21.8 – 76.8	5.2 (0.7)[b,g]	3.1 (2.4)
2 weeks	623	76.6	45.2 (14.5)[b]	1.3 – 20.4 – 78.3	5.1 (0.7)	3.2 (2.4)
4 weeks	295	71.5	42.4 (14.5)	2.0 – 23.1 – 74.9	5.1 (0.7)	3.3 (2.5)
3 months	167	69.5	45.7 (14.2)	1.2 – 18.6 – 80.2	5.1 (0.7)	3.0 (2.3)

[1]ANCOVA adjusted for age, sex, and educational level.
[a] p≤ .001 versus 2 weeks, [b] p≤ .05 versus 4 weeks, [c] p≤ .001 versus 4 weeks, [d] p≤.05 versus 3 months, [e] p≤ .001 versus 1 week, [f] p≤ .001 versus 3 months, [g] p≤ .05 versus 2 weeks.

Reliability

Cronbach's alpha was significantly higher in the 4 weeks' time frame (0.87, CI: 0.848-0.891) compared to the 24 hours (0.83, CI 0.818-0.842, p=0.006), the 1 week (0.84, CI: 0.824-0.856, p=0.043), and the 2 week (0.83, CI: 0.810-0.849, p=0.012) time frame. There was no significant difference in Cronbach's alpha between the 4 week and 3 months' time frame (0.84, CI:0.803-0.873, p=0.146), while the Cronbach's alpha of the 3 months' time frame did not significantly differ from the 24 hours, 1 week and 2 weeks' time frame.

Somatic symptom burden as assessed by the various time frames

The somatic symptom burden significantly increased with each step increase in the symptom assessment time frame, as shown in Figure 1. This increase was not found any more when the participants who filled out the questionnaire referring to somatic symptoms in the last 4 weeks and 3 months were compared (9.4 (SD 6.5) vs. 9.3 (SD 6.2); p=.898).

The pattern of somatic symptom burden increase with a longer time frame, was also seen when different somatic symptom clusters were studied, although this did not reach statistical significance in all instances (Figure 2). Comparable outcomes were found, when reanalysing the data while excluding the three somatic items with low factor loadings.

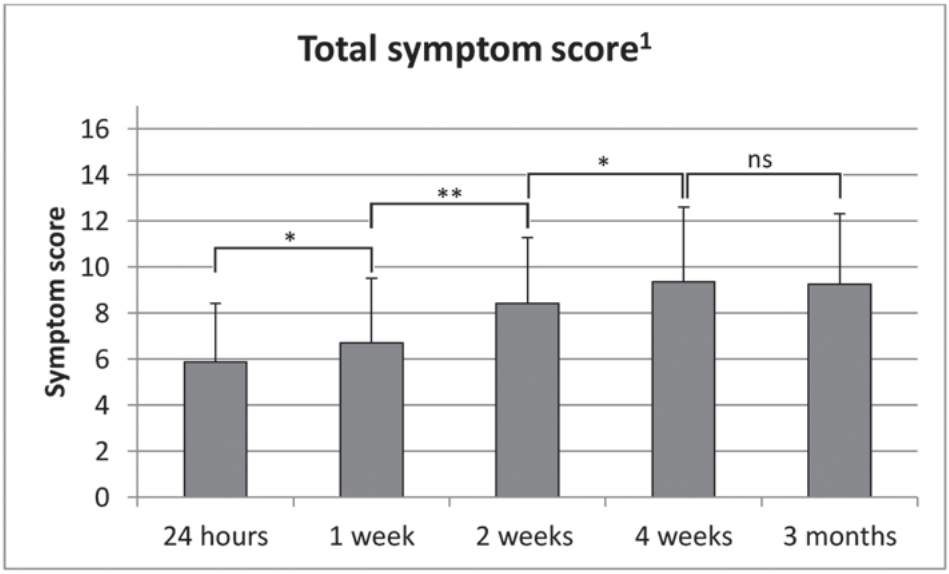


Figure 1. Total symptom score among the different time frames.
[1]ANCOVA adjusted for age, sex, and educational level.
Data are presented as mean and standard deviation.
Only comparisons between adjacent time frames are presented.
* p≤.05, ** p≤.001, ns= non-significant.

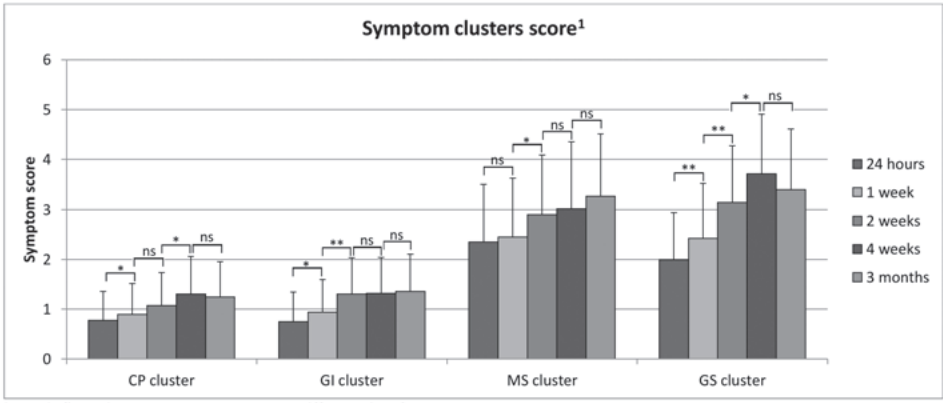


Figure 2. Symptom clusters score among the different time frames.
CP = cardiopulmonary, GI = gastrointestinal, MS = musculoskeletal, GS = general symptom.
[1]ANCOVA adjusted for age, sex, and educational level.
Data are presented as mean and standard deviation.
Only comparisons between adjacent time frames are presented.
* p≤.05, ** p≤.001, ns= non-significant.

Somatic symptom burden associated with quality of life or health anxiety
Multiple linear regression analyses were conducted to predict QoL and health anxiety based on somatic symptom burden as assessed by the questionnaires using different time frames. Somatic symptom burden was significantly associated with both QoL and health anxiety in all time frame groups (p≤.001), see Table 2.

The strongest association between somatic symptom burden and QoL was found in the participants who filled out the questionnaire referring to somatic symptoms in the past 3 months, followed by participants referring to somatic symptoms in the past 4 weeks. The association between health anxiety and somatic symptom burden was strongest among the participants in the time frame of 4 weeks, followed by the 1 week and 24 hour time frame.

Results of multiple linear regression analyses to predict QoL and health anxiety in the different symptom clusters are shown in Table 3. The time frame of 4 weeks resulted in the strongest associations with QoL for musculoskeletal and gastrointestinal symptoms, whereas the 3 months' time frame showed the strongest association with QoL for cardiopulmonary and general symptoms. The time frame of 4 weeks showed the strongest association between somatic symptoms and health anxiety for all different symptom clusters. Comparable outcomes were found, when reanalysing the data while excluding the three somatic items with low factor loadings.

Table 2. Regression analyses of somatic symptom score as a predictor of quality of life (MANSA) and health anxiety (WI).

	MANSA[1]			WI[1]		
	β	B	95% CI	β	B	95% CI
24 hours	-0.50	-3.73	-4.09, -3.35	0.51	1.07	0.96, 1.17
1 week	-0.45	-3.73	-4.33, -3.11	0.51	1.19	1.01, 1.36
2 weeks	-0.43	-3.45	-4.10, -2.78	0.45	1.08	0.90, 1.28
4 weeks	-0.52	-4.61	-5.47, -3.75	0.62	1.63	1.34, 1.92
3 months	-0.56	-4.83	-6.02, -3.71	0.50	1.33	0.92, 1.78

[1] Regression analysis adjusted for age, sex, and educational level.
All analyses p≤.001.

Table 3. Regression analyses of somatic symptom clusters as a predictor of quality of life (MANSA) and health anxiety (WI).

		MANSA[1]			WI[1]		
		β	B[2]	95% CI[2]	β	B[2]	95% CI[2]
24 hours	CP	-0.31	-0.53	-0.63, -0.43	0.39	0.18	0.15, 0.21
	GI	-0.27	-0.48	-0.58, -0.38	0.35	0.17	0.14, 0.20
	MS	-0.42	-1.41	-1.58, -1.24	0.45	0.42	0.37, 0.471
	GS	-0.47	-1.31	-1.44, -1.18	0.39	0.30	0.26, 0.33
1 week	CP	-0.31	-0.57	-0.70, -0.43	0.43	0.22	0.18, 0.27
	GI	-0.23	-0.45	-0.60, -0.31	0.32	0.17	0.13, 0.22
	MS	-0.38	-1.34	-1.54, -1.10	0.44	0.43	0.35, 0.50
	GS	-0.42	-1.38	-1.60, -1.14	0.40	0.36	0.29, 0.44
2 weeks	CP	-0.31	-0.57	-0.72, -0.41	0.29	0.16	0.11, 0.21
	GI	-0.24	-0.48	-0.67, -0.31	0.23	0.20	0.14, 0.25
	MS	-0.34	-1.13	-1.40, -0.88	0.39	0.39	0.32, 0.47
	GS	-0.40	-1.26	-1.59, -0.98	0.34	0.33	0.25, 0.41
4 weeks	CP	-0.37	-0.77	-0.99, -0.56	0.48	0.29	0.23, 0.37
	GI	-0.37	-0.71	-0.96, -0.47	0.42	0.25	0.18, 0.32
	MS	-0.43	-1.54	-1.93, -1.16	0.55	0.59	0.46, 0.76
	GS	-0.50	-1.63	-1.93, -1.32	0.52	0.51	0.41, 0.60
3 months	CP	-0.40	-0.80	-1.13, -0.51	0.42	0.26	0.17, 0.34
	GI	-0.29	-0.61	-0.90, -0.31	0.37	0.24	0.15, 0.35
	MS	-0.42	-1.49	-2.08, -0.85	0.46	0.50	0.31, 0.71
	GS	-0.56	-1.93	-2.44, -1.50	0.32	0.34	0.17, 0.52

CP = cardiopulmonary, MS = musculoskeletal, GI = gastrointestinal, GS = general symptoms.
[1] Regression analysis adjusted for age, sex, and educational level, [2] Based on bootstrapped analyses. All analyses p≤.001.

DISCUSSION

Our study suggests the time frame of 4 weeks to be the most suitable for the assessment of somatic symptom burden, since it reflects clinically relevant somatic symptom burden in terms of QoL and health anxiety best. Somatic symptom burden significantly increased with a longer time frame up to and including the time frame of 4 weeks, with no additional increase when the assessment time frame was extended to 3 months. Assessments based on the time frame of 4 weeks also showed the strongest associations with both QoL for the musculoskeletal and gastrointestinal symptoms and health anxiety for all symptom clusters, indicating clinical relevance. The burden of cardiopulmonary and general symptoms had the strongest association with assessments based on the 3 months' time frame.

Furthermore, somatic symptom questionnaires using the 4 weeks' time frame had the best psychometric properties, in terms of internal reliability.

This study has several strengths. Firstly, the assessed somatic symptoms covered all symptoms in the two most widely used somatic symptom questionnaires, which provided a comprehensive estimate of the somatic symptom burden of the participants. Secondly, QoL and health anxiety were assessed using questionnaires not referring to a specific time frame, which made it possible to investigate the association with somatic symptom burden in general.

In addition to strengths, there are also some limitations in the present study. Self-selection bias is the main limitation of this study that was performed in a convenience sample. Self-selection likely leads to a sample with a specific motivation to participate, which might be reflected in the overrepresentation of highly educated participants, women and participants above age 65. Self-selection bias might attenuate the generalizability of the results. To estimate the role of self-selection bias in our convenience sample, the characteristics of the HND participants were compared with the general Dutch population (22). Scores of HND participants on several psychological characteristics, mainly those associated with differences in education, deviated somewhat from population averages. This is also evident from the WI scores in our study, which were slightly higher compared to the general Dutch population, but comparable to general practice patients (26). Thus, the convenience sample might attenuate the generalizability of the results to the general population. Secondly, because participants of the HND study could register themselves online, inclusion rates fluctuated depending on several external factors such as media attention. The five versions of the questionnaire were assessed during different time periods (varying from several days to months) and contained severely unbalanced numbers of participants for each time period. Although the assessment periods for reporting symptoms with longer time periods (4 weeks, 3 months) were relatively long, the numbers of participants reporting on these time periods were substantially lower than for the shorter time periods. This raises the possibility of differential selection bias among study periods and confounding by time of administration. Furthermore, the unbalanced sample sizes may influence the results since they affect statistical power. Nevertheless, the 4 weeks and 3 months' time frame contained the least participants, but had the strongest associations between QoL and health anxiety.

Thirdly, because the different versions of the somatic symptom questionnaire were assessed during different time periods, somatic symptom burden may have been influenced by seasonal effects. Visual inspection revealed no indications for such seasonal effects. Fourthly, due to the study design, it was not possible to administer different versions of the questionnaire in one participant. Therefore, it was not possible to compare the association between somatic symptom score and the clinical parameters in the different time frames within a single participant. Lastly, the psychometric properties differ per time frame, which also can influence the association per time frame between somatic symptom score and the clinically relevant parameters.

This study found that somatic symptom burden significantly increased with a longer time frame until 4 weeks, with no further increase when comparing 4 weeks and 3 months. A possible explanation for this finding is that the short time frame questionnaire may not have included peaks in somatic symptom burden resulting in lower mean values. Extension of the assessment time frame simply increases the chance of having experienced somatic symptoms. Remarkably, somatic symptom burden did not further increase when prolonging the assessment frame from 4 weeks to 3 months, probably because of an increased influence of recall problems with the use of a longer time frame (14). Previous research indicated that participants frequently have forgotten previously reported somatic symptoms (12), and recall of somatic symptoms diminishes up to 100% over time (11). Furthermore, longer time frames might increasingly capture general beliefs based on personal experience with somatic symptoms (e.g. never experiencing or chronically suffering from symptoms), as opposed to the actual burden of symptoms experienced during the assessed time frame (27). The pattern of somatic symptom burden increasing with a longer time frame was not different when different types of somatic symptom clusters were studied. Based on these results, the assessment time frame of 4 weeks appears to provide the best balance between the increasing chance of capturing episodic symptoms and the increasing influence of recall problems of somatic symptoms with increasing time frames.

Our results indicate that the time frame of 4 weeks also provides the measure of subjective somatic symptom burden that is clinically most relevant. Somatic symptom burden of the different time frames were significant associated with QoL and health anxiety. However, the strongest associations were most commonly found

with the use of the assessment time frame of 4 weeks, except for the association between the burden of cardiopulmonary and general symptoms where the 3 months' time frame had the strongest association. As found in previous research (28,29), the impact of specific symptom clusters on patients' QoL and health anxiety varied. Nevertheless, the 4 weeks' time frame provided the strongest associations between the burden of musculoskeletal and gastrointestinal symptoms and QoL or health anxiety among all symptom clusters.

Currently, there are 46 different self-reported questionnaires available for the assessment of somatic symptoms, with varying time frames of assessment (8,9). This study used the PHQ-15 (19,20), with an original time frame referring to the past month, and the SCL-90 SOM (21), with an original time frame referring to the past week. Results of a previously conducted systematic review indicated that the PHQ-15 and the SCL-90 seem the most fit for purpose for use in large-scale studies (8,9). We now can add to these conclusions that the 4 weeks' time frame, which corresponds approximately to the time frame used in the PHQ-15, reflects clinically relevant somatic symptom burden best. Based on these results, other suitable questionnaires for the assessment of somatic symptoms are the 30-item Bodily Distress Syndrome Checklist (BDS checklist), that measures four symptom clusters: the cardiopulmonary/autonomic (arousal), gastrointestinal, musculoskeletal, and general symptoms (30), and the 29-item Subjective Health Complaints Inventory (SHC) (31).

In summary, our study suggests that the assessment time frame of 4 weeks is most suitable for somatic symptom questionnaires, since it reflects clinically relevant subjective somatic symptom burden in this sample. Further studies are necessary to gain more insight into the association between somatic symptom burden and external criteria that reflect clinical relevance, such as health care utilisation and work participation. Also other somatic symptom questionnaire characteristics could be studied. Remaining questions include the optimal number of response categories (e.g., binary, 3-points, 4-points, 5-points, or 7-points scale) which currently vary widely among somatic symptom questionnaires, as well as the most appropriate scoring algorithm (8,9). Furthermore, future studies may investigate whether the 4 weeks' time frame is also clinically relevant for measures of other health and mental health domains. Lastly, our recommendation is based on the quantification of symptom burden in a convenience sample from the general

population. The optimal time frame for somatic symptom questionnaires in clinical settings, in which the focus might be on recent symptoms or on quantification of treatment effects, remains unknown. Similar studies could be performed in different clinical settings (e.g. primary care, secondary care, tertiary care with patients suffering from somatoform disorders). Future studies could also investigate whether there is a difference in the optimal time frame between somatic symptoms that are episodic in nature, and symptoms that typically present more or less continuously.

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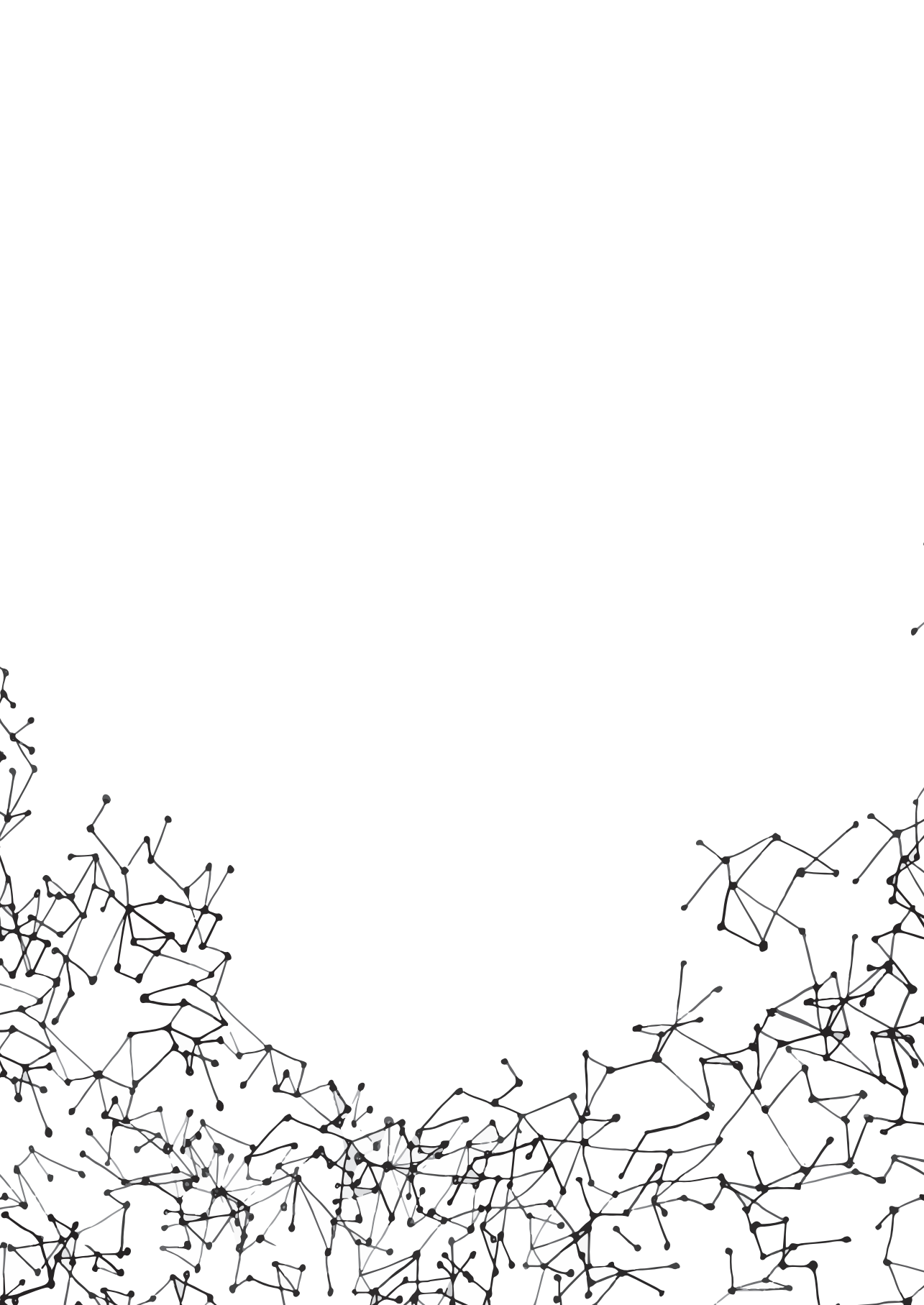

3

Functional limitations in functional somatic syndromes and well-defined medical diseases. Results from the general population cohort LifeLines

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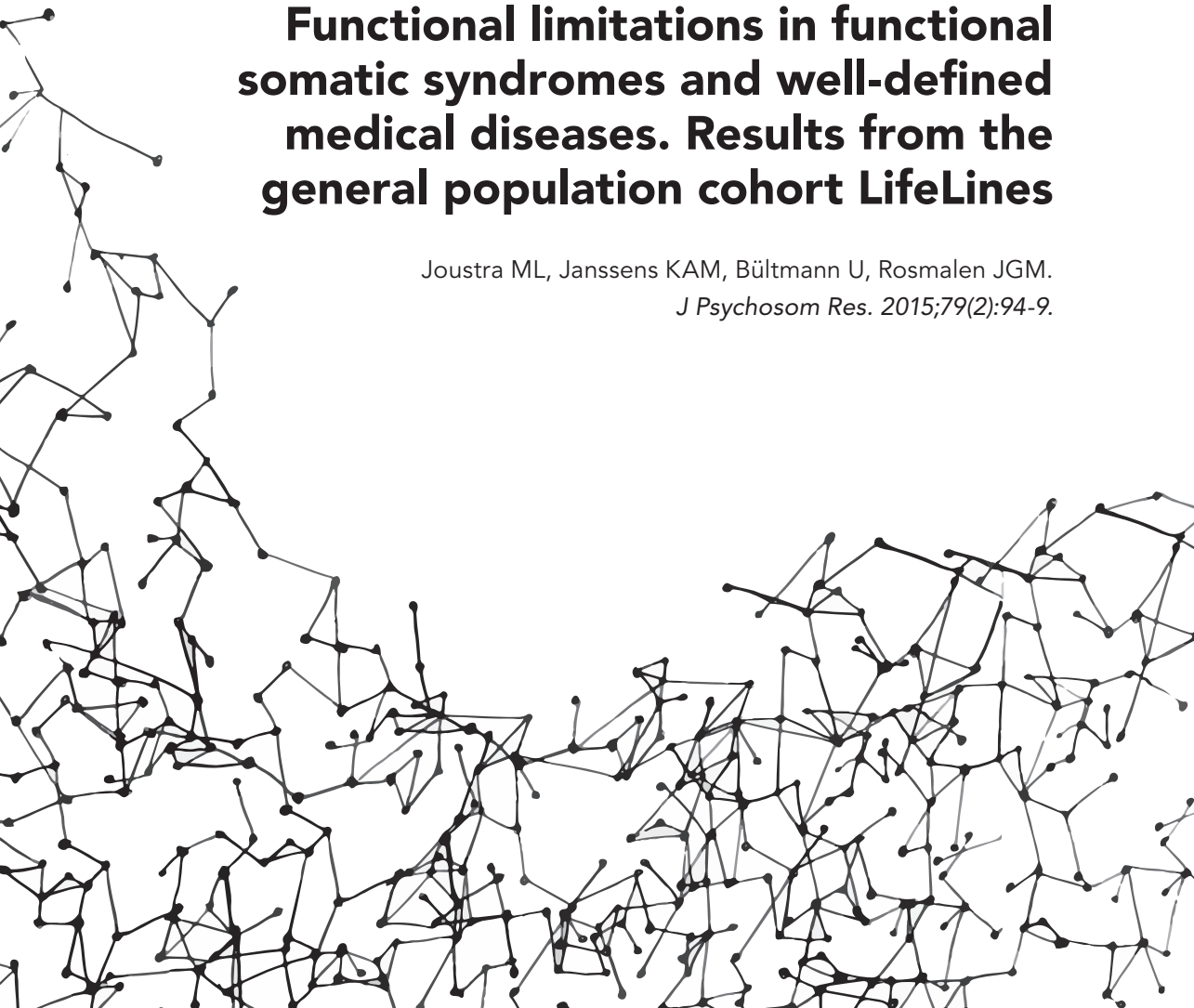
J Psychosom Res. 2015;79(2):94-9.



ABSTRACT

Objective: Functional somatic syndromes (FSS), defined as physical syndromes without known underlying organic pathology, are sometimes regarded as less serious conditions than well-defined medical diseases (MD). The aims of this study were to evaluate functional limitations in FSS, and to compare the results to MD patients with the same core symptoms.

Methods: This study was performed in 89,585 participants (age:44.4±12.4 years, 58.5% female) of the general-population cohort LifeLines. Quality of Life (QoL) and work participation were examined as indicators of functional limitations. QoL was assessed with two summary scales of the RAND-36: the physical component summary (PCS) and the mental component summary (MCS). Work participation was assessed with a self-reported questionnaire. QoL and work participation were compared between FSS and MD patients, using Chi-squared tests and ANCOVA-analyses, adjusted for age, sex, educational level, and mental disorders.

Results: Of the participants 11.0% (n=9,861) reported a FSS, and 2.7% (n=2,395) reported a MD. Total QoL, PCS and MCS were significantly lower in all the separate FSS and MD compared to controls ($p \leq 0.001$). Clinically relevant difference in QoL between chronic fatigue syndrome and multiple sclerosis patients, and fibromyalgia syndrome and rheumatoid arthritis patients were found. FSS and MD patients reported a comparable reduced working percentage, increased sick absence, early retirement due to health-related reasons and disability percentage, compared to controls ($p \leq 0.001$).

Conclusion: Functional limitations in FSS patients are common, and as severe as those in patients with MD when looking at QoL and work participation, indicating that FSS are serious health conditions.

INTRODUCTION

The experience of physical symptoms in the general population is common (1). When medical evaluation does not reval sufficient explanatory pathology, these symptoms are referred to as functional somatic symptoms. Functional somatic symptoms often occur together resulting in functional somatic syndromes (FSS). Chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS) are the most well-known FSS. CFS is mainly characterized by fatigue without sufficient explanatory pathology (2), FMS patients suffer from musculoskeletal pain with unknown etiology (3), and IBS patients suffer from bowel complaints with unknown underlying pathology (4). These core symptoms are typically accompanied by various additional symptoms. The etiology of all FSS is assumed to be multifactorial involving biological, psychological, and social factors (5).

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 are also often frustrated as a result of difficulties in controlling the symptoms and the patients' emotional responses to the syndromes (6). Furthermore, it is often assumed that functional limitations in FSS patients are less severe than in patients with well-defined medical diseases (MD). To date, relatively little is known about functional limitations in FSS patients compared to MD patients. FSS patients have been shown to suffer from productivity loss in daily activities, and from social isolation (7,8). Several studies suggest that Quality of Life (QoL) is impaired in FSS patients (9-11). For instance, overall QoL scores in CFS patients were significantly lower than in other chronic illness groups (12). QoL and functional disabilities among patients with FMS has been found to be similar to or worse than QoL in patients with rheumatoid arthritis (RA), Parkinson's disease, and other pain conditions (11,13-15). Also IBS patients had significantly lower QoL scores than the general population (16,17). QoL appeared to be similarly reduced in IBS and inflammatory bowel disease (IBD) (18). While previous studies only compared one FSS and MD, we aimed to compare multiple FSS and MD in one cohort, thereby avoiding differences in selection procedure or measurement.

FSS are associated with relevant indirect costs (8). A recent study showed that costs for healthcare services use and work-related costs in functional somatic

symptoms was estimated to be €6,815.91±10,923.14 per patient per year (19,20). Work-related costs are predominantly caused by productivity loss at work (56%), early retirement (29%), and sickness absence (14%) (21). Moreover, high levels of somatic symptoms are a determinant of long-term sickness absence, health-related job loss, and work disability (22). FSS patients often encounter difficulties at work, as a result of the somatic symptoms (8,23). For instance, fatigue is significantly influencing work participation in FSS patients resulting in more productivity loss at work and sickness absence (24,25). Because there are no studies that compare work participation between FSS and MD patients, it is unknown to what extent work participation is affected in FSS patients compared to MD patients.

The aim of the current study was to compare functional limitations in FSS patients, MD patients, and controls (defined by the absence of self-reported FSS or MD). We hypothesize that FSS and well-defined medical diseases are associated with equal functional limitations. This study is based on data of LifeLines, a large population-based cohort study of over 89,000 participants. To the best of our knowledge, there are no studies that evaluate functional limitations in both FSS and MD patients in one cohort. CFS patients were compared with patients who suffer from multiple sclerosis (MS), because fatigue is the most common symptom experienced by persons with MS (26). FMS patients were compared with RA patients, because they share similar symptoms including pain and sleep disorders (27). Lastly, IBS patients were compared with IBD patients, consisting of Crohn's disease and ulcerative colitis, because they share many of the clinical symptoms of IBS (28).

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study. LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of 165,000 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 (29).

Recruitment

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill in the questionnaires, and/or to understand the Dutch language were excluded. Parents and children were not excluded in case of the mentioned criteria when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until 6 months after pregnancy or 3 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.

Measures

Functional somatic syndromes and well-defined somatic diseases

FSS and MD were assessed by questionnaire, including a list of chronic disorders with three FSS (spastic or irritable bowel syndrome, fibromyalgia syndrome, chronic fatigue syndrome) and four MD (Crohn's disease and ulcerative colitis, multiple sclerosis and rheumatoid arthritis). Participants were asked to indicate which of these diseases they have or have had, with more than one answer allowed. IBD was defined as the presence of Crohn's disease or ulcerative colitis. Controls were defined by the absence of self-reported FSS or MD. To define a more strict diagnosis, FSS patients with a comorbid well-defined medical disease were excluded, including CFS patients who reported comorbid MS (N=6), FMS patients who reported comorbid RA (N=196), IBS patients who reported comorbid IBD (N=103), and other combinations (N=258). Furthermore, participants who

reported more than one FSS (N=1,281) (for more details, see 30) or well-defined medical disease (N=29) were excluded, so that the different groups present their own corresponding core symptom.

Functional limitations

The RAND-36 was used to evaluate health-related QoL (31). The RAND-36 consists of 36 closed-ended, structured questions that measure QoL in eight subscales (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health). The subscales were summarized in two components: the physical component summary (PCS) and mental component summary (MCS). The PCS includes physical function, role physical, bodily pain, and general health, while the MCS includes vitality, social function, role emotional, and mental health. The PCS, MCS, and total QoL score were calculated as recommended by the RAND-36 guideline (32), to generate a score from 0 to 100, with 0 being the lowest score and 100 being the best score for QoL. The outcome measures were transformed in T-scores performing a Z-score transformation ([Z * 10] + 50). The T-score with the mean of 50 and an SD of 10 is the average for the Dutch population. Thereafter, summary score coefficients of the RAND-36 were used to calculate the PCS, MCS and total QoL score correctly (32). A minimum difference of three points on any given RAND-36 scale was considered clinically relevant (31). The RAND-36 is validated in the general population and for patients suffering from several medical conditions (31).

Work participation was assessed with a self-reported questionnaire, including the following questions: "Which situation applies to you?" (answer categories: working, retired; early retired; unemployed/looking for work; disabled for work; welfare; homemaker; study), and "On average how many hours per week do you spend on paid work?". Participants who indicated they were early retired, the reason for stop working was asked (answer categories: retirement; illness/unfit for work; dismissal/unemployment; other). Participants who indicated that they were disabled for work were asked for what percentage they were disabled for work (ranging between 0- 100%). According to the definition of Statistics Netherlands, the working population was defined working ≥12 hours per week (33). Sick leave was assessed by the following questions: "In the past 3 months, how many days did you not work because of an illness or health problems?", and "In the past year, how often

did you stay home from work because of an illness or health problems?". Sick leave frequency was dichotomized (<4 and ≥4 days).

Covariates

Information on age and sex were obtained by questionnaire. Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low, middle, and high educational level. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education. Mental disorders, including current major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and generalized anxiety disorder were assessed with a standardized diagnostic interview: the Mini International Neuropsychiatric Interview (MINI) 5.0.0. The MINI is a brief structured interview for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10. A dichotomous variable for mental disorders (i.e. mood and/or anxiety disorders present or all absent) has been constructed from the MINI interview.

Statistical analyses

All analyses were performed using SPSS version 20. Analyses of covariance (ANCOVA) with Bonferroni correction were conducted to examine whether FSS, MD, and controls differed in age, QoL, working hours and days of sick leave. The percentage of participants that reported a frequency of sick leave of ≥4 times in the past year was described. Chi-squared tests were used to examine significant differences between FSS, MD and controls in sex, educational level, work participation, sick leave frequency, disability and retirement due to health-related reasons. Analyses with regard to QoL and work participation were adjusted for age, sex, and educational level. Analyses were repeated after an additional correction for mental disorders. Statistical analyses were corrected for age, sex, educational level, and mental disorders, because these factors are known to be related to FSS (2,3,30,34), MD (35-38), QoL (39,40), and work participation (25,41). Findings were considered statistically significant when $p \leq 0.05$, and clinically relevant with a minimum difference of three points on any given RAND-36 scale.

RESULTS

Demographic and work sample characteristics

Data were available for 89,585 participants, with a mean age of 44.4±12.4 years, and 58.5% female. Of these participants, 11.0% (n = 9,861) reported one FSS, 2.7% (n = 2,395) reported one of the specified MD, and 86.3% reported neither FSS nor MD (n = 77,329). An overview of prevalence rates of major medical conditions (lifetime) in the control population are presented in Table 1. Furthermore, prevalence rates of the separate FSS and MD, and their general characteristics are presented in Table 2. Lastly, prevalence rates of mental disorders in FSS and MD patients are presented in Table 3.

Table 1. Prevalence rates of major medical conditions in controls (lifetime).

	n	%
Arteriosclerosis	328	0.4
Cancer	3718	4.1
Diabetes	1621	2.1
Hypertension	15800	20.4
Stroke	475	0.6
Heart failure	517	0.7
Heart infarct	714	0.9
COPD	3545	4.6
Asthma	6162	8.0

Table 2. General characteristics of the study groups.

	n (%)	Female %	Age (years) mean (SD)	Education % Low – Middle -High
Controls	77329 (84.8)	55.6	44.2 (12.3)	28.7 39.1 30.0
Chronic fatigue syndrome	666 (0.8)	60.5[a,b]	44.8 (11.3)	30.5 40.8 24.8[a]
Multiple sclerosis	198 (0.2)	76.8[c,d]	44.9 (9.7)	30.3 42.9 25.3
Fibromyalgia syndrome	1686 (1.9)	90.4[c,e]	48.5 (10.5)[c,e]	44.0 38.3 14.5[c,e]

Table 2. Continued.

	n (%)	Female %	Age (years) mean (SD)	Education % Low – Middle -High
Rheumatoid arthritis	1572 (2.0)	60.8[c,f]	53.2 (13.2)[c,f]	44.0 31.0 21.8[c,f]
Irritable bowel syndrome	7509 (8.6)	79.2[c,g]	43.2 (12.1)[c,g]	29.1 40.1 28.4[a]
Inflammatory bowel disease	625 (0.7)	61.0[a,h]	45.9 (10.7)[c,h]	31.4 39.8 27.2

[a] p ≤ 0.05 versus controls, [b] p ≤ 0.001 versus MS patients, [c] p ≤ 0.001 versus controls, [d] p ≤ 0.001 versus CFS patients, [e] p ≤ 0.001 versus RA patients, [f] p ≤ 0.001 versus FMS patients, [g] ≤ 0.001 versus IBD patients, [h] ≤ 0.001 versus IBS patients.

Table 3. Prevalence rates of mental disorders.

	Mood disorder[1]	Anxiety disorder[2]	Mood and/or anxiety disorder
Controls	4.3	8.4	9.0
CFS	17.0	23.0	26.4
MS	6.6	9.6	11.1
CFS vs MS (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*
FMS	11.0	18.0	20.1
RA	6.0	10.3	11.3
FMS vs RA (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*
IBS	9.1	16.9	18.0
IBD	4.5	9.0	9.8
IBS vs IBD (p-value)[a]	*≤0.001*	*≤0.001*	*≤0.001*

Data are presented as %
CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.
[1] Major depressive disorder, dysthymia; [2] Generalized anxiety disorder, social phobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without panic disorder.
[a]Using Chi-squared test.

Functional limitations

Health-related QoL

Total QoL, PCS and MCS were significantly lower in all the separate FSS and MD compared to controls (Figure 1; p≤0.001). In the comparisons between FSS and MD patients, only FMS patients (42.9±8.7) reported a significantly lower total QoL score than RA patients (46.3±8.5). Without adjusting for mental disorder, the total QoL score differed significantly between CFS (39.0±10.8) and MS patients (40.8±10.5; p = 0.003), and IBS (47.3±8.0) and IBD patients (48.3±8.1; p≤0.001). After adjusting for mental disorders, these differences were not statistically significant anymore. Furthermore, the PCS was found to be statistically different between CFS (40.2±10.8) and MS patients (38.3±10.9), and FMS (39.8±10.2) and RA patients (42.5±10.7), both with and without adjusting for mental disorders. Lastly, the scores for the MCS were found to be statistically different in all three comparisons, both with and without adjustment for mental disorders.

When considering clinically relevant differences, CFS patients reported a clinically relevant lower mental component score compared to MS patients (39.7±11.3 and 45.5±9.0). FMS patients reported a clinically relevant lower physical component score, mental component score, and total QoL score compared to RA patients. No clinically relevant differences between IBS and IBD patients were observed.

Work participation and sick leave

Analyses regarding work participation and sick leave were limited to the working age population (18 to 65 years). Of our participants, 84,607 (94.4%) were of working age (age: 42.8±10.8 years, 58.8% female); 56,513 (63.1%) of these participants reported to work 12 hours per week or more (age: 42.1±9.8 years, 54.8% female).

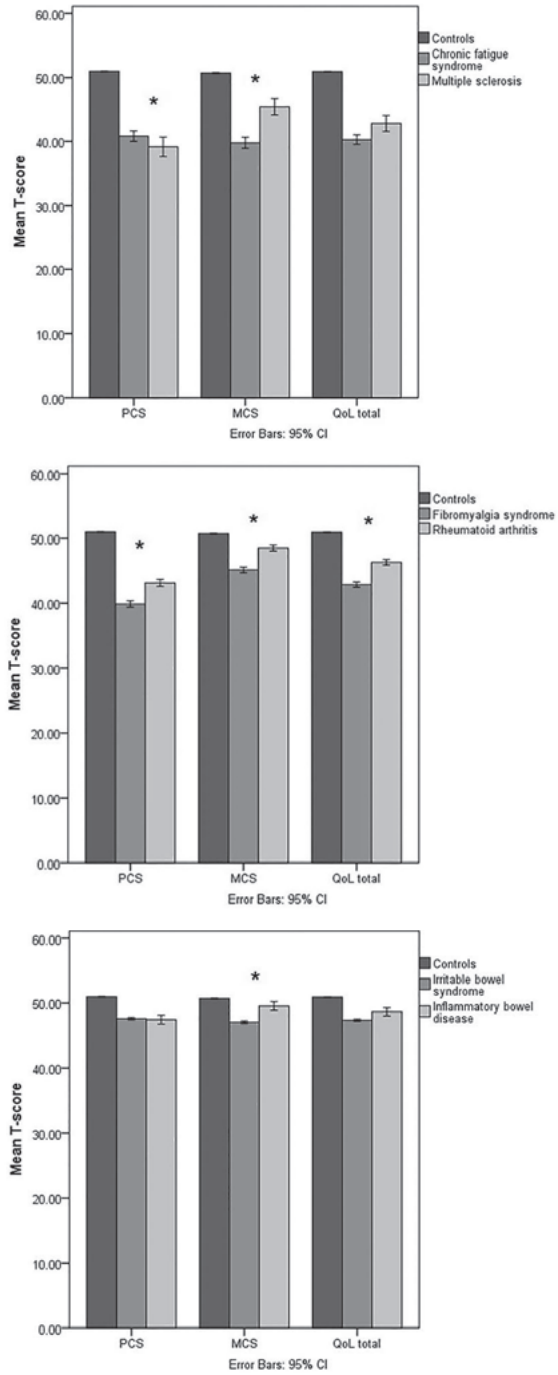


Figure 1. Differences between the groups with regard to the Quality of Life. QoL=quality of life, PCS=physical component summary, MCS=mental component summary. P ≤ .001 for all analyses that compared FSS or MD patients to controls. * P ≤ .001 for functional somatic syndrome patients versus well-defined medical disease patients.

As shown in Table 4, controls reported higher employment percentages (working ≥12 hours per week) than separate FSS and MD groups (p ranging from 0.02 to ≤0.001). When working, controls worked equally hours per week as FSS patients and MD patients, except for FMS (p=0.029), RA (p=0.046) and IBD patients (p=0.002) who worked less hours than controls. Working FSS and MD patients reported significantly more sick leave days, except for IBD patients (p=0.496), and a higher sick leave frequency than controls. When considering the separate syndrome comparisons, only statistically significant differences in work hours between IBS and IBD patients, and sick leave days between CFS and MS patients were found.

Retirement and work disability

Overall, controls retired less often due to health-related reasons, and reported a lower disability percentage than FSS and MD patients (Table 5; p≤0.001). When considering the separate syndrome comparisons, no statistically significant differences were found in early retirement due to health-related reasons, and disability percentage between FSS and MD patients.

Table 4. Work participation and sick leave among the working population (working ≥12hours/week).

	Working (%)[1,2]			Working (hours/ week) mean (SD)[3]			Sick leave (days/3 months) mean (SD)[3]	Frequent sick leave (%)[2,4]
	All	Men	Women	All	Men	Women		
Controls	67.8	73.8	63.1	33.6 (12.0)	40.5 (10.6)	27.2 (9.5)	0.8 (3.4)	3.6
CFS	50.3	59.6	44.1	33.5 (15.3)	40.6 (16.1)	27.1 (11.1)	1.5 (4.6)	13.7
MS	46.3	59.1	42.5	30.2 (12.6)	38.6 (14.0)	26.6 (10.0)	3.0 (7.8)	13.6
CFS vs MS (p-value)	*0.333[a]*			*0.593[b]*			*0.059[b]*	*0.983[a]*
				0.578[c]			*0.036[c]*	
FMS	51.9	61.3	50.9	27.2 (10.4)	40.0 (11.3)	25.6 (9.0)	1.3 (4.5)	7.6
RA	54.4	61.4	49.6	32.2 (12.3)	39.2 (11.2)	26.2 (9.7)	1.0 (3.1)	6.3
FMS vs RA (p-value)	*0.193[a]*			*0.885[b]*			*0.716[b]*	*0.296[a]*
				0.706[c]			*0.715[c]*	
IBS	64.0	70.4	62.4	30.1 (10.8)	39.9 (9.7)	27.3 (9.3)	1.1 (5.3)	6.6
IBD	63.4	70.6	58.8	31.2 (11.1)	37.5 (10.4)	26.5 (9.0)	0.8 (2.6)	7.4
IBS vs IBD (p-value)	*0.756[a]*			*0.015[b]*			*0.073[b]*	*0.532[a]*
				0.015[c]			*0.118[c]*	

CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.

[1] Percentage of all participants who are working ≥12 hours, [2] Chi-squared tests, [3] Analyses of Covariance, [4] ≥4 times of sick leave in the past year.

[a] Uncorrected using Chi-squared tests, [b]Adjusted for age, sex, and educational level, [c]Adjusted for age, sex, educational level, and mental disorders.

Table 5. Early retirement and work disability among the working age population.

	Early retirement due to health-related reasons (%)[1]	Disability % Mean (SD)[2]
Controls	2.0	53.5 (41.6)
CFS	15.4	75.8 (31.9)
MS	20.5	80.1 (28.5)
CFS vs MS (p-value)	*0.061*[a]	*0.307*[b] *0.094*[c]
FMS	10.8	70.7 (34.6)
RA	7.8	69.4 (34.5)
FMS vs RA (p-value)	*0.033*[a]	*0.991*[b] *0.852*[c]
IBS	3.4	63.0 (38.6)
IBD	4.7	62.2 (35.5)
IBS vs IBD (p-value)	*0.184*[a]	*0.806*[b] *0.431*[c]

CFS = chronic fatigue syndrome, MS = multiple sclerosis, FMS = fibromyalgia syndrome, RA = rheumatoid arthritis, IBS = irritable bowel syndrome, IBD = inflammatory bowel disease.
[1] Among the participant who indicated that they were early retired using Chi-squared tests, [2] Among the participants who indicated that they were disabled for work using Analyses of Covariance.
[a] Uncorrected using Chi-squared tests, [b]Adjusted for age, sex, and educational level, [c]Adjusted for age, sex, educational level, and mental disorders.

DISCUSSION

Our study revealed that functional limitations in FSS patients are comparable to those in patients with a MD. FSS and MD patients had a reduced QoL compared to controls. FSS patients reported a lower mental component score compared to MD patients, with relevant clinically differences between CFS and MS patients, and FMS and RA patients. Controls, FSS, and MD patients reported a comparable working percentage. But when working, FSS and MD patients worked less hours per week and reported higher sick absence compared to controls. Thus, functional

limitations in FSS patients are common, and as severe when looking at QoL and work participation, as those in MD.

The main strength of this study is the large population-based sample. This study included a sufficient number of participants with the various disorders, allowing meaningful cross-group statistical comparisons. Additionally, information about the three main FSS and related MD was available which enabled comparing these FSS and MD in one cohort, limiting differences in selection procedures or measurement. To the best of our knowledge, this is the first study that evaluates functional limitations in FSS and MD patients in one large population cohort.

There are also several limitations in our study. As a self-reported questionnaire was used for the diagnosis of FSS and MD as well as for the assessment of QoL and work participation common method variance can not be excluded. Although self-reports may underestimate the amount of persons with FSS (42), this underestimation seems unlikely in our study because the prevalence rates for CFS, FMS and IBS were comparable to those reported in previous studies (2,3,43). Another limitation is that lifetime diagnoses of FSS were available instead of current diagnoses. 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 (44). Moreover, the majority of the patients with CFS (>95%) and FMS (>93%) in the current study recently experienced fatigue and musculoskeletal pain in the past week(s). Unfortunately, no information about bowel complaints was available. To overcome the methodical weakness of self-reported questionnaires for the diagnosis of FSS and MD in the future, it is recommended to use patients' clinical records when possible. 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 more extensively assess the prevalence of the three FSS during the baseline assessment through practical limitations. We aim to assess FSS more extensively in future assessment waves, preferably by the use of clinical records. Lastly, because of the cross-sectional design, cause-effect relationships can not be examined. Furthermore, individuals who fulfil criteria for FSS and MD, but did not seek treatment and thus never received a diagnosis might differ from those who seek medical care and receive a diagnosis. Our study design may primarily have sampled FSS and MD

patients who received a diagnosis and sought medical care, and thus have more limitations than patients who did not seek medical care, thereby overestimating functional limitations in FSS.

Our study supports previous findings that FSS are associated with impaired QoL (9,10). Also in line with earlier studies, mental component scores were significantly lower in CFS and IBS patients than in MS and IBD patients (12,18). Furthermore, overall QoL, the PCS and MCS scores in FMS patients were significantly lower than in RA patients, which is also in accordance with previous findings (11,13-15). Although several QoL scores differed statistically between patients with FSS and well-defined medical diseases, not all of these differences were clinically relevant (i.e. differences larger than three points on the QoL scale). Nevertheless, CFS patients reported a clinically relevant lower mental component score compared to MS patients, and FMS patients reported a clinically relevant lower physical component score, mental component score, and total QoL, compared to RA patients. In addition to previous studies, we found that the lower QoL of FSS patients compared to MD patients is particularly related to mental limitations. The clinically relevant lower scores in the MCS in CFS and FMS patients might due to the difficulty in dealing with their disease symptoms. For instance, FSS patients 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 (45). Moreover, FSS patients felt stigmatized, since others tended to doubt the accuracy and truthfulness of patients' reported disabling symptoms (46,47).

Our findings also indicate that working FSS patients worked equal hours per week, and reported equal sick leave days and frequency compared to MD patients (21). This indicates that both FSS and MD are associated with relevant indirect costs (8). Regarding sick leave, it is likely that both FSS and MD patients often encounter difficulties at work (8,23). For example, fatigue is a significant problem in both FSS and MD patients, influencing work participation (24,25). Thus, this may suggest that FSS symptoms affect work participation just like in MD symptoms. In summary, this population-based study revealed that the functional limitations in FSS patients are common and as severe as those in patients with MD, despite the absence of underlying organic pathology. It shows that FSS have not only individual, but also societal consequences. Therefore, health care professionals

in public and occupational health, researchers and society should pay more attention to these disorders and their consequences in terms of QoL and work participation. Increased knowledge and understanding of the etiology and impact of FSS may eventually improve the treatment of a significant proportion of the population (in our cohort 11.0%) who is suffering from FSS. The study urges the need for more research on FSS, a relatively neglected research area, especially studies on a better understanding of the etiology and treatment of these disorders are needed. Specific suggestions for studies with regard to QoL and functional limitations are to examine the cause-effect relationships between FSS and QoL as well as work participation, and to gain insight in the working conditions and work accommodations of FSS patients.

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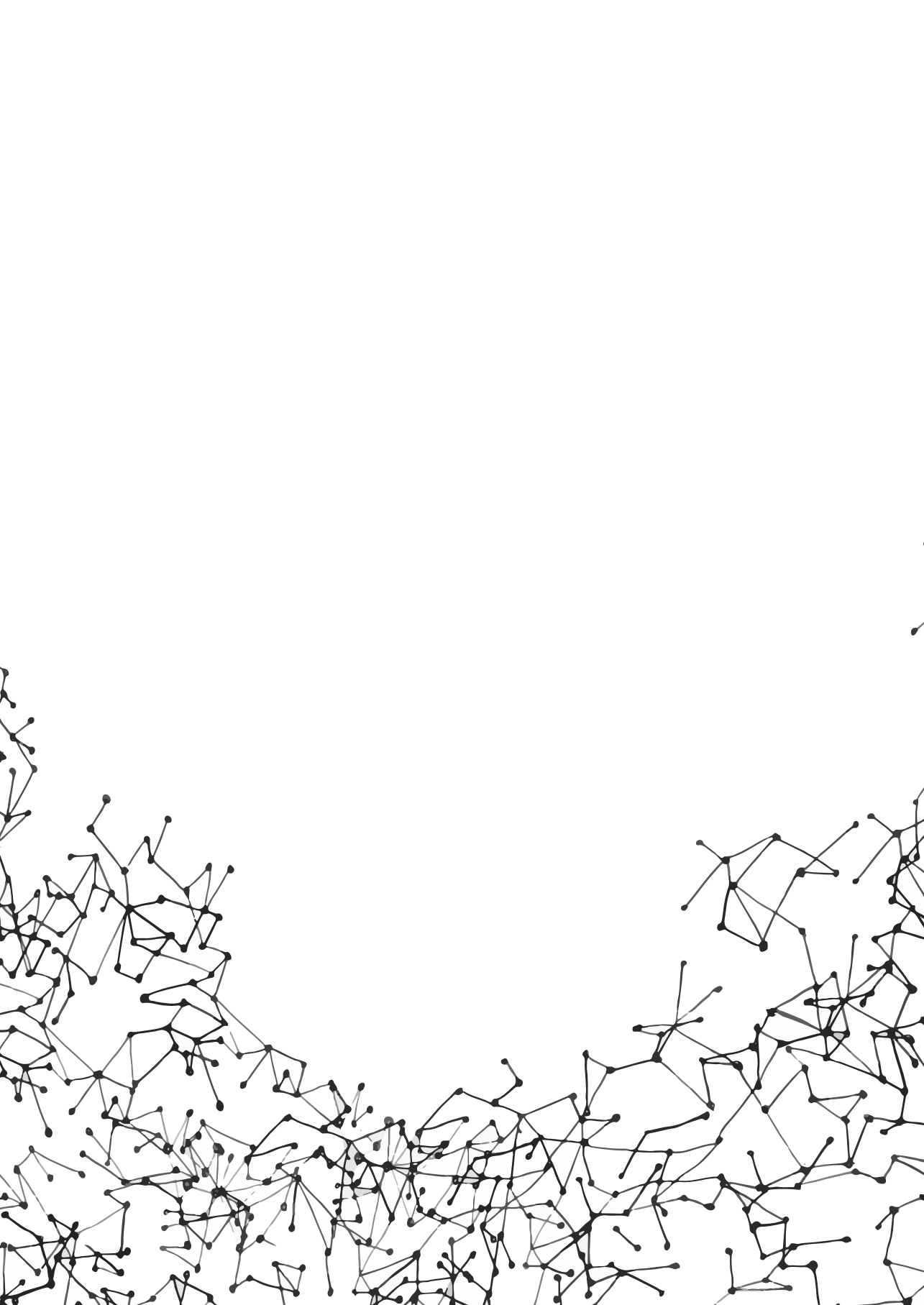

4

The network structure of diagnostic symptom criteria for functional somatic syndromes

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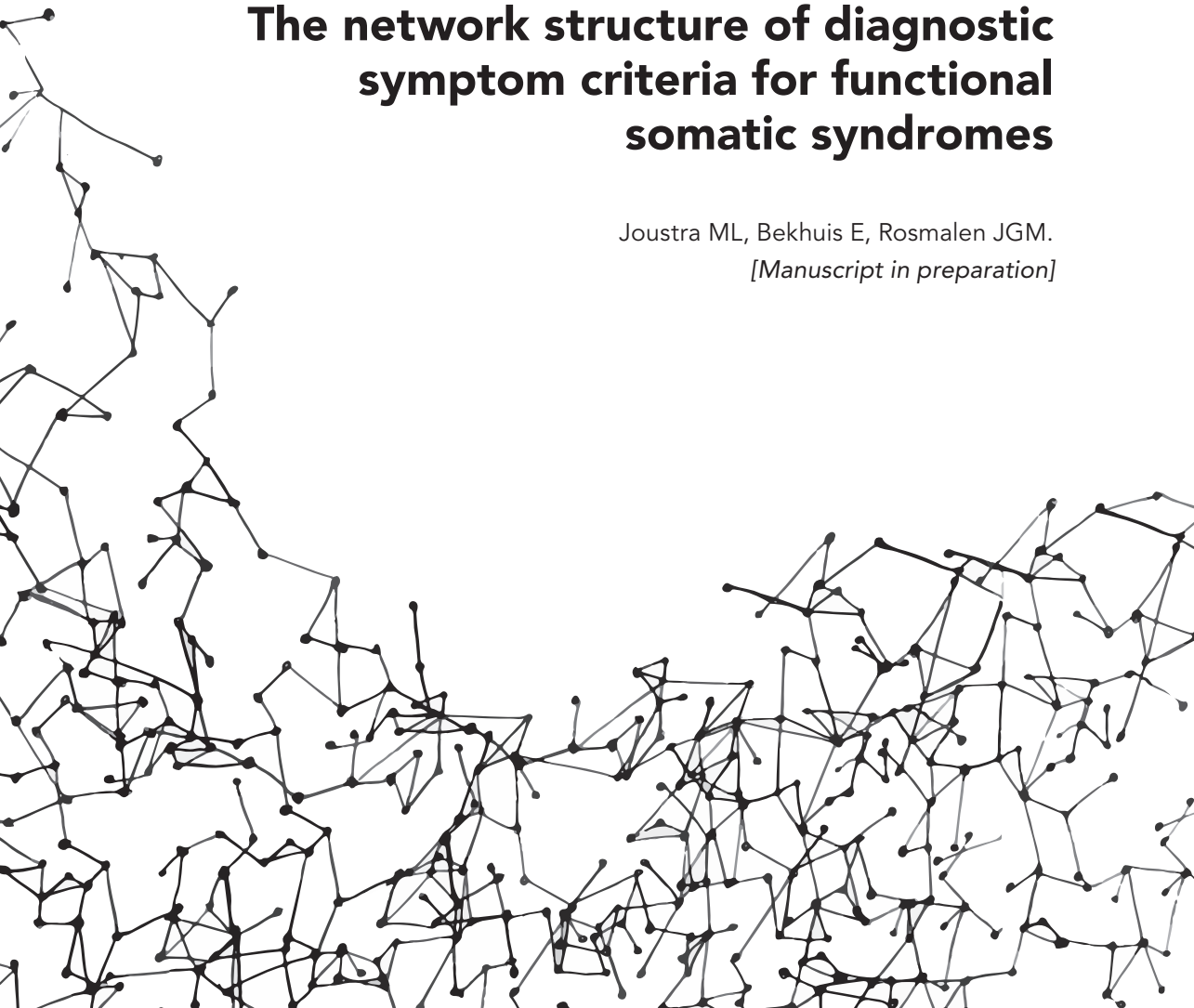
[Manuscript in preparation]



ABSTRACT

Background: There is a longstanding discussion on whether functional somatic syndromes (FSS) are different names for the same problem, since they are known for substantial clinical and diagnostic overlap.

Objectives: The aim of this study was to investigate the co-occurrence of the most well-known FSS (i.e., chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS)) on a symptom-level using network analyses, in the general population and in a subgroup consisting of patients fulfilling the diagnostic criteria for FSS.

Method: This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the LifeLines cohort study. The diagnostic symptoms of the three FSS were assessed by questionnaire. A partial correlation network of the diagnostic criteria was estimated to study how diagnostic symptoms were interrelated within and between diagnoses. Clustering of symptoms was examined using the walktrap algorithm.

Results: Network analyses showed that all diagnostic symptoms were highly connected, with similar levels of clustering in the general population and patients with FSS. The network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Clustering of diagnostic symptoms revealed 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.

Conclusions: 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. The diagnostic criteria for FSS should be further examined and reconsidered.

INTRODUCTION

Functional somatic syndromes (FSS) comprise clusters of persistent somatic symptoms for which no conclusive underlying organic pathology can be found (1). The main three syndromes are chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). FSS are often co-morbid: patients with CFS, FMS or IBS are more likely to meet lifetime symptom and diagnostic criteria for other FSS than control subjects (2). For example, lifetime rates of IBS were significantly higher in patients with CFS (92%) or patient with FMS (64%) compared with controls (18%) (2).

Since the three main FSS are known for substantial clinical and diagnostic overlap, there is a longstanding discussion in the literature on whether these syndromes are different names for the same problem, also known as the lumper-splitter discussion (3). Lumpers state that the different FSS identify one group of patients, while splitters state that the different FSS should be considered as distinct entities. One argument in favour of the lumpers is that the case definitions of FSS overlap. For example, both CFS and FMS diagnostic criteria describe both musculoskeletal symptoms, fatigue, cognitive symptoms, and sleep disturbance or waking unrefreshed. 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 or physiological patient characteristics (4).

In the current literature, attempts have been made to investigate whether FSS are different names for the same problem by examining the interrelatedness or clustering of symptoms that characterize FSS. Different statistical techniques have been used, including latent class analyses (5-7), principle component analysis (8-10), and cluster analysis (11,12). Most studies found multiple underlying classes or clusters and conclude that there are both similarities and dissimilarities between FSS. However, there were also some inconsistencies between these studies: some findings indicated that patients with FSS could be distinguished by the number of symptoms (7,9), while other findings suggested that both the number of symptoms and the type of symptoms were relevant (6,12,13). The number of classes or clusters also varied widely, ranging from two to eleven (9,12). A possible explanation for these inconsistencies is that different symptom clusters might be

the result of the experience of milder or lower numbers of symptoms, while in the more severe cases the overlap of clusters becomes larger (6,12-14). There are also several limitations of the current literature in the context of the lumper-splitter discussion: the somatic symptoms included more than those in the diagnostic algorithms of the different FSS, the time frame of symptom assessment was relatively long in most studies, and lastly, symptoms were frequently dichotomized (i.e. present or not), not taking into account the severity of symptoms.

Currently there is a new approach to analyze symptom patterns, known as the network approach (15). This approach focuses on individual symptoms and the unique patterns in which they co-occur with other symptoms (16). The advantage of the network approach compared to latent class analyses, principle component analysis, and standard cluster analysis, is that it naturally accommodates the unique role of each of the individual symptoms. As such, it can provide insight into how varying symptoms of a specific syndrome relate differentially to symptoms from the same or other syndromes. Recent studies have used the network approach to study co-morbidity and have shown promising results (13,17-19). One study investigated for example the network structure of psychiatric symptoms and showed that although clustering of the symptoms generally corresponded with the classification of symptoms in the DSM, symptoms within the same diagnosis could show unique patterns in which they co-occurred with each other (17). Another study showed that individual depressive/anxiety symptoms had different levels of importance in explaining their general co-occurrence with somatic symptoms (18). More recently, network analysis was performed in patients with CFS, FMS, or IBS and revealed that 61 symptoms could be classified into eleven categories, which showed more overlap as FSS severity increased (13). As the study did not focus on diagnostic criteria of the FSS and their individual roles in the network, however, important information about the role of individual diagnostic symptoms within the specific FSS syndromes as well as in their co-morbidity is missing in the context of the lumper-splitter discussion.

The aim of this study is to investigate networks of the diagnostic symptoms composing the criteria for the three most well-known FSS. To the best of our knowledge, no studies have investigated the relatedness of symptoms that compose the diagnostic algorithms of the different FSS using network analyses. This study will be performed in a large population-based cohort study. First, we

will examine the general network structure of the diagnostic criteria for FSS in both the entire cohort and in a subgroup consisting of patients with FSS experiencing more severe symptoms, to investigate the influence of experiencing more severe symptoms on network structure and clustering. Second, we will examine the role of the individual symptoms within and between the CFS, FMS and IBS diagnostic symptom criteria. Lastly, we will examine clustering of symptoms in the network models.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study (20). LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language were excluded. Parents and children were not excluded in case of the mentioned criteria when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website and then participate.

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

FSS diagnostic criteria

The diagnostic criteria for the three FSS were included in the LifeLines questionnaire. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) (21), FMS using the 2010 American College of Rheumatology criteria (ACR) (22), and the diagnosis for IBS was assessed using the ROME III criteria (23). However, the IBS criteria which were based on a minimal frequency of symptoms were adjusted in accordance with the ROME IV criteria (24),: instead of symptoms 3 days per month, participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (Appendix A: scoring algorithm).

Descriptives

Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational level. Medical diseases were assessed by a questionnaire asking to indicate for each disease whether the participant had or had had them.

Statistical analyses

The characteristics of the participants were described using SPSS version 22. For all continuous variables, means ± standard deviations (SDs) were calculated. Network analyses were performed on a combination of binary main criteria (fatigue for at least 6 months, locomotor pain complaints for at least 3 months, abdominal pain for at least 6 months with a frequency of at least 1 day/week), and categorical and continuous data on additional symptoms. Two diagnostic criteria of CFS and FMS were very similar, namely cognitive symptoms (forgetfulness or memory problems/difficulty with thinking or concentrating in CFS; thinking requires effort/I have trouble concentrating in FMS) and unrefreshed sleep (unrefreshing sleep in CFS; waking up unrefreshed in FMS). Therefore, these items were combined by taking the mean of the CFS and the FMS symptom. We performed the network analyses in both the general population cohort and in a subset with persons who fulfilled the diagnostic criteria for CFS, FMS and/or IBS. Weighted networks of symptoms for both the general population and FSS were estimated and visualized in R version 3.4.2 with package qgraph (25). A correlation matrix for all symptoms (with polyserial correlations for symptom pairs including categorical or binary symptoms and Pearson correlations for symptom pairs consisting only of continuous symptoms) was calculated. Partial correlations were calculated for all pairs of variables, which indicate correlations among symptoms while controlling for all other variables in the network. To prevent overfitting, an *l*1-penalty was used to estimate possible networks with different levels of sparsity (26). The model with the best fit to the data was selected using the extended Bayesian information criterion (EBIC) (27) with hyperparameter y=0.5 (28). This technique has been shown to yield adequate network structures (28-30). The accuracy of estimated connections in the networks was also investigated by calculating 95% confidence intervals around connection weights with R-package bootnet (31). Bootstrapped confidence intervals were calculated by drawing 1,000 bootstrap samples of the data and recalculating connection weights for each sample. The

lay-outs of the networks were based on the Fruchterman-Reingold algorithm, which places symptoms with stronger and/or more connections closer to each other (32).

First, we explored the general structure of the network. To examine the general connectivity of the network, the density of the network was calculated by determining the proportion of actual connections over the number of potential connections between all symptoms (33). In addition, the network clustering coefficient was calculated by determining the proportion of actual connections of adjacent nodes in the network over the number of potential connections between adjacent nodes. Subsequently, we focused on the strength of the individual FSS symptoms to symptoms of the same diagnosis, and the strength of all connections from an individual symptom to all symptoms of other FSS diagnoses by summing the weight of these connections (34). Strengths of 0.1, 0.3, and >0.5 were interpreted to reflect small, medium, large, and very large strengths, respectively (35). Lastly, clustering of symptoms was examined using the walktrap algorithm from package "Igraph" (36). This random walk method identifies groups of symptoms with high intragroup but low intergroup connectedness.

RESULTS

This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Of these participants, 11.5% (n=9,217) fulfilled criteria for one or more FSS: 3.1% of the participants fulfilled the CDC criteria for CFS, 6.4% fulfilled the ACR criteria for FMS, and 5.5% fulfilled the ROME IV criteria for IBS. Patients with FSS were more often female (75% female) and were slightly younger (52.3±12.4 years) than the general population (59.2%, 52.9±12.6; Table 1). In addition, patients with FSS were lower educated than the general population. The prevalence of medical health conditions is summarized in Table 2.

Table 1. General characteristics of the study groups.

	General population	One or more FSS	CFS	FMS	IBS
n (%)	79,966 (100)	9,217 (11.5)	2,490 (3.1)	5,122 (6.4)	4,377 (5.5)
Female n (%)	47,341 (59.2)	6,917 (75.0)	1,848 (74.2)	3,922 (76.6)	3,307 (75.6)
Age in years (SD)	52.9 (12.6)	52.3 (12.4)	54.2 (11.8)	52.8 (11.7)	50.9 (12.9)
Education (% low-middle- high)	2.6 65.9 29.2	3.5 69.9 24.0	4.7 72.7 19.6	3.9 73.6 19.9	2.5 66.4 28.6

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

Table 2. Prevalence rates of medical and psychiatric health conditions in the general population (lifetime).

	n	%
Anxiety disorder	5,712	7.1
Cancer	1,625	2.0
Celiac disease	381	0.5
Dementia	74	0.1
Eating disorder	1,107	1.4
Functional somatic syndrome	9,217	11.5
Heart failure	1,603	2.0
Hepatitis B	66	0.1
Inflammatory bowel disease	924	1.2
Mood disorder	2,368	3.0
Multiple sclerosis	185	0.2
Rheumatoid arthritis	2,858	3.6
Schizophrenia	65	0.1

General network structure

The network structure of FSS diagnostic symptoms in the general population is presented in Figure 1A and in patients with FSS in Figure 1B. Tables S1A and S1B show that accuracy of connection weights was excellent, reflected in very small confidence intervals of associations. The diagnostic symptoms were highly connected: 89.2% of potential connections in the general population network and 90% in the FSS group network were observed, with a mean strength of connections of r=0.055 in the general population and r=0.048 in patients with FSS. In addition, both networks had a high level of clustering (i.e., clustering coefficient = 0.79 in the general population and 0.80 in patients with FSS). Most connections were positive or slightly negative, except for the association of the main criterion of IBS (mIBS) with the widespread pain index of FMS (WPI, r=-0.17) and fatigue of FMS (Fat, r=-0.07) in patients with FSS.

Associations of symptoms within diagnoses

The associations of symptoms within FSS diagnoses in the general population and patients with FSS can be found in Table S2. The within-diagnosis density for the CFS diagnostic symptom criteria was respectively 86.1% in the general population and 69.4% in the FSS group, with a mean strength of connections of r=0.52 in both groups. The CFS symptom post-exertional malaise (PEM) had the highest within-diagnosis strength (r=0.73 in the general population and r=0.87 in patients with FSS), while headaches (Hea) had the lowest within-diagnosis strength in both the general population (r=0.27) and patients with FSS (r=0.32). Although sore throat (Thr) and lymph node tenderness (Lym) had a high within-diagnosis strength (r=0.62 and 0.58 in the general population and r=0.55 and 0.54 in the FSS group), this was mainly the result of their strong associations with each other (r=0.43 in both groups).

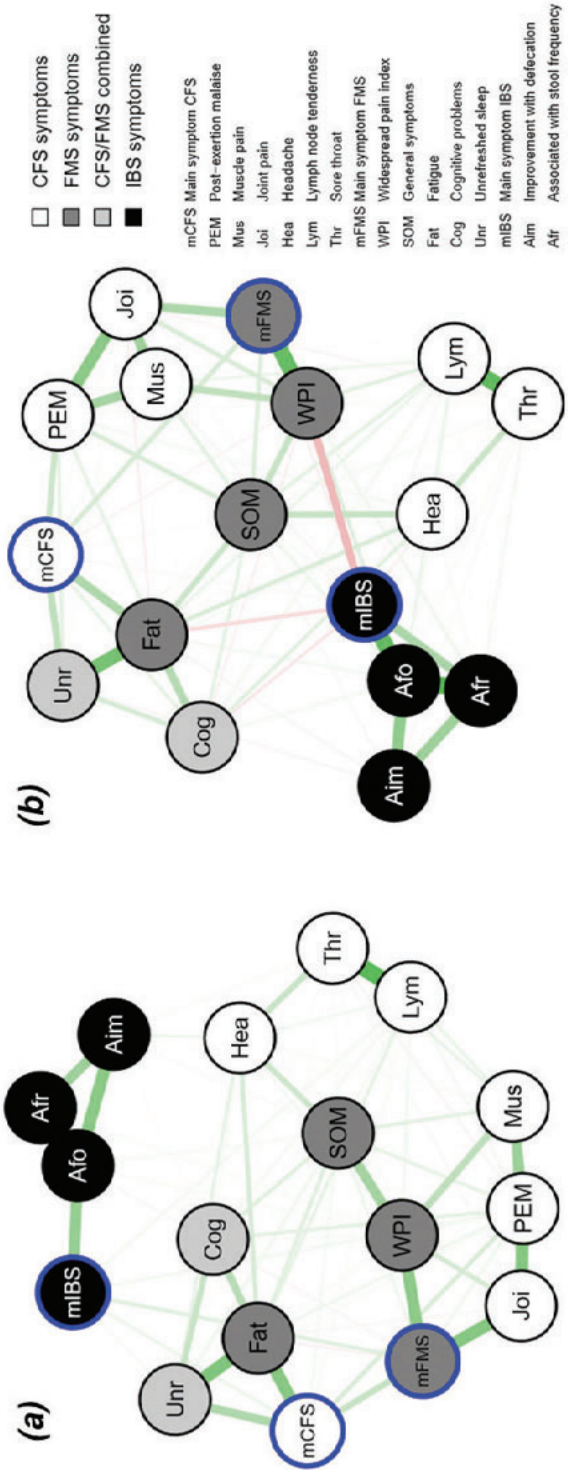


Figure 1. Estimated network structures of FSS diagnostic symptoms for (a) the general population and (b) patients with FSS.

Symptoms are represented by circles and associations between them by lines. The color of circles refers to the diagnosis symptoms belong to. Main criteria for CFS, FMS and IBS are delineated in blue. Green lines indicate positive associations and red lines negative associations. The thickness of lines is proportional to the strength of associations.

For the diagnostic symptom criteria of FMS, the within-diagnosis density was 80% in both the general population and patients with FSS, with a mean strength of connections of r=0.42 in the general population and r=0.51 in patients with FSS. The FMS symptom fatigue (Fat) had the highest within-diagnosis strength (r=0.57 in the general population and r=0.71 in patients with FSS), while the main criterion of FMS (mFMS) had the lowest within-diagnosis strength in the general population (r=0.24), and cognitive symptoms (Cog) in patients with FSS (n=0.34). The strongest connections between FMS symptoms were between the main criterion and the widespread pain index (WPI; r=0.26 in the general population and r=0.42 in patients with FSS), and fatigue and unrefreshed sleep (Unr; r=0.34 and r=0.37).

Lastly, the within-diagnosis density was 83.3% in the IBS symptom criteria of both groups, with a mean strength of connections of r=0.73 in the general populations and r=0.83 in patients with FSS. The IBS symptom abdominal pain associated with change in stool form (Afo) had the highest within-diagnosis strength (r=1.18 in both groups), while the symptoms with the lowest within-diagnosis strength were the main criterion in the general population (mIBS; r=0.15) and improvement of abdominal pain after defecation in patients with FSS (Aim; r=0.56). The strongest connections between IBS symptoms were between abdominal pain associated with change in stool form (Afo) and abdominal pain associated with change in stool frequency (Afr; r=0.73 in the general population and r=0.46 in patients with FSS).

Associations of symptoms between diagnoses

The associations of symptoms between FSS diagnoses in the general population and patients with FSS can be found in Table S3. The between-diagnosis density for CFS with FMS and IBS diagnostic symptom criteria was 66.2% in the general population and 74.6% in patients with FSS. The main criterion of CFS had the highest between-diagnosis strength (mCFS; r=0.92 in the general population and r=0.52 in patients with FSS respectively), while the symptom sore throat

(Thr) had the lowest between-diagnosis strength (r=0.10 in both groups). The strongest connections of CFS symptoms with FMS symptoms were between joint pain (Joi) and the main criterion of FMS (mFMS; r=0.23 in both groups), and with IBS symptoms between lymph node tenderness (Lym) and abdominal pain associated with change in form (Afo; r=0.05 in both groups).

The between-diagnosis density for FMS with CFS and IBS diagnostic symptom criteria was 73.1% in the general population and 80.8% in patients with FSS respectively. For FMS the symptom fatigue (Fat) had the highest between-diagnosis strength (r=1.07 in the general population and r=0.84 in patients with FSS), while cognitive symptoms in the general population (Cog; r=0.33) and the main criterion in FSS patients (mFMS; r=0.21) had the lowest between-diagnosis strength. The strongest connection between FMS and IBS symptoms was between the widespread pain index (WPI) and abdominal pain associated with change in form (Afo; r=0.08 in both groups).

Lastly, the between-diagnosis density was 44.2% and 50% for IBS with CFS and FMS diagnostic symptom criteria in the general population and patients with FSS respectively. The main symptom of IBS (mIBS) had the highest between-diagnosis strength in the general population (r=0.23), while it had a negative between-diagnosis strength in patients with FSS (r=-0.57).

Cluster analyses

Cluster analysis of the network in the general population revealed four clusters. Firstly, an abdominal symptom cluster with inclusion of all IBS diagnostic symptoms was found. Second, a general symptom cluster was identified including the main criterion of CFS (mCFS), the combined CFS/FMS symptoms cognitive problems (Cog) and unrefreshed sleep (Unr), and the FMS symptoms fatigue (Fat) and general somatic symptoms (SOM). Third, a musculoskeletal cluster was identified with inclusion of the main FMS criteria (mFMS), the widespread pain index (WPI), and the CFS diagnostic symptoms joint pain (Joi), muscle pain (Mus), and post-exertional malaise (PEM). Lastly, analyses revealed an "other symptoms" cluster with inclusion of the CFS criteria headaches (Hea), sore throat (Thr), and tender lymph nodes (Lym).

When analyzing clustering in the network of the FSS group, two clusters were found: one abdominal symptom cluster with inclusion of all IBS diagnostic symptoms, and a combined general and musculoskeletal symptom cluster including all diagnostic symptoms of CFS and FMS.

DISCUSSION

This was the first study that investigated the interrelatedness of symptoms that compose the diagnostic criteria of the different FSS using network analyses. First, we found that all diagnostic symptoms were connected, either directly or via other symptoms, with similar levels of clustering in the general population and patients with FSS. Second, the network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Main symptoms were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. Lastly, clustering of symptoms in the general population revealed a general, musculoskeletal, abdominal, and other symptom cluster, but in patients with FSS only an abdominal and a combined general and musculoskeletal symptom cluster were found.

The main strength of the current study is that the symptoms that compose the diagnostic criteria for the three main FSS were assessed concurrently in one cohort. We were therefore able to examine the networks of the diagnostic symptoms criteria in a large population-based sample, as well as in a subgroup consisting of patients fulfilling the diagnostic criteria for one or more FSS. Since we assessed the diagnostic symptom criteria for all three FSS, it was possible to examine the relatedness of symptoms that compose the diagnostic criteria of the different FSS irrespective of help-seeking behaviour or diagnostic biases. Lastly, instead of dichotomized additional symptoms, we used the continuous symptom variables taking into account the severity or frequency of symptoms.

There are also limitations in the current study. First, the FSS symptoms and diagnoses were based on the 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 met the diagnostic criteria for FSS based on clinical

examinations. Second, co-morbid conditions that could explain the FSS symptoms were not excluded when determining the FSS diagnoses, mainly because only the CFS diagnostic criteria and not the FMS and IBS criteria specifically mention the exclusion of medical health conditions. Nevertheless, FSS diagnoses rely heavily on subjective symptoms and to a lesser extent on the absence of objective clinical or laboratory findings. Furthermore, although we combined items with the same definitions (i.e., cognitive problems and unrefreshed sleep), the estimated network structures contained several symptoms with partially overlapping definitions. Examples include the main criterion of CFS and the additional symptom fatigue in FMS, and muscle pain or joint pain in CFS and the main symptom or the widespread pain index in FMS. The correlations between these variables will naturally be stronger, and therefore these (partially) overlapping symptoms might have changed clustering in the network structure. We decided not to combine these partially overlapping symptoms as they are included in this way in the diagnostic criteria and they differ in important aspects (e.g., their time frame).

Our networks had high density, and many connections within and between the different FSS diagnostic symptoms were found. The between-diagnosis density was comparable to the within diagnosis density for CFS and FMS, indicating that overlap among CFS and FMS diagnostic symptoms is very high. Despite strong within diagnosis connectedness of IBS symptoms, this symptom cluster seemed to be more isolated from the rest due to its lower between-diagnosis density. Within and between diagnoses of FSS, individual diagnostic criteria had differential roles. The highest within-diagnosis strengths were found for the additional criteria of post-exertional malaise in CFS, fatigue in FMS, and abdominal pain associated with change in stool frequency in IBS, while the syndromes' main criteria had low within-diagnosis. Main criteria, however, were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. This is interesting as it would be expected that main criteria have a central role in strengthening the internal connectedness of the diagnostic criteria of a syndrome, while they separate a syndrome from criteria of other syndromes. Indeed, previous studies have identified main criteria of mental disorders as the most central within-diagnosis symptoms (37,38).

Symptoms in the networks clustered based on bodily systems rather than their current classification into CFS, FMS and IBS symptoms. Recently, the Institute of

Medicine (IOM) published a new proposal for diagnostic criteria for CFS based on extensive literature review (39). These criteria are based on three main symptoms: disabling fatigue, post-exertional malaise and unrefreshing sleep; with at least one of two mentioned additional symptoms (cognitive impairment or orthostatic intolerance). In line with the literature review of the IOM, the networks revealed that fatigue symptoms clustered with cognitive problems and unrefreshed sleep, and that sore throat, lymph node tenderness, and headaches formed a separate symptom cluster. One remarkable finding is that the CFS symptom post-exertional malaise was included in the musculoskeletal cluster in the general population. In contrast to the 1990 diagnostic criteria (40), the revised 2010 FMS criteria also include non-pain symptoms that overlap with the CFS diagnostic symptom criteria such as fatigue, cognitive symptoms, unrefreshed sleep, and general symptoms (22). As mentioned by the IOM, the revised ACR diagnostic criteria for FMS may therefore greatly increase the overlap between CFS and FMS (39). Based on our results, the classification of the current diagnostic criteria for CFS or FMS could be questioned.

The level of clustering was similar in the general population and the FSS group. Nevertheless, the between-diagnosis density was higher in the FSS group than in the general population. In addition, the four clusters in the general population melted to an abdominal and combined general and musculoskeletal symptom cluster in the FSS group. This could have been the result of negative associations in the network of FSS patients, which may have been caused by the selection of patients based on the fulfilment of the criteria of either of the three syndromes. However, it is in line with an earlier network study showing that difference between network structure and symptom clusters in patient with FSS decreased as symptom severity increased (13). Furthermore, our findings may suggest that one mechanism underlies FSS which could be divided into a modest single-organ type with symptoms primarily from one bodily system (6,12,14). But also in a more severe, multiorgan type, which may have led to stronger symptom overlap in FSS patients than in the general population. Rather than the presence of such a latent variable, it has also been suggested that direct causal relations among symptoms, as is central in the network approach, could explain this higher overlap in patients with more severe symptomatology (13).

In summary, we revealed that all FSS diagnostic symptoms were connected, either directly or via other symptoms. Furthermore, we found that symptoms clustered based on bodily systems rather than their current classification into the different FSS. Our results are therefore in line with recent suggestions supporting both the lumpers' and splitters' views in that there is commonality as well as heterogeneity within and between FSS (4). Future studies will be necessary to examine and reconsider the diagnostic criteria for FSS.

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APPENDIX A: SCORING ALGORITHM TO DETERMINE THE FUNCTIONAL SOMATIC SYNDROME DIAGNOSIS

Chronic fatigue syndrome

The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention (CDC) criteria (1). To meet the CDC diagnostic criteria participants had to indicate [1] that they had experienced chronic fatigue for 6 or more months (box 1), and [2] that the fatigue significantly interfered with daily activities and work (box 2). In addition, [3] the participant had to report concurrently four or more of the eight mentioned additional symptoms (box 3)

BOX 1
Question chronic fatigue duration:

"I have had my tiredness complaints for about:"

Code	Label
1	not applicable because I do not have tiredness complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ….. years and ... months
6	I have been feeling tired my entire life

To meet the CDC diagnostic criteria, participants had to indicate that they experienced chronic fatigue for 6 or more months (code 4-6).

BOX 2
Question interference:
"To what extent did your tiredness hamper your normal activities (both work outside the home and household chores) in the past 6 months?"

Code	Label
1	not applicable, because I did not have any tiredness in the past 6 months
2	not at all
3	a little bit
4	quite a bit
5	a lot
6	very much

To meet the CDC diagnostic criteria, participants had to indicate that the fatigue significantly interfered with daily activities and work quite a bit, a lot or very much the past 6 months (code 4-6).

BOX 3
Question additional symptoms (items from the CDC CFS Symptom Inventory):
"How often did you have the complaints listed below in the past 6 months?
- *Sore throat;*
- *Tender lymph nodes;*
- *Muscle pain;*
- *Joint pain;*
- *Headaches;*
- *Unrefreshing sleep;*
- *Unusual fatigue after exertion;*
- *Forgetfulness or memory problems;*
- *Difficulty with thinking or concentrating."*

Code	Label
1	not at all
2	several times a month
3	several times a week
4	every day

To meet the CDC diagnostic criteria, participants had to indicate that they had concurrently four or more of the mentioned complaints several times a week or every day in the past 6 months (code 3 or 4), where forgetfulness and/or difficulty concentrating were scored as one symptom.

Fibromyalgia syndrome

The diagnosis for FMS was assessed using the 2010 American College of Rheumatology (ACR) criteria (2). To meet the ACR criteria participants had to indicate that they experienced pain symptoms for at least 3 months (box 4). Participants were asked to indicate in which of 19 mentioned body areas they had had pain during the last week using the widespread pain index (WPI, box 5). The Symptom Severity (SS) scale was calculated based on the severity of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms participants reported (box 6). The severity of fatigue and cognitive symptoms were determined using items of the Checklist Individual Strength (CIS) (3). An additional item that determined to which extent participants are waking unrefreshed was added. To determine the level of somatic symptoms, the 12-item somatization scale of the Symptom Checklist-90 (SCL-90 SOM) was used (4). To meet the ACR diagnostic criteria, participants were required to have a WPI score ≥7 and an SS-scale score ≥5 or a WPI score of 3-6 and an SS-scale score of ≥9.

BOX 4

Question musculoskeletal pain complaints duration:
"I have had my musculoskeletal pain complaints for about:"

Code	Label
1	not applicable because I do not have musculoskeletal pain complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ... years and ... months

To meet the ACR diagnostic criteria, participants had to indicate that they experienced musculoskeletal pain complaints for 3 or more months (code 3-6).

BOX 5

Questions Widespread Pain Index:
"Please indicate whether the parts of the body listed below were painful and/or tender in the past 7 days:
- *Abdomen;*
- *Chest;*
- *Left hip;*
- *Left lower arm;*
- *Left lower leg;*
- *Left shoulder;*
- *Left side of jaw;*
- *Left upper arm;*
- *Left upper leg;*
- *Lower back;*
- *Neck;*
- *Right hip;*
- *Right lower arm;*
- *Right lower leg;*
- *Right shoulder;*
- *Right side of jaw;*
- *Right upper arm;*
- *Right upper leg;*
- *Upper back."*

Code	Label
1	yes
2	no

The WPI score was determined by counting the number of body areas in which the participant had pain during the last week.

BOX 6

Questions symptom severity scale:

"The last two weeks in general:

- *I feel tired;*
- *I have difficulty thinking;*
- *It takes an effort to concentrate;*
- *I do not wake up rested."*

Code	Label
1	yes, true
2	2
3	3
4	4
5	5
6	6
7	no, not true

This scale was converted into a 0-3 scale (0) "No problem" (score 7), (1) "Slight or mild problems" (score 4-6); (2) "Moderate to considerable problems" (score 2, 3); and (3) "Severe, pervasive, continuous problems" (score 1).

Questions somatic symptoms (SCL-90 SOM items):

"In the previous week, how much were you bothered by:

- *Headaches;*
- *Faintness or dizziness;*
- *Pains in heart or chest;*
- *Pains in lower back;*
- *Nausea or upset stomach;*
- *Soreness of your muscles;*
- *Trouble getting your breath;*
- *Hot or cold spells;*
- *Numbness or tingling in parts of your body;*
- *A lump in your throat;*
- *Feeling weak in parts of your body;*
- *Heavy feeling in your arms or legs."*

Code	Label
1	not at all
2	a little bit
3	moderately
4	quite a bit
5	extremely

The symptoms of 12 items of the SCL-90-SOM were summed, and converted into (0) "No problem" (0 symptoms), (1) "Slight or mild problems" (1-3 symptoms); (2) "Moderate to considerable problems" (4-5 symptoms); and (3) "Severe, pervasive, continuous problems" (>=6 symptoms).
The SS scale score was created by summing the 0–3 scores of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms into a 0–12 scale.

Irritable bowel syndrome

The diagnosis for IBS was assessed using the ROME III criteria (5). However, the criteria including occurrence of symptoms was adjusted in accordance to the ROME criteria (6), namely participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (instead of 3 days per month), with a symptom onset at least 6 months in the past to meet the research diagnosis. And for women, this abdominal pain or discomfort should not only occur during menstrual bleeding (box 7). Participants were asked if [1] this recurrent abdominal pain or discomfort was associated with improvement after defecation, [2] the onset was associated with change in stool frequency or [3] the onset was associated with change in (appearance) of stool (box 8). To meet the ROME III diagnostic criteria participants should have indicated that the recurrent abdominal pain or discomfort was sometimes to always accompanied by at least 2 of the 3 additional symptoms.

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Table S1. Connection weights of the estimated network structures of FSS diagnostic symptoms for (A) the general population and (B) patients with FSS.

A. General population

	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.08	-															
Mus	-0.01	0.26	-														
Joi	-0.01	0.32	0.15	-													
Hea	0.01	0	0.03	-0.03	-												
Lym	0.03	0.01	0.03	0.01	0.02	-											
Thr	-0.01	-0.03	0.08	-0.02	0.15	0.43	-										
mFMS	0.17	0.05	0	0.35	0.01	-0.01	-0.01	-									
WPI	0	0.04	0.16	0.12	0.05	0.05	-0.01	0.26	-								
SOM	0.04	0.06	0.07	0.03	0.13	0.03	0.02	0.05	0.17	-							
Fat	0.33	0.04	0	-0.02	0.10	0.04	0.02	-0.04	0.02	0.07	-						
mIBS	0.07	0	0.08	-0.05	-0.02	0.14	0.03	-0.06	0.01	0.03	0	-					
Aim	0.01	0	0.01	0	0.07	0	0.03	0	0.01	0	0.03	0	-				
Afr	0	0	0	0	0	0	0	0	0.01	0	0	0.03	0.26	-			
Afo	0	0	0	0	0.01	0	0	0	0.02	0.02	0	0.13	0.32	0.73	-		
Cog	0.08	0.07	0	0	0.02	0.04	-0.01	-0.03	0	0.05	0.19	-0.02	0	0.01	0	-	
Unr	0.23	0.01	0.01	0	0.07	0	0.02	0	0	0.03	0.34	0.03	0	0	0.01	0.14	-

Table S1. Continued.

B. FSS patients

	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.14	-															
Mus	0.02	0.25	-														
Joi	0.02	0.32	0.26	-													
Hea	0	0.03	0	-0.01	-												
Lym	-0.01	0	0.05	0	0.03	-											
Thr	0	0	0	-0.03	0.14	0.43	-										
mFMS	0.10	0	0	0.23	0	-0.01	0	-									
WPI	-0.03	0.02	0.17	0.10	0	0.08	0.02	0.42	-								
SOM	0.02	0.10	0.07	0.02	0.15	0.07	0.03	0.09	0.15	-							
Fat	0.22	0.02	-0.01	-0.04	0.10	0.05	0.02	0.01	0	0.14	-						
mIBS	-0.02	-0.01	-0.03	-0.02	-0.04	-0.03	-0.01	-0.04	-0.19	-0.02	-0.09	-					
Aim	-0.01	0	0	-0.01	-0.01	-0.02	-0.02	0	0	-0.03	-0.03	0	-				
Afr	0	0	0	0	0.02	0.01	0.03	-0.02	0.05	0.02	0	0.23	0.26	-			
Afo	0	0	0	-0.01	0.03	0.05	0.02	-0.04	0.08	0.05	0.04	0.42	0.30	0.46	-		
Cog	0.07	0.07	0	0	0.08	0.04	0	0	-0.04	0.07	0.20	-0.06	0	0	0.03	-	
Unr	0.17	0.07	0.01	0.02	0.03	0	0.01	0	-0.01	0.02	0.37	-0.01	-0.03	0	0	0.10	-

mCFS = main symptom chronic fatigue syndrome; PEM=post-exertion malaise; Mus = muscle pain; Joi = joint pain; Hea = headaches; Lym = lymph node tenderness; Thr = sore throat; ACR = main symptom fibromyalgia syndrome; WPI = widespread pain index; SOM = general symptoms; Fat = fatigue; ROME = main symptom irritable bowel syndrome; Aim = improvement with defecation; Afr = associated with stool frequency; Afo = associated with stool form; Cog = cognitive problems; Unr = unrefreshed sleep.

Table S2. Associations of symptoms within FSS diagnoses in the general population and patients with FSS. Symptoms are ordered based on the strength of their connections.

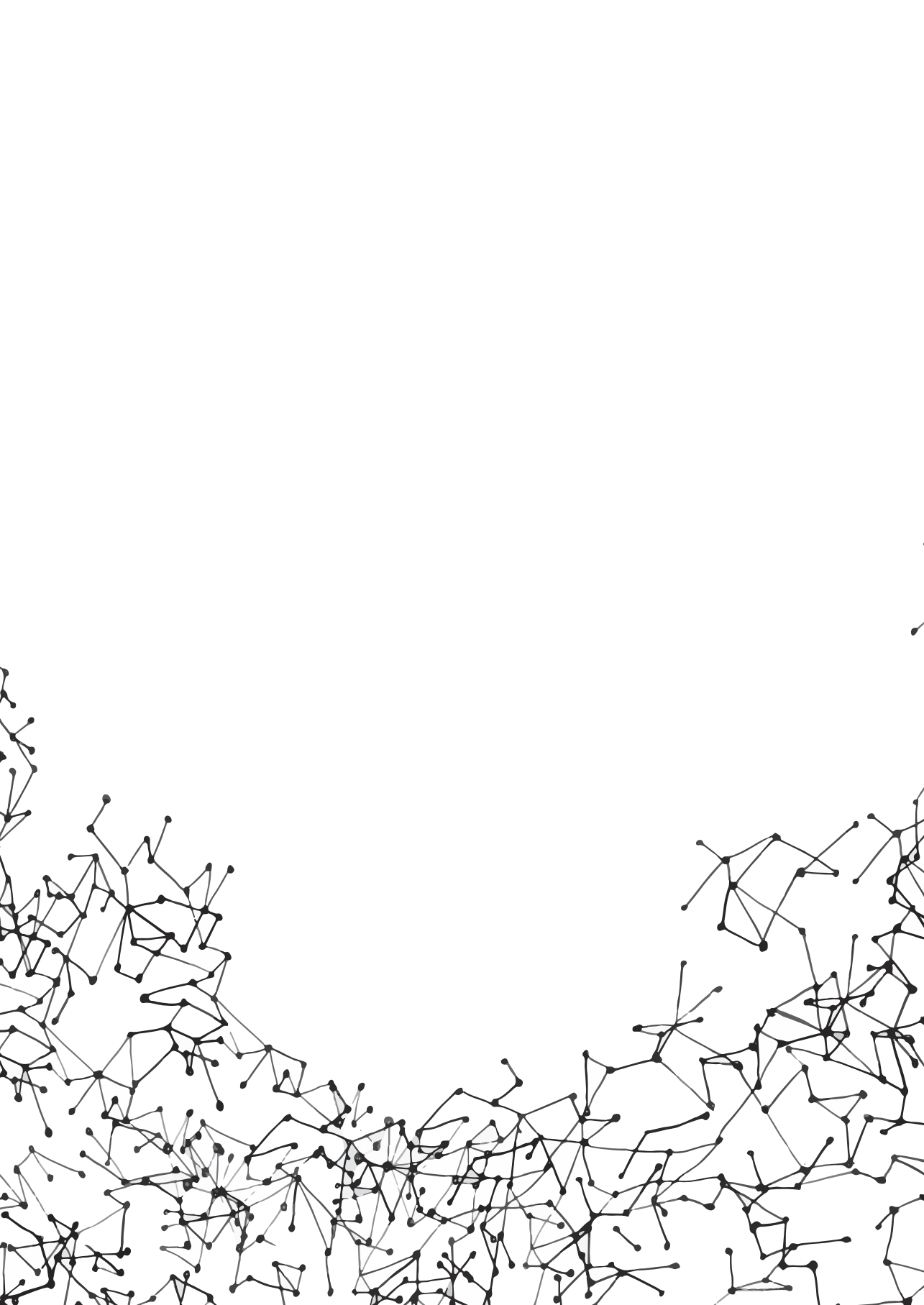
CFS				**FMS**				**IBS**			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
PEM	0.73	=	0.87	Fat	0.57	=	0.71	Afo	1.18	=	1.18
Thr	0.62	↑Mus	0.58	Unr	0.51	↑mFMS	0.52	Afr	0.95	=	0.95
Lym	0.58	↑Joi	0.57	WPI	0.45	=	0.52	Aim	0.65	↑mIBS	0.65
Mus	0.54	↓Thr	0.55	SOM	0.37	↓Unr	0.49	mIBS	0.56	↓Aim	0.56
Unr	0.49	↓Lym	0.54	Cog	0.36	↓SOM	0.46				
Joi	0.43	↓Unr	0.41	mFMS	0.24	↓Cog	0.34				
mCFS	0.4	=	0.4								
Cog	0.34	=	0.35								
Hea	0.27	=	0.32								

CFS = chronic fatigue syndrome; PEM = post-exertional malaise; Mus = musculoskeletal pain; Joi = joint pain; Thr = sore throat; Lym = tender lymph nodes; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Cog = cognitive symptoms; Hea = headaches; FMS = fibromyalgia syndrome; Fat = fatigue; mFMS = main criteria fibromyalgia syndrome; WPI = widespread pain index; SOM = symptoms in general; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; mIBS = main criteria irritable bowel syndrome; Aim: improvement of abdominal pain after defecation.

Table S3. Associations of symptoms between FSS diagnoses in the general population and patients with FSS. Symptoms are ordered based on the strength of their connections.

CFS				**FMS**				**IBS**			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
mCFS	0.92	=	0.52	Fat	1.07	=	0.84	mIBS	0.23	↑Afo	0.26
Unr	0.55	=	0.45	SOM	0.52	=	0.59	Aim	0.12	↑Afr	0.12
Hea	0.43	=	0.36	mFMS	0.47	↑Unr	0.38	Afo	0.02	↓Aim	-0.15
Joi	0.42	↑Cog	0.31	WPI	0.46	↑Cog	0.33	Afr	0	↓mIBS	-0.57
Cog	0.35	↓Joi	0.29	Unr	0.38	↓WPI	0.25				
Mus	0.33	↑PEM	0.26	Cog	0.33	↓mFMS	0.21				
Lym	0.31	=	0.25								
PEM	0.28	↓Mus	0.22								
Thr	0.1	=	0.1								

CFS = chronic fatigue syndrome; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Hea = headaches; Cog = cognitive symptoms; Joi = joint pain; PEM = post-exertional malaise; Lym = tender lymph nodes; Mus = musculoskeletal pain; Thr = sore throat; FMS = fibromyalgia syndrome; Fat = fatigue; SOM = symptoms in general; WPI = widespread pain index; mFMS = main criteria fibromyalgia syndrome; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; Aim: improvement of abdominal pain after defecation; mIBS = main criteria irritable bowel syndrome.



5

Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses

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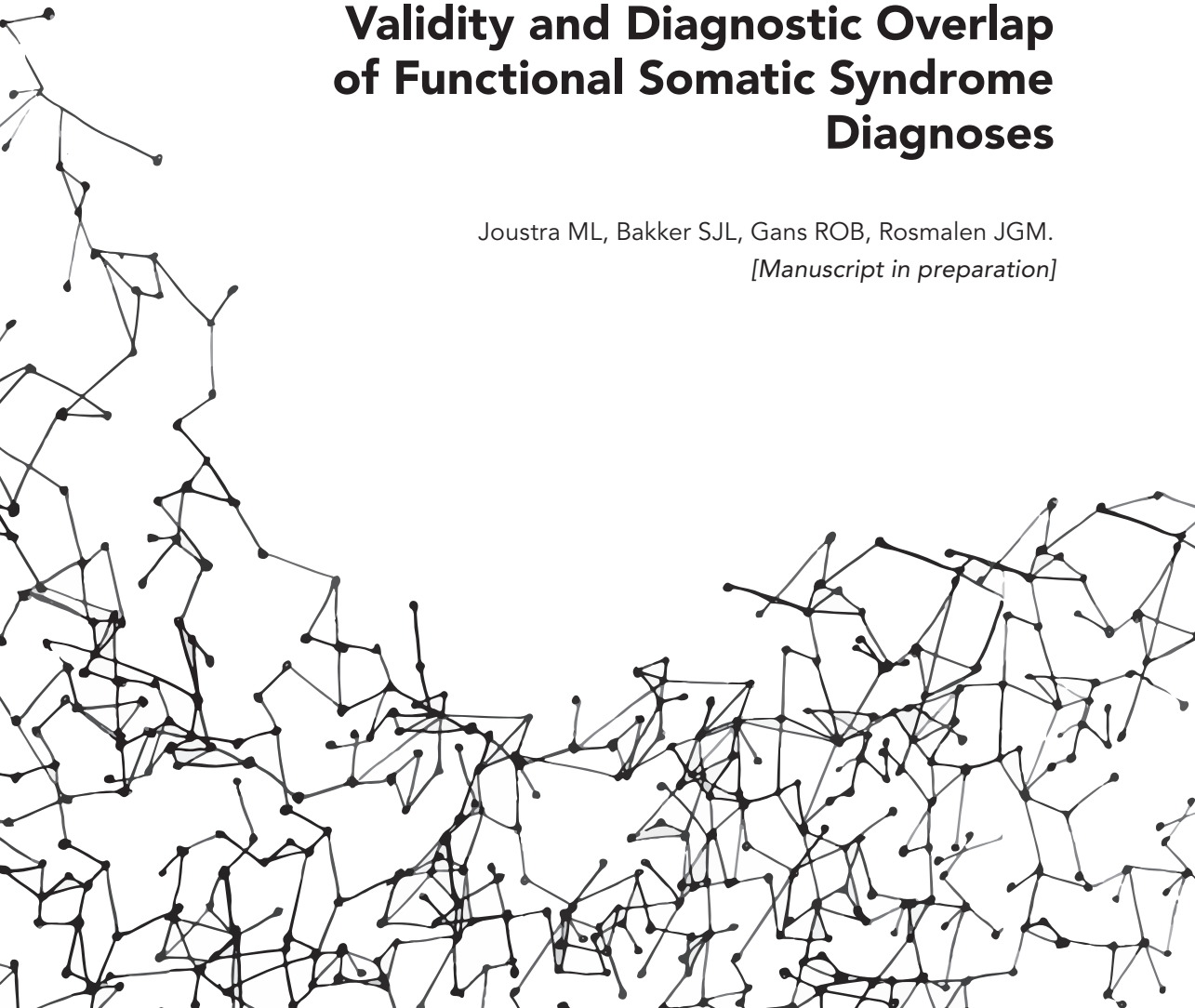
[Manuscript in preparation]



ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study.[16] LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North-East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language, were excluded. Parents and children were not excluded in case of the mentioned criteria, when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website.

All participants received written information on the purpose and methods of the study and written informed consent was obtained after the procedure was fully explained. All data are kept confidential and are only used for medical research. Approval by the Medical Ethical Committee of the University Medical Center Groningen was obtained for the study.

Data collection

The first participants were included at the end of 2006, and the recruitment period was closed after reaching the target number of participants in 2013. Participants who were included in the LifeLines study will be followed for at least 30 years. At baseline, participants visited one of the LifeLines research sites for a physical examination. Prior to these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires will be administered to all participants every 18 months, and they will be invited for a renewed physical examination at the LifeLines research site on average every five years. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and the CogState computerized cognitive battery and the digital neuropsychiatric questionnaire were conducted respectively. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. Data of the second assessment was used in the current study, since the diagnostic algorithms for FSS were included in the second assessment.

Diagnostic criteria

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

Medical and psychiatric health conditions

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

Statistical analyses

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

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

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

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

RESULTS

Prevalence rates and demographic characteristics

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

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

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

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

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

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

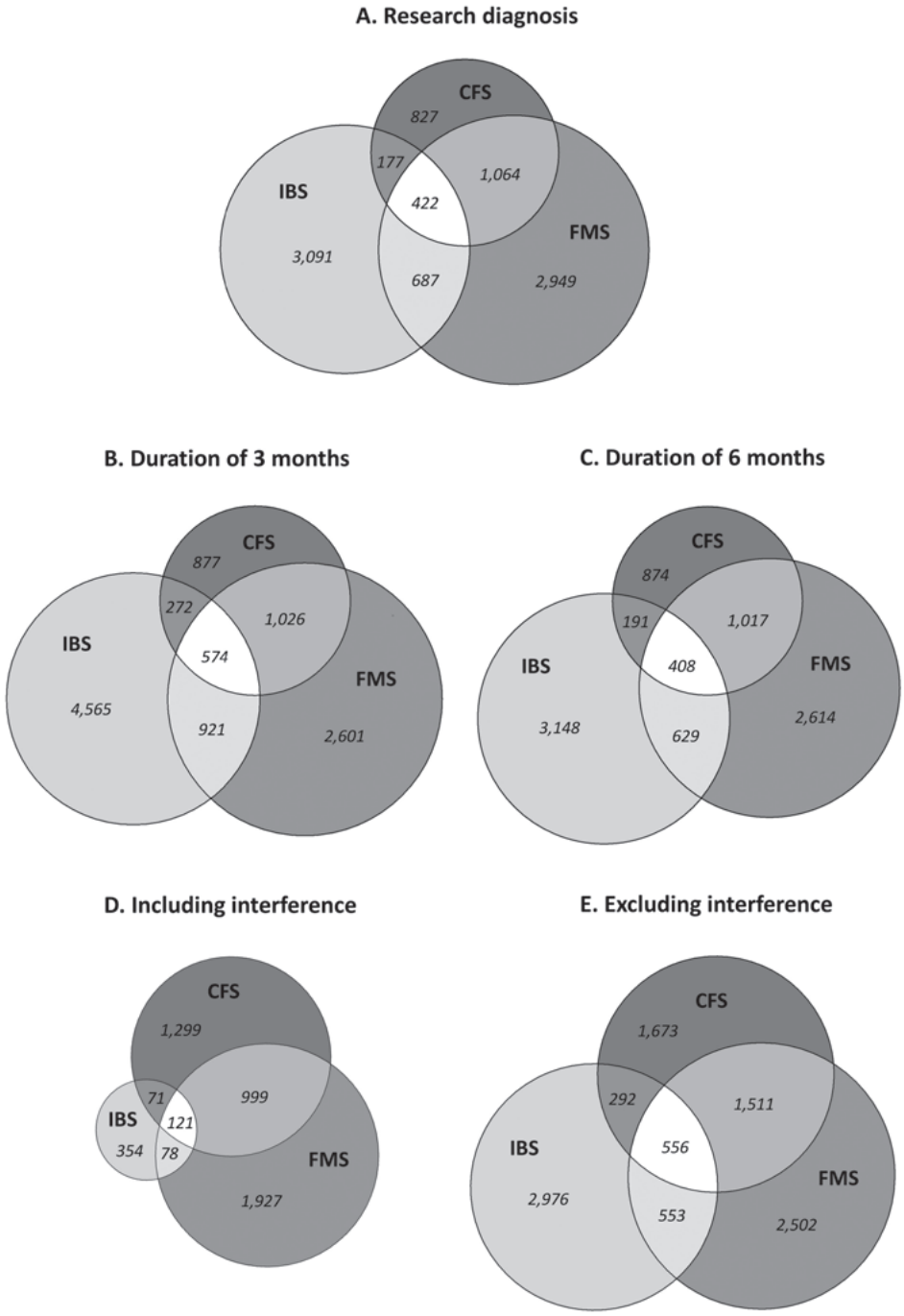


Figure 1. Diagnostic overlap presented in proportional Euler-diagrams.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

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

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

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

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

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

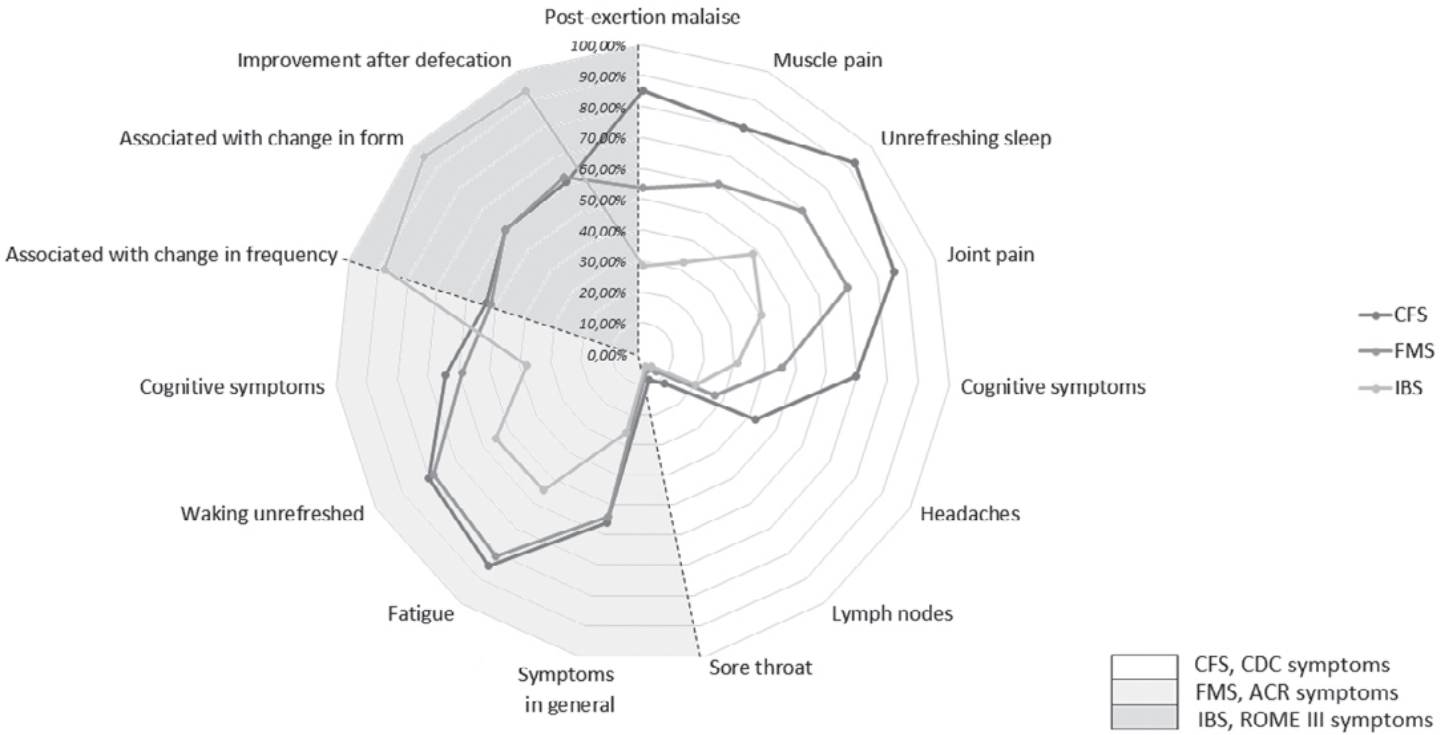


Figure 2. Percentage and distribution of symptoms mentioned in the diagnostic criteria, that participants who meet the official diagnostic criteria report.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

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

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

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

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

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

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

Table 5. Continued.

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

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

DISCUSSION

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

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

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

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

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

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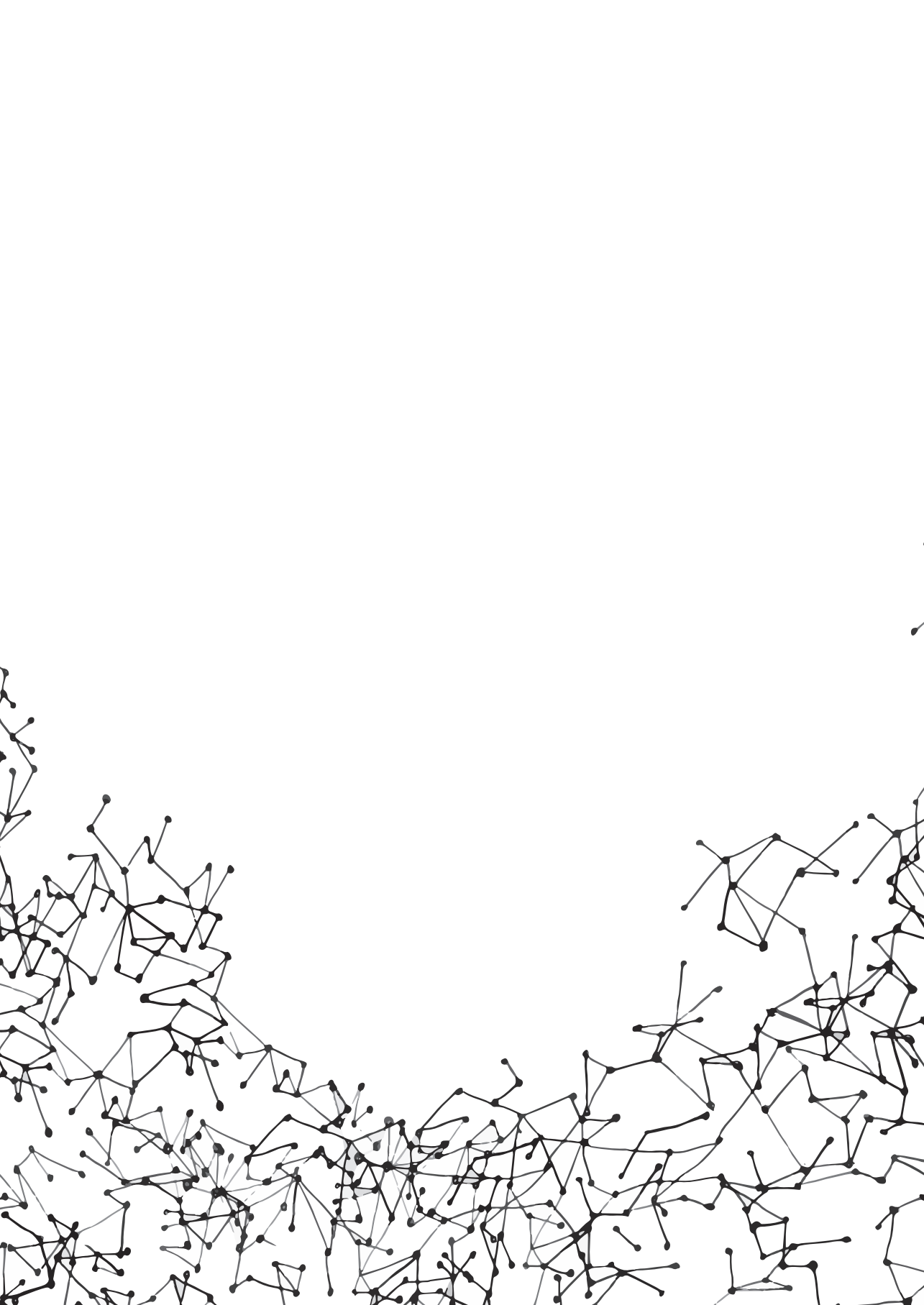
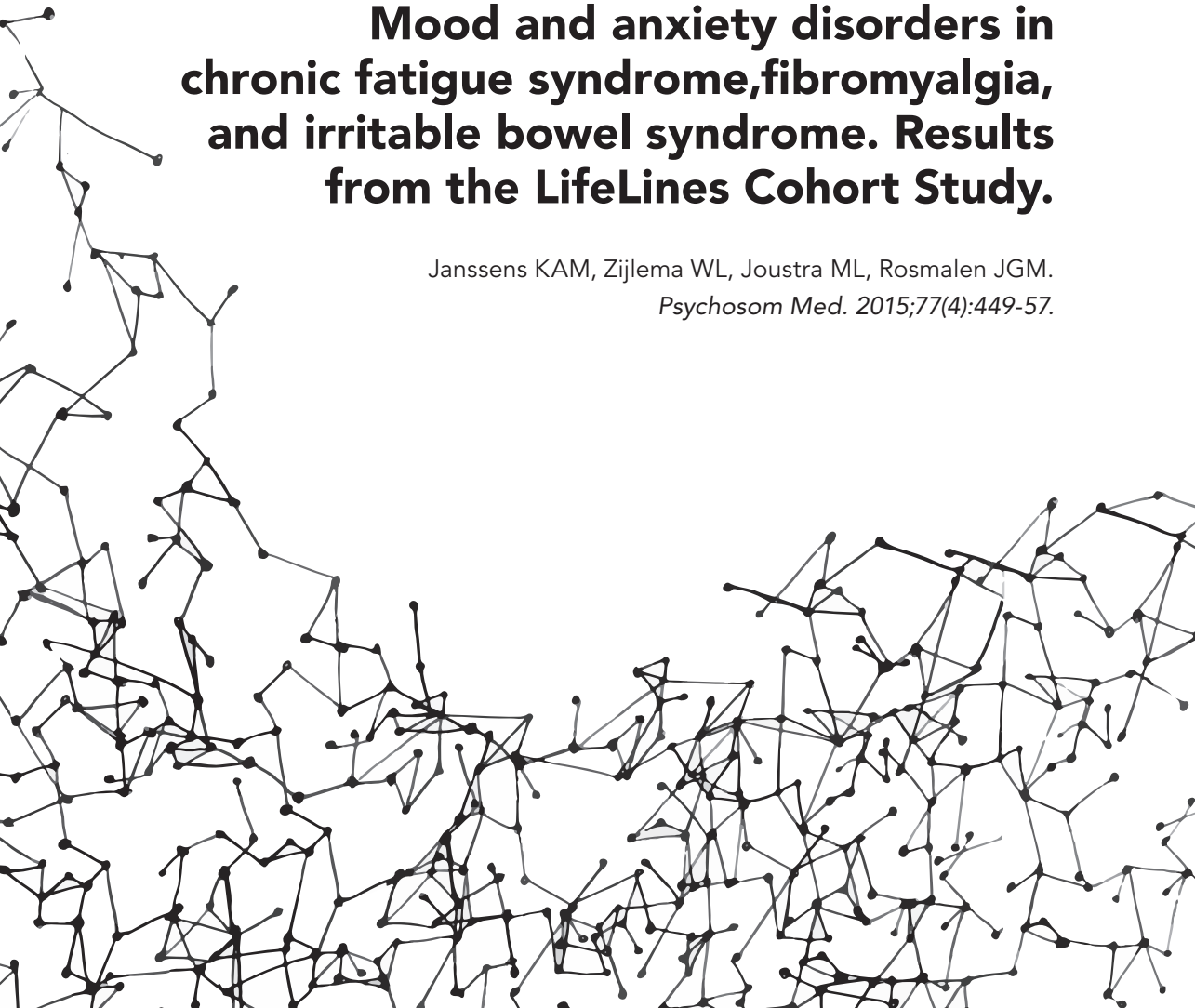


6

Mood and anxiety disorders in chronic fatigue syndrome,fibromyalgia, and irritable bowel syndrome. Results from the LifeLines Cohort Study.

Janssens KAM, Zijlema WL, Joustra ML, Rosmalen JGM.

Psychosom Med. 2015;77(4):449-57.



ABSTRACT

Objective: Functional somatic syndromes (FSS) have often been linked to psychopathology. The aim of the current study was to compare prevalence rates of psychiatric disorders between individuals with chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS).

Methods: This study was performed in 94,516 participants (mean age: 44.6 years, SD 12.5, 58.7 % female) of the general-population cohort LifeLines. FSS were assessed by self-reports. Mood disorders (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. generalized anxiety disorder, social phobia, panic disorder with/without agoraphobia, and agoraphobia) were assessed by means of the Mini International Neuropsychiatric Interview. Risks on psychiatric disorders were compared for individuals suffering from CFS, FMS, and IBS using logistic regression analyses adjusted for age and sex.

Results: Prevalence rates of CFS, FMS, and IBS were 1.3%, 4.0%, 9.7%, respectively. Individuals with CFS, FMS and IBS had significantly more mood (ORs 1.72 to 5.42) and anxiety disorders (ORs 1.52 to 3.96) than individuals without FSS, but prevalence rates were low (1.6 to 28.6%). Individuals with CFS had more often mood (ORs 2.00 to 4.08) and anxiety disorders (ORs 1.63 to 2.32) than individuals with FMS and IBS. Major depressive disorder was more common in FMS than IBS (OR 1.58, 95%CI=1.24-2.01) whereas these groups did not differ on dysthymia or anxiety disorders.

Conclusions: Mood and anxiety disorders are more prevalent in individuals suffering from FSS, and particularly CFS, than in individuals without FSS. However, most individuals with FSS do not suffer from mood or anxiety disorders.

INTRODUCTION

Somatic symptoms that cannot be sufficiently explained by underlying organic pathology are called functional somatic symptoms. Functional somatic symptoms tend to occur together and result in functional somatic syndromes (FSS). FSS are common, disabling and costly (1-4). Many FSS exist, and every medical specialty seems to have at least one. Chronic fatigue syndrome (CFS) is diagnosed by internists for patients suffering from unexplained fatigue; irritable bowel syndrome (IBS) is diagnosed by gastroenterologists for patients with unexplained bowel complaints; and fibromyalgia syndrome (FMS) is diagnosed by rheumatologists for patients having unexplained muscle pains.

Since several decades researchers have discussed co-morbidity of different FSS and wondered whether different FSS could result from the same underlying physiopathology (5, 6).Over 10 years ago, a landmark paper was published suggesting that the existence of different FSS is an artefact of medical specialization, and that in fact all patients with FSS (e.g. CFS, FMS, and IBS patients), suffer from the same syndrome (7). That paper has further fueled the lumper-splitter discussion that has been going on until today. "Lumpers" take the approach that all FSS result from the same etiology and thus can be studied together (7-9). "Splitters" believe that every particular FSS has its own specific background and should therefore be studied separately (10). More recent studies suggested a combination of both approaches (11-14). One argument in favor of the lumpers is that all FSS are associated with psychiatric symptoms and disorders, especially anxiety and depression.

FSS have indeed frequently been linked to psychopathology (12, 14, 15). However, these studies often relied on self-reports of anxiety and depression symptoms instead of diagnostic interviews. Therefore, information about prevalence rates of specific psychiatric disorders in FSS patients is scarce, while this information about psychiatric diagnoses is important since it might shed light on specific pathways underlying different FSS. Moreover, comparisons of psychiatric co-morbidity in different FSS within one study population are rare (16, 17), making it hard to examine whether psychiatric diagnoses are evenly prevalent in all FSS. A meta-analytic review comparing patients with FSS from different studies showed only minor differences in psychiatric co-morbidity between patients:

CFS patients were characterized by higher depression scores than IBS patients and FMS patients by lower anxiety scores than IBS patients (18). Persons with multiple FSS were not included in these studies, which hampered studying the influence of syndrome overlap. Moreover, most studies in this review concerned patients referred to tertiary care centers; these patients are more likely to resemble each other than patients that do not seek (specific) medical care. For example, help seeking behavior of FSS patients is related to higher levels of anxiety and depression (18, 19). Hence, differences in psychiatric co-morbidity between FSS might have been underestimated. Therefore, studies examining FSS patients in one population cohort are necessary.

The aim of the current study was to compare prevalence of mood and anxiety disorders in CFS, FMS and IBS patients based on diagnostic interviews in a large population-based cohort of over 90,000 adults.

METHODS

The sample

This study is based on data of LifeLines. LifeLines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the 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 (20).

Participants

Participants of LifeLines were obtained 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 probands 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. The general practitioners evaluated whether probands met the following exclusion criteria: severe psychiatric or physical illness; not being able to visit the general practitioner; not being able to fill in the questionnaires; not

being able to understand the Dutch language. Parents and children of probands were not excluded based on those criteria if a representative was willing to assist these participants in the fulfillment of the study. Inclusion of pregnant women was rescheduled until 6 months after pregnancy or 3 months after breast feeding. Second, persons who were interested to participate could register themselves via the LifeLines website. Data were collected between 8 November 2006 and 31 December 2012.

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 were 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. For this study, data of 94,516 participants were available, with an age range between 18 and 93 years, and a mean age of 44.6 (SD 12.5). The majority (58.7%) was female. More details about the sample can be found in Table 1.

Measures

Functional somatic syndromes

History of FSS was assessed by means of a questionnaire, which participants were asked to fill out at their homes. Within this questionnaire, a list of chronic disorders was presented, including CFS, FMS, and IBS. The participants were asked to indicate whether they ever suffered from each of these FSS. Although we thus asked for history of FSS within the LifeLines population, a previous study using a more extensive question in a general population cohort of 976 participants (21) suggests that a vast majority (i.e. 75-100%, depending on the syndrome) of persons indicating a history of CFS, FMS or IBS report to still being suffering from these syndromes. CFS patients also reporting multiple sclerosis (n = 6), FMS patients also reporting rheumatoid arthritis (n = 196) and IBS patients also reporting Crohn's disease or ulcerative colitis (n = 103) were excluded from our analyses, to exclude the possibility that the symptoms were caused by these underlying inflammatory diseases.

Co-morbid psychiatric disorders

Current major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and generalized

anxiety disorder were assessed with a standardized diagnostic interview: the Mini International Neuropsychiatric

Table 1. General description of the LifeLines cohort (n=94,516).

	Valid N	Mean (SD) or %
Age	94516	44.6 (12.5)
Sex (Male)	39007	41.3
Race (both parents born in the Netherlands)	88930	94.1
Education	28508	30.3
Low	36574	38.9
Middle	27187	28.9
High	1801	1.9
Other		
Netto income/month	3185	3.5
Lower than 750	2724	3.0
750-1000	7488	8.1
1000-1500	11531	12.5
1500-2000	12446	13.5
2000-2500	13524	14.7
2500-3000	11296	12.3
3000-3500	13950	15.2
Over 3500	15972	17.3
Unknown		
Marital status	61160	64.8
Married/Registered relationship		
Cohabiting	14906	15.8
Single	8689	9.2
Widow	1693	1.8
Divorced	3186	3.4
Partner, but non-cohabiting	3732	4.0
Other	989	1.0
Major medical conditions		
Arteriosclerosis (lifetime)	430	0.5
Cancer (lifetime)	4164	4.4
Diabetes (lifetime)	2238	2.4
Hypertension (lifetime)	19933	21.5
Stroke (lifetime)	688	0.7
Heart failure (lifetime)	668	0.7
Heart infarct (lifetime)	946	1.0
COPD	4919	5.2
Asthma	8018	8.5
Medication use (prescribed by doctor)	43081	46.9

Interview (MINI) 5.0.0. The MINI is a brief structured interview for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10 (22). LifeLines participants were interviewed by trained medical professionals during their visit to the research facilities. Sections on depressive disorder, dysthymia, panic disorders, agoraphobia, social phobia, and general anxiety disorder were administered. The DSM-IV criteria were used to determine whether participants suffered from these disorders. Previous studies suggested acceptable validity and reliability of the MINI (22). Valid interview data were available for 97.5% of the participants (n = 92164).

Statistical analyses

Descriptive statistics were performed to compare prevalence rates and sex ratios between individuals with CFS, IBS, or FMS. Additionally, syndrome overlap was studied and proportions of participants suffering from CFS, IBS or FMS were plotted per age category for males and females. To examine whether individuals with FSS had higher risk on psychiatric disorders than individuals without FSS, binary logistic regression analyses were performed with separate FSS as predictors and the psychiatric disorders as outcome variables. FSS were included simultaneously to adjust for co-morbidity between syndromes. Binary logistic regression analyses were also used to test for differences in psychiatric co-morbidity *between* individuals with CFS, IBS, or FMS. Analyses were performed in the subgroup of participants that suffered from one of these disorders, with type of FSS included as a predictor. When the main effect of type of FSS was significant, different contrasts were used to test which specific FSS differed from each other. All analyses were adjusted for age and sex, since they are known to be related to both FSS (7, 23, 24) and psychiatric disorders (25, 26). All analyses were performed using SPSS version 20. Results were considered statistically significant if the 95%-confidence interval (CI) did not include 1.

RESULTS

Prevalence rates and co-morbidity

After exclusion of participants that reported both a FSS and a medical condition resembling the core symptoms of their FSS, data on FSS were available for 91,153 participants. Of these participants, 1.3 % reported CFS (n = 1,166), 3.0 % (n =

2,765) reported FMS, and 9.7 % (n = 8,858) reported IBS. Exact prevalence rates of comorbidity can be found in Figure 1. The majority (n= 10,121, 79.1 %) of the persons that reported suffering from CFS, FMS, or IBS (n=12,789) did not report a co-morbid FSS. However, this was especially true for persons suffering from IBS. About 40 % of the participants suffering from CFS or FMS reported one or two other FSS. Binary logistic regression analyses also showed higher risk on additional FSS in presence of one FSS: OR 8.57 (95%-CI 7.39-9.96) of CFS when having FMS and vice versa, OR 3.72 (95%-CI 3.27-4.23) of CFS when having IBS and vice versa, and OR 5.18 (95%-CI 4.77-5.62) of FMS when having IBS and vice versa. Moreover, the number of persons that reported all three disorders (n=106) was 37.7 times higher than could be expected based on prevalence rates of the separate syndromes.

Demographic characteristics

All disorders were much more common in females than in males. The sex difference was smallest in participants with CFS of whom 30.9 % was male, and largest in participants with FMS of whom 8.0 % was male. Furthermore, 19.0 % of participants with IBS were male. Prevalence rates of CFS, IBS, and FMS showed a small peak around the age of 60, most pronounced for FMS (Figure 2). Exception to this pattern was that IBS prevalence decreased in females after their mid-twenties.

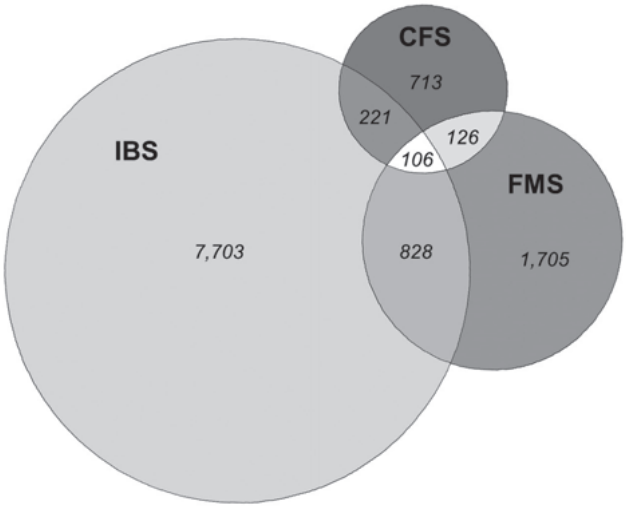


Figure 1. Overlap between chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. Depicted are the numbers of patients.
CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

Co-morbid mood and anxiety disorders

Results with regard to psychiatric co-morbidity showed that persons with FSS had higher prevalence rates of any of the mood or anxiety disorders than persons without FSS (Table 2). Moreover, when participants had multiple FSS, their risks of having a co-morbid psychiatric disorder were higher than when they had only one FSS. However, it should be stressed that the majority of persons suffering from FSS did not fulfill the criteria of an anxiety or mood disorder.

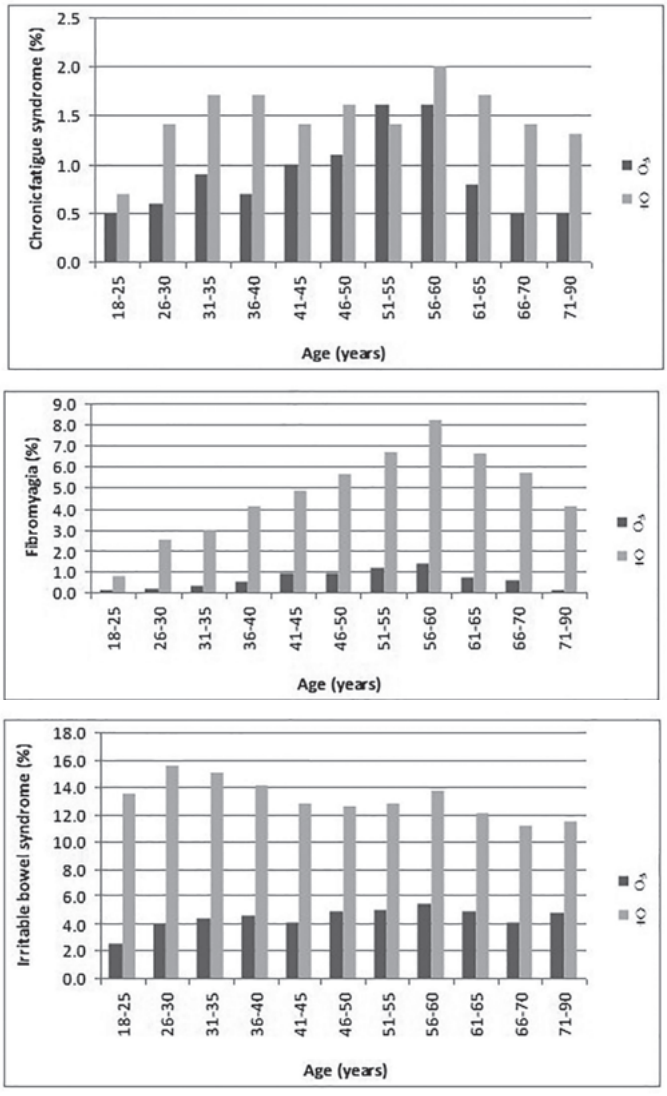


Figure 2. Prevalence rates of chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome for males and females in different age categories.

Table 2. Prevalence of psychiatric disorders in patients suffering from chronic fatigue syndrome, fibromyalgia, and/or irritable bowel syndrome.

		Major depressive disorder	Core symptoms depression	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder	Any mood disorder	Any anxiety disorder
No FSS	N	1412	1219	670	2810	599	487	1532	2231	2082	6726
	%	1.8	1.6[a]	0.9	3.6	0.8	0.6	2.0	3.0	2.7	8.4
Only CFS	N	74	59	39	86	25	13	32	61	113	171
	%	10.7	8.6[a]	6.5	12.5	3.6	1.9	4.6	8.9	17.2	24.0
Only FM	N	100	87	36	130	29	32	65	109	136	307
	%	5.9	5.2[a]	2.3	7.7	1.7	1.9	3.9	6.5	8.2	18.0
Only IBS	N	295	245	127	592	123	129	330	415	710	1305
	%	3.9	3.3[a]	1.8	7.9	1.6	1.7	4.4	5.5	5.7	16.9
2 FSS	N	124	79	46	177	37	36	75	61	170	327
	%	10.7	6.8[a]	4.5	15.3	3.2	3.1	6.5	8.9	15.4	27.8
3 FSS	N	20	14	7	30	5	6	6	15	27	43
	%	19.0	13.3[a]	8.3	28.6	4.8	5.7	5.7	14.3	29.1	40.6

FSS = functional somatic syndrome, CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; [a] When depressive disorder is defined as the two core symptoms of depression (i.e. depressed mood and anhedonia) being present.

Since the diagnostic criteria for MDD overlap with FSS, the MDD prevalence in FSS patients might have become artificially high. To control for this overlap, we examined prevalence rates of depression when defining depression as the two core symptoms of MDD (i.e. depressed mood and anhedonia, which are both cognitive) being present. Prevalence rates were indeed lower when taking this approach, particularly in participants with CFS in whom the prevalence rate was now 2.1 % lower than when the original diagnostic criteria were used (Table 2).

Logistic regression analyses showed that participants with CFS, FMS, and IBS had higher levels of mood (ORs 1.72 to 5.42) and anxiety disorders (ORs 1.52 to 3.96) than persons without FSS. Comparisons of individuals with CFS, FMS or IBS showed that participants with CFS patients had higher levels of mood (ORs 2.00 to 4.08) and anxiety disorders (ORs 1.63 to 2.32) than participants with FMS or IBS, except for panic disorders (Table 3). Individuals with FMS had higher levels of MDD (OR 1.58), but not dysthymia or anxiety disorders than individuals with IBS (Table 3).

Patients showing complaints in the past week(s)

Since lifetime diagnoses of FSS were assessed, the question remained whether patients were still suffering from the reported syndrome. Analyses were therefore repeated after exclusion of individuals with CFS who did not report fatigue in the past four weeks (n = 44), individuals with FMS that did not report muscle pain in the past week (n =148), and individuals with IBS that did not report nausea in the past week (n = 5,251). Due to the absence of assessment of gastrointestinal symptoms other than nausea, it was not possible to base this selection on bowel complaints. Fatigue was assessed using one item from the RAND-36 (27), and muscle pain and nausea were assessed by two items from the somatization scale of the Symptom Checklist-90 (28). Results are shown in Table 4. In this sample, participants with CFS did not have more anxiety disorders than participants with IBS anymore, and participants with FMS did not have more MDD than IBS patients. Results regarding the comparison between individuals with CFS and individuals with FMS in mood or anxiety disorders remained essentially the same.

Table 3. Odds ratios and 95%-CIs of psychiatric disorders in patients suffering from chronic fatigue syndrome (n= 689), fibromyalgia (n = 1683), and irritable bowel syndrome (n = 7505).

	Major depressive disorder	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder
Only CFS vs controls	**5.06 (4.20-6.10)**	**5.42 (4.12-7.12)**	**3.53 (2.99-4.17)**	**3.96 (2.92-5.39)**	**2.68 (1.86-3.85)**	**1.83 (1.40-2.40)**	**2.45 (2.00-3.01)**
Only FMS vs controls	**2.42 (2.05-2.84)**	**1.98 (1.53-2.56)**	**1.94 (1.70-2.22)**	**1.83 (1.37-2.43)**	**2.03 (1.54-2.67)**	**1.59 (1.32-1.93)**	**1.52 (1.30-1.77)**
Only IBS vs controls	**1.87 (1.67-2.10)**	**1.72 (1.44-2.04)**	**2.00 (1.84-2.18)**	**1.85 (1.54-2.22)**	**2.19 (1.82-2.63)**	**1.94 (1.72-2.17)**	**1.67 (1.51-1.85)**
CFS vs IBS	**3.16 (2.40-4.15)**	**4.08 (2.80-5.95)**	**1.77 (1.39-2.26)**	**2.32 (1.49-3.62)**	n.a.	n.a.	**1.75 (1.31-2.32)**
CFS vs FMS	**2.00 (1.45-2.76)**	**2.90 (1.80-4.67)**	**1.69 (1.26-2.27)**	**2.04 (1.17-3.56)**	n.a.	n.a.	**1.63 (1.17-2.28)**
FMS vs IBS	**1.58 (1.24-2.01)**	1.41 (0.96-2.06)	1.05 (0.86-1.28)	1.14 (0.75-1.73)	n.a.	n.a.	1.07 (0.86-1.34)

Odss ratio (95%-CI); CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; adjusted for gender and age, n.a.= not applicable, since the main effect of "type of disorder" is not significant.

Table 4. Odds ratios and 95%-CIs of psychiatric disorders in patients suffering from chronic fatigue syndrome (n = 659), fibromyalgia (n = 1578), and irritable bowel syndrome (n = 2914) who did report the core symptoms in the past weeks.

	Major depressive disorder	Dysthymia	Generalized anxiety disorder	Social phobia	Panic disorder with agoraphobia	Panic disorder without agoraphobia	Agoraphobia without panic disorder
Only CFS vs controls	**4.86 (3.98-5.93)**	**4.98 (3.69-6.72)**	**3.45 (2.89-4.13)**	**4.11 (2.98-5.67)**	**2.43 (1.65-3.58)**	**1.93 (1.45-2.56)**	**2.35 (1.88-2.94)**
Only FMS vs controls	**2.41 (2.02-2.87)**	**2.00 (1.51-2.66)**	**2.00 (1.72-2.32)**	**1.76 (1.29-2.42)**	**2.10 (1.56-2.82)**	**1.57 (1.27-1.95)**	**1.51 (1.27-1.80)**
Only IBS vs controls	**1.41 (1.28-1.57)**	**2.54 (2.05-3.16)**	**2.96 (2.66-3.30)**	**2.56 (2.04-3.22)**	**3.60 (2.90-4.47)**	**2.58 (2.23-3.00)**	**2.19 (1.91-2.51)**
CFS vs IBS	**1.72 (1.29-2.30)**	**2.54 (1.68-3.83)**	1.18 (0.91-1.53)	1.60 (0.99-2.57)	n.a.	n.a.	1.26 (0.93-1.72)
CFS vs FMS	**1.94 (1.40-2.71)**	**2.81 (1.72-4.59)**	**1.70 (1.26-2.29)**	**2.10 (1.19-3.68)**	n.a.	n.a.	**1.57 (1.11-2.22)**
FMS vs IBS	0.88 (0.68-1.14)	0.90 (0.59-1.38)	0.69 (0.56-0.87)	0.76 (0.49-1.19)	n.a.	n.a.	0.80 (0.63-1.03)

Odds ratio (95%-CI); CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, IBS = irritable bowel syndrome; adjusted for gender and age, n.a.= not applicable, since the main effect of "type of disorder" is not significant.

DISCUSSION

Co-morbidity of CFS, FMS, and IBS in our population based-cohort study was much higher than could be expected based on the prevalence rates of 1.3 %, 3.0 % and 9.7 %, respectively. Participants that suffered from one or more of these FSS showed higher rates of mood and anxiety disorders than participants without FSS, but the majority of participants with FSS did not show a mood or anxiety disorder. Participants with CFS had higher rates of mood (MDD and dysthymia) and anxiety disorders (generalized anxiety disorder, social phobia and agoraphobia without panic disorders; but not panic disorders) than participants with IBS or FMS. Participants with FMS and participants with IBS did only differ in amount of MDD which was more prevalent in participants with FMS.

The main strength of this study is that diagnoses of psychiatric disorders were based on psychiatric interviews that in general give better estimates of psychiatric diagnoses than self-reports. Another strength is the large sample size, which enabled us to study relatively large groups of participants with FSS, hence increasing the robustness of our findings. Additionally, information about the three main FSS was available which enabled comparing these three FSS in one cohort. Comparing patients included in different cohorts is difficult, since these patients are not comparable due to different selection procedures and different measurements for psychopathology.

One limitation of this study is that diagnoses for FSS were based on self-report. An American study showed that self-reports often underestimate the amount of persons that suffer from FSS (29). This seems not likely in our study, since the prevalence rates for CFS, FMS, and IBS were comparable to previous studies (30-33), among which studies using diagnoses based on physical examination. Also demographic characteristics, like prevalence rates being highest in females and around midlife, were in line with previous studies (23, 24). Nevertheless, our choice to assess FSS using self-report was based on practical limitations associated with a cohort study of this size which aims to study a wide spectrum of mental and somatic disorders. We aim to assess FSS more extensively in future assessment waves. Another limitation is that lifetime diagnoses of FSS were available instead of current diagnoses, which might have given an overestimation of persons who are currently suffering from FSS. However, as mentioned, data of another cohort

study in the same geographical area showed that persons who reported to have experienced CFS, FMS, or IBS usually report still being suffering from the syndrome. So the overestimation of participants currently suffering from FSS is likely to be minor. Moreover, the majority (>95%) of participants reporting CFS experienced fatigue, and the majority (>93%) of participants reporting FMS experienced musculoskeletal pain in the past week(s). Thirty-nine per cent of the participants with IBS patients reported nausea. Unfortunately, no information about gastrointestinal complaints other than nausea was available for the entire sample. Further, the prevalence rates of FSS per age category also indicate that diagnoses represent current rather than lifetime diagnoses of FSS, given the absence of a linear increase during ageing. Nevertheless, as a sensitivity analysis, analyses were repeated after exclusion of patients who did not report the core symptoms in the past week(s). After exclusion of these patients, participants with CFS did not have more anxiety disorders than participants with IBS anymore, and participants with FMS did not have MDD more frequent than participants with IBS. It should be noted that IBS patients in this subsample might not be representative of average IBS patients, since only patients who reported nausea in the past week were included. Results regarding the comparison between participants with CFS and FMS in frequency of mood or anxiety disorders remained essentially the same. Finally, it is good to note that although self-reported lifetime diagnoses of FSS might have complicated the adequate characterizing of participants with FSS, the main aim of this paper was to compare psychiatric co-morbidity of the three FSS. Obtaining diagnoses for all FSS in the same way (i.e. by self-report) probably enhanced the comparability of syndromes.

To the best of our knowledge, only one previous study compared participants with chronic fatigue, widespread pain and IBS within one general-population cohort on scores of anxiety and depression (17). This previous study of 2,290 subjects did not show significant differences in anxiety and depression scores between participants with different FSS. These results might have been due to insufficient power in that study. It should be stressed that differences between FSS in frequency of mood or anxiety disorders in the current study were only small. Moreover, the previous study examined prevalence of symptoms of anxiety and depression instead of specific mood and anxiety disorders. In line with our study, (small) differences in anxiety and depression scores between CFS, FMS, and IBS patients were found in a meta-analytic review (18). This meta-analytic

review showed that CFS patients had higher depression scores than patients suffering from FMS or IBS. In contrast to that study, we found participants with FMS to have higher MDD rates than participants with IBS, while the meta-analysis found FMS patients to show lower anxiety scores than IBS patients. These differences might be due to different study characteristics or to the fact that we studied specific mood and anxiety disorders, whereas the meta-analytic review examined general mood and anxiety symptoms. An explanation for individuals with CFS reporting the highest levels of psychiatric co-morbidity might be that symptoms of psychiatric disorders, especially depressive disorder, overlap with CFS symptoms. Prevalence rates of depressive disorder in participants with CFS were indeed lower when taking the two core depression symptoms into account. Therefore, symptom overlap should be taken into account in psychiatric examination of individuals with CFS.

Because of the cross-sectional nature of our study, 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. We previously found evidence for all three hypotheses in a longitudinal population-based study of adolescents, with most pronounced evidence for depression and anxiety being risk factors of FSS (34). What can be concluded from the current study is that FSS, mood and anxiety disorders only partially overlap, and that most individuals with FSS do not suffer from mood and anxiety disorders. This finding is in line with previous studies (18, 23). Therefore, these syndromes should not be simply considered somatic expressions of anxiety and depression.

With regard to differences between CFS, FMS, and IBS, our study supports both the lumper and the splitter approach. In line with the lumper approach and previous studies (17, 35), FSS co-occurred much more often than could be expected based on separate prevalence rates, which might imply a generic etiology. Moreover, psychiatric co-morbidity, in the form of mood and anxiety disorders, was characteristic of all three FSS. In keeping with the splitter approach, mood and anxiety disorders were more common in some than in other FSS, and sex differences were more pronounced in some syndromes than in others. This finding of both specific and general characteristics of FSS is in line with factor analyses in recent population-based studies and in a twin cohort (11-13).Upcoming studies

from the LifeLines cohort will further investigate the lumper-splitter discussion, by investigating syndrome-specificity of different biological, psychological and social factors. With regard to biological factors, several potential biomarkers could be examined in the plasma, serum and urine stored for all LifeLines participants. In addition, hair and faeces have been collected providing the opportunity to study cortisol levels and alterations in microbial flora. Several other relevant data have been collected, including cardiovascular parameters (e.g. blood pressure recordings and electrocardiogram), pulmonary function as assessed by spirometry, anthropometry, muscular strength, and cognitive function as assessed by a computerised test battery. LifeLines also provides the opportunity to study lifestyle factors, including physical activity and diet.

In summary, this population-based study suggests that although individuals with CFS, FMS, and IBS suffer from mood and anxiety disorders more often than individuals without FSS, most of them do not have these psychiatric disorders. Individuals with CFS have higher rates of mood and anxiety disorders than individuals with FMS and IBS. Individuals with FMS have more MDD, but not dysthymia or anxiety disorders than individuals with IBS, but differences are small.

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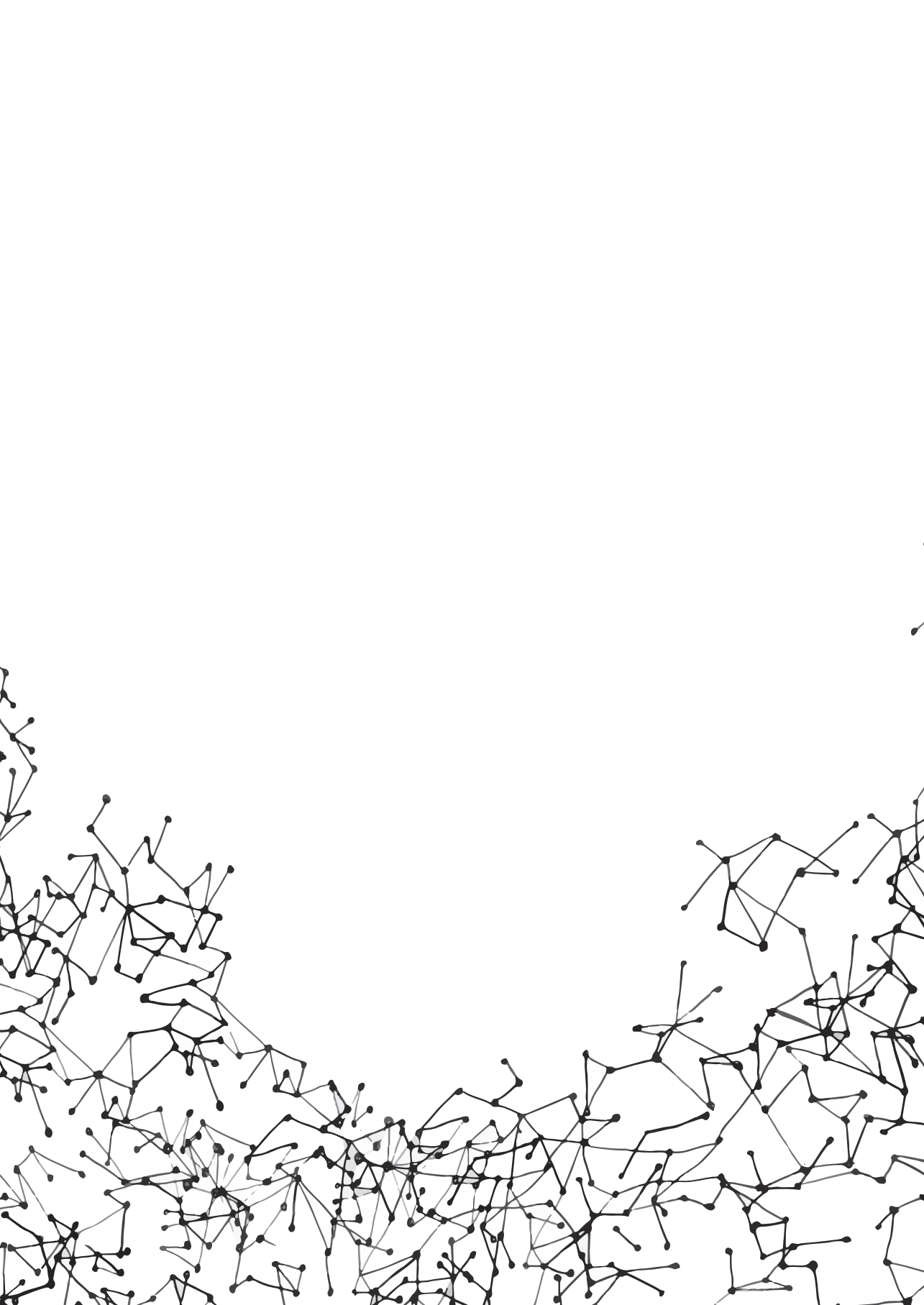

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Cognitive functioning in patients with chronic fatigue and fibromyalgia syndrome

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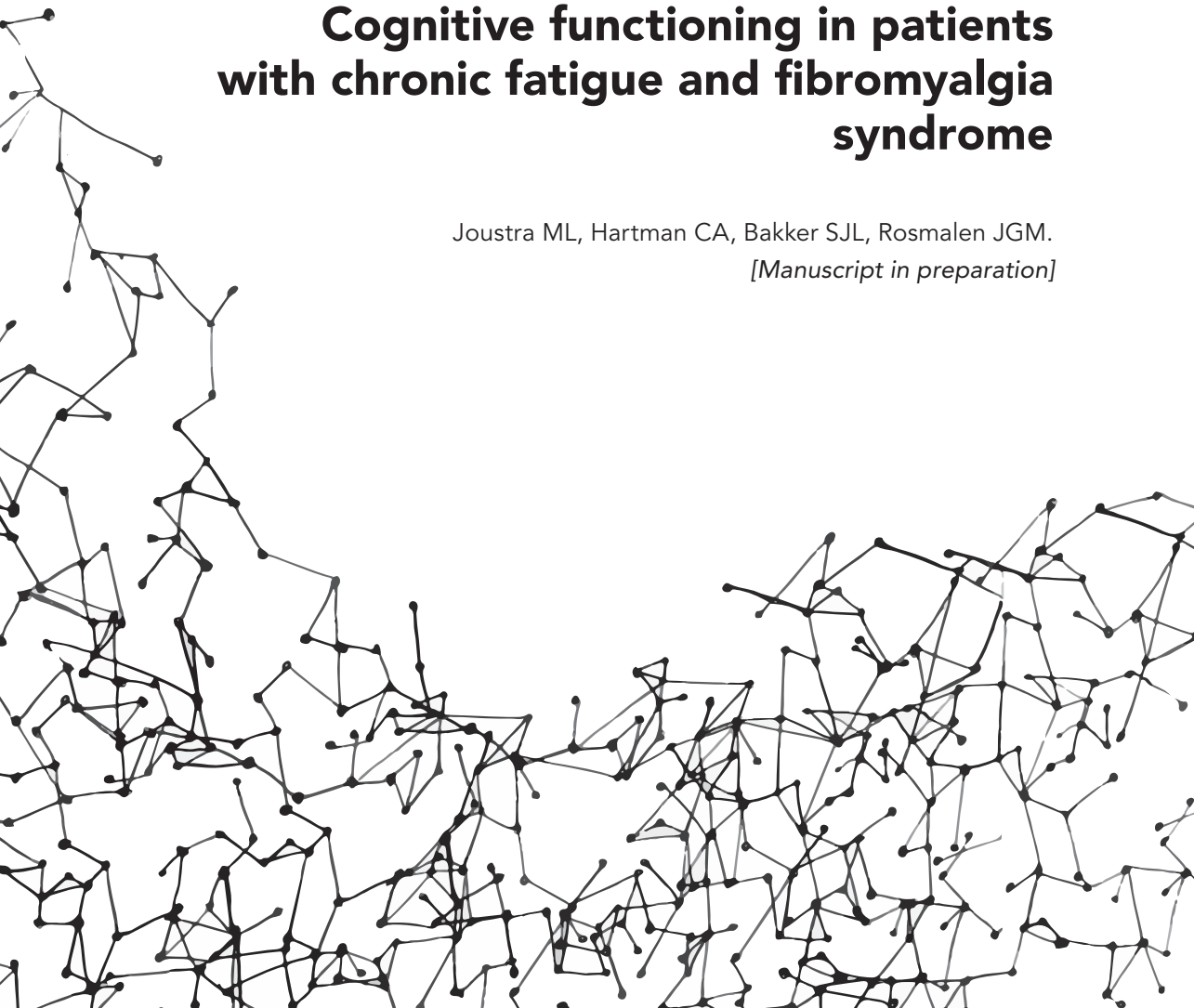
[Manuscript in preparation]



ABSTRACT

Background: The aims of this study were to examine cognitive functioning in patients with chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) compared to controls and patients with well-defined medical diseases, and to investigate their relationship with mood or anxiety disorders, and somatic symptomatology.

Methods: This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Diagnostic criteria for CFS and FMS were assessed by questionnaire. Objective cognitive functioning was determined using the CogState computerized cognitive battery, while subjective cognitive functioning was assessed using items from the Checklist Individual Strength.

Results: Patients with CFS (n=2,461) and FMS (n=4,626) reported significantly more subjective cognitive impairments compared to control participants and patients with well-defined medical diseases. Objective cognitive impairments were particularly present in patients with CFS, although they were rather mild. These differences remained essentially the same when excluding participants with comorbid mood or anxiety disorders. In addition, the associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between the groups. General symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups.

Conclusions: Subjective cognitive impairments are more prevalent than objective cognitive impairments in patients with CFS or FMS compared to control participants and patients with well-defined medical diseases. Importantly, these impairments do not appear to be the consequence of mood or anxiety disorders.

INTRODUCTION

Functional somatic symptoms are persistent physical symptoms that cannot be adequately explained in the context of a well-defined medical disease. The term functional somatic syndromes (FSS) refers to specific combinations of persistent functional somatic symptoms. FSS are serious disabling health conditions that are associated with a reduced quality of life and reduced social participation (Collin *et al* 2011, Dickson *et al* 2009, Hoffman and Dukes 2008, Joustra *et al* 2015). Two well-known FSS are chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS).

FSS are symptom-based diagnoses, since they require the presence of specific clusters of somatic symptoms (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). The diagnostic criteria for FSS include a description of the main symptom and additional symptoms. FSS diagnostic criteria attempt to distinguish these syndromes from well-defined medical diseases that present with comparable symptoms, but they also require the absence of detectable pathological explanations for these symptoms (Drossman 2006, Drossman 2016, Fukuda *et al* 1994, Wolfe *et al* 2010). The main and additional symptoms in CFS and FMS partly overlap; for example, both patient groups can suffer from cognitive symptoms, unrefreshing sleep, fatigue or post-exertional malaise (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). Commonalities among these FSS have resulted in a discussion on whether or not these syndromes share etiological pathways, also known as the lumper-splitter discussion (Wessely *et al* 1999).

Cognitive impairment is one of the most frequently reported symptoms in both CFS and FMS (Fukuda *et al* 1994, Teodoro *et al* 2018, Thomas and Smith 2009, Wolfe *et al* 1990, Wolfe *et al* 2010). In 2010, *Psychological Medicine* published a meta-analysis of research examining cognitive functioning in patients with CFS (Cockshell, Susan Jayne and Mathias 2010). This meta-analysis found that studies examining objective cognitive impairments reported inconsistent results. The authors suggested that these inconsistencies could be explained by methodological differences, since the studies used a wide variety of cognitive tasks that could not be directly compared. They also identified several limitations of the existing literature: most studies contained small samples, did not include a control group, or did not report the diagnostic algorithm that was used to select

the patient group (Cockshell, Susan Jayne and Mathias 2010). Similar conclusions were drawn in a review focusing on cognitive functioning in patients with FMS (Glass 2009). In particular, the authors recommend a study with a large sample of subjects with varying levels of mood and anxiety disorders, pain, fatigue, and sleep disruption, which would allow for assessment of the contribution of these comorbid symptoms to cognitive functioning. Therefore, larger studies investigating both subjective and objective cognitive functioning in CFS and FMS patients and controls are needed.

In the current study, we will examine cognitive functioning in patients with CFS and patients with FMS in a large population-based cohort study of over 79,000 participants. First, we will examine whether patients with CFS and patients with FMS differ significantly from each other and from controls or patients with a well-defined medical disease with the same core symptoms (CFS versus multiple sclerosis (MS) and FMS versus rheumatoid arthritis (RA)), on the subjectively and objectively measurable aspects of cognitive functioning. We will additionally explore the effects of current mood and anxiety disorders on cognitive functioning. Lastly, the relationship between somatic symptomatology and objective cognitive functioning will be examined, and whether it differs between patient groups.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study (Scholtens *et al* 2015). LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all

their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language, were excluded. Parents and children were not excluded in case of the mentioned criteria, when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website and then participate.

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 were administered to all participants approximately every 18 months, and participants have been invited for a renewed physical examination at the LifeLines research site on average every five years. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and lastly, the CogState computerized cognitive battery and psychiatric assessment were conducted respectively.

Functional somatic syndromes and medical or psychiatric health conditions
The diagnostic criteria for CFS and FMS were assessed by questionnaire. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) (Fukuda *et al* 1994), and for FMS using the 2010 American College of Rheumatology criteria (ACR) (Wolfe *et al* 2010) (Appendix A: scoring algorithm, chapter 4).

MS and RA were assessed by questionnaire. CFS with comorbid MS (n=29), and FMS with comorbid RA (n=496) were excluded from the analyses. Controls were defined as participants that did not fulfill the diagnostic criteria for CFS and FMS and did not report MS or RA.

Psychiatric health conditions, including current mood (i.e. major depressive disorder, dysthymia) or anxiety disorders (i.e. panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, generalized anxiety disorder) were assessed with a standardized instrument, which was completed by participants at the LifeLines location. This instrument was a digitalized self-report version of the Mini International Neuropsychiatric Interview (MINI). The MINI is a brief structured instrument for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10 (Sheehan *et al* 1998).

Objective cognitive functioning
The CogState computerized cognitive battery was used to measure cognitive functioning, because it measures multiple domains of cognitive functioning and is brief, using automated data processing and scoring. It is suitable for research among people from the general population with a wide range of ages and educational levels (Fredrickson *et al* 2010, Maruff *et al* 2009). Furthermore, the CogState battery has shown to have good test-retest reliability (Darby *et al* 2002) and validity (Hammers *et al* 2012).

The CogState Brief Battery is a collection of four short card tasks. Different cognitive functioning domains are tested: 1) speed of processing (Detection task (DET); 2 min), visual attention/vigilance (Identification task (IDN); 2 min), working memory (One back (OBK); 2 min), and visual learning & memory (One Card Learning task (OCL); 5 min). During the CogState Brief Battery, a supervisor was available in case participants needed assistance.

Detection task
The DET is a simple reaction time task that measures speed of processing. In this task, the participant is instructed to attend to the center of the screen and follow the rule "Has the card turned face up? Subjects were instructed to press the "Yes" key as soon as the card turned face up. The task ended after 35 correct trials had been recorded. The primary outcome measure was reaction time (in milliseconds), which was normalized using log10 transformation.

Identification task
The IDN is a choice reaction task that measures visual attention. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question: "Is the card red"? Participants were instructed to press the "Yes" key if it is and the "No" key if it is not. This task continued until 30 correct responses had been recorded. Reaction time (in milliseconds and log10 transformed) was the primary outcome measure.

One back
The OBK is a measure of attention and working memory. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question "Is this card the same as that on the immediately previous trial"? If the answer was yes, participants were instructed to press the "Yes" key, and the "No" key if the answer was no. The task ends after 30 correct trials. The primary outcome measure was the proportion of correct answers, which was normalized using arcsine transformation.

One Card Learning task
The OCL is a visual learning and memory task. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question "Have you seen this card before in this task"? If the answer was yes, participants were instructed to press the "Yes" key, and the "No" key if the answer was no. The task ended after 42 trials. The primary outcome measure was the proportion of correct answers, normalized using arcsine transformation.

Subjective cognitive functioning
The Checklist Individual Strength (CIS) is a 20-item self-report questionnaire that covers four domains of the subjective fatigue experience, including fatigue

severity (8 items; e.g. physically I feel exhausted), concentration (5 items; e.g. thinking requires effort), motivation (4 items; e.g. I don't feel like doing anything), and physical activity levels (3 items; e.g. I think I do very little in a day) (Vercoulen *et al* 1994). Participants were asked to indicate how they recognize themselves in the mentioned statements during the past two weeks on an (1) "No, that is not true" to (7) "Yes, that is true" scale. A CIS total score (ranging from 20 to 140) can be obtained by adding the individual scores on the 20 questions. Furthermore, the summary scores can be calculated for the four domains (fatigue severity range 8-56, concentration range 5-35, motivation range 4-28, physical activity level range 3-21). Higher scores indicate a higher degree of fatigue severity, more concentration problems, reduced motivation, or less physical activity. Since motivation is also known to reflect cognitive functioning (Avlar *et al* 2015), the CIS-concentration and motivation scale were used to reflect subjective cognitive functioning.

Fatigue, pain, and general symptom severity

Fatigue severity was assessed using the results of the CIS-fatigue severity subscale (Vercoulen *et al* 1994). To assess subjective pain, participants were asked to indicate in which of 19 mentioned body areas they had pain during the last week using the Widespread Pain Index (WPI; Appendix A, chapter 4) (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). The WPI score was determined by counting the number of body areas in which the participant reported pain during the last week.

To determine general symptom severity, the 12-item somatization scale of the Symptom Checklist-90 (SCL-90 SOM) was used (Derogatis *et al* 1974). This scale consists of 12 somatic symptoms, including: headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach, soreness of your muscles, numbness or tingling in your body, hot or cold spells, feeling weak in parts of your body, heavy feelings in arms or legs, a lump in your throat, and trouble getting your breath. Participants were asked to what extent they had been limited by these symptoms in the past seven days. Items were scored on a 5-point scale ranging from (0) "Not at all" to (4) "Extremely". The outcomes of 12 items of the SCL-90-SOM were summed (total scale ranging 0-48).

Covariates

Age, sex and educational level were included as covariates due to their associations with FSS and cognition. Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational level.

Statistical analyses

All analyses were performed using SPSS version 22. First, the characteristics of the different study groups were described. For continuous outcomes, means ± standard deviations (SDs) were calculated. One-way analyses of variance (ANOVA) were performed for continuous data, to test the differences in sample characteristics. In addition, $\chi 2$ tests were performed for categorical data. Cohen's *d* effect sizes were calculated for the differences between study groups in objective and subjective cognitive functioning, based on the estimated means and standard deviations using ANCOVA analysis adjusted for age, sex, and educational level. To determine 95% CIs for effect sizes, the following formulas were used (Cohen 1988, Hedge and Olkin 2014):

$$\sigma\,(d) = \sqrt{\frac{N1 + N2}{N1 \times N2} + \frac{d^2}{2(N1 + N2)}}$$

$$95\%\ CI\ d = [d - 1{,}96 \times \sigma(d), d + 1{,}96 \times \sigma(d)]$$

Effect sizes of 0.2, 0.5, 0.8, and 1.3 were interpreted to reflect small, medium, large, and very large effects, respectively (Cohen 1988, Cohen 1992). If applicable, effect sizes were reversed to ensure that a positive effect reflected better cognitive function, as reflected in better performance on a cognitive task or less subjective cognitive symptoms. Lastly, to investigate whether fatigue severity, pain severity and general symptom severity were related to objective cognitive functioning, multivariable linear regression analyses were performed using standardized variables, adjusted for age, sex and educational level. Cases with missing data were deleted listwise. To investigate whether the regression coefficients differed significantly between groups (i.e. b1 ≠ b2), a dummy variable for group and the interaction term (independent variable*dummy) were added to the regression models. Statistical significance was defined as $p<0.05$.

RESULTS

Sample characteristics

This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Of the included participants, 3.1% (n=2,461) fulfilled the CDC criteria for CFS, 0.2% reported MS (n=339), 5.8% fulfilled the ACR criteria for FMS (n=4,626), 3.0% reported RA (n=4,440), and 89.4% were considered controls since they did not fulfil the diagnostic criteria for CFS or FMS and did not report MS or RA (n=71,466). An overview of the general sample characteristics is presented in Table 1. Patients with CFS or FMS reported significantly higher fatigue severity, subjective cognitive problems, pain complaints, and general symptom severity compared to both controls and patients with MS or RA. Lastly, both patients with CFS and FMS had significantly higher current comorbid mood or anxiety disorder than controls and patients with MS or RA.

Cognitive functioning in CFS and FMS as compared to controls, MS and RA

In the current sample, 74% of the control group (n=52,914), 65.4% of patients with CFS (n=1,609), 71.8% of patients with MS (n=112), 68.7% of patients with FMS (n=3,179), and 62.2% of patients with RA (n=1,470) completed the CogState computerized cognitive battery. Figure 1 shows the differences between groups in objective and subjective cognitive functioning. Patients with CFS had a significantly slower reaction time on the IDN task (visual attention), and had significantly less correct answers on the OBK (attention/working memory) and OCL tasks (visual learning/memory), compared to controls with only small effect sizes (Figure 1A). Patients with FMS performed significantly less on the OCL task compared to controls with small effect size, while no significant differences were found for the other three tasks. Furthermore, patients with CFS or FMS reported significantly more subjective cognitive problems compared to controls with large to very large effect sizes.

Table 1. General characteristics of the study groups.

	Controls	CFS	MS	FMS	RA
N (%)	71,466 (89.4)	2,461 (3.1)	156 (0.2)	4,626 (5.8)	2,362 (3.0)
Female n (%)	41,178 (57.6)	1,823 (74.1)[1]	121 (77.6)	3,541 (76.5)[1,3,4]	1,531 (64.8)
Age (years), mean (SD)[#]	52.7 (12.6)	54.2 (11.8)[1]	51.9 (9.8)	52.1 (11.4)[1,3,4]	61.2 (11.9)
Education (% low-middle-high)[$]	2.4 – 65.2 – 30.2	4.8 – 72.6 – 19.6[1,2]	1.9 – 69.2 – 26.9	3.5 – 73.5 – 20.3[1,3,4]	5.5 – 70 – 21.1
CIS-fatigue, mean (SD)[#]	21.1 (10.5)	44.2 (8.0)[1,2]	33.2 (11.5)	40.3 (9.5)[1,3,4]	24.6 (11.6)
CIS-concentration, mean (SD)[#]	12.0 (6.3)	21.7 (7.4)[1,2]	16.2 (7.4)	19.9 (7.3)[1,3]	12.5 (6.4)
CIS-motivation, mean (SD)[#]	10.3 (5.0)	17.2 (5.5)[1,2]	13.9 (5.4)	15.5 (5.5)[1,3,4]	11.5 (5.4)
CIS-physical activity, mean (SD)[#]	6.9 (3.9)	13.1 (4.7)[1,2]	10.5 (5.0)	11.0 (5.0)[1,3,4]	7.8 (4.4)
WPI, mean (SD)[#]	2.0 (2.1)	7.6 (4.1)[1,2]	2.9 (2.7)	8.6 (3.0)[1,3,4]	3.4 (2.9)
General symptom severity, mean (SD)[#]	1.3 (0.4)	2.1 (0.6)[1,2]	1.5 (0.4)	2.0 (0.5)[1,3,4]	1.5 (0.5)
DET, mean (SD)[#]	2.57 (0.18)	2.59 (0.19)[1]	2.61 (0.21)	2.58 (0.18)[3,4]	2.63 (0.21)
IDN, mean (SD)[#]	2.69 (0.094)	2.70 (0.096)[1]	2.70 (0.087)	2.69 (0.095)[3,4]	2.72 (0.11)
OBK, mean (SD)[#]	1.29 (0.23)	1.26 (0.25)[1]	1.28 (0.22)	1.29 (0.23)[3,4]	1.24 (0.26)
OCL, mean (SD)[#]	0.95 (0.12)	0.93 (0.13)[1]	0.93 (0.12)	0.94 (0.13)[1,3]	0.93 (0.13)
Current mood disorder n (%)[$]	1,400 (2.0)	544 (22.1)[1,2]	3 (1.9)	682 (14.7)[1,3,4]	69 (2.9)
Current anxiety disorder n (%)[$]	4,141 (5.8)	754 (30.6)[1,2]	14 (9.0)	1098 (23.7)[1,3]	134 (5.7)

CFS = chronic fatigue syndrome; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis; CIS = checklist individual strength; WPI = widespread pain index.
[#] using ANOVA; [$] using $\chi 2$ tests.
[1] $p<0.01$ versus controls, [2] $p<0.05$ versus MS, [3] $p<0.01$ versus RA, [4] $p<0.01$ versus CFS.

When comparing patients with FSS and patients with well-defined medical diseases (Figure 1B), patients with FMS had significantly more correct answers on the OBK task (attention and working memory) compared to patients with RA with a small effect size. No significant differences were found for the other tasks between patients with CFS or FMS compared to patients with MS or RA. For subjective cognitive functioning, patients with CFS or FMS reported significantly

more concentration and motivation problems compared to patients with MS or RA with medium to large effect sizes.

Lastly, when comparing patients with CFS and FMS (Figure 1C), patients with CFS scored significantly lower on the DET (speed of processing) and OBK (attention/working memory) tasks compared to patients with FMS with a small effect size. In addition, patients with CFS reported significantly more concentration and motivation problems compared to FMS patients with small effect sizes.

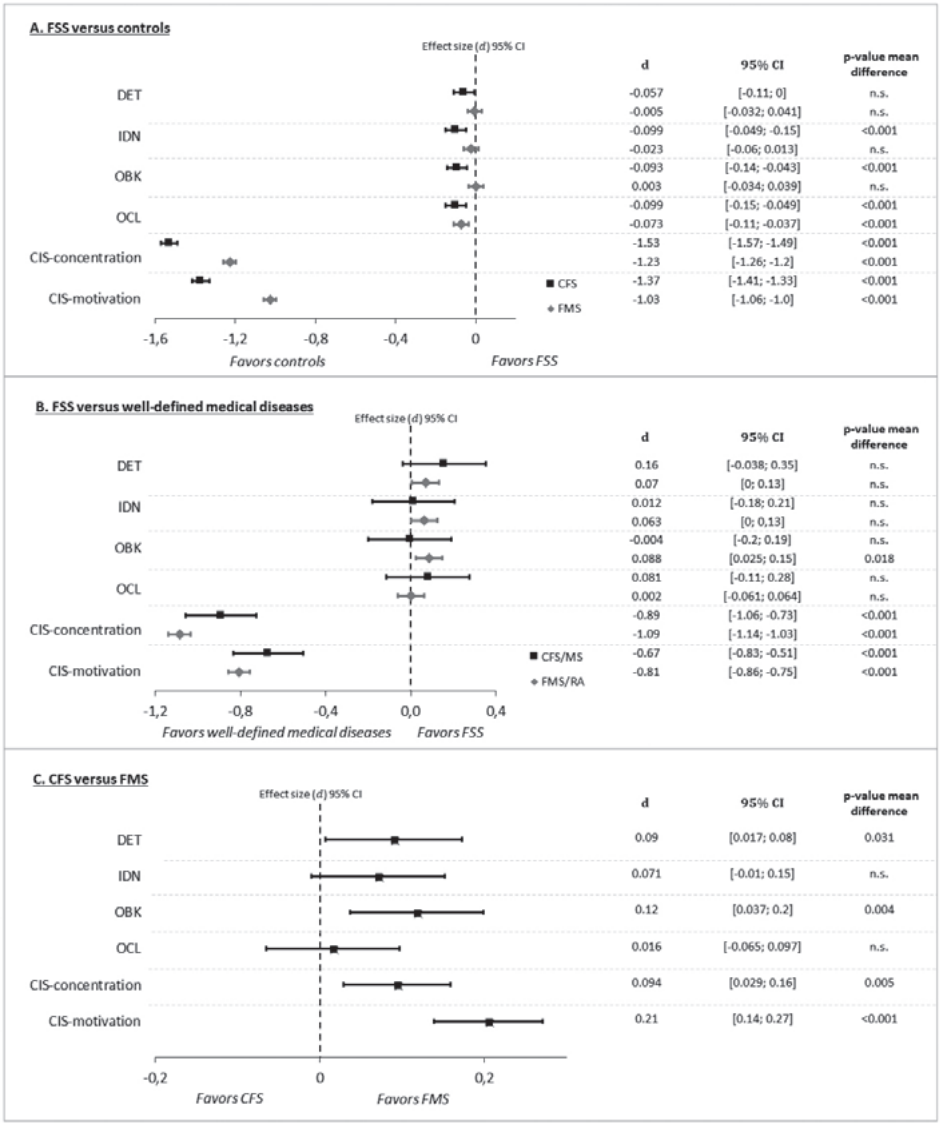


Figure 1. Effect sizes objective and subjective cognitive functioning.
Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms.
Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level.
CFS = chronic fatigue syndrome; FSS = functional somatic syndromes; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis.

The effects of comorbid mood or anxiety disorder

The influence of comorbid mood or anxiety disorder on objective and subjective cognitive functioning was tested by repeating the analyses excluding participants with comorbid mood or anxiety disorders. Among all comparisons, the results with regard to differences between groups in cognitive functioning remained essentially the same (Figure 2). In contrast to the main analyses, the exclusion of participants with mood or anxiety disorders resulted in significantly lower scores on the DET task (speed of processing) in patients with CFS compared to controls (Figures 2A&B). When comparing patients with FSS and patients with well-defined medical diseases (Figure 2C&D), the effect sizes of concentration problems for the comparison CFS/MS and the effect sizes of motivation problems for the comparison FMS/RA reduced from large to medium.

Lastly, scores on the IDN task became significantly lower in patients with CFS compared to FMS, whereas the difference in the OBK task (attention and working memory) between patients with CFS and FMS lost significance when excluding participants with anxiety disorders (Figure 2E&F).

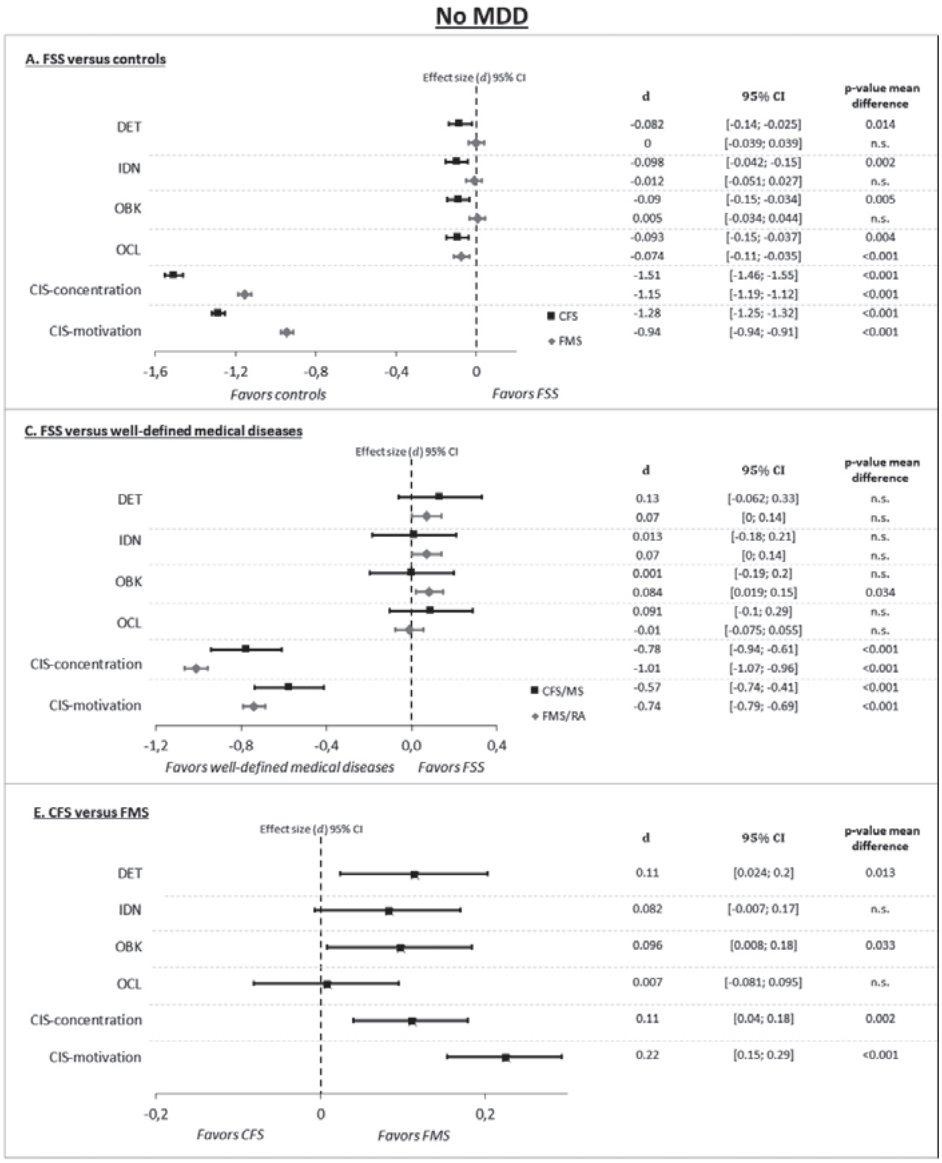


Figure 2. Effect sizes objective and subjective cognitive functioning, when excluding comorbid major depressive disorder or generalized anxiety disorder.

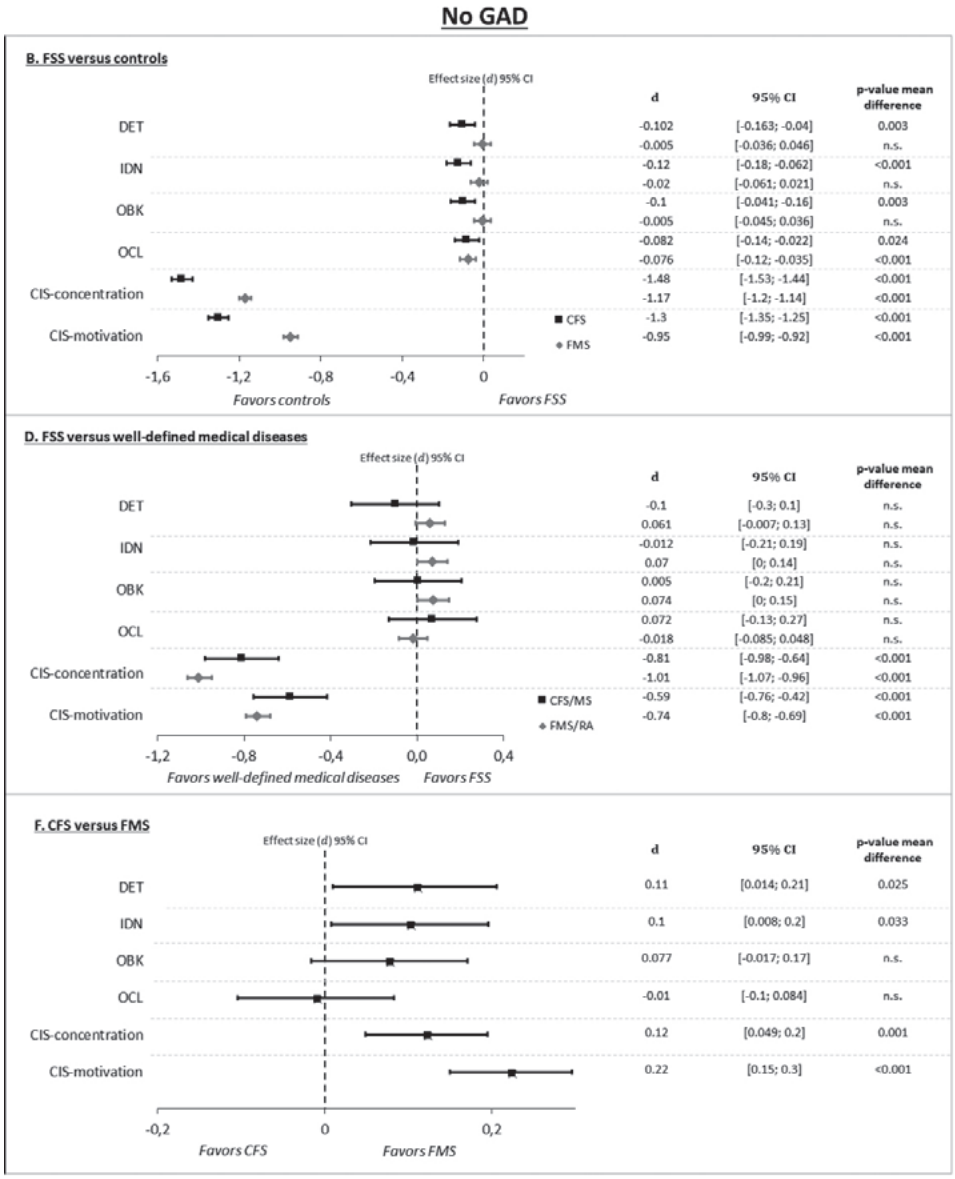


Figure 2. Continued.
Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms.
Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level.
CFS = chronic fatigue syndrome; FSS = functional somatic syndromes; GAD = generalized anxiety disorder; MDD = major depressive disorder; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis.

Associations between symptom severity and objective cognitive functioning

Results of the multivariable regression analyses investigating the association between fatigue, pain or general symptom severity and objective cognitive functioning can be found, per patient group, in Table 2. In controls, severity of fatigue and pain were significantly negatively associated with DET, but not significantly associated with IDN, OBK or OCL scores. General symptom severity was positively associated with all four tasks. In CFS patients, severity of fatigue was significantly negatively associated with DET, and general symptom severity was significantly positively associated with DET, IDN, and OBK. Lastly, general symptom severity was significantly positively related to all four tasks in FMS patients.

Statistical tests of differences in regression coefficients between groups (see note under Table 2), indicated some differences between groups. Although one association was significantly different in patients with CFS from that in controls, and two from those in patients with MS, the estimates were very small and mainly non-significant. In patients with FMS, a few associations were significantly different from controls, and one association was significantly different from patients with RA. However, estimates were again very small and in one case non-significant within the group of FMS patients.

Table 2. Associations between symptom severity and objective cognitive functioning.

	DET	IDN	OBK	OCL
Controls				
CIS-fatigue	-0.016 [-0.026, -0.007]	0.001 [-0.008, 0.01]	0.007 [-0.003, 0.016]	0.007 [-0.003, 0.017]
WPI	-0.013 [-0.024, -0.002]	-0.011 [-0.022, 0]	-0.002 [-0.014, 0.009]	-0.001 [-0.013, 0.01]
SCL-90 SOM	0.012 [0.001, 0.023]	0.018 [0.007, 0.029]	0.032 [0.021, 0.044]	0.026 [0.015, 0.038]
CFS				
CIS-fatigue	-0.09 [-0.16, -0.023][1,2]	0.005 [-0.066, 0.076][2]	-0.029 [-0.11, 0.048]	-0.042 [-0.12, 0.032][3]
WPI	-0.011 [-0.043, 0.02]	0.015 [-0.018, 0.049]	-0.004 [-0.04, 0.032]	0.018 [-0.017, 0.053]
SCL-90 SOM	0.037 [0.002, 0.071]	0.042 [0.006, 0.078]	0.048 [0.009, 0.088]	0.032 [-0.006, 0.07]
MS				
CIS-fatigue	0.15 [-0.054, 0.35]	0.20 [0.031, 0.38]	-0.12 [-0.31, 0.07]	0.069 [-0.12, 0.26]
WPI	-0.048 [-0.26, 0.16]	0.011 [-0.17, 0.19]	-0.043 [-0.24, 0.15]	0.076 [-0.12, 0.27]
SCL-90 SOM	0.22 [0.002, 0.43]	0.10 [-0.082, 0.29]	-0.052 [-0.24, 0.13]	0.01 [-0.18, 0.21]
FMS				
CIS-fatigue	-0.03 [-0.07, 0.011]	-0.002 [-0.044, 0.04]	0.01 [-0.033, 0.052]	-0.034 [-0.076, 0.008][1,4]
WPI	-0.002 [-0.033, 0.028]	0.009 [-0.023, 0.04]	-0.003 [-0.035, 0.029]	0.012 [-0.02, 0.044]
SCL-90 SOM	0.043 [0.016, 0.07][1]	0.052 [0.024, 0.08][1]	0.043 [0.014, 0.071]	0.047 [0.076, 0.19]
RA				
CIS-fatigue	0.001 [-0.055, 0.057]	0.034 [-0.023, 0.091]	0.054 [-0.005, 0.11]	0.053 [0, 0.11]
WPI	-0.037 [-0.093, 0.02]	0.023 [-0.035, 0.08]	0.032 [-0.028, 0.092]	0.016 [-0.038, 0.07]
SCL-90 SOM	0.004 [-0.05, 0.058]	0.039 [-0.017, 0.094]	0.065 [0.007, 0.12]	0.075 [0.023, 0.13]

Multivariable regression analyses, adjusted for age, sex, and educational level. Reported as standardized B [95%CI]. Significant associations are underlined. A positive association indicates that the experience of more symptoms was associated with worse performance on the objective cognitive tasks. CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, MS = multiple sclerosis, RA = rheumatoid arthritis, DET = detection task, IDN = identification task, OBK = one back, OCL= one card learning task, CIS-fatigue = fatigue subscale of the checklist individual strength, WPI = widespread pain index, SCL-90 SOM = 12-item somatization scale of the Symptom Checklist-90.

[1,2,3,4] refer to associations that differed between groups [1] $p < 0.05$ versus controls, [2] $p < 0.05$ versus MS, [3] $p < 0.05$ versus FMS, [4] $p < 0.01$ versus RA.

DISCUSSION

This is the first large population-based study that assessed both subjective and objective cognitive functioning in patients with CFS and FMS compared to patients with MS and RA and a control group, including relevant confounding variables. We found that subjective cognitive impairments are more prevalent in both patients with CFS and FMS than in controls and patients with MS and RA, respectively. Patients with CFS had significantly more subjective and objective cognitive impairments compared to patients with FMS, which could not be attributed to the presence of comorbid mood or anxiety disorders. In addition, associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between patients with FSS and controls or patients with well-defined medical diseases. General symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups.

The main strength of the current study is that it was performed in a large population-based sample, in which data were collected on subjective and objective cognitive functioning and relevant confounding variables. This enabled comparing patients with FSS and patients with well-defined medical diseases in a single cohort, avoiding differences in selection procedures or measurement. Since we selected the groups from the general population, it was possible to examine subjective and objective cognitive functioning of the different study groups irrespective, help-seeking behavior, referral by clinicians, and differences in diagnostic assessment. Lastly, FSS were based on the official positive diagnostic criteria instead of the self-reported diagnoses.

There are also limitations of the current study. First, we used a brief battery covering only basic domains of cognitive functioning. We therefore may have missed some differences in objective cognitive functioning between patients with FSS and controls or patients with well-defined medical diseases. In addition, cognitive tasks assess specific cognitive functions, while questionnaires cover more global cognitive functions, which makes it difficult to compare results on objective cognitive functioning and subjective cognitive functioning. Second, FSS diagnoses were based on the 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 met the diagnostic criteria for FSS based on clinical examinations. We excluded patients that fulfilled the criteria for one of the FSS and reported the corresponding well-defined medical disease, but we cannot fully exclude the presence of other somatic pathology explaining the symptoms.

Our study supports previous findings that cognitive impairments are more prevalent and severe in both patients with CFS and FMS compared to controls (Teodoro *et al* 2018, Thomas and Smith 2009). Furthermore, we found that patients with CFS had reduced visual learning and working memory, and both patients with CFS or FMS had reduced visual attention scores compared to controls. Patients with CFS or FMS did not differ from controls in speed of processing, so differences in this most basic cognitive process cannot serve as an explanation for the differences in other, more complex cognitive functions. These findings are in accordance with a recent meta-analysis that concluded that patients with FSS have primarily cognitive impairments in the domains of attention, memory, and tasks requiring working memory (Cockshell, Susan Jayne and Mathias 2010, Glass 2009). In contrast to earlier research, we found only small effect sizes for the differences, and we found that the objective cognitive impairments of FSS patients are comparable to those in patients with MS and RA (Krupp *et al* 1994). A possible explanation for these differences might be that we have addressed some limitations of previous research, including the use of small samples and self-report diagnoses. In addition, previous research mostly recruited referred patients, while we selected patients from the general population. Thus, the results in previous research might be the affected by help-seeking behavior, referral practices by clinicians, or differences in diagnostic assessment.

This study found that subjective cognitive impairments were more prevalent in patients with FSS compared to control participants and patients with well-defined medical diseases, while differences in objective cognitive performance between the groups were rather mild. Similar findings have been reported in previous studies, investigating both healthy participants as well as patients with FSS (Ray *et al* 1993, Stulemeijer *et al* 2007, Tucker-Drob 2011). The difference between the outcomes of subjective and objective cognitive functioning may be due to the fact that questionnaires measure different domains of cognitive function than cognitive

tasks (Cockshell, Susan Jayne and Mathias 2010, Ray *et al* 1993). Questionnaires cover more global and overarching cognitive functions, whereas tasks assess much smaller and specific functions. In addition, the CogState brief battery covered four basic domains of cognitive functioning, while adequate cognitive functioning in daily life requires much more, and more complex, processing. Furthermore, in accordance with previous research, the presence of comorbid mood or anxiety disorders did not explained the differences in cognitive performance between groups (Cockshell, Susan J. and Mathias 2013). Thus, although mood or anxiety disorders are relatively common in patients with FSS (Janssens *et al* 2015), we found no evidence to suggest that they contribute to cognitive impairments. We also found that the associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between patients with FSS and controls or patients with well-defined medical diseases. Moreover, general symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups. The associations between the experience of somatic symptoms and the performance on the cognitive tasks were therefore not unique to patients with FSS, as shown by the results in controls or the MS/RA groups.

Lastly, we investigated differences between patients with CFS and patients with FMS in the context of the lumper-splitter discussion (Wessely *et al* 1999). We found that patients with CFS patients had significantly more subjective cognitive impairments and performed significantly worse on tasks measuring speed of processing and attention/working memory, compared to patients with FMS. Since we found both similarities and differences between CFS and FMS, our results support suggestions that FSS have both specific and general characteristics (Lacourt *et al* 2013).

While our study addresses many limitations of previous research, our cross-sectional design provides only a first step. Future studies will be necessary to understand the causes of and contributors to impaired subjective cognitive functioning in FSS patients. Furthermore, the fluctuations that occur in FSS symptoms (e.g. pain, fatigue) may result in unstable results on objective cognitive tasks (Fuentes *et al* 2001). We recommend to use a more extensive cognitive battery that measures more aspects of cognitive functioning, in correctly diagnosed CFS and FMS patients compared to a well-matched control group, including relevant confounding variables and taking into account the fluctuations of symptoms experienced.

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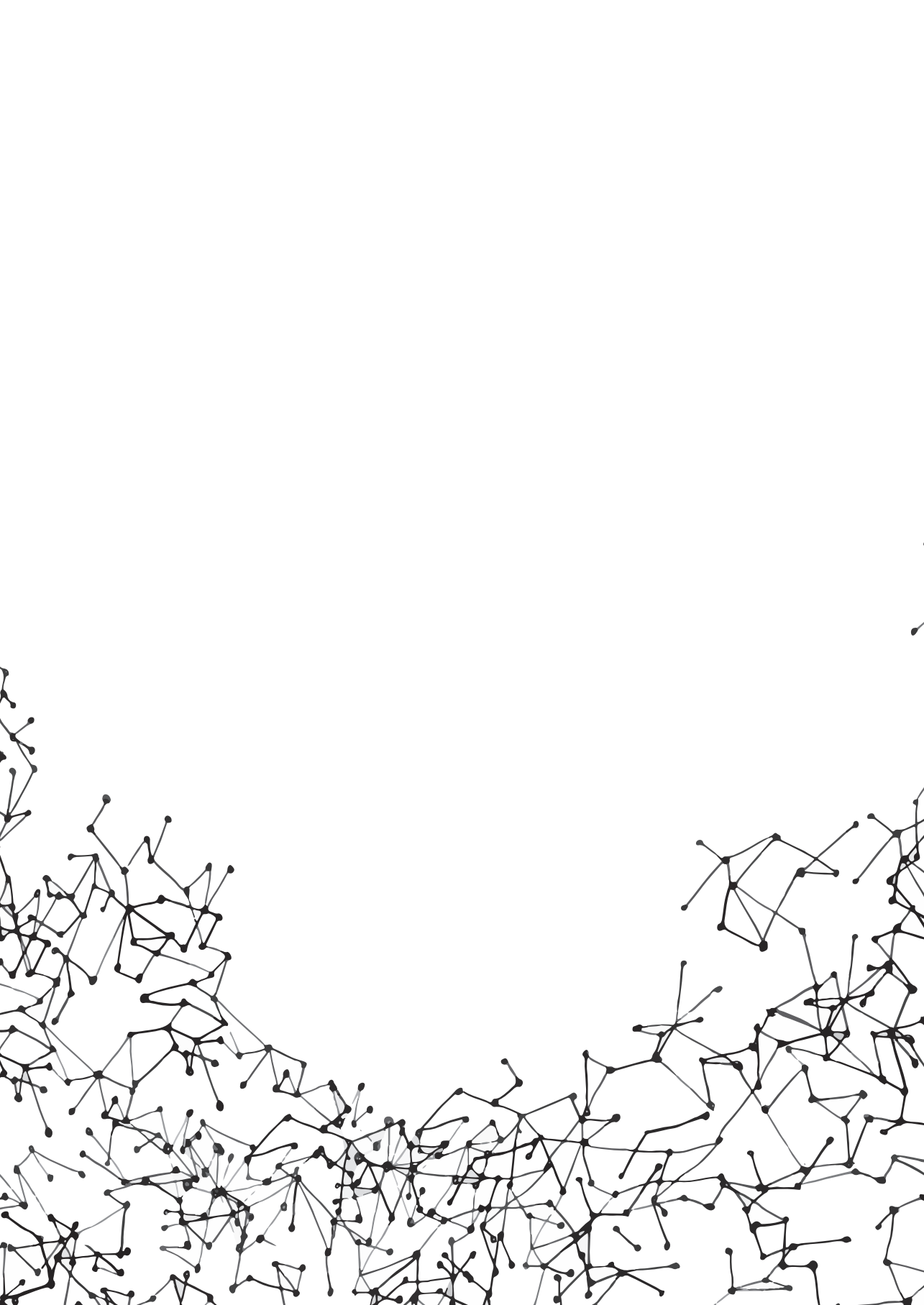

8

Physical activity and sleep in chronic fatigue syndrome and fibromyalgia syndrome: associations with symptom severity in the general population cohort LifeLines

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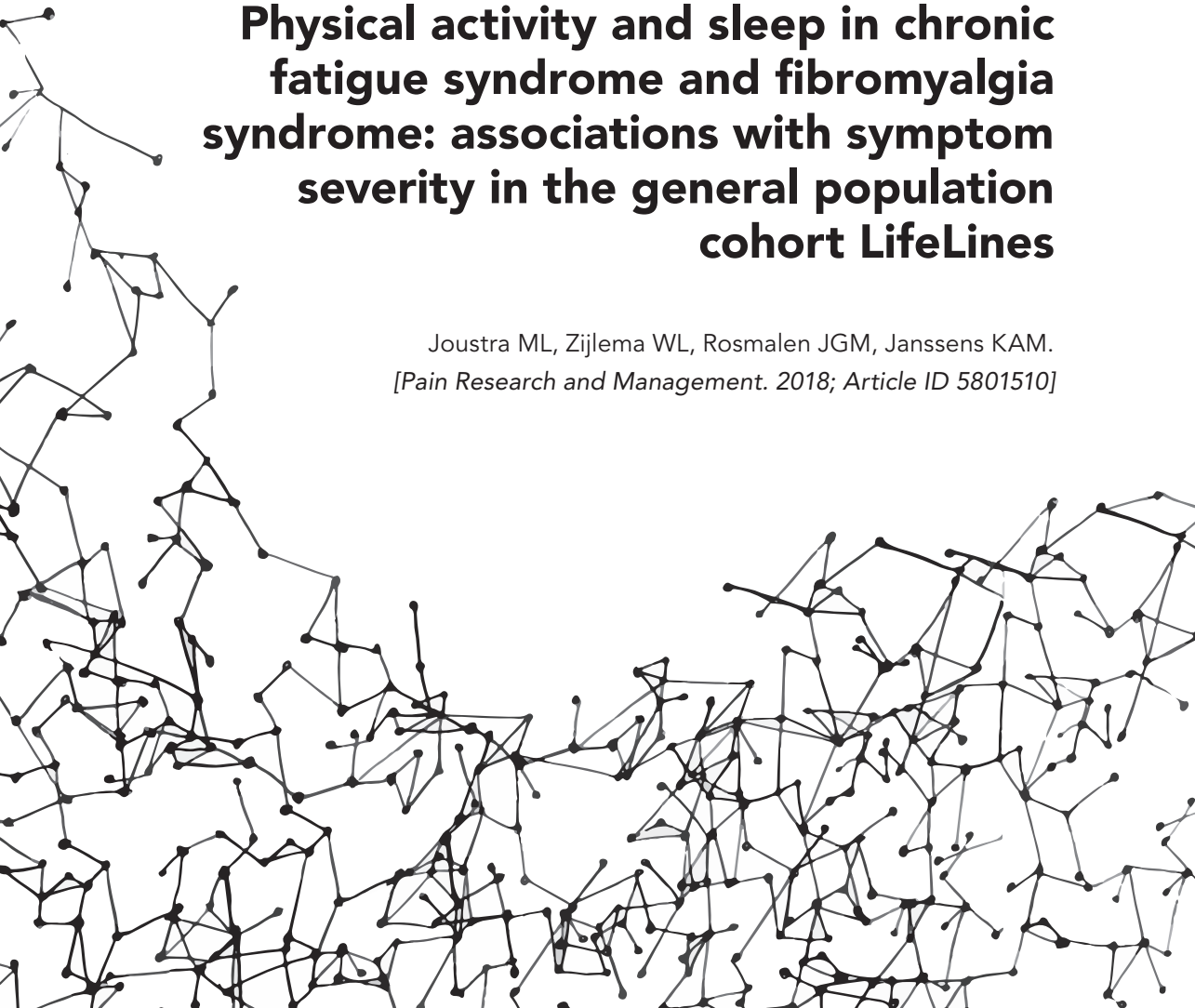

ABSTRACT

Objective: The aim of the current study was to compare physical activity and sleep duration between patients with chronic fatigue syndrome (CFS), patients with fibromyalgia syndrome (FMS), and controls and to examine the association between physical activity level and sleep duration with symptom severity within these patient groups.

Methods: This study used data of LifeLines, a general population cohort in which 1.0% (n = 943; 63.7% female, age 44.9 (SD 11.6) years) reported CFS, 3.0% (n = 2,714; 91.6% female, age 48.4 (SD 10.7) years) reported FMS, and 95.7% (n = 87,532; 57.9% female, age 44.3 (SD 12.4) years) reported neither CFS nor FMS. Physical activity, sleep duration, and symptom severity were assessed by questionnaires and analysed using ANCOVA and regression analyses, adjusted for age, sex, body mass index, smoking, and educational level

Results: Patients with CFS and FMS had significantly lower physical activity scores (8834 ± 5967 and 8813 ± 5549 MET*minutes) than controls (9541±5533; $p<0.001$). Patients with CFS had the longest sleep duration (466 ± 86 minutes) compared to patients with FMS and controls (450 ± 67 and 446 ± 56; $p<0.001$). A linear association between physical activity, sleep duration, and symptom severity was only found in controls, in whom higher physical total activity scores and longer sleep duration were associated with a lower symptom severity. In contrast, quadratic associations were found in all groups: both relatively low and high physical activity scores and relatively short and long sleep duration were associated with higher symptom severity in CFS, FMS, and controls.

Conclusion: This study indicates that patients with CFS or FMS sleep longer and are less physically active than controls on average. Both low and high levels of physical activity and short and long sleep duration are associated with higher symptom severity, suggesting the importance of patient-tailored treatment.

INTRODUCTION

Functional somatic syndromes (FSS), including chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS), are common, disabling, and costly health conditions without known underlying organic pathology [1–4]. CFS is an illness characterised by profound disabling unexplained fatigue [5], while the primary complaint of patients with FMS is unexplained musculoskeletal pain [6]. Both core symptoms are typically accompanied by various additional symptoms. The etiology of CFS and FMS is assumed to be multifactorial including biological, psychological, and social contributing factors [7].

The role of physical activity and sleep in the pathophysiology of CFS and FMS is not well understood. Regarding physical effort, various studies have evaluated the ability of patients with CFS or FMS to perform physical activity, but the results are conflicting [8–10]. There are also different approaches in the way individuals with CFS and FMS cope with physical activity. Recent research suggests that both avoidance of activity and overactivity are associated with an increase in symptom severity, including pain and fatigue [9, 11, 12]. This indicates that, in patients with CFS and FMS, both high and low levels of physical activity may result in higher symptom severity, comparable to what is observed in the general population [13]. Regarding recovery, sleep difficulties have been associated with negative effects on pain and fatigue [14, 15]. A study found that nights with an unusually long or short sleep duration resulted in greater fatigue and that moderate sleep duration was associated with the least fatigue [15]. As with physical activity, an association between sleep duration and symptom severity may thus exist in these patient groups [16].

CFS and FMS are known for substantial clinical and diagnostic overlap. The two conditions are comorbid: 35% to 75% of patients with CFS met the criteria for FMS [17]. This phenomenon resulted in the lumper-splitter discussion [18]. "Lumpers" believe that all FSS result from the same etiology, and "splitters" take the approach that every separate FSS has its own specific background. It is not known to which extent patients with CFS and FMS differ with regard to physical activity and sleep. Studies that compare these associations between patients of one population-based cohort are, to the best of our knowledge, lacking.

The aim of this study was to examine whether patients with CFS, patients with FMS, and controls have different levels of physical activity and sleep duration. Furthermore, we will examine the degree to which physical activity or sleep duration is associated with the severity of physical symptoms, in CFS, FMS, or controls. We hypothesize that both too much and too little physical activity and sleep are related to symptom severity and expect this association to be stronger in patients with CFS and FMS than controls. Furthermore, we hypothesize that CFS is more strongly related to sleep difficulties and FMS is more strongly related to physical activity. These hypotheses were tested within LifeLines, a large population-based cohort study.

METHODS

This study is conducted within the sampling frame of the LifeLines cohort study [19-21], a general population cohort in which 1.0% (n = 943; 63.7% female, age 44.9 (SD 11.6) years) reported CFS, 3.0% (n = 2,714; 91.6% female, age 48.4 (SD 10.7) years) reported FMS, and 95.7% (n = 87,532; 57.9% female, age 44.3 (SD 12.4) years) reported neither CFS nor FMS. The LifeLines cohort study is a multidisciplinary prospective population-based cohort study with a unique three-generation design. LifeLines aims to examine the health and health-related behaviours of more than 167,000 persons living in the North East region of the Netherlands, with a special focus on multimorbidity and complex genetics. It uses a broad range of research procedures to assess biomedical, sociodemographics behavioural, physical, and psychological factors that contribute to health and/or disease of the general population.

Participants

Participants were recruited in two different ways. First, participants aged 25–50 years were invited through a number of general practitioners from the three northern provinces of the Netherlands. Second, persons who were interested to participate in the study could register themselves via the LifeLines website. Patients who agreed to participate were asked to invite their partner, parents, parents-in-law, and children to as well participate in the LifeLines cohort study. Therefore, participants of all age were included in the study. General practitioners evaluated eligibility for participation, whereby persons with severe psychiatric

or physical illness, and those not being able to visit the general practitioner and to fill in the LifeLines questionnaires, and/or persons those who did not understand the Dutch language were excluded from the study. However, children and parents were not excluded in the case of the mentioned exclusion criteria, when a representative was willing to assist these persons in the performance of the study. In case of pregnancy, participation was rescheduled until 6 months after pregnancy or 3 months after breastfeeding.

The LifeLines cohort study obtained approval by the Medical Ethical Committee of the University Medical Center Groningen. All participants received written information on the purpose and methods of the LifeLines cohort study. Written informed consent of participants was obtained after the procedure of the LifeLines cohort study was fully explained. Data of the LifeLines cohort study are kept confidential and are only used for medical research.

Measures

Chronic fatigue syndrome and fibromyalgia syndrome
CFS and FMS were assessed by means of a self-report questionnaire, including a list of chronic disorders including CFS and FMS. The participants were asked to indicate which of these disorders they had or have had. More than one answer to this question was allowed. Participants who reported both CFS and FMS were excluded (n=264), since we were interested in differences between both conditions. Controls were defined by the absence of CFS and FMS.

Physical activity and sleep duration
Physical activity was assessed by means of the validated Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [22]. This self-report questionnaire assesses physical activity undertaken in an average week in the past months across a set of domains. These domains include commuting activities (walking or bicycling to/from work or school), leisure-time activities (walking, bicycling, gardening, and odd jobs), sports activities, household activities, and activities at work and school. It is a reliable and valid questionnaire [22]. The SQUASH discusses three questions per activity: days per week of the activity (frequency), average time per day (duration in minutes), and intensity of the

activity. The intensity of the physical activity was scored on a 3-point scale ranging between (1) "*Slow*," (2) "*Moderate*," and (3) "*Fast*."

The answers collected with the SQUASH can be examined as a continuous measure by weighting each type of activity by its energy requirements defined in intensity scores, also referred to as metabolic equivalent of tasks (METs). METs are defined as multiples of the resting metabolic rate, thus the energy expenditure at rest. Selected MET values are derived using the Ainsworth's Compendium of Physical Activities [23]. Based on age and assigned MET values, physical activities were subdivided into three intensity categories: light, moderate, and vigorous. For adults aged 18–54 years, the following cutoff values were used: <4.0 MET (light intensity), 4.0 to 6.5 MET (moderate intensity), and ≥6.5 MET (vigorous intensity), and for adults aged ≥55 years, these cutoff values were <3.0 MET (light), 3.0 to 5.0 MET (moderate), and ≥5.0 MET (vigorous). The three MET categories were combined with self-reported intensity for each activity, resulting in a combined intensity score ranging from 1 to 9, with 1 being light MET and light self-reported intensity and 9 being vigorous MET and vigorous self-reported intensity. The classification of physical activities according to the combined intensity score was <3 (light intensity), 3 to 6 (moderate intensity), and ≥6 (vigorous intensity). The physical activity scores of the different domains were calculated by multiplying duration (minutes per week) with the MET value, taking into account the combined intensity score. Subjects with unlikely values were excluded if separate activity categories exceeded plausible values, more than two activity categories of the questionnaire were missing, and/or ≥18 hours/day were spent on all activities together.

Sleep duration was assessed using the question: "How many minutes do you sleep on average per day?"

Symptom severity

Symptom severity was assessed with the 12-item somatization scale of the Symptom CheckList-90 (SCL-90 SOM) [24]. The SOM scale measures self-reported intensity of somatic symptoms. This scale consists of 12 somatic symptoms, including a lump in your throat, faintness or dizziness, feeling weak in parts of your body, headaches, heavy feelings in arms or legs, hot or cold spells, nausea or upset stomach, numbness or tingling in your body, pains in heart or chest, pains in lower

back, soreness of your muscles, and trouble getting your breath. Participants were asked to what extent they have been limited by these somatic symptoms in the past seven days. The somatic symptoms were scored on a 5-point scale ranging from (1) "*Not at all*" to (5) "*Extremely*." An additional item assessing fatigue was used from the RAND-36 [25]: "How much of the time during the past four weeks did you feel tired?" This item was scored on a six-point scale ranging from (1) "*All of the time*" to (6) "*None of the time*." The fatigue score was transformed to a 5-point scale with (1) "*None of the time*" to (5) "*All of the time*," with a combined score of (3) "*A good bit of the time*" and (4) "*Some of the time*" into (3) "*quite a bit*" to obtain consistency with the SOM scale. Symptom severity was calculated by taking the mean score of the 13 somatic symptoms. Therefore, the total symptom severity ranged from (1) all symptoms endorsed as "*Not at all or none of the time*" to (5) all symptoms endorsed as "*Extremely or all of the time*."

Covariates

Length in centimetres and weight in kilograms were assessed during a basic medical examination at a local LifeLines research facility. Subsequently, body mass index (BMI) was calculated as kg/m^2. The smoking status was assessed using the following question: "Do you smoke now, or have you smoked in the past month?" Participants could fill in "*yes*" or "*no*." Educational level was assessed using the following question: "What is your highest completed education?," resulting in information about low, middle, and high educational level. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education.

Statistical analyses

For all continuous variables, means ± standard deviations (SDs) were calculated. One-way analyses of variance (ANOVA) were performed for continuous data, to test the differences in sample characteristics. Differences in symptom severity were also investigated between males and females within the different study groups. In addition, χ^2 tests were performed for categorical data. For continuous variables, analyses of covariance (ANCOVA) with post hoc Bonferroni correction were performed to examine differences in physical activity level and sleep duration between patients with CFS, patients with FMS, and controls. In addition,

sex differences in physical activity and sleep duration were explored. Linear and quadratic regression analyses were conducted using standardized variables to examine how physical activity and sleep duration were associated with symptom severity in the different groups. Four regression models were performed: both linear and regression analyses for physical activity and for sleep duration. All analyses were adjusted for age, sex, BMI, smoking status, and educational level, since they are known to be related to CFS [26, 27], FMS [28–30], physical activity [31, 32], and sleep [33, 34]. All analyses were performed using SPSS version 20. All analyses were performed using SPSS version 20. Statistical significance was defined as $p<0.05$.

RESULTS

Sample characteristics

Data were available for 91,453 participants; descriptives, including age, BMI, education, SOM-score, sex and smoking are shown in Table 1. Of these participants, 1.0% reported CFS (n = 943), 3.0% (n = 2,714) reported FMS, and 95.7% (n = 87,532) reported neither CFS nor FMS. Women were most prevalent in all groups. The mean age varied between 44.3 ± 12.4 for controls, 44.9 ± 11.9 for patients with CFS, and 48.4 ± 10.7 years for patients with FMS. Female CFS patients and controls reported significantly higher symptom severity (2.1 ± 0.6 and 1.5 ± 0.4 respectively) compared to males (1.9 ± 0.6 and 1.4 ± 0.3), while no difference in symptom severity was found in female FMS patients (2.0 ± 0.5) compared to male FMS patients (1.9 ± 0.5).

Physical activity and sleep duration

Physical activity levels in patients with CFS, patients with FMS, and controls are shown in Figure 1A. ANCOVA analysis revealed significant groups differences ($F(7,76182) = 303$, $p<0.001$). Posthoc comparisons with Bonferroni correction indicated that patients with CFS and FMS had a significantly lower physical total activity score than controls (8834 ± 5967 and 8813 ± 5549 MET * minutes, respectively, versus 9541 ± 5533; both $p<0.001$). There was no significant difference in physical total activity score between patients with CFS and FMS ($p=0.99$). Lastly, males were significantly more physically active than females among all three study groups.

Sleep duration in patients with CFS, patients with FMS, and controls is shown in Figure 1B. ANCOVA analysis revealed significant groups differences (F(7,39438) = 222, p=<0.001). Posthoc comparisons with Bonferroni correction indicated that patients with CFS had the longest sleep duration (466 ± 86 minutes) compared to patients with FMS and controls (450 ± 67 and 446 ± 56 respectively; both p<0.001), while no difference was found between patients with FMS and controls (p=0.846). Furthermore, female CFS patients and controls reported significantly longer sleep duration (474 ± 84 and 453 ± 59 minutes respectively) than males in the corresponding groups (453 ± 87 and 437 ± 50 minutes), while no difference in sleep duration was found between female FMS patients (451 ± 66 minutes) and male FMS patients (442 ± 80 minutes).

Table 1. Sample characteristics.

				Pairwise comparisons[c], p value		
	CFS	**FMS**	**Controls**	**CFS vs FMS**	**CFS vs controls**	**FMS vs controls**
	Mean (SD)					
Number (%)	943 (1.0)	2714 (3.0)	87532 (95.7)			
Age[a]	44.9 (11.6)	48.4 (10.7)	44.3 (12.4)	<0.001	0.137	<0.001
BMI (kg/m^2)[a]	26.4 (4.8)	27.8 (5.3)	26.0 (4.3)	<0.001	0.407	<0.001
Symptom severity (1-5)[a]	2.0 (0.6)	2.0 (0.5)	1.5 (0.4)	0.038	<0.001	<0.001
	n (%)					
Education[b]						
Low	319 (33.8)	1193 (44.0)	25,418 (29.0)	<0.001	<0.001	<0.001
Middle	377 (40.0)	1055 (38.9)	34,211 (39.1)			
High	213 (22.6)	377 (13.9)	25,697 (29.7)			
Female[b]	601 (63.7)	2485 (91.6)	50,705 (57.9)	<0.001	<0.001	<0.001
Smoking[b]	257 (27.3)	609 (22.4)	18,520 (21.2)	0.002	<0.001	0.145

CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome.
[a]ANOVA; [b]χ^2 test; [c]Bonferroni correction for continuous and χ^2 test for categorical variables.

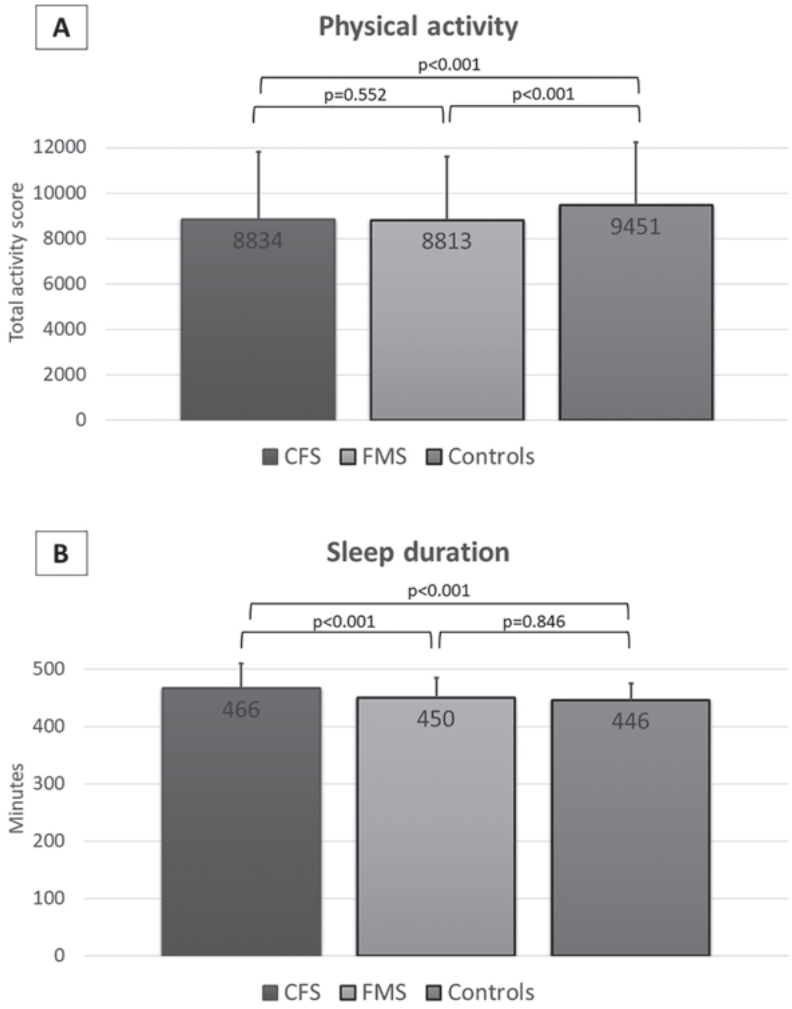

Figure 1. Physical activity and sleep duration.
CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome.
[1]Analyses of Covariance and Bonferroni correction, adjusted for age, sex, BMI, smoking and education.

Physical activity or sleep duration associated with symptom severity

Physical activity and sleep duration showed both linear and quadratic associations with symptom severity. Results of both linear and quadratic regression analyses are shown in Table 2. Linear regression analyses showed that, only in controls, physical total activity score (model 1) and sleep duration (model 2) were related to symptom severity: controls with a higher physical total activity score or longer sleep duration reported a slightly lower symptom severity. No significant linear

associations were found in patients with CFS or FMS between physical total activity score or sleep duration and symptom severity.

Quadratic regression analyses indicated a significant association between total physical activity score in CFS, FMS and controls (model 3). Both linear and quadratic terms were significant in FMS and controls, and only the quadratic term, but not the linear was significant in CFS. Thus, patients with CFS, patients with FMS and controls with relatively low and high physical activity scores reported higher symptom severity than those with moderate physical activity scores. Furthermore, all three groups showed significant quadratic associations between sleep duration and symptom severity (model 4). Both linear and quadratic sleep terms were significant in patients with CFS and controls, while only the quadratic but not the linear sleep term was significant in patients with FMS. Thus, patients with CFS, patients with FMS and controls with short or long sleep duration reported a higher symptom severity than those with moderate sleep duration.

Table 2. Regression analyses for physical activity or sleep duration predicting symptom severity.

	CFS		**FMS**		**Controls**	
	B	95% CI	B	95% CI	B	95% CI
	Linear					
Total activity score	-0.007	-0.047, 0.032	-0.009	-0.031, 0.012	-0.007**	-0.009, -0.004
Sleep duration	-0.005	-0.045, 0.036	-0.009	-0.036, 0.017	-0.004*	-0.008, -0.001
	Quadratic					
Total activity score (linear term)	-0.042	-0.091, 0.008	-0.046**	-0.073, -0.020	-0.009**	-0.012, -0.006
Total activity score (quadratic term)	0.020*	0.003, 0.038	0.019**	0.011, 0.027	0.001**	0.001, 0.002
Sleep duration (linear term)	-0.045*	-0.089, 0.00	-0.021	-0.047, 0.005	-0.007**	-0.011, -0.003
Sleep duration (quadratic term)	0.017**	0.008, 0.025	0.040**	0.031, 0.049	0.00**	0.00, 0.00

CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome.
* p≤0.05; ** p≤ 0.001.
Regression analyses using standardized variables, adjusted for age, sex, BMI, smoking, and education.

DISCUSSION

This study revealed that patients with CFS and FMS were significantly less physically active than controls. Furthermore, patients with CFS reported longer sleep duration than patients with FMS and controls. Only in controls, physical total activity score and sleep duration were linearly related to symptom severity, with both higher physical total activity score and higher sleep duration being associated with slightly lower symptom severity. Quadratic associations were present in all groups; both relatively high and low physical activity levels were associated with higher symptom severity in patients with CFS, patients with FMS, and controls; and both relatively long and short sleep duration were associated with higher symptom severity in patients with CFS, patients with FMS, and controls.

The main strength of this study is the large population cohort. To the best of our knowledge, this is the first study that evaluates physical activity and sleep duration in patients with CFS and FMS in one large population cohort. A sufficient number of patients with CFS and FMS were identified, allowing for meaningful statistical comparisons. Moreover, the large number of patients enabled examining the association between sleep duration, physical activity, and symptom severity in CFS, FMS, and controls. Both patients and controls with different physical activity or sleep duration outcomes were therefore present in the cohort. Finally, since LifeLines is a large cohort study with extensive measurements, adjusting for important covariates such as age, sex, BMI, smoking status, and educational level was possible.

Our study also contained limitations, including the use of a self-report questionnaire for the assessment of CFS and FMS. Instead of current diagnoses, our questionnaire asked for a history of CFS and FMS. A previous study in a general population cohort from the same geographical area indicated that about 75% and 100% of the participants that reported a history of CFS and FMS, respectively, still had this syndrome at the time of reporting [35]. In addition, self-reports may underestimate the amount of persons with FSS. This seems not likely in our study because the prevalence rates for CFS and FMS were comparable to previous studies [27, 29]. Moreover, the majority of the patients with CFS and FMS in the current study recently experienced fatigue and musculoskeletal pain. Furthermore, subjective measurements were used to assess sleep duration and physical activity, instead

of objective measures. For example, sleep duration was assessed using a single question, so participants may have interpreted this differently (e.g.,time in bed, actual time sleep, and inclusion of naps). A final limitation is that the cross-sectional design did not allow conclusions on cause-and-effect relationships.

In line with previous findings, this study revealed that both patients with CFS and FMS were significantly less physically active than controls [36, 37]. However, it should be mentioned that self-reported questionnaires to assess physical activity levels in these patient groups have shown a low reliability [38, 39]. In contrast to our hypothesis, no difference in physical activity was found between patients with CFS and FMS. Lower activity levels in patients with CFS or FMS might be explained by the substantial limitations in physical functioning that may be caused by their symptoms [9]. In addition, a lack of physical activity might also contribute to physical deconditioning, further increasing symptom severity [12, 40]. We found that both low and high physical activity levels in patients with CFS, patients with FMS, and controls were associated with the reporting of more symptoms. This finding stresses the close relationship between physical activity and the experience of symptoms. Thus, on the one hand, low activity levels may be associated with the experience of more and more severe symptoms, while on the other hand, high physical activity level may exacerbate symptoms in CFS and FMS [9, 11, 12].

Differences between patients with CFS and FMS were found for sleep duration, since patients with CFS were found to report longer sleep duration than patients with FMS and controls. However, misestimation of sleep duration appears common in patients with CFS and FMS, particularly in patients having a poor sleep quality [41, 42]. Nevertheless, our results are in accordance with our hypothesis and might be due to the primary complaint of disabling fatigue in patients with CFS [5, 43, 44]. Furthermore, our results are in line with a recent study that reported that nights with an unusually long or short sleep duration resulted in greater fatigue, and that moderate sleep duration was associated with the least fatigue [15].

Our study also revealed differences between patients, as illustrated by the finding of quadratic associations of symptom severity with physical activity and sleep. These quadratic associations indicate that the pathophysiological role of physical activity and sleep varies not only between but also within patient groups with

CFS or FMS. Treatment aimed at reducing symptoms might therefore better be tailored to individual patients. This is mainly important since both CFS and FMS are characterised both by nonrestorative sleep and intolerance to physical exercise. Since the LifeLines cohort is a large population cohort study that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to more extensively assess lifestyle factors such as physical activity and sleep in CFS and FMS during the baseline assessment because of practical limitations. We aim to include objectively measured lifestyle factors in CFS and FMS in future assessment waves. Further studies will be necessary to determine the effect of objectively measured physical activity or sleep duration, by using, for instance, polysomnography or accelerometers. Furthermore, the association between sleep duration and symptom severity was found to vary between different patients. Therefore, studies that evaluate how sleep duration and physical activity are related to symptom severity within individual patients, so called idiographic research [45], is recommended to further study the role of sleep and physical activity in patients with CFS and FMS.

Conclusion

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 levels of physical activity and sleep duration are associated with higher symptom severity. Differences were found within patient groups, suggesting etiological heterogeneity in these patients and thus the importance of patient-tailored treatment.

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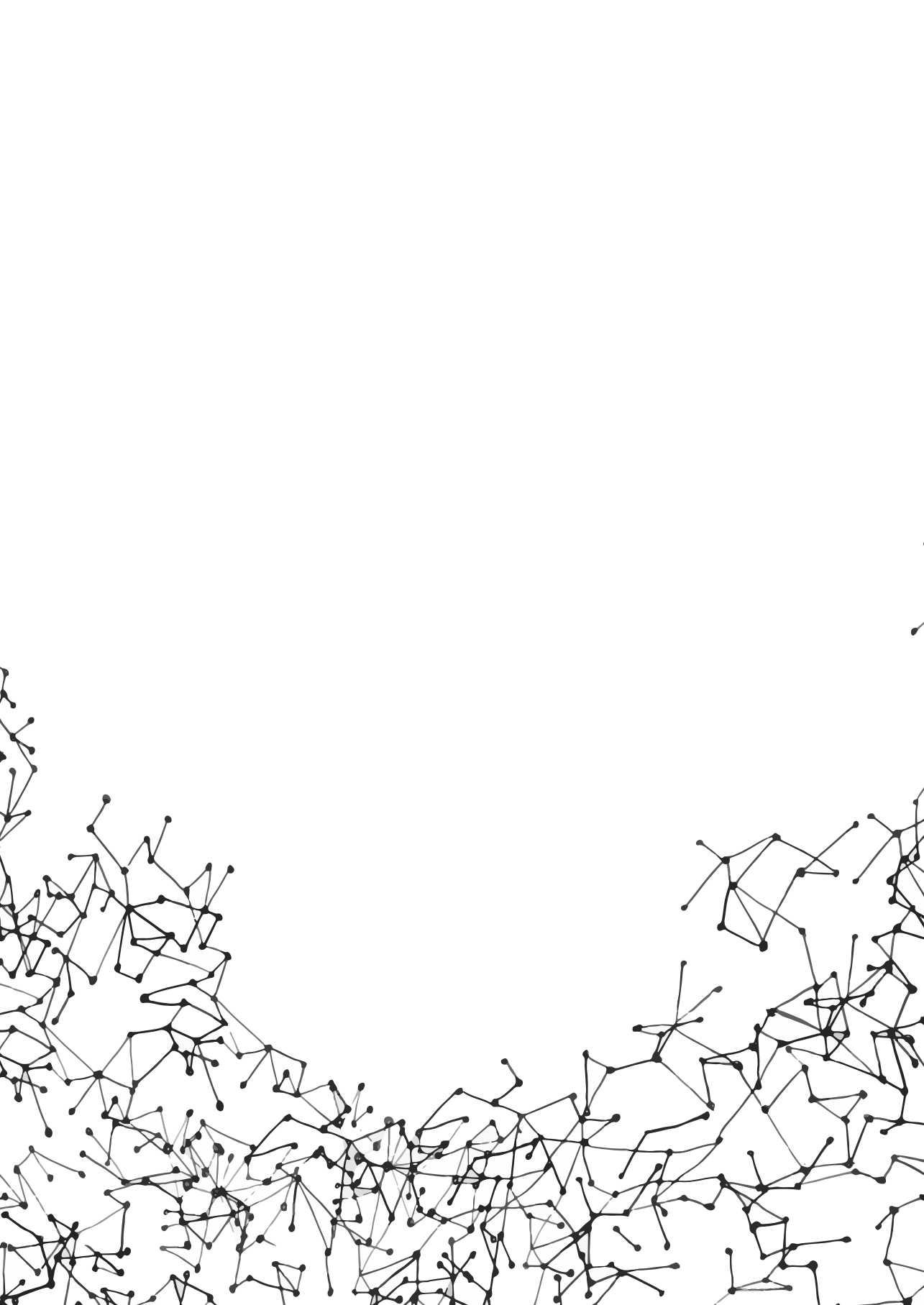

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Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: a systematic review and meta-analysis

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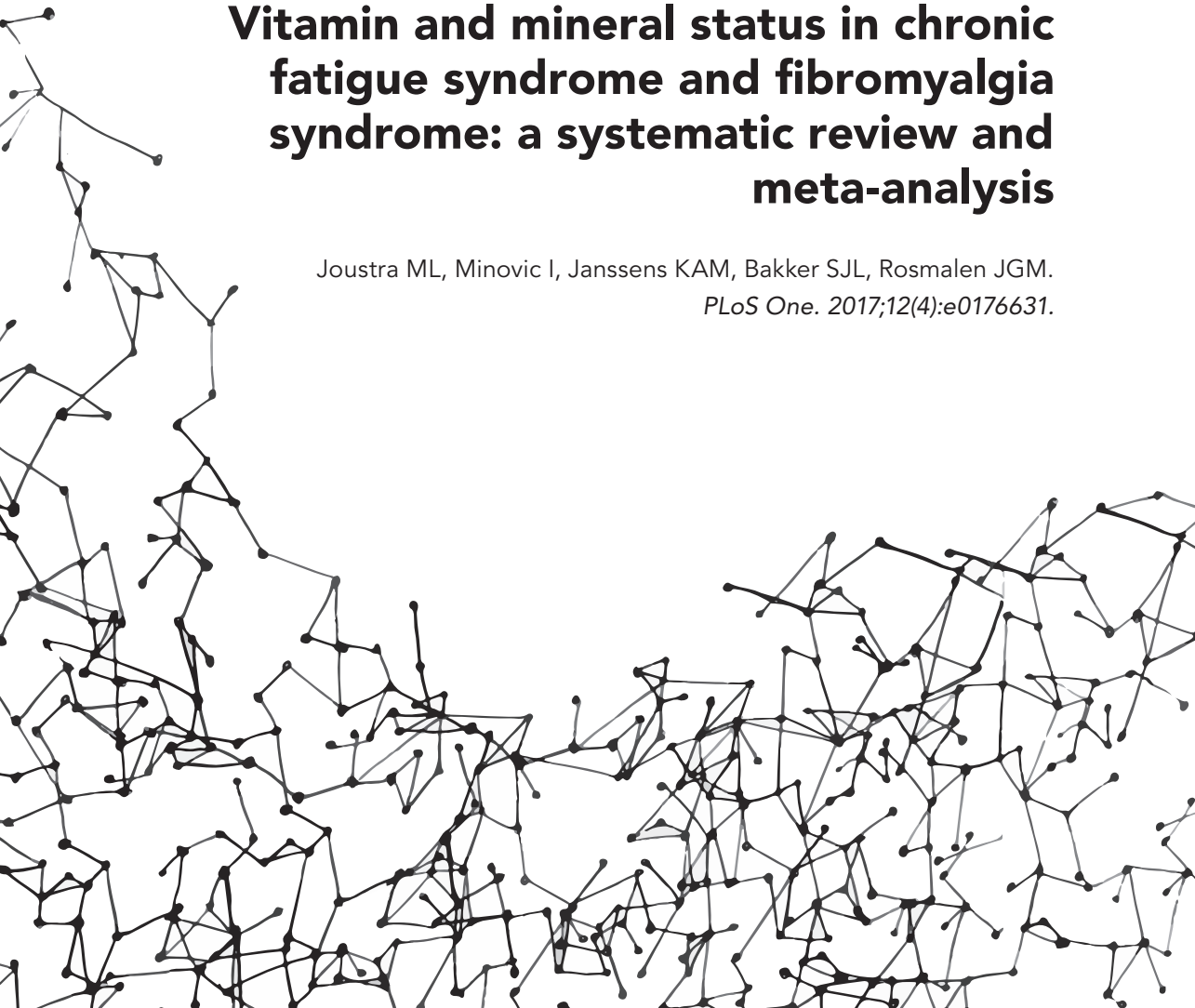


ABSTRACT

Background: Many chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) patients (35-68%) use nutritional supplements, while it is unclear whether deficiencies in vitamins and minerals contribute to symptoms in these patients. Objectives were (1) to determine vitamin and mineral status in CFS and FMS patients as compared to healthy controls; (2) to investigate the association between vitamin and mineral status and clinical parameters, including symptom severity and quality of life; and (3) to determine the effect of supplementation on clinical parameters.

Methods: The databases PubMed, EMBASE, Web of Knowledge, and PsycINFO were searched for eligible studies. Articles published from January 1st 1994 for CFS patients and 1990 for FMS patients till March 1st 2017 were included. Articles were included if the status of one or more vitamins or minerals were reported, or an intervention concerning vitamins or minerals was performed. Two reviewers independently extracted data and assessed the risk of bias.

Results: A total of 5 RCTs and 40 observational studies were included in the qualitative synthesis, of which 27 studies were included in the meta-analyses. Circulating concentrations of vitamin E were lower in patients compared to controls (pooled standardized mean difference (SMD): -1.57, 95%CI: -3.09, -0.05; p=.042). However, this difference was not present when restricting the analyses to the subgroup of studies with high quality scores. Poor study quality and a substantial heterogeneity in most studies was found. No vitamins or minerals have been repeatedly or consistently linked to clinical parameters. In addition, RCTs testing supplements containing these vitamins and/or minerals did not result in clinical improvements.

Discussion: Little evidence was found to support the hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of CFS and FMS, and that the use of supplements is effective in these patients.

Registration: study methods were documented in an international prospective register of systematic reviews (PROSPERO) protocol, registration number: CRD42015032528.

INTRODUCTION

Chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) are syndromes of unknown origin. The core symptom of CFS is profound disabling fatigue [1], whereas FMS is characterized by chronic widespread pain [2,3]. CFS and FMS are known for substantial clinical and diagnostic overlap, for example, chronic pain and fatigue are common in both patient groups. The two syndromes are often comorbid; up to 80% of CFS patients reported a history of clinician-diagnosed FMS [4,5]. This has resulted in the hypothesis that these syndromes share etiological pathways [6].

Vitamin and mineral deficiencies may play a role in the pathophysiology of both CFS and FMS, although mechanisms behind this hypothesis are not entirely clear [7,8]. In addition, results of studies investigating the effects of nutritional supplementation or dietary intake on, for example, symptom severity in these patient groups, are conflicting [9-12]. Nevertheless, a large proportion of CFS and FMS patients indicate they use nutritional supplements (35%-68%) [10,13-15], compared to the Dutch general population (27-56%) [16]. The higher nutritional supplement use among patients may be due to encouragements by specialty stores, the internet or (complementary medicine) clinics. Vitamins and minerals in these products are sometimes supplemented in doses high enough to cause health problems, for example gastric discomfort, insomnia, dizziness and weakness [17]. More information is needed on the evidence for (marginal) vitamin and mineral deficiencies in CFS and FMS, and the potential benefits in taking nutritional supplements.

Recently, a review investigating hypovitaminosis D in both chronic pain and FMS patients showed that these patients were at significantly higher risk of hypovitaminosis D than healthy controls [18]. Unfortunately, further reviews on vitamin and mineral deficiencies among CFS and FMS patients are lacking. We therefore carried out this first systematic review on vitamin and mineral status in CFS and FMS. We explored the following research questions: first, what is the evidence for deficiencies in vitamin and mineral status in CFS and FMS patients as compared to healthy controls? Second, is vitamin and mineral status associated with clinical parameters, including symptom severity and quality of life, in CFS and FMS? Third, what is the evidence for an effect of vitamin and

mineral supplementation, as compared to placebo, on clinical parameters in CFS and FMS patients? Because it is currently unknown whether CFS and FMS result from the same etiology, we analyzed results both for the combined and for the separate syndromes.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (S1 Table) [19]. Prior to start of article inclusion, we documented study methods in an international prospective register of systematic reviews (PROSPERO) protocol, registration number: CRD42015032528, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015032528.

Data Sources and Searches

The databases PubMed, EMBASE, Web of Knowledge, and PsycINFO were systematically searched. Articles published between January 1st 1994 and 1990, for CFS and FMS respectively, and March 1st 2017 were included. We focused on the most recent diagnostic guidelines, namely the International Center of Disease Control (CDC) diagnostic criteria for CFS that was established in 1994 [1], and the American College of Rheumatology (ACR) criteria for FMS in 1990 [2]. To retrieve relevant articles from PubMed, we formulated a search string (S1 Appendix) that consisted of CFS, FMS, and synonyms, vitamins, minerals, micronutrients and synonyms, while excluding systematic reviews or animal studies. This search string was adapted according to the thesaurus of the databases EMBASE, Web of Knowledge, and PsycINFO. All included studies were screened for potential references that were not included in the first search. Duplicates were removed, as well as studies including pediatric participants. There were no language restrictions; included non-English articles were translated (French, Italian, Polish, and Turkish articles) by native speakers.

Study Selection

Title and abstract were screened by two independent reviewers (M.L.J. and I.M.) for the following criteria: (1) CFS or FMS patients; (2) vitamin or mineral status; and (3) study design. Studies which were in agreement with the eligibility criteria were retrieved as full text. Discrepancies between the two researchers

were resolved by consensus, and when needed a third assessor was consulted (J.G.M.R.). Reasons for exclusion and percentage of agreement, as Cohen's kappa, between the assessors were documented.

Participants of the included studies had to be adults (i.e. ≥18 years) suffering from CFS or FMS according to the official diagnostic criteria [1-3]. Studies that involved patients with a combination of CFS and FMS or other comorbid medical conditions were excluded. Furthermore, the vitamin or mineral status had to be assessed or reported in the article, or there had to be an intervention concerning vitamins or minerals. Patients were compared with healthy controls in observational studies, or vitamin and mineral supplementation were compared with placebo in intervention studies. Lastly, cross-sectional studies comparing cases and controls, cohort studies and randomized controlled trials (RCTs) were included. Case reports, clinical cohorts without appropriate controls (e.g. controls with musculoskeletal pain or fatigue), (systematic) reviews, expert opinion, and other study designs were excluded.

Data Extraction

Two reviewers (M.L.J. and I.M.) independently extracted data and assessed the risk of bias for each study. The first ten articles were screened together to pilot the data extraction and risk of bias form. Reasons for exclusion and percentage of agreement between the assessors were documented.

From the included articles, the following information was extracted: name first author, publication year, type FSS, number and age of the participants, and vitamin or mineral status. In addition, data on smoking habits or alcohol use, diet (and assessment tool used), BMI (or waist circumference, waist-hip ratio), physical activity (assessment tool), socioeconomic status, ethnicity, severity of illness (assessment tool), duration of illness, co-morbidities (somatic and psychiatric), medication use, clinical parameters including symptom severity and quality of life, and in case of RCTs the relevant co-intervention(s) were also extracted.

Quality Assessment

To assess quality of RCTs, the Cochrane Collaboration's tool for assessing risk of bias was employed [20]. For observational studies, literature indicates lack of a single methodological assessment tool [21,22]. Therefore, we adjusted a

previously developed quality tool for observational studies in this field [23], for use in studies that focus specifically on the association between vitamin and mineral status and CFS or FMS. Eight of the nine items in this original quality tool originated from guidelines or tools for either reporting or appraising observational research [24-26]. These items were adjusted to the specific question on vitamins and minerals and classified into three key domains: appropriate selection of participants (validated disorder, representative controls, in- and exclusion criteria, disease characteristics), appropriate quantification of vitamin and mineral status (duplicate quantification, appropriate outcome), and appropriate control for confounding (assessed confounders, analyses adjusted). The item: "Is the assessor blind for disease status", was excluded since from the original quality tool since it is not applicable in the current review. Furthermore, we added the item "Are methods for assessment of vitamin and mineral status clearly stated", based on the adapted Newcastle Ottawa scale for cross-sectional studies (S2 Appendix) [27]. RCTs that contained relevant observational data (n=4/5), were assessed with both the Cochrane tool and the observational studies quality tool. For both quality tools, items were rated as (0) low risk, (1) medium risk, and (2) high risk of bias. The maximum attainable quality score was 14 for RCTs, and 18 for observational studies.

Data Synthesis and Analysis

We first constructed an overview of available data on the different vitamins and minerals. Characteristics of the included studies were systematically listed to generate a clear overview of the current literature on vitamins and minerals in CFS and FMS patients. For those vitamins and minerals with more than five studies available, we did quantitative syntheses on aggregated data. For these syntheses, data was pooled with the random effects model of meta-analysis, using Stata statistical software, version 14 (Statacorp LP, Texas). To allow pooling across studies that used different outcomes of vitamin or mineral plasma or serum levels, we calculated the standardized mean difference (SMD). For proportions of deficiencies, the odds ratio (OR) was calculated and pooled. Subsequently, the SMD and OR for each study were weighted by their inverse variance and the corresponding 95%CI were calculated. The existence of heterogeneity among studies was assessed by Q-tests, and the degree of the heterogeneity was quantified by calculating the I-squared (I^2) value. Publication bias was inspected visually by a funnel plot, and an Egger's test was conducted to quantify funnel

plot asymmetry [28]. The Tweedie's Trim and Fill test was performed as an additional sensitivity analysis to identify and correct for funnel plot asymmetry arising from publication bias [29]. When the Trim and Fill test was performed, and additional studies were added to the analyses, contour-enhanced funnel plots were used instead of regular funnel plots to examine whether asymmetry in the funnel plots was due to publication bias [30]. Subgroup analyses were performed including studies with more than half of the maximum study quality score (>9 quality points), if more than three studies with a sufficient quality score were available. Furthermore, vitamin and mineral status of CFS and FMS patients were investigated separately if more than three studies were available. Findings were considered statistically significant if $p<0.05$.

RESULTS

Study inclusion

Results of the systematic review and meta-analysis are presented in a flow diagram (Fig 1). Cohen's kappa's for the abstract and full text selection were 0.96 and 0.89 respectively, indicating very good consistency of agreement [31]. Out of 108 studies included for the full text review, 45 studies were included in the current review.

Characteristics of the included studies are presented in Table 1, and results of the quality assessment in Table 2. Most studies involved FMS patients (n=35/45); 4 of the 5 RCTs also contained relevant observational data. Vitamin and mineral status was mainly assessed in plasma or serum (n=40/45). Furthermore, quality scores revealed poor study quality (i.e. equal or less than half of the maximum study quality score) in the vast majority of observational studies (n=27/44; range 4-14 points) and RCTs (n=3/5; range 5-12 points). Only few observational studies defined all described in- and exclusion criteria for the investigated population, including medication use, somatic morbidity, and psychiatric morbidity (n=10/44). The CFS or FMS diagnostic criteria were often described in observational studies, but researchers failed to state whether or not the syndromes were diagnosed by a physician (n=40/44). Disease characteristics were frequently not fully presented (n=15/44), or were completely absent (n=18/44) in observational studies. Almost all observational studies did not assess vitamin or mineral in duplicate (n=38/44). Most studies that assessed vitamin or mineral status did not clearly state the

methods for assessment of vitamin and mineral status (n=27/44). Furthermore, most observational studies did not adjust their analyses for any potential confounders (n=43/44). Lastly, most RCTs had a medium to high risk of bias for random sequence generation (n=3/5), allocation concealment (n=3/5), blinding of outcome assessment (n=4/5), incomplete data (n=4/5), selective reporting quantification (n=3/5), and other bias (n=5/5).

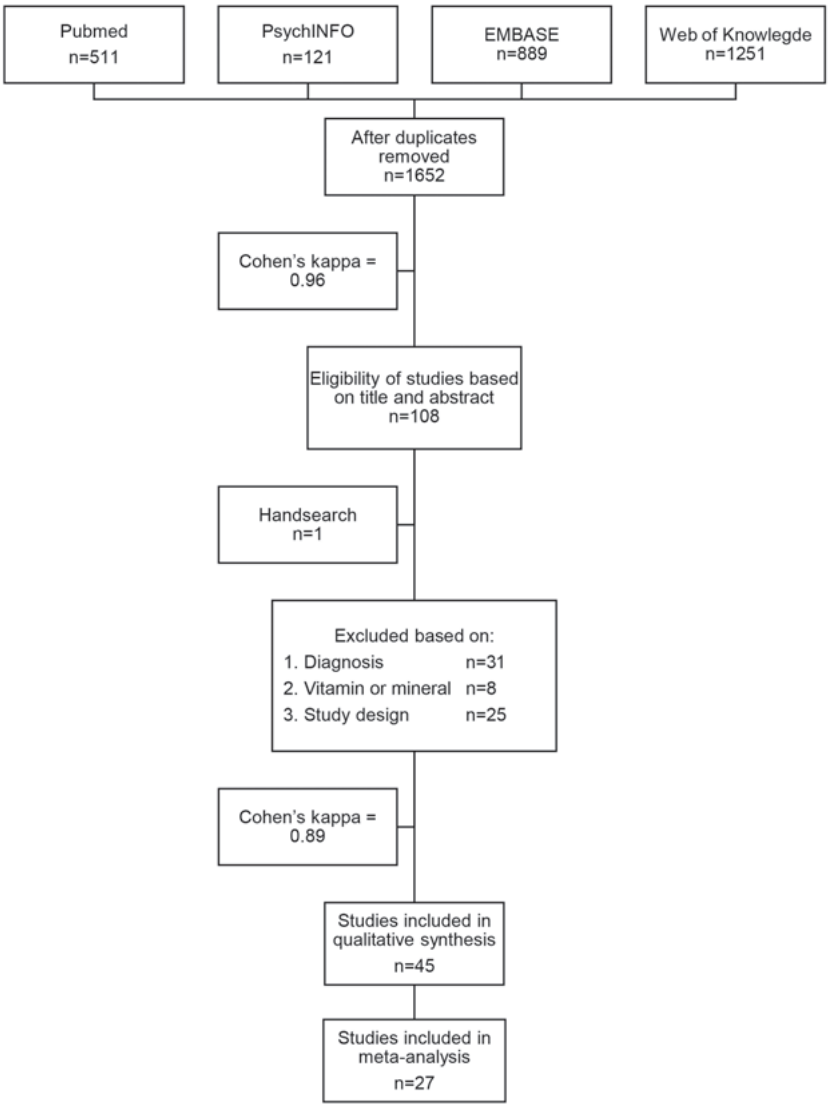


Figure 1. Flow diagram.

Table 1. Characteristics of included studies.

Study	Setting	Type of FSS	N of cases	Study design	Mean age in years (SD)	Mean FSS severity (SD) and/or mean duration in months (SD)	Comparison group (n)	Vitamin and/or mineral	Material
Akkus et al, 2009 [32]	Secondary care	FMS	30	Case-control	40.1 (5.2)	FIQ: 59.8 (7.9) 68.8	Healthy controls (30)	Vitamin A, C, E	Plasma
Al-Allaf et al, 2003 [33]	Secondary care	FMS	40	Case-control	42.5 (3.6)	FIQ (score out of 10): 6.5 (2.2) 48 (31)	Healthy controls (37)	Vitamin D, calcium	Serum
Bagis et al, 2013 [34]	Secondary care	FMS	60	RCT and case-control	40.7 (5.2)	FIQ: 38.8 (10.4) 4.4 (1.2)	Healthy controls (20)	Magnesium	Serum, erythrocytes
Baygutalp et al, 2014 [35]	Secondary care	FMS	19	Case-control	35 (7.5)	FIQ: 19.3 (21.5)	Healthy controls (21)	Vitamin D	Serum
Bazzichi et al, 2008 [36]	Secondary care	FMS	25	Case-control	48.8 (9.3)	FIQ: 57.9 (17.3)	Secondary care patients without FMS or musculo-skeletal pain (25)	Calcium, magnesium	Platelets
Brouwers et al, 2002 [37]	Tertiary care	CFS	24	RCT	40.0 (9.9)	CIS: 51.4 (4.2) Disease duration (years, median (IQR)) 8.0 (2–15)	Placebo, CFS patients (25)	Polynutrient supplement	NA
Costa et al, 2016 [38]	Secondary care	FMS	100	Case-control	42.4 (8.4)	NR	Healthy controls (57)	Calcium	Serum
Eisinger et al, 1997 [39]	NR	FMS	25	Case-control	40	NR	Healthy controls (20)	Vitamin A, E, magnesium, selenium, zinc	Plasma
Eisinger et al, 1996 [40]	NR	FMS	25	Case-control	40	NR	Healthy controls (20)	Magnesium	Serum, erythrocytes, lencocytes

Table 1. Characteristics of included studies.

Study	Setting	Type of FSS	N of cases	Study design	Mean age in years (SD)	Mean FSS severity (SD) and/or mean duration in months (SD)	Comparison group (n)	Vitamin and/or mineral	Material
Heidari et al, 2010 [41]	Secondary care	FMS	17	Case-control	40.6 (8.3)	NR	Secondary care patients without FMS or musculoskeletal pain (202)	Vitamin D	Serum
Jammes et al, 2011 [42]	NR	CFS	5	Case-control	39 (8)	72 (12)	Healthy controls (23)	Vitamin C, potassium, sodium	Plasma
Jammes et al, 2009 [43]	Secondary care	CFS	18	Case-control	38 (5)	NR	Medical checkup patients (9)	Vitamin C	Plasma
Kasapoğlu Aksoy et al, 2016 [44]	Secondary care	FMS	53	Case-control	48.2 (9.6)	VAS pain (0-10) median, min-max: 8.0 (4.0-10.0)	Healthy controls (47)	Vitamin D	Serum
Khalifa et al, 2016 [45]	Secondary care	FMS	31	Case-control	40.2 (13.3)	FIQR mean: 32.4	Healthy controls (21)	Calcium, copper, magnesium, zinc	Serum
Kim et al, 2011 [46]	Secondary care	FMS	44	Case-control	42.5 (6.9)	NR	Healthy controls (122)	Calcium, copper, ferritin, magnesium, manganese, phosphorus, potassium, selenium, sodium, zinc	Hair
Kurup et al, 2003 [47]	Secondary care	CFS	15	Case-control	30–40 range	NR	Healthy controls (15)	Vitamin E, magnesium	Plasma, RBC
La Rubia et al, 2013 [48]	NA	FMS	45	Case-control	52.2 (7.5)	FIQ: 61.4 (13.1)	Healthy controls (25)	Copper, ferritin, iron, zinc	Serum

Table 1. Continued.

Study	Setting	Type of FSS	N of cases	Study design	Mean age in years (SD)	Mean FSS severity (SD) and/or mean duration in months (SD)	Comparison group (n)	Vitamin and/or mineral	Material
Maafi et al, 2016 [49]	Tertiary care	FMS	74	Case-control	37.9 (9.8)	FIQR: 51.8 (17.2) 13.2 (6.2)	Healthy controls (68)	Vitamin D, calcium, phosphorus	Serum
Mader et al, 2012 [50]	Secondary care	FMS	84	Case-control	52 (12)	FIQ: 57.1 (20.2)	Healthy controls (87)	Ferritin, iron	Serum
Maes et al, 2006 [51]	Secondary care	CFS	12	Case-control	41.9 (13.2)	NR	Healthy controls (12)	Zinc	Serum
Mateos et al, 2014 [52]	Secondary care	FMS	205	Case-control	51.5 (9.6)	NR	Healthy controls (205)	Vitamin D, calcium	Serum
McCully et al, 2005 [53]	NR	CFS	20	Case-control	NR	NR	Healthy sedentary controls (11)	Magnesium	Skeletal muscle
Mechtouf et al, 1998 [54]	NR	FMS	54	Case-control	Min-max: 20-75	NR	Healthy controls (36)	Vitamin B1	Plasma
Miwa et al, 2010 [55]	Secondary care	CFS	27	Case-control	29 (6)	NR	Secondary care patients free from fatigue for at least a month (27)	Vitamin E	Serum
Miwa et al, 2008 [56]	NR	CFS	50	Case-control	NR	NR	Healthy controls (40)	Vitamin E	Serum
Nazıroğlu et al, 2010 [57]	Secondary care	FMS	31	RCT and case-control	40.1 (5.2)	Number tender points: 15 (2)	Healthy controls (30)	Vitamin A, C, E	Plasma
Ng et al, 1999 [58]	Secondary care	FMS	12	Case-control	44.6	NR	Healthy controls (12)	Calcium, magnesium	Hair
Norregaard et al, 1994 [59]	NR	FMS	15	Case-control	49	NR	Healthy controls (15)	Potassium	Plasma
Okyay et al, 2016 [60]	Tertiary care	FMS	79	Case-control	37 (9)	NR	Healthy controls (80)	Vitamin D	Serum

Table 1. Characteristics of included studies.

Study	Setting	Type of FSS	N of cases	Study design	Mean age in years (SD)	Mean FSS severity (SD) and/or mean duration in months (SD)	Comparison group (n)	Vitamin and/or mineral	Material
Olama et al, 2013 [61]	Secondary care	FMS	50	Case-control	32.3 (9.4)	47 (24)	Healthy controls (50)	Vitamin D, calcium, phosphorus	Serum
Ortancil et al, 2010 [62]	Secondary care	FMS	46	Case-control	46.9 (10.6)	FIQ: 60.0 (10.9)	Healthy controls (46)	Vitamin B12, ferritin, folic acid	Serum
Özcan et al, 2014 [63]	Secondary care	FMS	60	Case-control	41.9 (9.8)	FIQ: 58.6 (10.3) 27.3 (17.3)	Healthy controls (30)	Vitamin D	Serum
Reinhard et al, 1998 [64]	Secondary care	FMS	68	Case-control	47	NR	Blood donors without FMS or musculoskeletal pain (97)	Selenium	Serum
Rezende Pena et al, 2010 [65]	Secondary care	FMS	87	Case-control	44.9 (8.6)	Number tender points: 14 (5)	Secondary care patients without FMS or musculoskeletal pain (92)	Vitamin D	Serum
Rosborg et al, 2007 [66]	Secondary care	FMS	38	Case-control	Median (min-max): 49 (31-71)	NR	Healthy controls (41)	Calcium, copper, ferritin, iodine, magnesium, molybdenum, potassium, selenium, sodium, zinc	Whole blood, fasting urine
Sakarya et al, 2011 [67]	NR	FMS	40	Case-control	33.6 (7.6)	FIQ: 61.3 (9.2)	Healthy controls (40)	Vitamin A, C, E, magnesium	Plasma
Samborski et al, 1997 [68]	Secondary care	FMS	60	Case-control	46,4 (9.8)	NR	Healthy controls (20)	Calcium	Plasma
Sendur et al, 2008 [69]	NR	FMS	32	Case-control	42.9 (7.7)	FIQ: 53.3 (7.9)	Healthy controls (32)	Magnesium, selenium, zinc	Serum

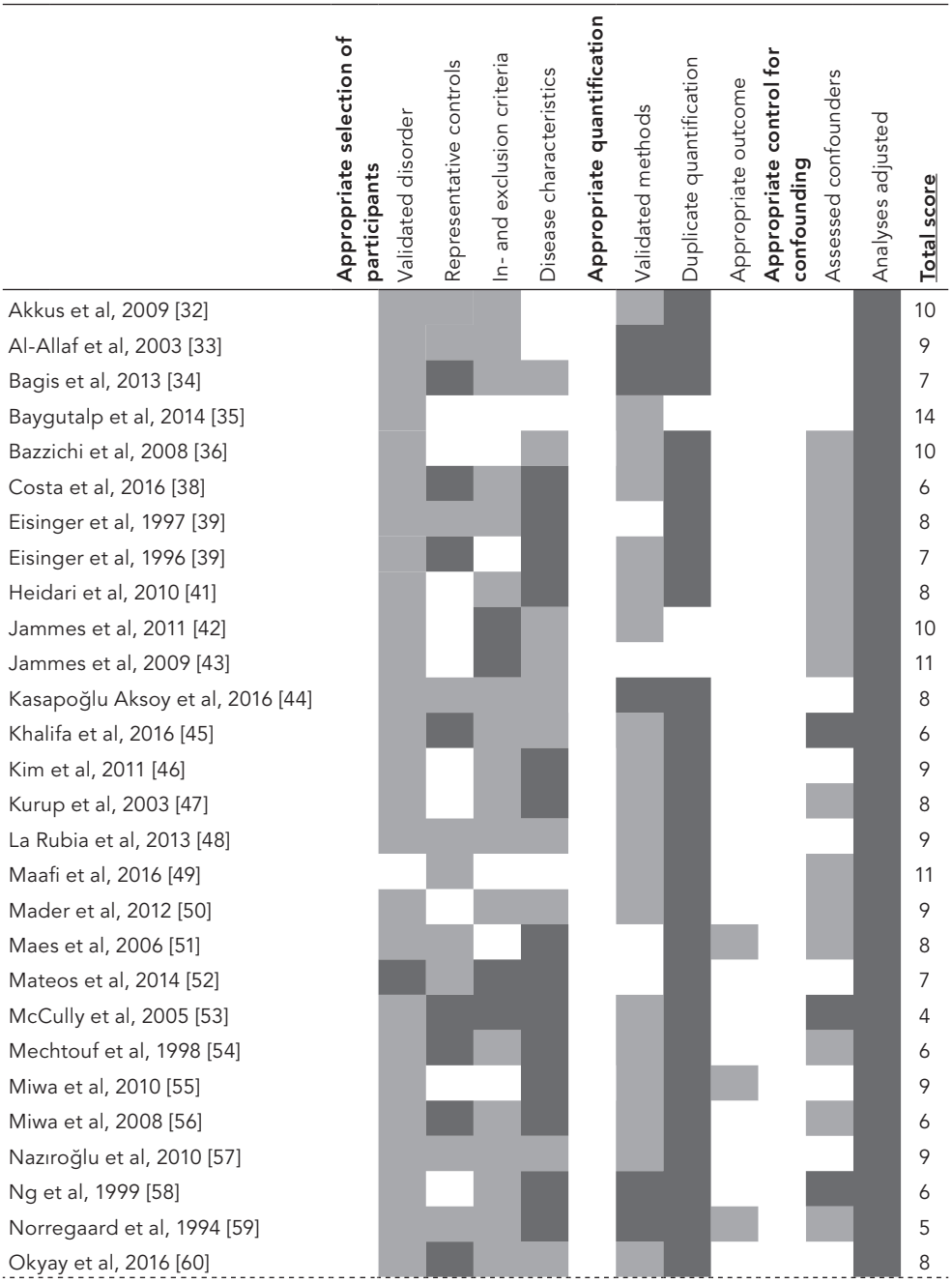
Table 1. Continued.

Study	Setting	Type of FSS	N of cases	Study design	Mean age in years (SD)	Mean FSS severity (SD) and/or mean duration in months (SD)	Comparison group (n)	Vitamin and/or mineral	Material
Tandeter et al, 2009 [70]	Secondary care	FMS	68	Case-control	43.8 (7.6)	NR	Regular periodic blood tests patients with no FMS (82)	Vitamin D	Serum
Türkyilmaz et al, 2010 [71]	Secondary care	FMS	30	Case-control	39.8 (6.2)	SF- 36: 47.4 (17.3) 72 (62.2)	Healthy controls (30)	Vitamin D, calcium, phosphorus	Serum
Ulusoy et al, 2010 [72]	NR	FMS	30	Case-control	32.2 (6.8)	FIQ: 64.7 (14.3) 32.7 (19.7)	Healthy controls (30)	Vitamin D, calcium, phosphorus	Serum
Vecchiet et al, 2002 [73]	Secondary care	CFS	21	Case-control	42 (8)	VAS muscle fatigue (0-100): 52.9 (4.9) 44.5 (27.6)	Healthy controls (20)	Vitamin E	Plasma, LDL
Wepner et al, 2014 [74]	General population and secondary care	FMS	15	RCT and cross-sectional	Overall (n=30) 48.3 (5.3)	Number tender points: 15 (2)	Placebo, FMS patients (15)	Vitamin D	Serum
Witham et al, 2015 [75]	Secondary care	CFS	25	RCT and case-control	48.1 (12.0)	Piper fatigue scale: 6.3 (1.6)	Placebo, CFS patients (25)	*RCT*: depending on serum levels 2400 or 1200 IU cholecalciferol *Observational*: Vitamin D	Serum
Yildirim et al, 2016 [76]	NR	FMS	99	Case-control	49.4 (9.2)	FIQ: 62.9 (17.7)	Healthy controls (99)	Vitamin D	Serum

CFS = chronic fatigue syndrome, CIS = checklist individual strength (8-56), FIQ = fibromyalgia impact questionnaire (0-100), FIQR = revised fibromyalgia impact questionnaire (0-100), FMS = fibromyalgia syndrome, FSS = functional somatic syndrome, NR = not reported, RBC = red blood cells, RCT = randomised controlled trail, VAS = visual analogue scale.

Table 2. Results of the quality assessment.

A) Quality scores observational studies.



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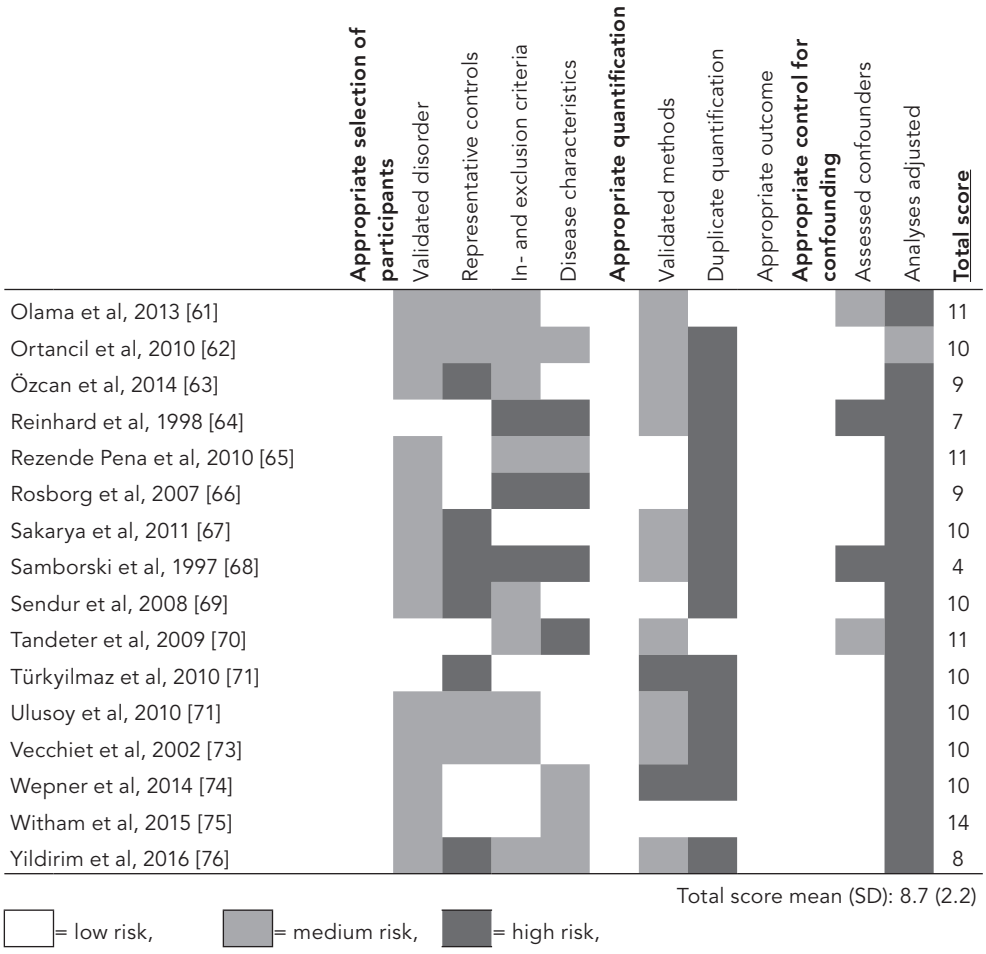
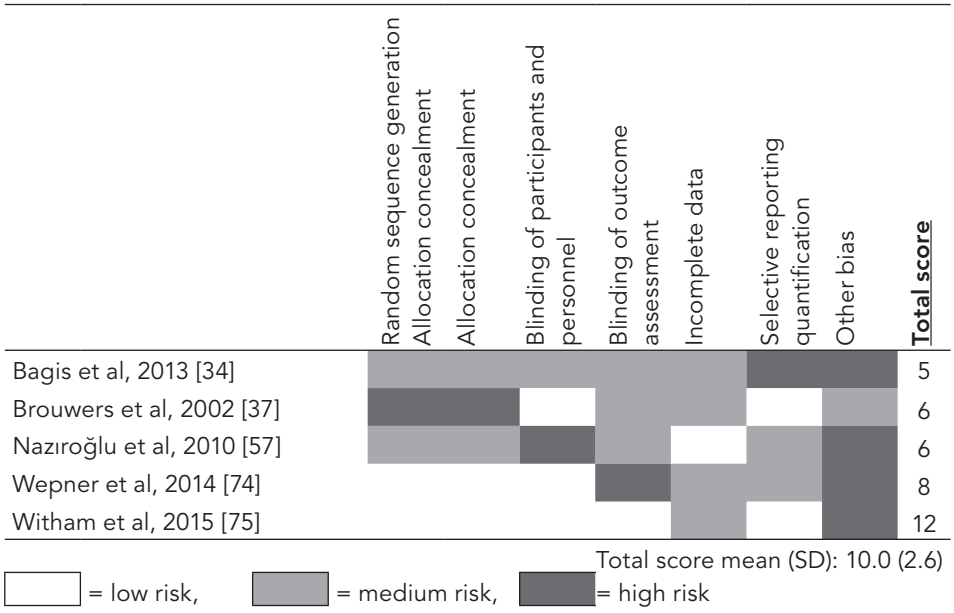


According to the quality tool to assess methodological quality of vitamin and mineral studies in CFS and FMS (S2 Appendix).

Table 2. Continued.

B) Quality scores randomized controlled trails.



According to the Cochrane Collaboration's tool.

Systematic review

Studies that were not included in the meta-analyses are presented in Table 3.

Table 3. Vitamin and mineral status in the included studies.

	Patients		Controls			
Study	**Mean**	**SD**	**Mean**	**SD**	**Statistically significant**	**Linked to clinical parameter**
Vitamin A						
Akkus et al, 2009 [32]	0.30 µmol/l	0.10	0.45	0.16	p<.01	NR
Eisinger et al, 1997 [39]	2.7 µmol/l	1.5	2.3	0.9	NS	NR
Nazıroğlu et al, 2010 [57]	1.5 µmol/l	0.5	2.4	0.2	p<.05	NR
Sakarya et al, 2011 [67]	1.46 mmol/l	0.47	1.25	0.26	NS	*FIQ Pearson's correlation coefficient*: -0.083 (NS)
Vitamin B1						
Mechtouf et al, 1998 [54]	58 ng/ml	38.9	49.6	14.8	p<.05	NR

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Vitamin B12						
Ortancil et al, 2010 [62]	297.6 pg/ml	120.7	295.7	113.0	NS	NR
Vitamin C						
Sakarya et al, 2011 [67]	x	x	x	x	x	*FIQ Pearson's correlation coefficient*: -0.115 (NS)
Vitamin D						
Al-Allaf et al, 2003 [33]	<20nmol/l (n (%)):	18 (45)	n (%):	7 (18.9%)	p<0.015	NR
Baygutalp et al, 2014 [35]	x	x	x	x	x	*FIQ Spearman correlation:* 0.231 (NS)
Kasapoğlu Aksoy et al, 2016 [44]	x	x	x	x	x	*<30 ng/ml vs >30 ng/ml in FMS:* *VAS pain:* 8.4 (1.6) *vs* 6.7 (2.0) p=.002 *FIQ:* 65.4 (12.0) *vs* 57.2 (16.1) p=.088
Maafi et al, 2016 [49]	x	x	x	x	x	*FIQR Spearman correlation:* -0.093 (NS) *Number of tender points:* -0.194 (NS) *VAS pain*: -0.097 (NS)
Okyay et al, 2016 [60]	x	x	x	x	x	*<20 ngl/ml vs 20-30 vs >30 ng/ml in FMS:* *FIQ:* 56.6 (8.9) *vs* 48.8 (2.8) *vs* 41.4 (8.2) p=.000 *VAS pain*: 7.4 (1.4) *vs* 6.4 (0.5) *vs* 5.1 (1.0) p=.000 *FIQ Spearman correlation*: -0.621 (p=.000) *VAS pain Spearman correlation*: -0.578 (p=.000)

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Vitamin D						
Rezende Pena et al, 2010 [65]	x	x	x	x	x	*Number of tender points Pearson's correlation coefficient*: -0.160 (NS) *VAS pain*: -0.196 (NS)
Ulusoy et al, 2010 [72]	<20ng/l (n (%)):	26 (86.7)	n (%):	29 (96.7)	NS	*FIQ Pearson's correlation coefficient*: 0.071 (NS)
Wepner et al, 2014 [74]	19.94 ng/ml	6.066	NR	NR	NR	NR
Witham et al, 2015 [75]	44 and 48 nmol/l	15 and 20	NR	NR	NR	*Piper fatigue scale*: no improvement after vitamin D3 treatment
Yildirim et al, 2016 [76]	x	x	x	x	x	*FIQ Pearson's correlation coefficient:* r=0.112 (NS) *VAS pain:* r=0.104 (NS)
Vitamin E						
Kurup et al, 2003 [47]	5.22 µg/ml RBC	0.31	5.25	0.33	NS	NR
Miwa et al, 2010 [55]	2.81 mg/g lipids	0.73	3.88	0.65	p<.001	NR
Miwa et al, 2008 [56]	3.03 mg/g lipids	0.72	3.78	0.66	p<.001	NR
Sakarya et al, 2011 [67]	x	x	x	x	x	*FIQ Pearson's correlation coefficient:* −0.171 (NS)
Vecchiet et al, 2002 [73]	9.5 µmol/mg LDL	1.0	18.0	1.5	p<.001	*Linear regression analyses fatigue versus vitamin E in plasma:* Y=56.674-0.4467X r=-0.6098 (p < 0.004)

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Calcium						
Bazzichi et al, 2008 [36]	231.0 nM platelet	13.75 (SEM)	198.3	10.40	NS	NR
Kim et al, 2011 [46]	775 µg/g	439-1,366 (95%CI)	1,093	591-2,020	p=.001	NR
Ng et al, 1999 [58]	2288.4 µg/g hair	1486.2	846.3	645.7	p=.025	NR
Rosborg et al, 2007 [66]	49 mg/l (median whole blood) 72.8 mg/l (median urine)	28.5-62.2 <29 – 258 (range)	48.0 74.5	39.7-58.5 <29 - 519	NS	NR
Copper						
Khalifa et al, 2016 [45]	145.8 µg/dl	17.34	116.50	14.35	p<.05	NR
Kim et al, 2011 [46]	28.3 µg/g	11.8-68.1 (95%CI)	40.2	16.1-100.0	p=.029	NR
La Rubia et al, 2013 [48]	105.99 mg/dl	17.03	83.55	9.20	p<.001	NR
Rosborg et al, 2007 [66]	971 µg/l (median whole blood) 28.1 µg/l (median urine)	620-1740 6.7-186 (range)	855 34.7	690-1475 8.6-92.2	p=.002 NS	NR
Ferritin						
Kim et al, 2011 [46]	5.90 µg/g	4.21-8.26 (95%CI)	7.10	4.73-10.66	p=.007	NR
La Rubia et al, 2013 [48]	52.33 g/dl	15.07	57.42	17.01	NS	NR
Mader et al, 2012 [50]	63.68 ng/ml ≤30 ng/mL n (%): 23 (27.4)	49.72	53.70 n (%): 38 (43.7)	46.24	p=.18 p<.04	*FIQ Spearman correlation*: NS
Ortancil et al, 2010 [62]	27.3 ng/ml <50 ng/mL n (%): 40 (87.0)	20.9	43.8 n (%): 26 (56.5)	30.8	p=.035 p=.001	*FIQ Spearman correlation:* NS
Rosborg et al, 2007 [66]	422 mg/l (median)	245-585 (range)	400	273-465	p=.046	NR
Folic acid						
Ortancil et al, 2010 [62]	9.2 ng/ml	3.1	8.9	2.5	NS	NR

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Iodine						
Rosborg et al, 2007 [66]	<650 µg/l (median whole blood) 788 µg/l (median urine)	<650-1900 <130-5395 (range)	<650 2000	<650-693 <130-12145	NS p=.001	NR
Iron						
La Rubia et al, 2013 [48]	81.82 mg/dl	34.64	83	30.07	NS	NR
Mader et al, 2012 [50]	82.32 µg/dl	32.75	75.31	29.13	NS	*FIQ Spearman correlation*: NS
Magnesium						
Bagis et al, 2013 [34]	Erythrocyte: 2.27/2.70/2.91 mmol/l	0.41/0.47/0.42	3.22 mmol/l	0.36	p<.001	*FIQ Pearson's correlation serum Mg*: -0.426 (p<.001) *Erythrocyte Mg*: -0.309 (p=.013)
Bazzichi et al, 2008 [36]	1.30 mM platelet	0.079 (SEM)	1.07	0.056	p=.02	NR
Eisinger et al, 1997 [39]	2.36 mmol/l erythrocyte	0.24	2.39	0.24	NS	NR
Eisinger et al, 1996 [40]	4.9 fmol/cell lencocyte	1.7	3.9	1.3	NS	NR
Kim et al, 2011 [46]	52 µg/g	25-107 (95%CI)	72	36-147	p=.008	NR
McCully et al, 2005 [53]	0.47 mM muscle	0.07	0.36	0.06	p<.01	NR
Ng et al, 1999 [58]	84.7 µg/g hair	73.3	46.8	28.9	p=.05	NR
Rosborg et al, 2007 [66]	28.6 mg/l (median whole blood) 47.1 mg/l (median urine)	24.5-37.8 <25-189 (range)	28.2 60.5	23.2-37.2 <25-171	NS	NR
Sakarya et al, 2011 [67]	x	x	x	x	x	*FIQ Pearson's correlation coefficient*: 0.014 (NS)
Sendur et al, 2008 [69]	x	x	x	x	x	*FIQ Pearson's correlation coefficient*: -0.040 (NS)
Manganese						
Kim et al, 2011 [46]	140 ng/g	80-260 (95%CI)	190	80-480	p=.029	NR

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Molybdenum						
Rosborg et al, 2007 [66]	0.6 µg/l (median)	<0.25-4.4 (range)	0.6	<0.25-5.7	NS	NR
Phosphorus						
Kim et al, 2011 [46]	146 µg/g	116-183 (95%CI)	143	116-176	NS	NR
Maafi et al, 2016 [49]	3.6 mg/dl	0.47	3.66	0.54	NS	NR
Olama et al, 2013 [61]	3.55 mg/dl	0.12	3.6	0.16	NS	NR
Türkyilmaz et al, 2010 [71]	3.2 mg/dl	0.4	3.3	0.5	NS	NR
Ulusoy et al, 2010 [72]	3.54 mg/dl	0.56	3.57	0.46	NS	NR
Polynutrient supplement						
Brouwers et al, 2002 [37]	Baseline CIS: 51.4 Follow up CIS: 48.6	4.2 7.4	51.3 48.2	3.6 7.6	NS	NR
Potassium						
Jammes et al, 2011 [42]	3.92 mmol/l	0.12	3.99	0.08	NS	NR
Kim et al, 2011 [46]	75 µg/g	25-219 (95%CI)	56	23-138	NS	NR
Norregaard et al, 1994 [59]	3.25 mmol/l (median)	NR	3.9	NR	NS	NR
Rosborg et al, 2007 [66]	926 mg/l (median urine)	205-3300 (range)	1410	378-5200	p=.013	NR
Selenium						
Eisinger et al, 1997 [39]	83 ng/ml	17	87	12	NS	NR
Kim et al, 2011 [46]	75 µg/g	25-219 (95%CI)	56	23-138	NS	NR
Reinhard et al, 1998 [64]	Median: 70.8 µg/l	67.7-75.3 (95%CI)	76.8	73.4-81.6	p<.05	NR
Rosborg et al, 2007 [66]	117 µg/l (median whole blood) 18.4 µg/l (median urine)	77.6-207 5.5-55.7 (range)	105 23.5	66.4-137 2.3-52.2	p=.015 NS	NR
Sendur et al, 2008 [69]	44.4 µg/dl	12.1	38.7	13.9	NS	*FIQ Pearson's correlation coefficient*: 0.011 (NS)

Table 3. Continued.

Study	Patients Mean	SD	Controls Mean	SD	Statistically significant	Linked to clinical parameter
Sodium						
Jammes et al, 2011 [42]	138 mmol/l	0.5	140	0.4	NS	NR
Kim et al, 2011 [46]	78 µg/g	31-195 (95%CI)	72	27-195	NS	NR
Rosborg et al, 2007 [66]	1560 mg/l (median urine)	90.8-3705 (range)	1700	510-4790	NS	NR
Zinc						
Eisinger et al, 1997 [39]	16.9 mmol/l	1.8	16.1	1.9	NS	NR
Khalifa et al, 2016 [45]	75.87 µg/dL	5.5	93.21	11.94	p<.05	NR
Kim et al, 2011 [46]	167 µg/g	120-232 (95%CI)	165	125-217	NS	NR
La Rubia et al, 2013 [48]	66.48 ng/ml	18.82	106.8	22.41	p<.001	*PCS-12 Pearson's correlation coefficient:* 0.402 (p=.017)
Maes et al, 2006 [51]	73.5 mg/dl	NR	87	NR	p=.0001	*Fibrofatigue scale Pearson's correlation coefficient:* -0.039 (NS)
Rosborg et al, 2007 [66]	6000 µg/l (median whole blood) 294 µg/l (median urine)	3720-9400 35.8-1230 (range)	5450 290	3900-7300 35.0-66.5	p=.026 NS	NR
Sendur et al, 2008 [69]	102.8 µg/dl	24.7	77.2	31	p=.001	*FIQ Pearson's correlation coefficient*: -0.106 (NS)

CI = confidence interval, CIS = checklist individual strength, FIQ = fibromyalgia impact questionnaire, FIQR = revised fibromyalgia impact questionnaire, NR = not reported, NS = not significant, PCS = physical component summary, SD = standard deviation, VAS = visual analogue scale, x = reported in meta-analyses.

Interventions

Five RCTs were included. The first RCT determined the effect of magnesium citrate treatment in combination with amitriptyline versus amitriptyline only, on FMS symptoms, over a period of 8 weeks [34]. They found that amitriptyline and

magnesium supplementation was more effective on all measured outcomes than amitriptyline alone. The second RCT investigated the effect of a polynutrient supplement (containing several vitamins (including A, B, C, D, E), minerals (including calcium, magnesium) and (co)enzymes), on fatigue and physical activity of patients with CFS, over a period of 10 weeks [37]. They found no significant difference between the placebo and treatment group on any of the outcome measures. A third RCT examined vitamin C and E treatment combined with exercise versus exercise only, in FMS patients, over a period of 12 weeks [57]. Although both interventions lead to significantly higher vitamin A, C, and E serum levels, the FMS symptoms did not improve in both groups. Furthermore, the most recent RCT investigated the effect of vitamin D, on symptoms in CFS patients, over a period of 6 months [75]. Despite a statistically significant increase in vitamin D, they found no evidence of improvement in symptoms of fatigue or depression. Lastly, in the fifth RCT, cholecalciferol was administered for 20 weeks in FMS patients, with the dosage depending on patients calcifediol levels [74]. A significant treatment effect on intensity of pain was found in the treatment group versus placebo. No changes in somatization, depression and anxiety, physical and mental health, and FMS symptom severity were observed in both the treatment and placebo group.

Clinical parameters

All studies investigating vitamin A (n=1) [67], vitamin C (n=1) [67], ferritin (n=2) [50,62], iron (n=1) [50], and selenium (n=1) [69], found no significant associations between vitamin and mineral status and clinical parameters in FMS patients (Table 3). Most studies investigating vitamin D (n=6) found no significant associations between vitamin D and clinical parameters in CFS [75] and FMS [35,49,65,72,76] patients. However, two studies found significantly higher VAS-score for pain in patients with vitamin D levels <30 ng/ml compared to FMS patients with vitamin D levels of >30ng/ml [44,60]. Significant negative associations were found for vitamin E in plasma and fatigue in CFS patients (n=1/2) [73], and serum and erythrocyte magnesium and fibromyalgia symptoms (n=1/3) [34]. A significant positive association was found for serum zinc and somatic symptoms in fibromyalgia patients (n=1/3) [48].

Vitamin and mineral status

All studies that investigated vitamin B12 (n=1) [62], folic acid (n=1) [62], iron (n=2) [48,50], molybdenum (n=1) [66], phosphorus (n=4) [46,49,61,71,72] sodium (n=3)

[42,46,66], and iodine (n=1) [66], and the majority of studies that investigated potassium (n=3/4) [42,46,59], and selenium status (n=4/5) [39,46,66,69] found no statistically significant difference between patients and controls (Table 3). In contrast, all studies that investigated vitamin B1 (n=1/1) [54], and manganese (n=1/1) [46], and the majority of studies that investigated vitamin A (n=2/4) [39,67], found statistically significant lower serum values in patients versus controls. The majority of the studies that were not suitable for inclusion in the meta-analyses reported significantly lower vitamin E in patients versus controls (n=3/4) [55,56,73]. Statistically significant results were found in the majority of the included studies investigating copper (n=3/4) [46,48,66], ferritin (n=4/5) [46,50,62,66], and zinc (n=5/7) status [48,51,66,69]. However, the direction of the differences was equivocal for all three minerals: levels of copper were higher among patients in 3 studies and lower in 1, levels ferritin were higher among patients in 2 studies and lower in 2, and levels of zinc were lower in 3 studies and higher in 2.

Meta-analysis

Vitamin C, vitamin D, vitamin D deficiency (<20ng/ml), vitamin E (Fig 2), and the minerals calcium, and magnesium status, and were reported in more than five studies and were therefore investigated using meta-analysis (Fig 3). Meta-analysis revealed that circulating concentrations of vitamin E were lower in patients compared to controls (patients n=162, controls n=140; pooled SMD:-1.57, 95%CI:-3.09,-0.05; p=.042). No differences were found in patients compared to controls in circulating concentrations of vitamin C (patients n=124, controls n=132; pooled SMD:-0.55, 95%CI:-1.38,0.28; p=.19), vitamin D (patients n=871, controls n=1039; pooled SMD:-0.17, 95%CI:-0.41,0.06; p=.15), and vitamin D deficiency (patients n=435, controls n=604; pooled OR:0.23, 95%CI:-0.54,0.99; p=.17). There were no differences between patients and controls in circulating concentrations of the minerals calcium (patients n=620, controls n=518; pooled SMD:-0.15, 95%CI:-0.50,0.19; p=.38), and magnesium (patients n=218, controls n=148; pooled SMD:-0.59, 95%CI:-1.33,0.15; p=.12). All analyses revealed substantial to considerable heterogeneity in the effect sizes, as can be found in Fig 2.

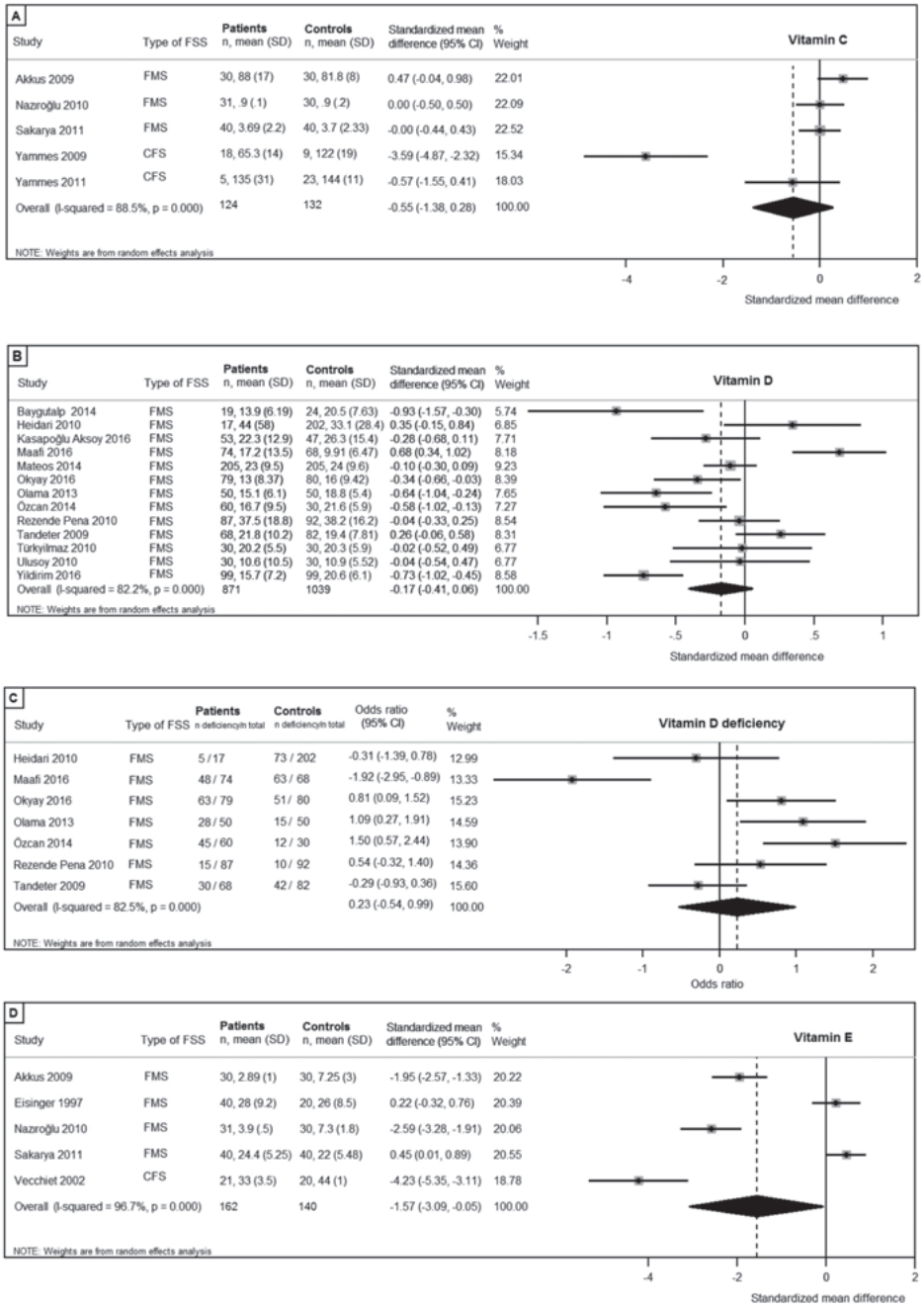


Figure 2. Forest plots of studies investigating vitamins.
(A) Vitamin C; (B) Vitamin D; (C) Vitamin D deficiency (<20ng/ml); (D) Vitamin E.

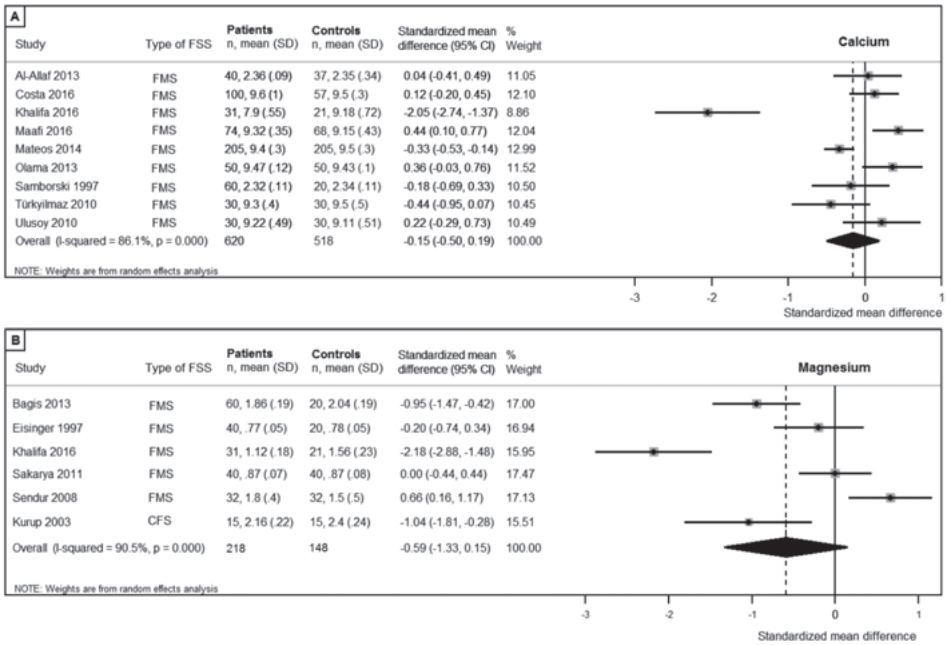


Figure 3. Forest plots of studies investigating minerals. (A) Calcium; (B) Magnesium.

Subgroup analyses

Subgroup analyses were performed including studies with more than half the maximum study quality score (>9 quality points), if more than three studies with a sufficient quality score were available. The additional analysis was not possible for magnesium, since only two studies achieved more than half of the maximum quality score. No differences in circulating concentrations of vitamin C (patients n=93, controls n=102, pooled SMD:-0.78, 95CI:-1.95, 0.39; p=.19) [32,42,43,67], vitamin D (patients n= 358, controls n= 376, pooled SMD:-0.07, 95%CI:-0.44,0.30; p=.71) [35,49,61,65,70-72], vitamin D deficiency (patients n=121, controls n=130; pooled OR:-0.12, 95%CI:-1.24,1.01; p=.84) [49,61,65,70], and calcium = (patients n=184, controls n=178; pooled SMD:0.18 95%CI:-0.18,0.54; p=.34) [49,61,71,72] were found. The significant difference in circulating concentrations of vitamin E between patients and controls disappeared when studies with low quality score were excluded (patients n=91, controls n=90, pooled SMD: -1.86, 95%CI:-4.28, 0.56; p=.13) [32,67,73].

Subgroup analyses were performed separately for the syndromes, when more than three studies were available per syndrome. Since vitamin D, vitamin D

deficiency and calcium were only determined in FMS patients, additional subgroup analyses were possible for vitamin C, vitamin E and magnesium. No statistically significant difference between patients and controls was found in the three studies investigating circulating concentrations of vitamin C in FMS patients (patients n=101, controls n=100; pooled SMD:0.14, 95%CI:-0.16,0.44; p=.32). However, the heterogeneity was substantially lower (I^2=13.3% versus 88.5% in the overall analysis including CFS patients), indicating a high consistency of studies' results. The significant difference in circulating concentrations of vitamin E between patients and controls disappeared when the single CFS study was excluded (patients n=141, controls n=120; pooled SMD:-0.95, 95%CI:-2.41,0.50; p=.20. Lastly, no considerable differences were found in analyses of the five studies investigating circulating concentrations of magnesium in FMS patients (patients n=203, controls n=133; pooled SMD:-0.51, 95%CI:-1.34,0.32; p=.23).

Publication bias

Finally, we tested whether publication bias could have affected the results. Corresponding funnel plots can be found in Fig 4. Egger's test showed that there was significant funnel plot asymmetry in vitamin E (p=.039), with no significant asymmetry among the other analyses. Trimming was performed in the calcium studies using the Trim and Fill test, and the contour-enhanced funnel plot revealed two added studies in the statistically significant areas. No studies were trimmed or filled among the vitamin C, vitamin D, vitamin D deficiency, vitamin E, and magnesium studies, indicating absence of substantial publication bias.

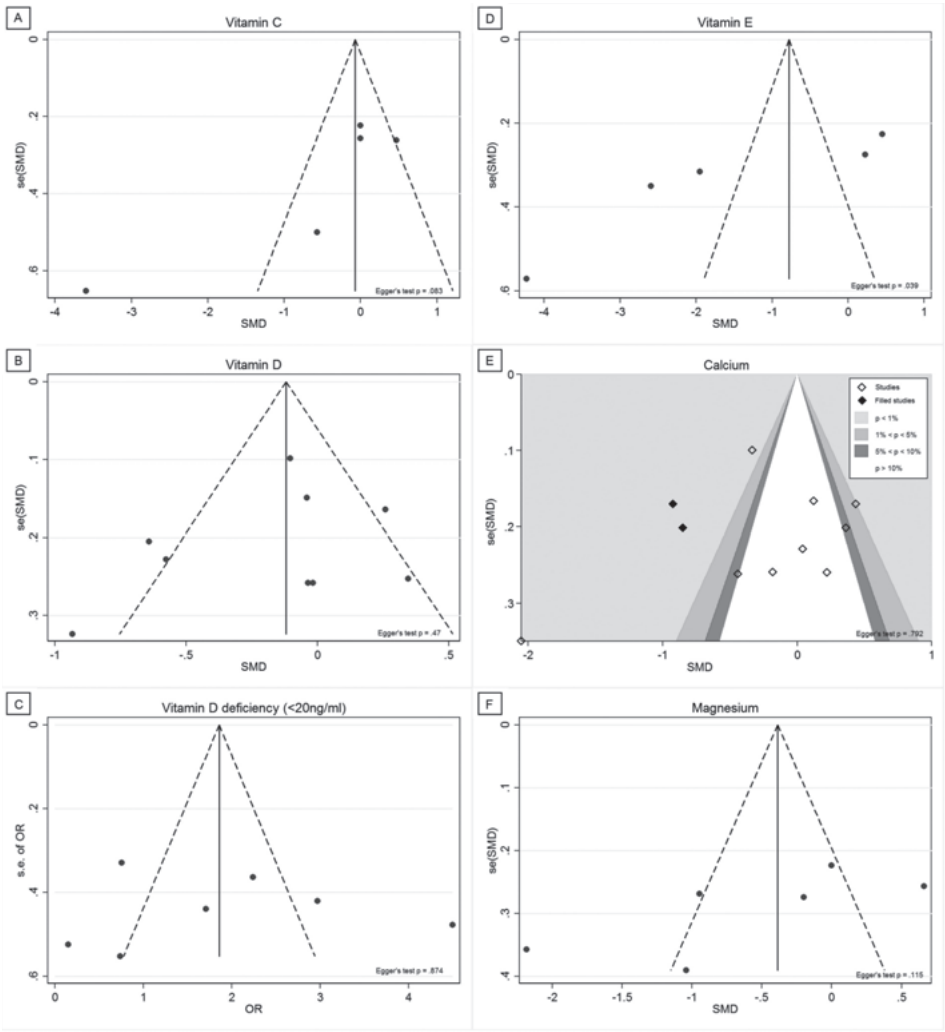


Figure 4. Funnel plots. (A) Vitamin C; (B) Vitamin D; (C) Vitamin D deficiency (<20ng/ml); (D) Vitamin E; (E) Calcium; (F) Magnesium.

DISCUSSION

We found little evidence 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. Poor study quality and considerable heterogeneity in most studies was found, which makes it difficult to reach a final conclusion. Consistent significant lower circulating concentrations

were found repeatedly and in the majority of studies for vitamin A and vitamin E in patients compared to controls. However, the significant difference in circulating concentrations of vitamin E between patients and controls disappeared when excluding low quality studies. None of these or other vitamins and minerals have been repeatedly or consistently linked to clinical parameters. In addition, RCTs testing supplements containing these vitamins and/or minerals did not result in clinical improvements.

This review has several strengths. First, this is the first review focusing on vitamin and mineral deficiencies among CFS and FMS patients. We were able to give a clear overview of the current knowledge existing in literature. Second, we included only studies that examined CFS and FMS patients according to the official diagnostic criteria. We therefore have included relatively homogeneous groups of patients. Third, because we defined strict in- and exclusion criteria, e.g. patients should meet the official diagnostic criteria, or clinical cohorts must have an appropriate control group, poor quality studies were filtered out. Nevertheless, the vast majority of the included studies scored a quality score below a reasonable study quality. Fourth, enough studies that investigated similar vitamins or minerals were available, which made it possible to conduct six meta-analyses. Lastly, we had no language restrictions for the included abstracts or full text articles, which enabled us to include all relevant articles.

We must acknowledge that this study also has its limitations, which are mostly due to limitations in original studies on which this review was based. First, most studies were observational in nature. In general, observational studies have a lower validity than RCTs, and they are more susceptible to bias (e.g. selection and information bias) and confounding factors. Potential confounders were assessed in about half of the studies, but almost no studies adjusted their analyses for potential confounders. Consequently, the results of the current review may be affected by the methodological weaknesses that are accompanied by the observational study designs. Second, quality assessment revealed a poor study quality in the majority of studies. This demonstrates that substantial improvements can be made in terms of study quality, especially in specification of in- and exclusion criteria, presenting disease characteristics of the participants, making use of validated methods to assess vitamin and mineral status, to perform the vitamin and mineral assessments in duplicate, and, as mentioned earlier, to adjust analyses for potential

confounders. Furthermore, a quality issue in research on CFS and FMS patients is that of careful selection of control groups. Our quality assessment showed that many included studies fell short because of the selection of the controls, which could result in inaccurate study results. Third, a problem that affects the validity of meta-analyses is the presence of publication bias. Funnel plots indicated the absence of publication bias in the majority of the meta-analyses. Trimming was performed among the calcium studies, and two "missing" studies were added, while no significant funnel plot asymmetry was present. However, trimming was performed in the statistically significant areas, which argues against the presence of publication bias. Although Egger's test is preferred for more than 10 studies, it revealed significant funnel plot asymmetry in vitamin E, while no trimming was performed. It is therefore possible that the significant outcomes of vitamin E in patients are influenced by publication bias. Lastly, a substantial to considerable heterogeneity in most studies was found, which makes it difficult to reach a final conclusion about vitamin status in CFS and FMS patients.

This review reveals that very few RCTs have investigated the effect of vitamin and mineral supplementation versus placebo in CFS and FMS patients. Most published RCTs found no treatment effect of vitamin and mineral supplementation on clinical parameters. So, the evidence for beneficial effects of supplementation in CFS and FMS patients is not proportional to the large quantity of supplements that are used by these patients. Nevertheless, the industry of vitamin and minerals supplements is increasing, for example, Americans spend an estimated $36.7 billion each year on supplements [77]. This is important information, since the vitamins and minerals in these products are sometimes supplemented in doses high enough to cause side effects, for example gastric discomfort, insomnia, dizziness or weakness [17]. The vast majority of available studies concerned FMS patients. Several FMS studies investigated vitamin D, whereas most CFS studies have focused on vitamin E. Only one CFS study that investigated vitamin E was suitable for inclusion in the meta-analysis. It is remarkable that the significant difference of vitamin E between patients and controls disappeared when the single CFS study was excluded in the sensitivity analysis, while the studies that were not suitable for inclusion in the meta-analysis reported significant lower vitamin E concentrations in particularly CFS patients versus controls. Further research is needed to determine whether this may indicate that vitamin E levels are lower in CFS patients, but not in FMS patients. This systematic review and

meta-analysis provides no further insights in whether the remaining vitamins and minerals differ between these two medical conditions.

We conclude that there is little evidence to support the hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of both CFS and FMS. Furthermore, the current literature on vitamins and minerals in CFS and FMS is of poor quality and stresses the need for well-performed intervention research, and large population-based and age-matched prospective studies in CFS and FMS, in order to gain more insight in the role of vitamins and minerals in the pathophysiology of CFS and FMS. According to our results, potential vitamins and minerals that should be further examined include vitamin A and vitamin E.

Acknowledgements
The authors wish to acknowledge the translators of the non-English articles (Léopold Brunet, Jurek Cislo, Anne-Marie Daubigney, Michele Eisenga, Giulia Iozzia, Akin Ozyilmaz, Mehmet Suludere), which made it possible to include all the articles in the current review.

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SUPPORTING INFORMATION

S1 Table. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Appendix

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7, 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8, 9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, 9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9, 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9, 10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8, 9, 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9, 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3, Figure 2, 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	28-30, Fig 2 + 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	30, Fig 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	29, 30
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	31-34
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32, 33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	34
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	35

S1 APPENDIX. SEARCH STRINGS.

PubMed:

("Fatigue Syndrome, Chronic"[Mesh] OR "Fibromyalgia"[Mesh] OR functional somatic syndrome*[tw] OR chronic fatigue*[tw] OR postviral fatigue[tw] OR post-viral fatigue[tw] OR fatigue syndrome*[tw] OR myalgic encephalomyelit*[tw] OR royal free disease*[tw] OR fibromyalg*[tw] OR fibrositis*[tw])
AND
("Micronutrients"[Mesh] OR "Minerals"[Mesh] OR "Vitamins" [Pharmacological Action] OR vitamin*[tw] OR mineral*[tw] OR nutrient*[tw] OR micronutrient*[tw] OR retinol*[tw] OR Thiamin*[tw] OR Riboflavin*[tw] OR Niacin*[tw] OR Pantothenic*[tw] OR Pyridoxin*[tw] OR Biotin*[tw] OR Folic*[tw] OR folate*[tw] OR Cobalamin*[tw] OR Ascorbic*[tw] OR Calciferol*[tw] OR Tocopherol*[tw] OR Phylloquinone*[tw] OR Menaquinone*[tw] OR Calcium*[tw] OR Chromium*[tw] OR Chlorine*[tw] OR Copper*[tw] OR Fluoride*[tw] OR Iodine*[tw] OR Iron*[tw] OR Manganese*[tw] OR Magnesium*[tw] OR Molybdenum*[tw] OR Phosphor[tw] OR phosphorus[tw] OR phosphoric[tw] OR Potassium*[tw] OR Selenium*[tw] OR Sodium*[tw] OR natrium*[tw] OR Zinc*[tw])
NOT
(("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Review" [Publication Type] OR systematic review [ti] OR animal* [ti] OR mouse[ti] OR mice[TI] OR rodent*[TI] OR rat[TI] OR rats[TI])

EMBASE:

'chronic fatigue syndrome'/exp OR 'fibromyalgia'/exp OR 'functional somatic syndrome':ab,ti OR 'chronic fatigue':ab,ti OR 'postviral fatigue':ab,ti OR 'post viral fatigue':ab,ti OR 'fatigue syndrome':ab,ti OR 'myalgic encephalomyelitis':ab,ti OR 'royal free disease':ab,ti OR fibromyalg*:ab,ti OR fibrositis*:ab,ti AND
('trace element'/exp OR 'mineral'/exp OR 'vitamin'/exp OR vitamin*:ab,ti OR mineral*:ab,ti OR nutrient*:ab,ti OR micronutrient*:ab,ti OR retinol*:ab,ti OR thiamin*:ab,ti OR riboflavin*:ab,ti OR niacin*:ab,ti OR pantothenic*:ab,ti OR pyridoxin*:ab,ti OR biotin*:ab,ti OR folic*:ab,ti OR folate*:ab,ti OR cobalamin*:ab,ti OR ascorbic*:ab,ti OR calciferol*:ab,ti OR tocopherol*:ab,ti OR phylloquinone*:ab,ti OR menaquinone*:ab,ti OR calcium*:ab,ti OR chromium*:ab,ti OR chlorine*:ab,ti OR copper*:ab,ti OR fluoride*:ab,ti OR iodine*:ab,ti OR iron*:ab,ti OR manganese*:ab,ti OR magnesium*:ab,ti OR molybdenum*:ab,ti OR phosphor:ab,ti OR phosphorus:ab,ti OR phosphoric:ab,ti OR potassium*:ab,ti OR selenium*:ab,ti OR sodium*:ab,ti

OR natrium*:ab,ti OR zinc*:ab,ti)
NOT
('animal experiment'/exp OR ('animal'/exp NOT 'human'/exp) OR 'systematic review'/exp OR 'review'/exp OR 'systematic review':ti OR animal*:ti OR mouse:ti OR mice:ti OR rat:ti OR rats:ti OR rodent*:ti)

Web of Knowledge:
TS=("chronic fatigue" OR "fatigue syndrome" OR "fibromyalgia" OR "postviral fatigue" OR "post viral fatigue" OR "myalgic encephalomyelitis" OR "royal free disease" OR "fibrositis")
AND
TS=(micronutrient* OR nutrient* OR vitamin* OR mineral* OR retinol* OR thiamin* OR riboflavin* OR niacin* OR pantothenic* OR pyridoxin* OR biotin* OR folic* OR folate* OR cobalamin* OR ascorbic* OR calciferol* OR tocopherol* OR phylloquinone* OR menaquinone* OR calcium* OR chromium* OR chlorine* OR copper* OR fluoride* OR iodine* OR iron* OR manganese* OR magnesium* OR molybdenum* OR "phosphor" OR "phosphorus" OR "phosphoric" OR potassium* OR selenium* OR sodium* OR natrium* OR zinc*)
NOT
TI=(review* OR animal* OR "mouse" OR "mice" OR "rat" OR "rats" OR rodent*)

PsycINFO:
(DE "Fibromyalgia" OR DE "Chronic Fatigue Syndrome" OR TX ("chronic fatigue" OR "fatigue syndrome" OR "fibromyalg*" OR "postviral fatigue" OR "post viral fatigue" OR "myalgic encephalomyelitis" OR "royal free disease" OR "fibrositis"))
AND
(DE "Vitamins" OR DE "Ascorbic Acid" OR DE "Choline" OR DE "Folic Acid" OR DE "Nicotinamide" OR DE "Nicotinic Acid" OR TX (micronutrient* OR nutrient* OR vitamin* OR mineral* OR retinol* OR thiamin* OR riboflavin* OR niacin* OR pantothenic* OR pyridoxin* OR biotin* OR folic* OR folate* OR cobalamin* OR ascorbic* OR calciferol* OR tocopherol* OR phylloquinone* OR menaquinone* OR calcium* OR chromium* OR chlorine* OR copper* OR fluoride* OR iodine* OR iron* OR manganese* OR magnesium* OR molybdenum* OR "phosphor" OR "phosphorus" OR "phosphoric" OR potassium* OR selenium* OR sodium* OR natrium* OR zinc*))
NOT
TI (review* OR animal* OR "mouse" OR "mice" OR "rat" OR "rats" OR rodent*)

S2 APPENDIX. QUALITY TOOL TO ASSESS METHODOLOGICAL QUALITY OF VITAMIN AND MINERAL STUDIES IN CFS AND FMS.

Key domain 1 (items 1-4): appropriate selection of participants.
Patients have to meet the international criteria; the CDC case definition for CFS [1], and the ACR criteria for the classification of FMS [2, 3]. An appropriate control group has to represent the population from which the cases arose. Poor reporting of recruitment strategies and the recruitment of healthy controls from medical students or hospital staff may lead to selection bias and may threaten the validity of reported results [4].

Several somatic conditions, for example celiac disease, inflammatory bowel disease [5], diabetes [6], hypertension [7], cancer [8], and psychiatric conditions, such as anorexia or bulimia nervosa [9], and major depressive disorder [10], have been associated with the vitamin and mineral status. Additionally, medication use is important to consider, since use of several drugs, such as antidepressants [11], antihypertensive medication [12], corticosteroids [13], and anticonvulsants [14], are associated with vitamin or mineral status.

It is difficult to assess the length of disease as the formal diagnosis is typically made much later than the onset of somatic symptoms. However, in the initial phase of CFS or FMS other characteristics may be present than in the chronic course of CFS or FMS. Therefore, studies should report the central tendency of disease duration with an appropriate measure of distribution. Since there is currently no validated tool that indicates severity of CFS or FMS, measurements of for example somatic symptoms or quality of life should be reported as best available measure of severity.

Key domain 2 (items 5-7): quantification of vitamin and mineral status.
In addition to selection of participants, it is important to assess the reliability of vitamin and mineral quantification. We have chosen to incorporate three important requirements that a reliable analysis and data presentation should meet: presence of a detailed description of the analytical method or a statement of validation, measurements performed in duplicate and a clear mention of appropriate units and dispersion measures.

Validation was assumed when explicitly mentioned in the methods; analyses which were not stated as validated were also classified as such. Vitamin and mineral data were regarded as appropriate when reported in conventional or Système International (SI) units, e.g. concentration as unit of amount – mole, gram or international unit (IU) – per unit of volume – liter.

Key domain 3 (items 8 and 9): appropriate control for confounding.
There are potential confounders in the relationship between vitamin and mineral status and CFS or FMS. Age [15], sex [15,16], smoking [15,17], diet [15,18], body mass index [11] socioeconomic status [19], and psychiatric morbidity, are associated with the vitamin and mineral status. Age, sex, smoking, diet, body mass index, socioeconomic status [20-22], and psychiatric morbidity [23], are also associated with CFS and FMS. Therefore, these variables were included in the quality assessment tool.

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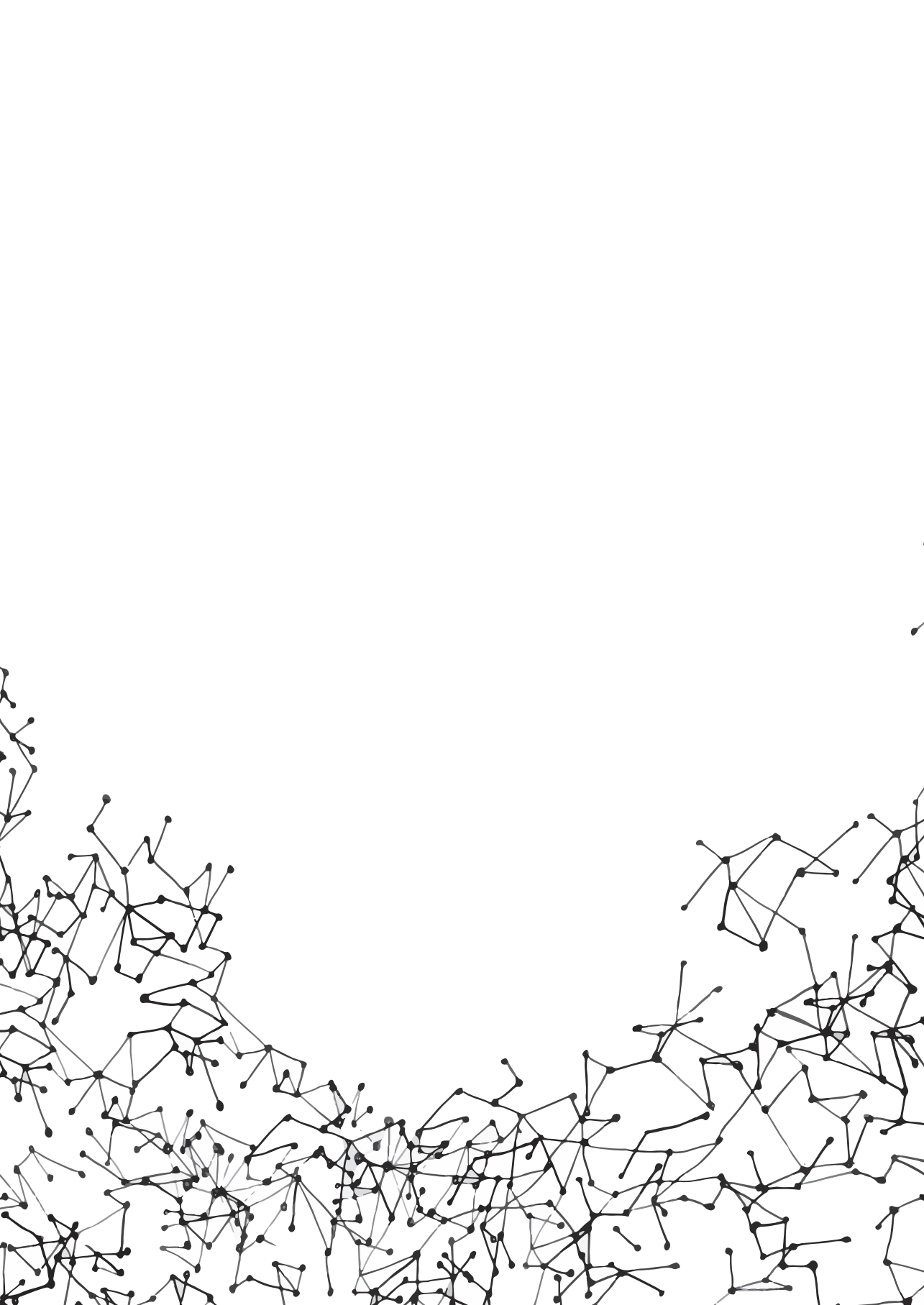
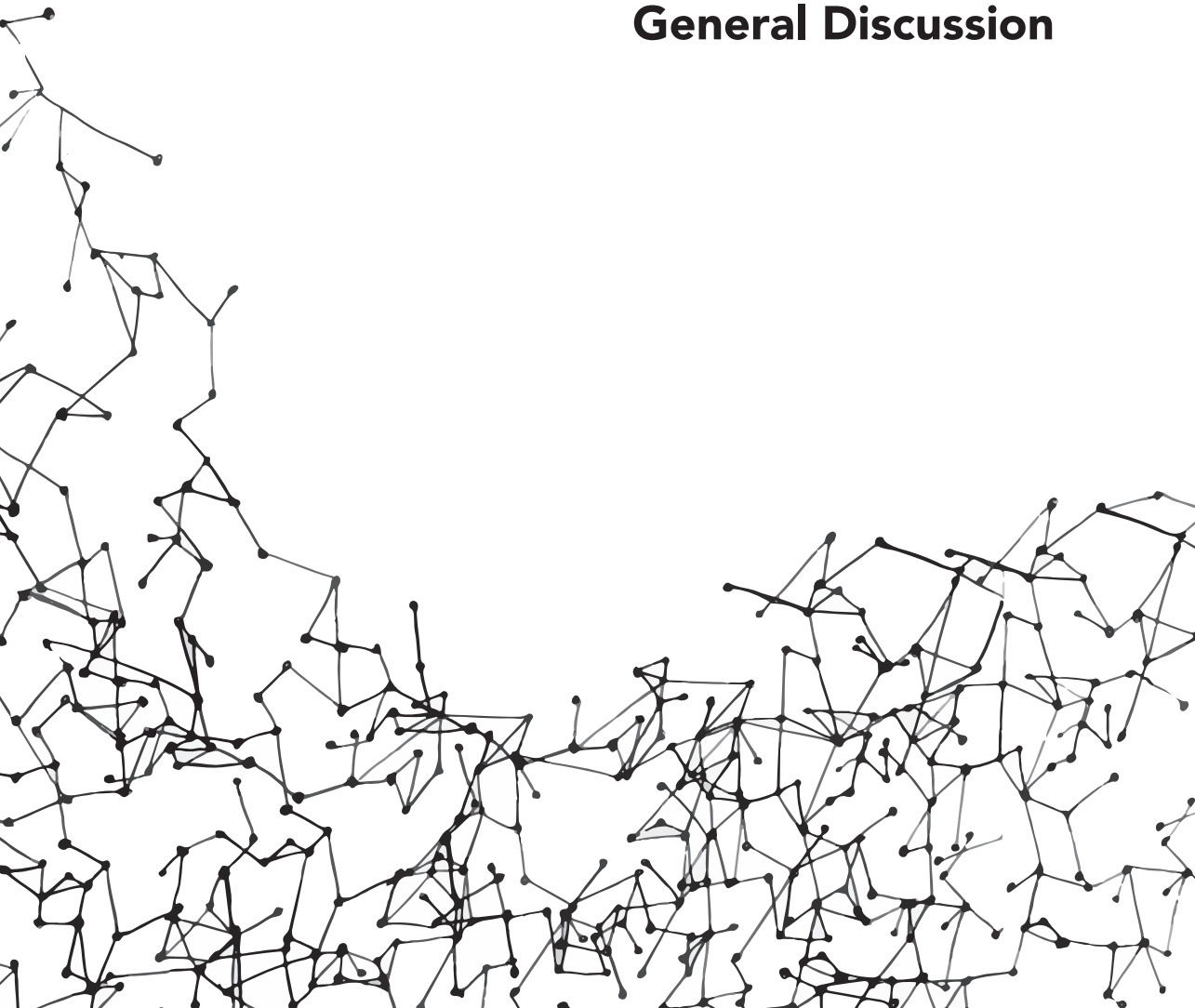


10

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 lumper-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 lumper-splitter discussion. I will start from the four main observations that initiated the lumper-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 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 lumper as well as the splitter 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 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 lumper-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 lumper-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 lumper-splitter discussion.

Concluding remarks

This thesis provided more insight into the validity of FSS diagnoses in the context of the lumper-splitter discussion. It revealed that, although there is overlap in case definitions, the four arguments of the lumper-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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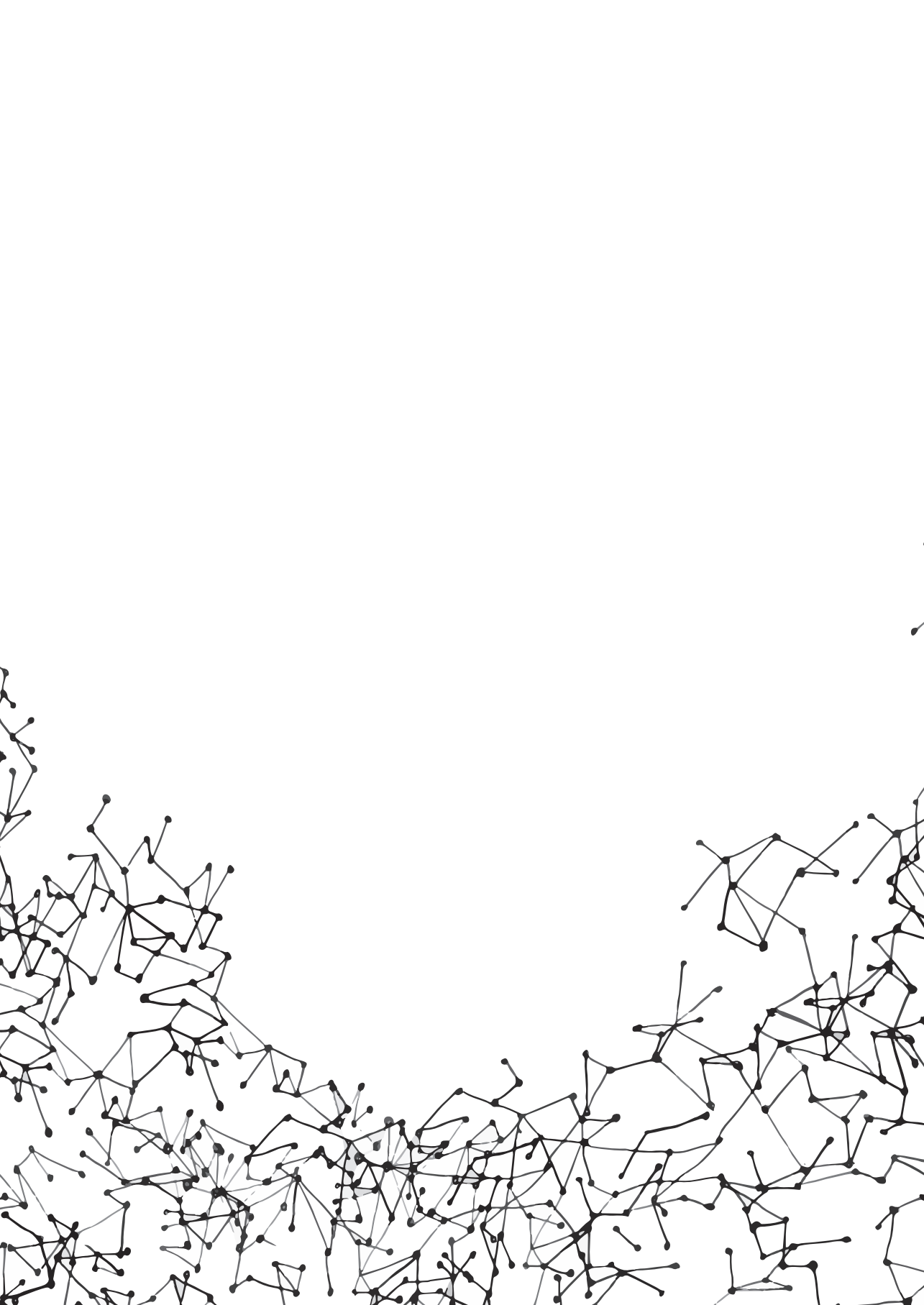

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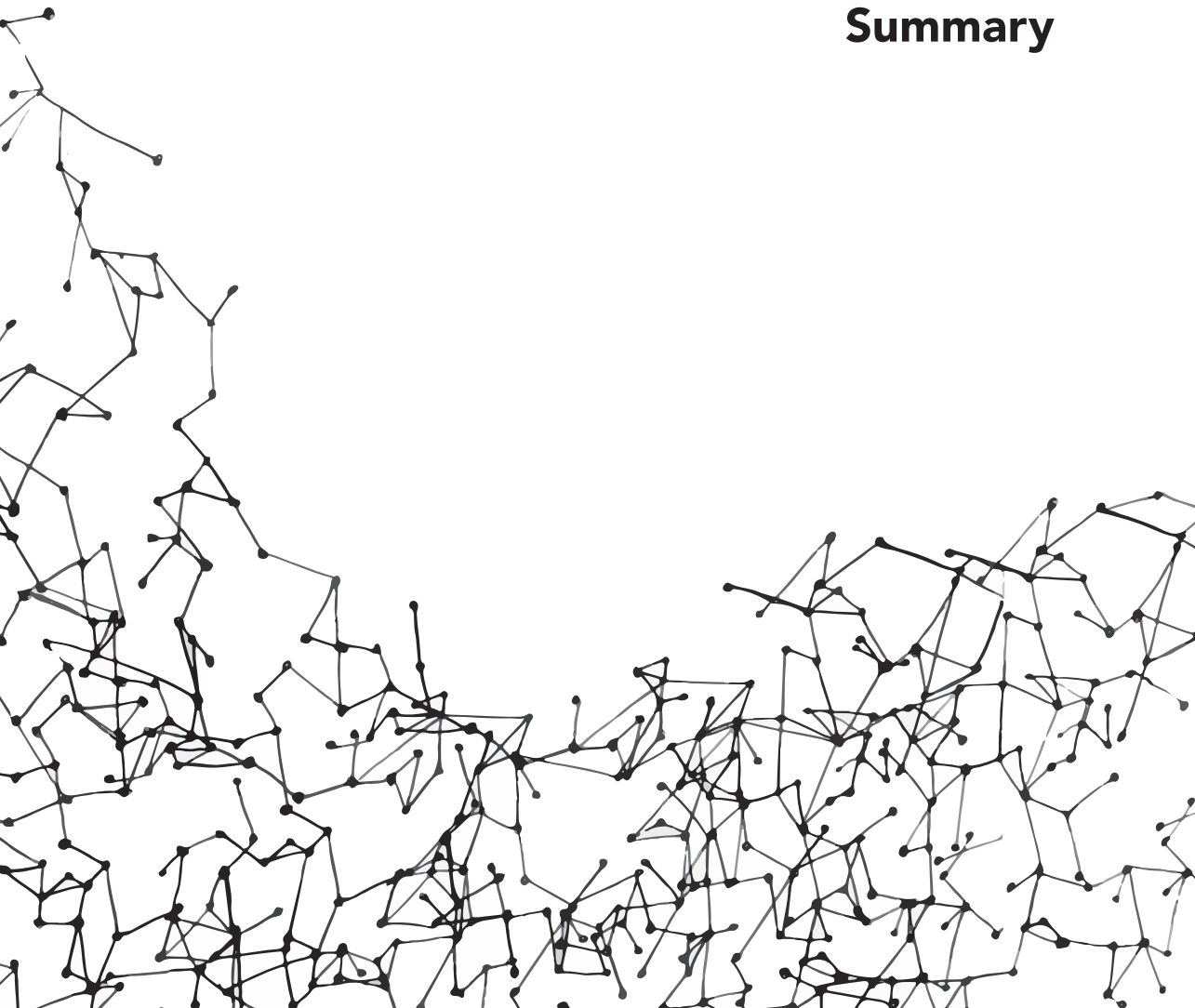


SUMMARY

Clusters of somatic symptoms with no detectable well-defined structural organic pathology can be classified as functional somatic syndromes (FSS). Many functional somatic syndromes (FSS) exist, and every medical specialty seems to have at least one. The exact etiology that underlies the different FSS is not fully understood, but it is assumed to be multifactorial involving biological, psychological, social, and healthcare factors. The phenomenon that FSS are known for substantial clinical and diagnostic overlap has resulted in the so-called lumper-splitter discussion. Lumpers believe that all FSS result from the same etiology, while splitters take the approach that every separate FSS has its own specific background. 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. A large part of this thesis is based on data of the LifeLines cohort study, a multi-disciplinary, prospective cohort study, examining health in the general population.

Since FSS are symptom-based diagnoses, we first examined the most clinically relevant assessment time frame for somatic symptoms in **chapter 2**. We defined relevance as the time frame that best reflects subjective symptom burden in daily life, in terms of quality of life and health anxiety. Our results indicate that the time frame of 4 weeks provided the measure of subjective somatic symptom burden that is clinically most relevant. Furthermore, somatic symptom questionnaires using the 4 weeks' time frame had the best psychometric properties, in terms of internal reliability. This finding may be important, since self-report questionnaires are useful tools to assess symptom burden in patients with an FSS.

We examined the idea that FSS are less serious health conditions than well-defined medical diseases (MD) in **chapter 3**. The aim was to compare functional limitations, defined as quality of life and work participation, in the three main FSS compared to MD. Our study revealed that functional limitations in patients with an FSS are comparable to those in patients with an MD. Patients with an FSS and patients with an MD had a reduced quality of life compared to controls. Controls, patients with an FSS, and patients with an MD reported a comparable frequency of work participation, but working patients with an FSS or an MD worked less hours per week and reported higher sick leave compared to controls.

Thus, functional limitations in patients with an FSS are common, and as severe as those in patients with an MD.

In **chapter 4**, we investigated whether FSS are different names for the same problem by examining networks of the symptoms that compose the diagnostic criteria for chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). Different findings emerged from this study. First, we found that all diagnostic symptoms were connected, either directly or via other symptoms. Second, the network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Main symptoms were important in connecting the different FSS diagnoses. Lastly, clustering of symptoms in the general population revealed a general, musculoskeletal, abdominal, and other symptom cluster. This study suggests that symptom clusters reflecting the different FSS can be identified, but also that these symptom clusters are strongly related.

The validity and the diagnostic overlap between the three main FSS diagnoses based on the official diagnostic criteria was examined in **chapter 5**. Two key findings emerged from this study. First, the diagnostic overlap between the FSS was much higher than would be expected by chance. The diagnostic overlap substantially increased when FSS were more chronic and serious in nature. Second, participants who met the criteria for a specific FSS frequently reported symptoms that were included in the diagnostic criteria of other FSS. This chapter also suggests that the different FSS diagnoses are related.

The hypothesis that FSS are the result of psychological distress, defined as mood or anxiety disorders, was examined in **chapter 6**. We found that patients with CFS, FMS, and IBS suffer from mood and anxiety disorders more often than individuals without FSS, however, in most of them we did not find any indications for psychiatric disorders.

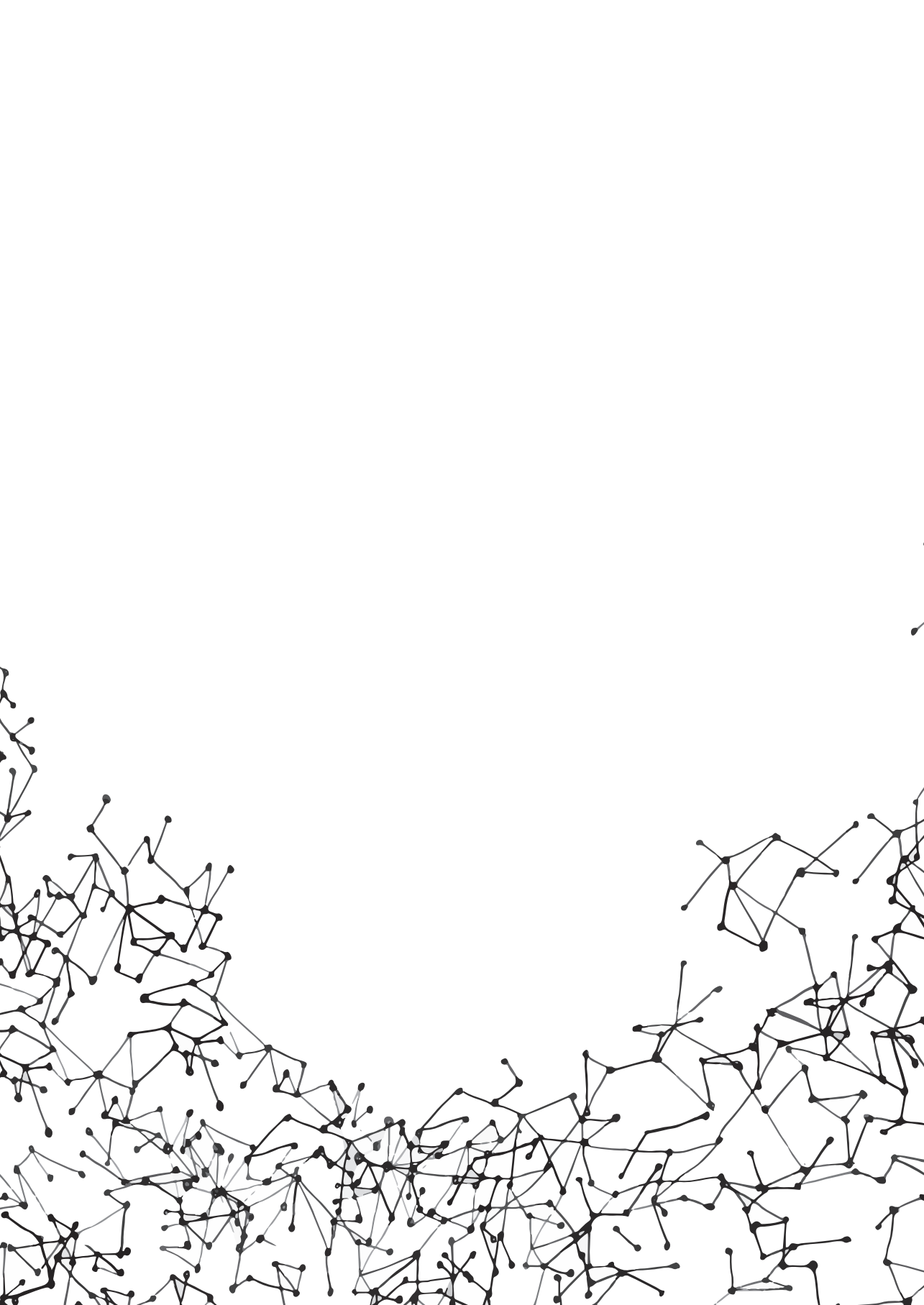
Cognitive symptoms are part of the diagnostic criteria of both CFS and FMS. We therefore examined objective and subjective cognitive functioning in patients with CFS and FMS in **chapter 7**. We revealed that subjective cognitive symptoms are more prevalent in patients with CFS and patients with FMS compared to controls and patients with an MD. We found small differences in objective cognitive

impairments in patients with CFS compared to controls on the domains of visual learning, working memory, and visual attention. These differences could not be explained by comorbid mood or anxiety disorders or the severity of symptoms.

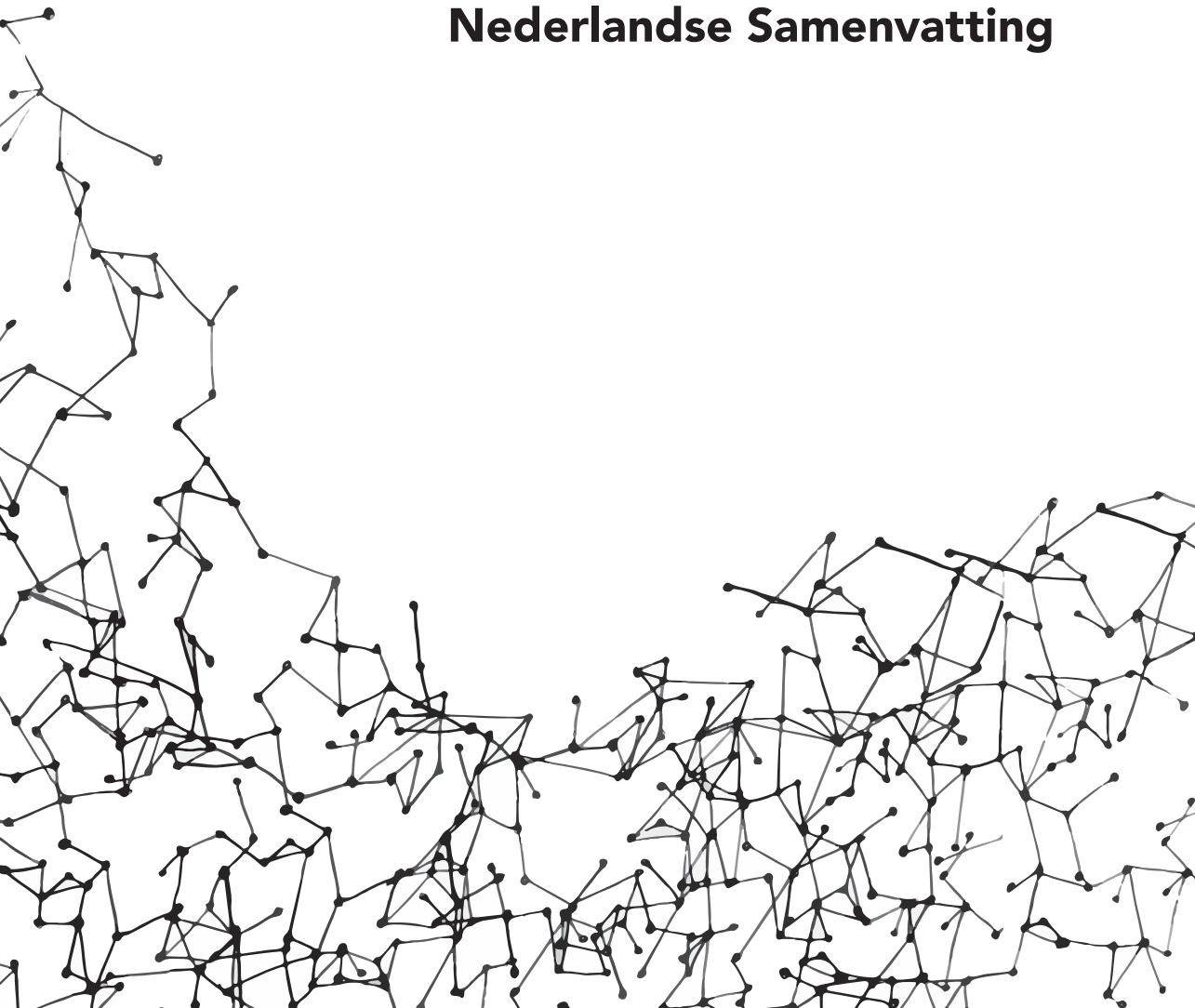
The role of physical activity and sleep in patients with CFS and FMS was examined in **chapter 8**. Our study suggested a role of physical activity and sleep duration in CFS and FMS. We found that Patients with CFS and patients with FMS were significantly less physically active than controls. Patients with CFS reported longer sleep duration than patients with FMS and controls. Both relatively high and low physical activity levels were associated with higher symptom severity in patients with CFS and FMS; this was also true for both relatively long and short sleep duration.

A systematic review and meta-analysis was carried out to examine vitamin and mineral status in patients with CFS and FMS in **chapter 9**. We found little evidence to support our hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of both CFS and FMS, or that use of nutritional supplements is effective in these patients. Poor study quality and considerable heterogeneity in most studies was found, which makes it difficult to reach a final conclusion.

In **chapter 10**, all findings were summarized and discussed. In this thesis, we found evidence to support both the lumpers' and splitters' perspective. Arguments in favor of the lumpers perspective are the diagnostic overlap, the overlap in reported symptoms, and patient characteristics such as sex, age, lifestyle factors, and functional limitations. Arguments in favor of the splitters perspective include symptom clusters reflecting FSS diagnoses, differences in symptoms between patients with different FSS, and indications for differences in contributing factors. In summary, we can state that, although there is overlap in case definitions, the differences between FSS cannot be ignored. We suggest that FSS may reflect the same underlying syndrome with different subtypes. These subtypes may have their own unique manifestation of specific symptom patterns based on symptoms' bodily systems and share both common as well as unique factors. This underlying syndrome should be more extensively investigated in the future to establish valid and generally accepted diagnostic criteria across medical specialties.



Nederlandse Samenvatting



NEDERLANDSE SAMENVATTING

Voor lichamelijke klachten kan niet altijd een duidelijke onderliggende lichamelijke oorzaak gevonden worden. Wanneer onvoldoende verklaarde lichamelijke klachten in clusters voorkomen, spreekt men ook wel van functioneel somatische syndromen (FSS). Er bestaan vele soorten FSS en ieder medisch specialisme lijkt er tenminste één te kennen. De etiologie die ten grondslag ligt aan FSS is nog niet geheel duidelijk, maar er wordt verondersteld dat deze multifactorieel is, en dat zowel biologische, psychologische, sociale als gezondheidszorgfactoren bijdragen. Het fenomeen dat verschillende FSS substantiële klinische en diagnostische overlap kennen, heeft geresulteerd in de zogenoemde lumper-splitter discussie. Lumpers veronderstellen dat FSS voortkomen uit eenzelfde etiologie, terwijl splitters ervan uitgaan dat elk afzonderlijk FSS een eigen specifieke achtergrond heeft. Het doel van dit proefschrift was om de validiteit van de FSS-diagnoses te onderzoeken, en om te kijken in welke mate deze diagnoses in staat zijn om aparte patiëntengroepen te identificeren. Een groot deel van dit proefschrift is gebaseerd op data van de LifeLines cohortstudie, een multidisciplinaire, prospectieve studie naar gezondheid in de algemene populatie.

Omdat FSS-diagnoses gebaseerd zijn op symptomen, hebben we eerst in **hoofdstuk 2** het klinisch meest relevante tijdsbestek voor het uitvragen van somatische symptomen onderzocht. Relevantie werd gedefinieerd als het tijdsbestek dat het beste de subjectieve symptoomlast in het dagelijks leven reflecteert, in termen van kwaliteit van leven en ziekteangst. Onze resultaten laten zien dat een tijdsbestek van 4 weken het beste de klinisch relevante subjectieve symptoomlast reflecteert. Ook hadden de somatische symptoomvragenlijsten die gebruik maakten van een tijdsbestek van 4 weken de beste psychometrische eigenschappen, in de vorm van interne betrouwbaarheid. Deze bevindingen zijn van belang, omdat zelf gerapporteerde vragenlijsten nuttige hulpmiddelen zijn om symptoomernst in patiënten met FSS in kaart te brengen.

We onderzochten het idee dat FSS minder ernstige aandoeningen zijn dan erkende medische aandoeningen (MD) in **hoofdstuk 3**. Het doel was om functionele beperkingen, gedefinieerd als kwaliteit van leven en arbeidsparticipatie, te vergelijken tussen patiënten met FSS en MD. Onze studie liet zien dat de functionele beperkingen van patiënten met een FSS vergelijkbaar zijn met de beperkingen

van patiënten met een MD. Zowel patiënten met een FSS als patiënten met een MD hadden een verminderde kwaliteit van leven in vergelijking met een controlegroep. De controlegroep, patiënten met een FSS en patiënten met een MD rapporteerden een vergelijkbare arbeidsparticipatie, maar werkende patiënten met een FSS of een MD werkten wel minder uur per week en rapporteerden een hoger ziekteverzuim dan de controlegroep. Kortom, functionele beperkingen in patiënten met een FSS zijn veelvoorkomend, en minstens zo ernstig als in patiënten met een MD.

In **hoofdstuk 4** onderzochten wij of verschillende FSS mogelijk verschillende namen zijn voor eenzelfde probleem. Wij deden dit door het onderzoeken van netwerken van de symptomen die de diagnostische criteria vormen voor chronisch vermoeidheidssyndroom (CVS), fibromyalgie syndroom (FMS) en prikkelbare darm syndroom (PDS). Uit deze studie kwamen diverse bevindingen naar voren. Ten eerste vonden we dat alle diagnostische symptomen met elkaar waren verbonden, zowel direct als via andere symptomen. Ten tweede was de netwerkdichtheid tussen de diagnoses in de meeste gevallen wat lager dan binnen de diagnoses, hoewel de verschillen klein waren. Hoofdsymptomen waren belangrijk bij het verbinden van de verschillende FSS-diagnoses. Tot slot, clustering van symptomen in de algemene populatie onthulde een algemeen, een musculoskeletaal, een abdominaal en een overige symptomen cluster. Deze studie suggereert dat er symptoomclusters te herkennen zijn die de verschillende FSS weerspiegelen, maar ook dat deze symptoomclusters sterk gerelateerd zijn.

De validiteit van en de diagnostische overlap tussen de drie belangrijkste FSS-diagnoses werd onderzocht in **hoofdstuk 5**. Uit deze studie kwamen twee belangrijke bevindingen naar voren. Ten eerste was de diagnostische overlap tussen de FSS veel groter dan op basis van kans zou mogen worden verwacht. De overlap nam substantieel toe wanneer FSS chronischer en ernstiger van aard werden. Ten tweede rapporteerden deelnemers die voldeden aan de criteria voor een specifieke FSS frequent symptomen die onderdeel waren van de diagnostische criteria van andere FSS. Ook dit hoofdstuk suggereert dus dat de verschillende FSS diagnoses aan elkaar gerelateerd zijn.

De hypothese dat FSS zoals CVS, FMS en PDS het resultaat zijn van psychische stress, gedefinieerd als stemmings- en angststoornissen, werd onderzocht in

hoofdstuk 6. We vonden dat mensen met CVS, FMS en PDS vaker lijden aan stemmings- en angststoornissen dan mensen zonder FSS, maar bij de meesten van hen zijn er geen aanwijzingen voor deze psychiatrische aandoeningen.

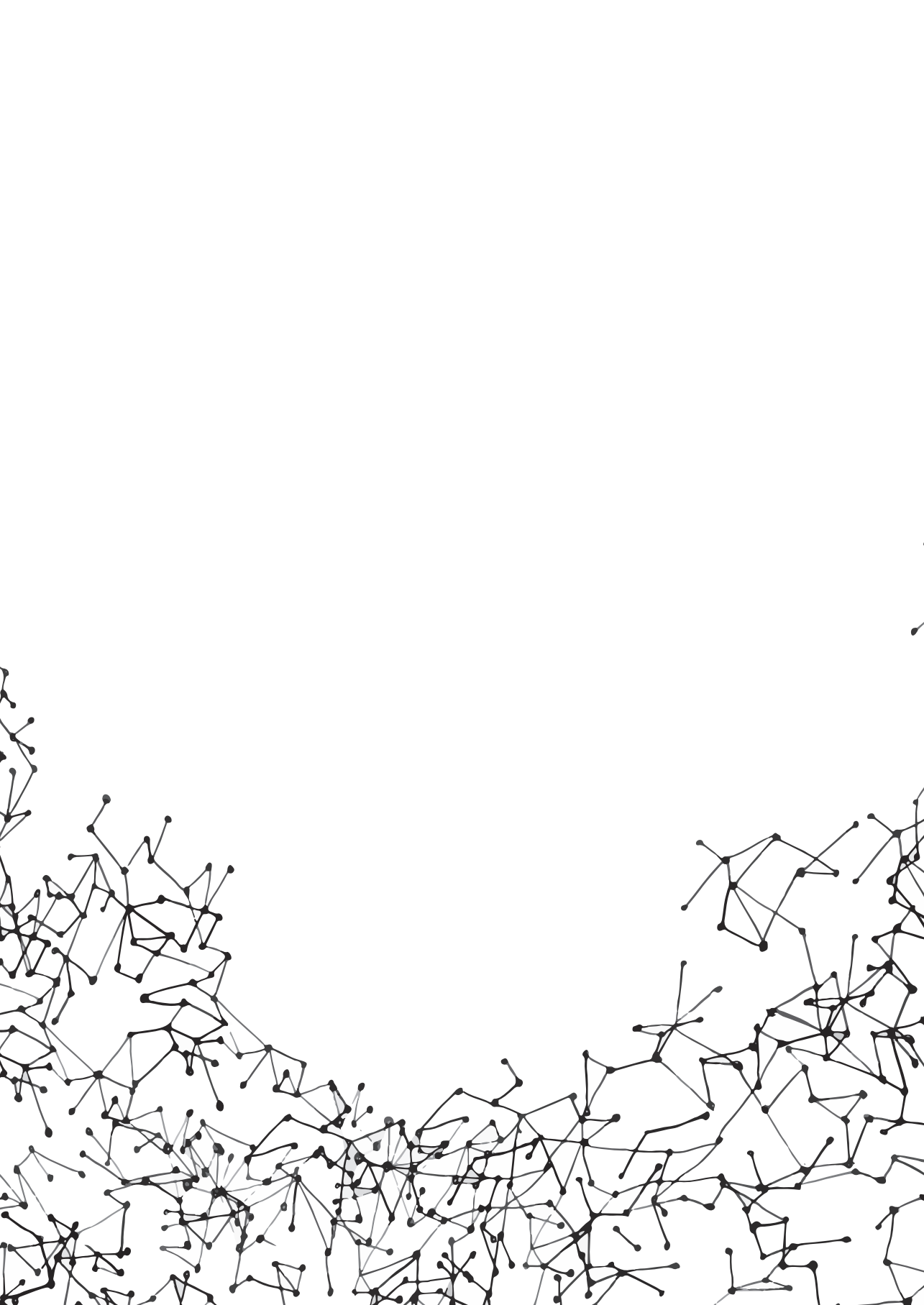
Cognitieve symptomen zijn onderdeel van de diagnostische criteria van zowel CVS als FMS. Objectief en subjectief cognitief functioneren in patiënten met CVS en FMS werd daarom onderzocht in **hoofdstuk 7**. We vonden dat subjectieve cognitieve symptomen vaker voorkomen bij zowel patiënten met CVS als patiënten met FMS, in vergelijking met controles en patiënten met een MD. Bovendien vonden we kleine verschillen in objectief cognitief functioneren tussen controles en patiënten met CVS op de gebieden van visueel leren, werkgeheugen en visuele aandacht. Deze verschillen konden niet worden verklaard uit comorbide stemmings- of angststoornissen of ernst van de symptomen.

De rol van fysieke activiteit en slaap bij patiënten met CVS en FMS werd onderzocht in **hoofdstuk 8**. Onze studie suggereerde een rol van fysieke activiteit en slaapduur bij CVS en FMS. We vonden dat patiënten met CVS en FMS significant minder fysiek actief waren dan controles. Patiënten met CVS rapporteerden een langere slaapduur dan patiënten met FMS en controles. Zowel relatief hoge als lage fysieke activiteitsniveaus waren geassocieerd met een hogere ernst van de symptomen bij beide patiëntgroepen; dit gold ook voor zowel de relatief lange als korte slaapduur.

Een systematische review en meta-analyse werd uitgevoerd om de vitamine- en mineraalstatus in patiënten met CVS en FMS te onderzoeken in **hoofdstuk 9**. We vonden weinig ondersteuning voor de hypothese dat vitamine- en mineralentekorten een rol spelen in de pathofysiologie van CVS en FMS, of dat het gebruik van voedingssupplementen effectief is bij deze patiënten. De meeste onderzoeken werden gekenmerkt door een slechte studiekwaliteit en aanzienlijke heterogeniteit, waardoor het moeilijk is om tot definitieve conclusies te komen.

In **hoofdstuk 10** werden alle bevindingen samengevat en besproken. In dit proefschrift hebben we aanwijzingen gevonden die zowel het perspectief van de lumpers, alsmede dat van de splitters ondersteunen. Argumenten voor het lumpers perspectief zijn de diagnostische overlap, de overlap in gerapporteerde symptomen en patiënt karakteristieken zoals geslacht, leeftijd, leefstijlfactoren,

en functionele beperkingen. Argumenten voor het splitters perspectief zijn onder andere de symptoomnetwerken die de FSS diagnoses reflecteren, de verschillen in symptomen tussen patiënten met verschillende FSS, en aanwijzingen voor verschillen in bijdragende factoren. Samenvattend kunnen we stellen dat, hoewel er overlap is in de definities, de verschillen tussen de FSS niet genegeerd kunnen worden. We suggereren daarom dat FSS hetzelfde onderliggende syndroom weerspiegelen met verschillende subtypen. Deze subtypen hebben mogelijk hun eigen unieke manifestatie van specifieke symptoompatronen gebaseerd op lichamelijke systemen, en hebben zowel gemeenschappelijke als unieke factoren. Dit onderliggende syndroom zal in de toekomst uitgebreider onderzocht moeten worden om tot valide en algemeen aanvaarde diagnostische criteria te komen.



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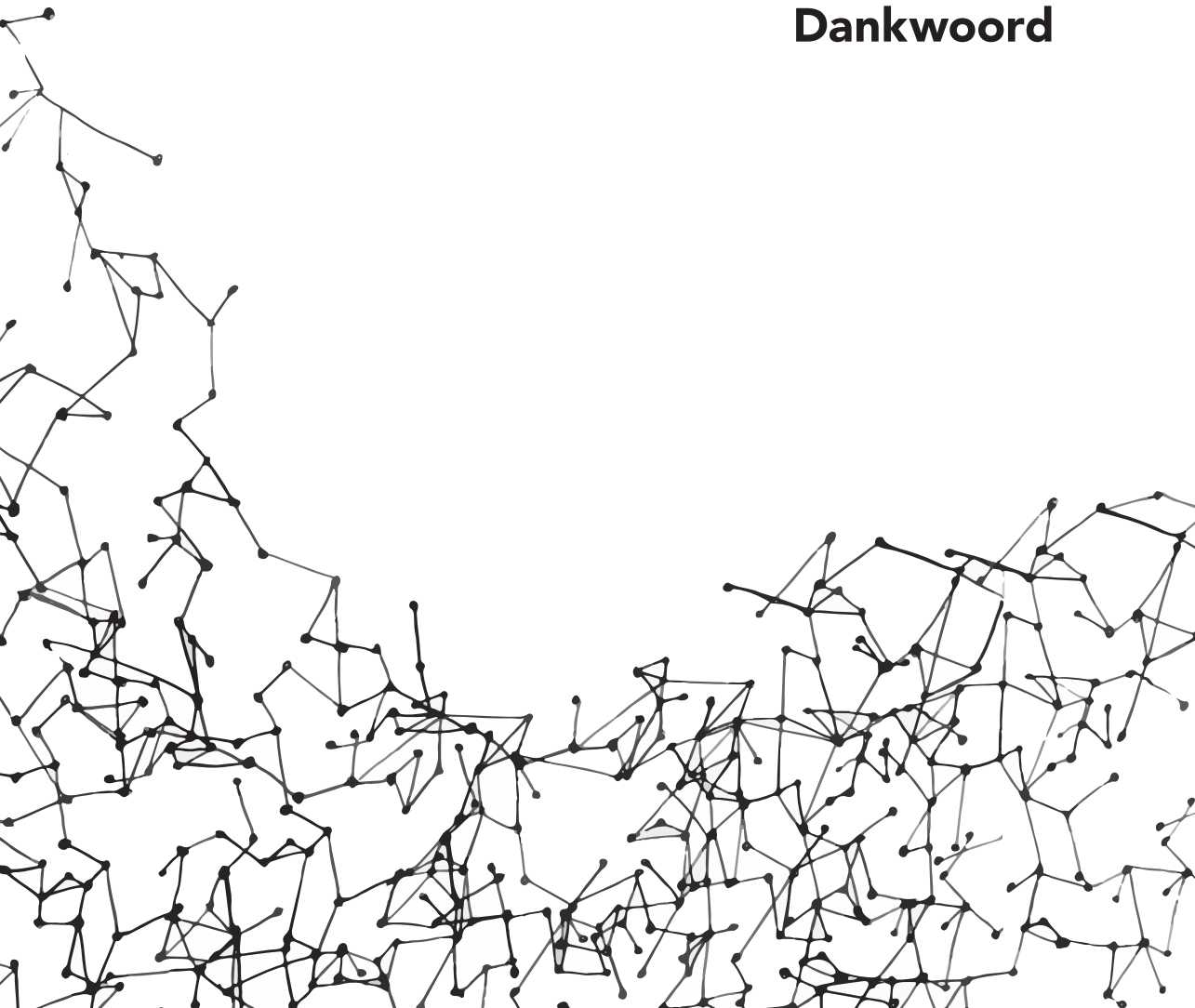
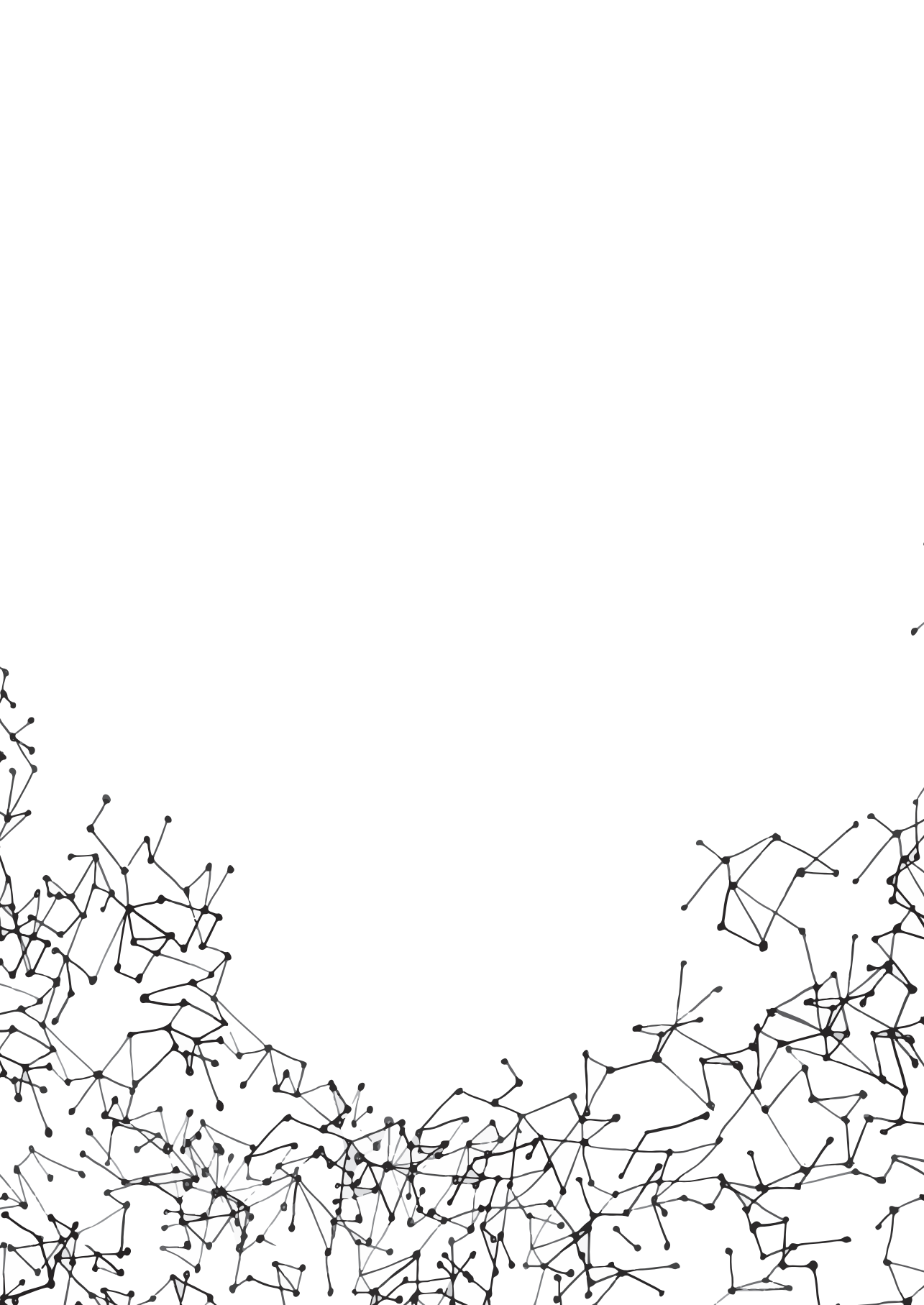
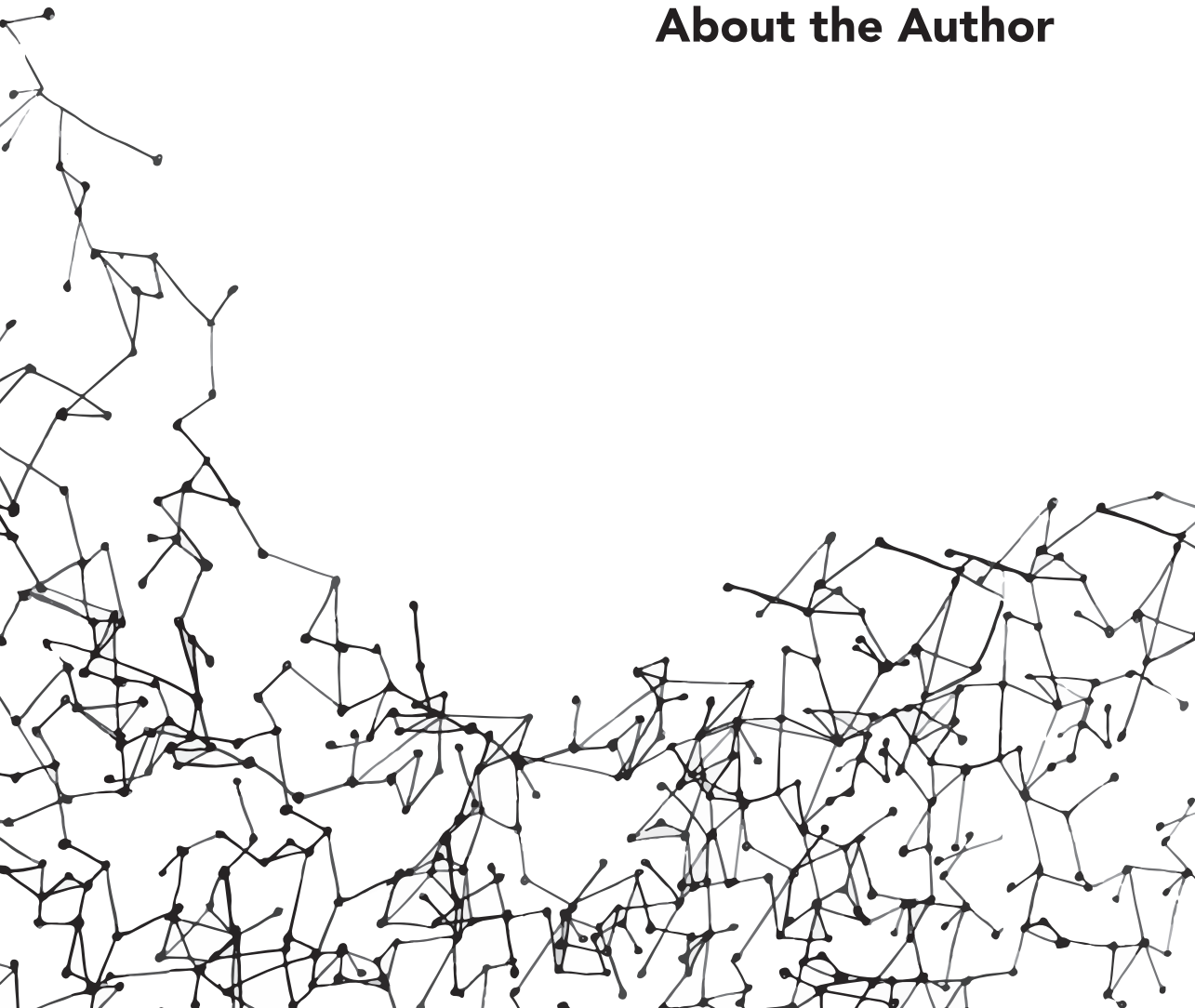


DANKWOORD

Alles behalve terecht dat alleen mijn naam op de omslag van dit proefschrift staat. Ik ben ontzettend dankbaar voor iedereen die direct of indirect betrokken is geweest bij mijn MD/PhD-traject. Promotoren, coauteurs, collega's, vrienden en familie, allen hebben zij bijgedragen aan deze bijzondere periode, met dit proefschrift als resultaat. Daarom, speciaal voor jullie:



About the Author



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Monica Laura Joustra was born on 29 October 1991 in Leeuwarden, the Netherlands. She graduated from pre-university education (VWO) in 2010 at the Stellingwerf College in Oosterwolde. In the same year she started her study Medicine at the University of Groningen. In 2015 she started her MD/PhD trajectory at the Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE) of the University Medical Center of Groningen (UMCG) under the supervision of Judith Rosmalen, Stephan Bakker and Karin Janssens. Her PhD project aimed to investigate the validity of functional somatic syndrome 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. At the ICPE she was involved in teaching and supervising medical and PhD students. She presented her research a various national and international conferences. In 2017 she graduated after her final internship at the emergency department and the department of internal medicine at the Hospital location Wilhelmina in Assen. After finishing her MD/PhD trajectory in 2018, Monica started to work as medical doctor at the department of internal medicine at the Hospital location Scheper in Emmen.