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# Stigma perceived by patients with functional somatic syndromes and its effect on health outcomes – A systematic review

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ABSTRACT

*Background:* Patients with functional somatic syndromes (FSS) experience stigma which arguably affects their health.
*Aim:* To determine the presence of perceived stigma and its effects on physical and mental health in patients with FSS compared to patients with comparable explained conditions.
*Methods:* A comprehensive search of PubMed, Embase, PsycINFO, CINAHL and Cochrane Library was performed to select studies focusing on stigma perceived by patients with irritable bowel syndrome (IBS), fibromyalgia (FM) or chronic fatigue syndrome (CFS), comparing these patients to patients with comparable but explained conditions.
*Results:* We identified 1931 studies after duplicate removal. After screening we included eight studies: one study about all three FSS, one about IBS, five about FM and one about CFS. We found that patients with IBS did not consistently experience higher levels of stigma than those with a comparable explained condition. Patients with CFS and FM experienced higher levels of stigma compared to patients with comparable explained conditions. All studies showed a correlation between stigma and negative health outcomes.
*Discussion:* Patients with FSS experience stigma and negative health outcomes. However, experiencing stigma is not restricted to patients with FSS, as many patients with explained health conditions also experience stigma. Whether stigma has more negative health consequences in patients with FSS compared to patients with explained health conditions remains unclear and should be assessed in future research.

## 1. Introduction

The term functional somatic syndromes (FSS) relates to several syndromes characterized by a specific combination of persistent somatic symptoms, rather than by structural bodily abnormalities [1]. FSS are highly prevalent: approximately 13% of the patients older than 65 years that visit the GP present with FSS [2]. The three most prevalent functional syndromes in the general population are irritable bowel syndrome (IBS), fibromyalgia (FM) and chronic fatigue syndrome (CFS), with a point prevalence of 8.6%, 1.9% and 0.8% respectively [3].

Patients with FSS often suffer from an impaired (health-related) quality of life (HRQoL), as was found in a large-scale study including 89,985 participants [3–7]. Multiple studies found that patients with FSS experience higher levels of negative health outcomes compared to patients with comparable, but organically explained physical complaints. For instance, a study that included 110 CFS patients found significantly lower overall HRQoL scores in CFS patients than in other explained chronic illness groups [8]. FM patients had similar or significantly worse physical and mental health status scores, HRQoL scores and functional disabilities compared to those with rheumatoid arthritis (RA), Parkinson's disease, Systemic Lupus Erythematosus (SLE) and other pain conditions [5,9–11]. Significantly lower HRQoL scores were also found in IBS patients as compared to inflammatory bowel disease (IBD), diabetes mellitus, dialysis-dependent end-stage renal disease, panic disorder, and RA [12,13].

Patients with FSS are frequently unable to provide explanations about the cause of their symptoms to others, because healthcare professionals experience problems with providing explanations when

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symptoms are medically unexplained [14]. Many FSS patients experience that their feelings of being physically ill are not validated, either by people important to them (for example, parents, siblings) or healthcare professionals, and that their condition is dismissed as an emotional problem [15–17]. Patients with FSS experience doubt about the truthfulness and accuracy of their symptoms and their character. They feel that their symptoms are ascribed to psychological causes [18,19].

Being negatively assessed and not being believed by others are important features of both stigmatization and invalidation. These concepts are used interchangeably in literature, although they are different but overlapping concepts. Stigma is a complex phenomenon with many definitions [19,20]. In the current study we define stigma as "a social process, in which social groups or individuals accept, endorse or enact negative attitudes, characterized by exclusion, rejection, blame and devaluation, against people with FSS". It concerns a negative social judgment towards a group of people, in this case patients with FSS, because of their FSS. It is important to distinguish the belief of being stigmatized by others (perceived stigma) and the actual experience of being stigmatized (experienced stigma) [21]. Experienced stigma refers to real-life experiences while perceived stigma refers to an expected reaction by others. Finally, internalized stigma occurs when a person believes and applies the negative messages and stereotypes related to a health condition to themselves. The term 'invalidation' is used to describe the patients' perception that their medical condition is not recognized, not accepted, received with scepticism, not acknowledged, or even dismissed by their social environment. Invalidation has two dimensions: lack of understanding and discounting [22]. Lack of understanding reflects a lack of positive social responses such as not recognising, comprehending and emotionally supporting the patient. Discounting represents active negative social responses including disbelieving, admonishing, dismissing inability to work, not acknowledging symptom fluctuations, and offering unusable advice [23].

It has been shown that patients with FSS experience stigma or invalidation for CFS [24,25], FM [26,27] and IBS [28,29]. The same studies showed an association of the degree of stigma with negative health outcomes such as depression and low quality of life. However, patients with comparable explained conditions also experience stigma and negative health outcomes such as depression and psychological distress [30,31]. It is unclear whether stigma and associated negative health outcomes are related to the unexplained nature of the FSS. Therefore, this systematic review aims to explore the differences between patients with FSS and patients with comparable explained conditions concerning perceived and experienced stigma and associated negative health outcomes.

We hypothesized that: (1) patients with FSS will experience statistically significantly higher levels of stigma compared to patients with explained conditions; (2) patients with FSS will experience statistically significantly higher levels of negative health outcomes compared to patients with comparable explained conditions; (3) the level of perceived or experienced stigma will be statistically significantly associated with negative health outcomes.

## 2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Methods and inclusion criteria were included in a protocol (PROSPERO 2020 CRD42020191932) prior to the study. The study was not sponsored, and the authors have no conflicts of interest to declare.

### 2.1. Data sources and search strategy

We have searched the following sources from their inception till October 2021: PubMed (starting 1946), Embase (starting 1974), PsycINFO (starting 1806), CINAHL (starting 1981) and Cochrane Library. The search strategy for this study consists of two search strings combined with the Boolean operator AND. The first search string refers to the three most prevalent functional syndromes (IBS, FM, CFS), and the second string refers to stigma and invalidation (Supplement 1). Reference lists of retrieved studies were searched for additional studies. We included peer-reviewed observational (cohort studies, case-control studies) or experimental studies. We had no restrictions concerning the date of publication or language.

### 2.2. Study selection

The results of the electronic searches were combined, and duplicates were removed. Next, two reviewers (CK, PL) independently selected studies based on title and abstract screening. Following a full-text screening, we definitively included studies. Problems encountered during the inclusion process were discussed with a third reviewer (TOH). If any data were missing in the included studies, we contacted the authors. We included all studies comparing stigma experienced by patients with FSS with stigma experienced by patients with comparable explained conditions. Studies also had to provide data about the negative health consequences of stigma. We excluded all studies describing the experience of stigma in patients with FSS without comparison with patients with explained comparable conditions. We also excluded studies with populations younger than 18 years. We calculated Cohen's kappa as an indication of agreement in the selection process.

### 2.3. Data extraction and management

One reviewer (CK) performed the extraction of relevant characteristics, and a second reviewer (PL) independently checked the extracted data for its completeness and accuracy. We extracted the following data from the included studies: first author, year of publication, country, setting, study design, response rate and differences between responders and non-responders, duration of follow-up (in cohort studies), (mean) age, sex, ethnicity, comorbidities, inclusion and exclusion criteria, number of included patients, definition of the functional somatic syndrome, type of outcome, illness duration, instruments to measure stigma and negative health outcomes, method of analysis of the relation between stigma and negative health outcome, definition of health outcomes, their measurement method and validity, analysis applied to determine health outcomes, time between measurement and start of experience of stigma.

### 2.4. Data analysis

We could not perform a meta-analysis of the data due to the high heterogeneity in the study populations, methodologies, and outcome measures of included studies. Two review authors (CK, PL) independently assessed the quality of each included study. Disagreement on quality assessment was solved by consensus discussion or by consulting a third author (TOH). We used the National Heart, Lung and Blood Institute (NIH) assessment tool to judge the risk of bias (Fig. S1) [32]. We ranked the risk of bias in the included studies as 'high', 'moderate' or 'low' risk. The developers of the tool recommend to 'think about the questions in the tool and how each one tells you something about the potential for bias in a study [32].

## 3. Results

We retrieved 3178 publications, of which 1931 remained after duplicates were removed. Of these, eight studies fulfilled the inclusion criteria (Fig. 1). Major reasons for excluding studies were a lack of focus on patients with FSS (IBS, CFS or FM), lack of comparisons made between FSS and comparable explained conditions and lack of focus on stigma perceived by the patient. Interobserver agreement for inclusion between the two reviewers (CK, PL) was $\kappa = 0{,}61$ (95% CI: 0.37–0.84),

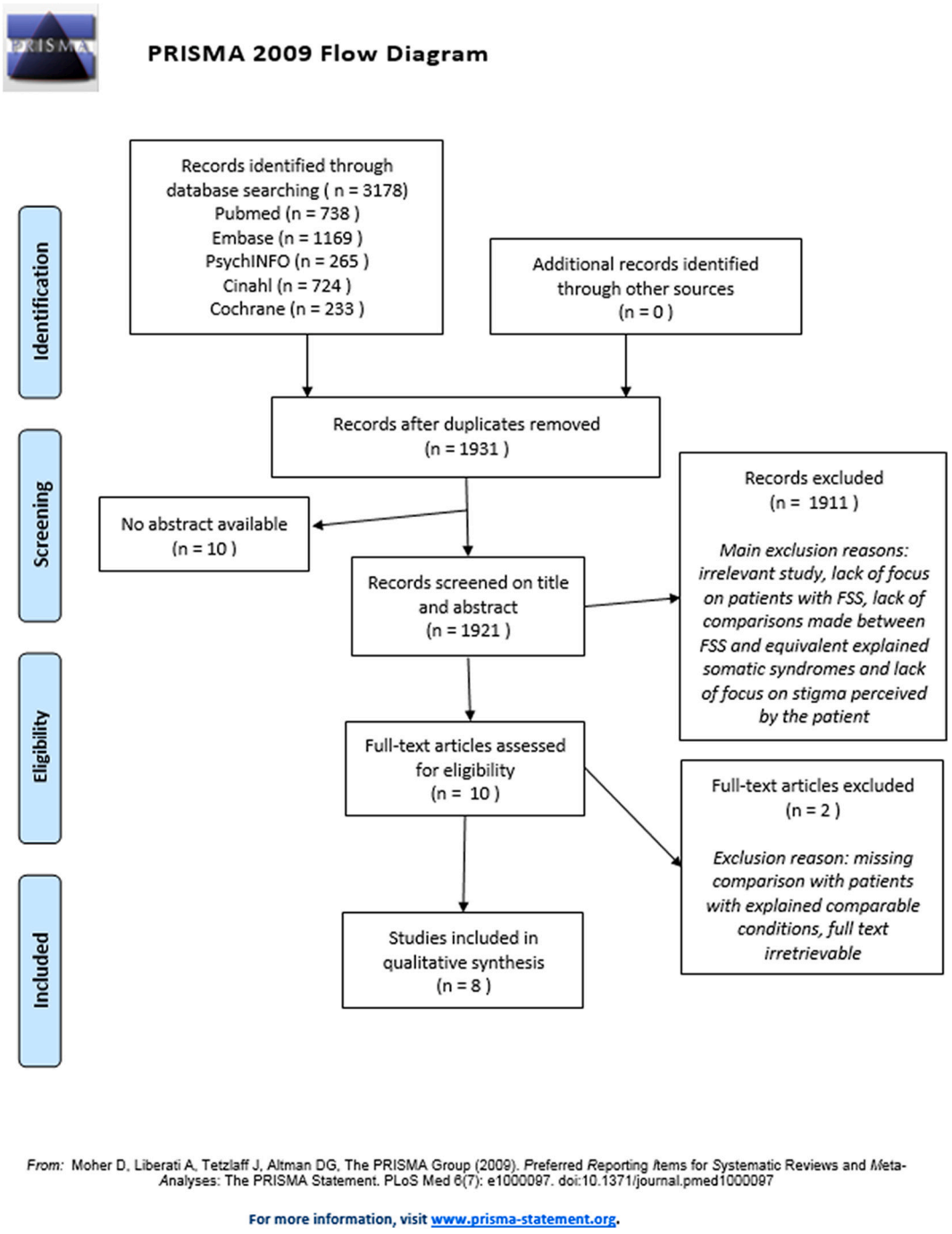


**Fig. 1.** PRISMA flowchart.

**Table 1**
Quality assessment of observational cohort and cross-sectional studies [32].

| Reference (first author and year of study) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Taft 2011 | Y | Y | NR | Y | Y | N | N | Y | Y | N | Y | NA | NA | Y |
| Kool 2013 | Y | Y | Y | Y | N | N | N | Y | Y | N | Y | NA | NA | Y |
| Kool 2010 | Y | Y | Y | Y | N | N | N | Y | P | N | P | N | N | Y |
| Santiago 2017 | Y | Y | Y | Y | N | N | N | Y | Y | N | Y | NA | NA | Y |
| Singh 2021 | Y | Y | NR | Y | N | N | N | Y | Y | N | Y | NA | NA | Y |
| Van Alboom 2021 | Y | Y | Y | Y | N | N | N | Y | Y | Y | Y | NA | NA | Y |
| Baken 2016 | Y | P | Y | Y | N | N | N | Y | Y | N | N | NA | NA | NR |
| Looper 2004 | Y | Y | Y | Y | N | N | N | Y | Y | N | Y | NA | NA | Y |

NA, not applicable; N, No; NR, not reported; P, partially; Y, Yes.

which is substantial. The reference lists of the retrieved studies did not reveal any relevant publications. In total we included eight studies: one study reported on all three FSS [15], one was about IBS [33], five about FM [34–38], and one about CFS[39] Seven studies had a cross-sectional design, using questionnaires for their data collection. One study was a diary study with daily questionnaires and diaries but compared mean values from the registration period for analysis. The risk of bias in the included studies was moderate to high (Table 1). Table 2 shows an overview of all the studies main characteristics.

### 3.1. Irritable bowel syndrome

Two studies compared IBS with inflammatory bowel diseases (IBD: ulcerative colitis or Crohn's disease) [15,33]. Looper et al. (2004) included 38 IBS and 51 IBD patients, diagnosed by a specialist or general practitioner (GP), in which no statistically significant difference was found in perceived stigma between IBS and IBD patients (mean ± SD; IBS 42.9 ± 10.4; IBD 45.7 ± 10.9; scale range 22–88) [15]. Taft et al. (2011) included 269 patients with IBS and 227 with IBD, recruited from an outpatient gastroenterology clinic and online via support message boards [33]. This study found that more than three times as many IBS patients reported moderate to high levels of perceived stigma (27%), compared to IBD patients (8%) [33]. The level of perceived stigma was significantly higher in IBS patients compared to IBD patients (mean ± SD; IBS 86.88 ± 50.0; IBD 61.93 ± 37.4; scale range 0–240). However, the overall level of perceived stigma in both groups was in the mild range of the stigma scale (which ranged from 60 to 119) [40]. The higher levels of perceived stigma in the second study might be related to method of recruitment, which was partly online, inducing selection bias. These patients might perceive more stigma and therefore have more motivation to participate in the study.

The first study showed no differences in health outcomes between IBS and IBD patients, neither in depression scores nor in physical functioning scores (Table S1) [15]. In the second study IBS patients reported significantly higher levels of depression (mean ± SD; IBS 59.5 ± 9.4; IBD 55.8 ± 10.3, scale range < 50; 50–56, 57–62; >63) with women more likely to score higher than men ($p = 0.02$). There were no differences for anxiety, somatization, HRQoL or global severity of symptoms.

Concerning the association of stigma and negative health outcomes, the first study found a significant association between stigma and depression for both IBS and IBD patients, with the correlation being stronger in IBS patients than in IBD patients (IBS $r = 0.43$, $p > 0.01$; IBD $r = 0.25$, $p > 0.01$) [15]. The second study found no significant correlations between perceived stigma and depression, physical quality of life, and overall quality of life for IBS patients in contrast to IBD patients. IBD patients reported a significant positive relationship between stigma and depression ($r = 0.37$) and a significant negative association with physical health quality of life ($r = -0.36$), and overall quality of life ($r = -0.39$).

### 3.2. Fibromyalgia

The six studies about fibromyalgia (FM) compared FM with other rheumatic diseases. Four of the six studies concerned the relationship of invalidation with mental and physical health; the other two focussed on stigma and health outcomes. Kool et al. (2013) examined whether invalidation was significantly associated with physical and mental health [36]. Participants included 1.455 patients with FM ($n = 341$), RA ($n = 171$), ankylosing spondylitis (AS, $n = 152$), osteoarthritis (OA, $n = 150$), or other rheumatic disease ($n = 641$) diagnosed by a specialist, GP or nurse practitioner. However, since reported results were stratified by disease, we could not compare FM with comparable explained conditions. Furthermore, data concerning stigma were not described in the study. The second study (Kool et al. 2010) was a diagnostic study, but it presented relevant data comparing FM and RA patients [34]. It included 167 patients with FM and 142 patients with RA, diagnosed by a rheumatologist. The study investigated the two dimensions of invalidation (discounting and lack of understanding) and 5 different sources of invalidation (spouse, family, medical professionals, work environment and social services). Patients with FM experienced significantly more

**Table 2**
Main characteristics of the included studies.

| First author (year of publication) | Functional syndrome vs explained comparable condition | Design | Concept that is measured | Number of included patients | Stigma/invalidation tool | Statistical technique |
|---|---|---|---|---|---|---|
| Taft (2011) [ 33] | IBS vs IBD | Cross-sectional | Perceived stigma | 496 (IBS $n = 269$, IBD $n = 227$) | Perceived Stigma Scale for IBS/IBD (PSS-IBS/IBD) | Pearson's correlation and simple linear regression |
| Kool. (2013) [ 36] | FM vs RA, AS, OA, or other rheumatic disease | Cross-sectional | Invalidation | 1.455 (FM n = 341, RA, n = 171, AS, n = 152, OA, $n = 150$, other rheumatic disease $n = 641$) | The Illness Invalidation Inventory (3*I) | Pearson's correlation coefficients |
| Kool (2010) [ 34] | FM vs RA | Cross-sectional | Invalidation | 309 (FM $n = 167$, RA $n = 142$) | The Illness Invalidation Inventory (3*I) | Pearson's correlation coefficients |
| Santiago (2017) [ 35] | FM vs RA, SpA and SLE | Cross-sectional | Invalidation | 562 (FM $n = 241$, RA $n = 124$, SpA $n = 85$, SLE $n = 112$) | The Illness Invalidation Inventory (3*I) | Multivariate regression analysis |
| Singh (2021) [ 37] | FM vs RA | Cross-sectional | Invalidation | 157 (FM $n = 55$, RA $n = 102$) | The Illness Invalidation Inventory (3*I) | Pearson's correlation coefficients |
| Van Alboom (2021) [38] | FM vs RA | Cross-sectional | Perceived stigma | 165 (FM $n = 79$, RA $n = 86$) | Adaption of The Illness Invalidation Inventory (3*I) | Lme4 package in R linear mixed models |
| Baken (2018) [ 39] | CFS vs adult epilepsy, Parkinson's disease, and MS | Cross-sectional | Experienced stigma | 206 (CFS $n = 206$)* | Stigma Short-form | Pearson's correlation coefficients |
| Looper and Kirmayer (2004) [ 15] | IBS vs IBD, FM vs RA, CFS vs MS | Cross-sectional | Perceived stigma | 238 (IBS $n = 38$, IBD $n = 51$, FM $n = 35$, RA $n = 39$, CFS $n = 42$, MS $n = 33$) | 1. Attitudes of Others Scale (including adapted items from the Explanatory Model Interview Catalogue (EMIC-SS)) 2. Pain-Stigma scale | Bivariate and multivariate analyses |

IBS = Irritable Bowel Syndrome, IBD = Inflammatory Bowel Diseases, FM = Fibromyalgia, RA = Rheumatoid Arthritis, AS = Ankylosing Spondylitis, OA = Osteoarthritis, Spa = Spondylarthritis, SLE = Systemic Lupus Erythematosus, CFS = Chronic Fatigue Syndrome, MS = Multiple Sclerosis.

* The CFS patients were compared to normative samples for adult epilepsy, Parkinson's disease, and multiple sclerosis populations.

invalidation from all sources, except spouses, than patients with RA did (Table S2). Santiago et al. (2017) distinguished invalidation in (a) invalidation by family members and (b) invalidation by health professionals [35]. The study included 562 adults with FM ($n = 241$), RA ($n = 124$), spondylarthritis (SpA $n = 85$) and SLE ($n = 112$), with the diagnosis established by a physician. Invalidation levels in patients with FM were significantly higher than in each of the other diagnoses. Patients with FM perceived more discounting and more lack of understanding from family as well as from health professionals (Table S3). There were no significant differences between RA, SpA, and SLE [35]. Singh et al. (2021) investigated the two dimensions of invalidation (discounting and lack of understanding) from four different sources of invalidation (spouse, family, medical professionals and work environment) [37]. The study included 55 patients with FM and 102 patients with RA. Patients with FM experienced significantly more discounting from spouses, family and medical professionals and significantly lower understanding from spouses and medical professionals compared to RA patients [37]. Van Alboom et al. (2021) studied perceived stigma and physical, psychological and social well-being among patients with FM and RA [38]. The study included 79 patients with FM and 86 patients with RA. Individuals with FM reported more daily stigmatizing reactions compared with participants with RA, although the difference was not significant ($p = 0.06$) [38]. Looper et al. (2004) studied the levels of stigma, depression and physical functioning among patients with FM and RA [15]. The study included 35 FM patients and 39 RA patients, diagnosed by a specialist or GP. The study showed no significant differences in perceived stigma between FM or RA (mean ± SD; FM 48.9 ± 13.0; RA 44.2 ± 11.4; scale range 22–88) [15]. The difference between the latter study and the other studies might be explained by the different selection of patients. However, the available data provided insufficient information about this.

From the six studies, three assessed negative health outcomes in FM and RA patients. Singh et al. (2021) assessed physical and psychological health [37], showing that FM patients had significantly lower quality of life on both domains (physical health: FM 46.3 ± 11.8; RA 51.2 ± 10.6; psychological health: FM 45.2 ± 11.4; RA 52.8 ± 11.8; both scales range 0–100; mean ± SD) [37]. Van Alboom et al. (2021) evaluated pain intensity, physical well-being, psychological well-being and social well-being [38]. They found that individuals with FM had significantly higher levels of pain intensity and lower levels of social well-being. No significant difference was found for physical and psychological well-being between the FM and RA groups, with the FM group reporting poorer well-being for both domains [38]. Looper et al. (2004) showed that FM patients had significantly increased levels of depression compared to RA patients (mean ± SD; FM 13.3 ± 8.1; RA 9.2 ± 6.7; scale range 0–39). There was no difference in physical functioning between the groups (Table S1) [15].

All six studies investigated the relationship between stigma and/or invalidation and negative health outcomes. Although the first study did not analyse the different patient groups separately, the authors calculated the correlation of discounting and lack of understanding with health variables for the study population as a whole [36]. They established that greater discounting and lack of understanding correlated significantly with poorer physical health ($r = -0.23$; $p < 0.001$ and $r = -0.13$; $p < 0.001$) and mental health ($r = -0.38$; $p < 0.001$ and $r = -0.35$; $p < 0.001$) [36]. There were no data to compare FM and the other rheumatic diseases. The second study showed several significant associations of the two dimensions of invalidation with health status (Table S4) [34]. Discounting by medical professionals and the work environment correlated most strongly with health status. Correlations were stronger in patients with RA than in those with FM. The third study showed a significant association between the domains of invalidation by family members and health professionals with higher levels of pain and loneliness (Table S5) [35]. All correlations were weak to moderate in strength [35]. The fourth study also showed statistically significant correlation of the two dimensions of invalidation and poorer HRQoL (Table S6) [37]. Invalidation by spouses and medical professionals correlated most strongly with health status for both groups. The correlations were stronger in patients with RA than in those with FM. For RA patients a lack of understanding from family also correlated with poorer health status. All correlations were weak to moderate in strength [37]. The fifth study did not analyse the different patient groups separately but found that perceived stigma overall was significantly correlated with poorer physical, psychological and social well-being (Table S7) [38]. The sixth study also showed a significant association between stigma and negative health outcomes [15]. For FM, perceived stigma was significantly correlated with depression ($r = 0.60$, $p < 0.001$) and physical functioning ($r = -3.3$, $p < 0.1$) on bivariate analysis. For RA, perceived stigma was significantly correlated with depression ($r = 0.31$, $p < 0.1$) and physical functioning ($r = -0.41$, $p < 0.05$) on bivariate analysis.

### 3.3. Chronic fatigue syndrome

We included two studies about CFS. The first compared CFS with MS [15]; the second compared CFS with conditions such as adult epilepsy, Parkinson's disease, and multiple sclerosis (MS) [39]. Looper et al. (2004) compared 42 CFS patients with 33 MS patients, all diagnosed by a specialist or GP, and found stigma scores to be higher in CFS than in MS (mean ± SD; CFS 61.5 ± 10.8; MS 52.6 ± 8.1; scale range 22–88) (Table S1) [15].

Baken et al. (2018) studied 206 patients who self-reported a ME/CFS diagnosis given by a GP or specialist [39]. The ME/CFS patients were compared to normative samples for adult epilepsy, Parkinson's disease, and multiple sclerosis populations [41]. The study found that the CFS patients scored high on the stigma questionnaire (mean ± SD: 60.2 ± 4.8), indicating more perceived stigma; they scored on average at least one standard deviation higher than patients with adult epilepsy (mean: 49.7), Parkinson's disease (mean: 48.4) and MS (mean: 49.4), which are all close to the average value for clinical populations (mean: 50).

The first study found no significant differences in depression or physical functioning between CFS and MS patients (Table S1) [15]. The second study found that compared to the three control neurological conditions, CFS participants reported lower executive functioning, less ability to perform roles and activities and less satisfaction with that ability [39].

Both studies investigated the relationship between stigma and negative health outcomes. Looper et al. (2004) found statistically significant correlations between stigma scores and negative health outcomes. Stigma significantly correlated with depression for both CFS ($r = 0.46$, $p < 0.01$) and MS ($r = 0.40$, $p < 0.05$) [15]. Baken et al. (2018) showed that the increased experience of stigma in CFS patients was significantly associated (strength of association not provided in the study) with poorer self-reported physical health, poorer mental health, and poorer executive functioning as well as lowered ability and less satisfaction in performing roles and activities of daily life [39].

## 4. Discussion

### 4.1. Main results

Patients with FSS perceive or experience at least moderate levels of stigma/invalidation, but patients with comparable explained conditions also perceive or experience stigma/invalidation. For studies about IBS the results were ambivalent; sometimes IBS patients perceived or experienced more stigma, and sometimes there were no statistically significant differences in stigma compared to the patients with comparable explained conditions. Patients with FM perceived more stigma than those with RA in the majority of the studies [34,35,37], albeit not statistically significant in two included studies [15,38]. One study failed to provide sufficient data about perceived stigma [36]. The results in the CFS studies were consistent: patients with CFS experienced more stigma

than patients with neurological disease. Therefore, our hypothesis that FSS patients perceive or experience more stigma compared to medically diagnosed diseases can largely be confirmed although we could not demonstrate this for IBS.

Both patients with FSS and patients with comparable explained conditions experienced negative health outcomes. Therefore, based on the gathered data we cannot confirm our second hypothesis: that patients with FSS will experience significantly higher levels of negative health outcomes compared to patients with comparable explained conditions.

Our third hypothesis was that the level of perceived or experienced stigma will be significantly associated with the negative health outcomes and that this association will be stronger in patients with FSS. This can only be partially confirmed. We found that perceived or experienced stigma was consistently and positively associated with the level of negative health outcomes: the more stigma perceived by the patient the more negative health outcomes. Therefore, we can confirm the first part of the hypothesis. However, we cannot conclude that the association of perceived stigma with negative health outcomes is greater in patients with FSS compared to patients with comparable explained conditions.

### 4.2. Comparison with the literature

Although our study did not find a substantial difference in perceived or experienced stigma between FSS and their medically diagnosed counterparts, patients with FSS do perceive stigma. Among medical conditions, the relatively high levels of stigma have been associated with mental illnesses [42]. The association of FSS with mental health – 'it's all in the mind' - could explain the experience or perception of stigma by patients with FSS, but it does not explain why patients with comparable explained conditions also perceive or experience stigma. The difference between CFS and FM on the one hand and IBS on the other hand can be due to different levels of stigma for the reference group. It is possible that for example IBD evokes more negative attitudes than for example epilepsy because research has shown that the more visible a condition, the more stigma is provoked. A striking example hereof is leprosy [43,44].

The finding that patients with FSS experience negative health outcomes and lower quality of life are understandable, because patients who experience stigma or invalidation are more likely to get distanced from others (initiated by themselves or by others), become socially isolated, loose their social support network, and experience more loneliness and stress [18,45].

### 4.3. Strengths and limitations

In this systematic review, we used an extensive search strategy to identify relevant studies. We searched relevant databases without time or language restrictions. We independently selected the articles for inclusion and had substantial interobserver agreement.

The certainty of the evidence is low because of the heterogeneity of the studies and the scarcity of the available evidence. There are further limitations. Firstly, not all studies presented data enabling a comparison between patients with FSS and their medically explained counterparts. Second, we could not pool data because of the diversity of health outcomes and because not all studies provided raw data. Further, we could only use the bivariate analysis from Looper et al. (2004) since their multiple linear regression analysis used perceived stigma as the dependent variable, whereas we used it as the independent variable. Third, the cross-sectional design of the studies does not allow the direction of causality between stigma and outcomes to be established. Their moderate to high risk of bias may distort the studies' generalizability. Patients experiencing FSS with increased levels of perceived stigma may also experience increased levels of depressive symptoms: perceived stigma may result in depressive symptoms, but the experience of depressive symptoms may also result in an increased sensitivity to negative of rejecting attitudes coming from the social environment. Fourth, all of the included studies had a relatively small sample size, which may have hampered the power of the studies.

### 4.4. Implications for practice and further research

The experience of stigma may lead to a feeling of non-acceptance by health professionals, resulting in the concealment of symptoms and delayed help-seeking behaviour. Health professionals should be aware of stigma and invalidation and their consequences during the clinical management of patients with FSS. Health professionals should try to reduce stigma and invalidation, thus preventing additional negative health effects and lower quality of life. Training in appropriate communication skills related to stigma and invalidation could improve clinical outcomes for patients with FSS [46,47]. Health professionals should also be aware that there are many important sources of stigma and/or invalidation, including themselves.

The fact that there were only eight included studies in this systematic review (regarding stigma and health outcomes inpatients with FSS, compared to patients with organically diagnosed diseases), demonstrates the need for further research into this topic. To determine the level of perceived and experienced stigma and the influence of perceived stigma on health outcomes, there should be increased use of longitudinal studies. We would advise researchers to use a broad set of health outcomes, concerning both physical and mental outcomes, augmented with outcomes considered relevant by patients. These studies should include a large study population to obtain enough statistical power, as the effect size of potential associations remains unknown. Future studies should also be developed with consideration of the control conditions as these conditions may also generate feelings of stigma. Moreover, future studies should deal with all sources of stigma (such as family members and health professionals) and all kinds of stigma (such as perceived, internalized, and enacted stigma).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2021.110715.

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