Predictors of persistent somatic symptoms in the general population: a systematic review of cohort studies

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Predictors of Persistent Somatic Symptoms in the General Population: A Systematic Review of Cohort Studies

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ABSTRACT

Objective: Up to 10% of the general population experiences persistent somatic symptoms (PSS). Numerous studies in a variety of health domains are dedicated to identifying factors that are associated with PSS onset. The present study aimed to provide an overview of predictors for PSS onset in the general population and the related health domains.

Methods: A systematic search was performed identifying longitudinal cohort studies that examined factors associated with PSS onset in the general population. Included studies measured potential predictors before PSS onset and were categorized according to the dynamic biopsychosocial model. Four levels of evidence were discerned for predictors, based on the number of studies and percentage of consistent findings.

Results: In the 154 articles eligible for analysis, 27 PSS subtypes were studied, with primary focus on fibromyalgia (25.0%) and irritable bowel syndrome (23.3%). Of the >250 predictors of PSS onset, 46 were investigated more than once and showed consistent results. Strong evidence identifies biological (e.g., infections, body weight–related metrics), psychological (e.g., sleep problems, psychopathology), interpersonal (life events, childhood/interpersonal stress), contextual (employment), and health behavioral (health care utilization) predictors.

Conclusions: The results provide strong evidence for factors from all dynamic biopsychosocial domains, although interpersonal and health behavioral factors are relatively under investigated. Thus, evidence suggests that reduction of predictors of PSS onset to a specific factor/domain may be too restrictive. There is no evidence that this differs per PSS subtype. Exploring all domains and measuring common factors across subtypes are essential to improve the clinical course of PSS.

Key words: persistent somatic symptoms, risk factors, systematic review, biopsychosocial model, medically unexplained symptoms, functional somatic symptoms.

INTRODUCTION

Up to 10% of the general population experience persistent somatic symptoms (PSS) that are not fully explained by established biomedical pathophysiology. These symptoms cannot be fully attributed to objectively determined anatomical or functional disease severity (1–4). So-called PSS—symptoms without identified biomedical pathophysiology—are prevalent in both patients with well-understood disorders, such as cancer (5) and cardiovascular disease (6), as well as in patients without well-understood disorders (7–9). PSS has a high burden of disease, for both the patient and the health care system. Diagnostic difficulties and delays may contribute to this burden (10).

Terminology and classification for PSS vary widely across and within health care domains and disciplines (11). Although umbrella terms such as medically unexplained (physical) symptoms, functional somatic symptoms, and PSS are used more or less interchangeably, symptoms may also be diagnosed as syndromes, which cluster around bodily symptoms (e.g., chronic low back pain, chronic fatigue syndrome [CFS], or irritable bowel syndrome [IBS]). The diagnostic distinctiveness of these syndromes in the context of PSS is debatable, because patients with syndromes, which use bodily symptoms as diagnostic criteria, often fulfill the diagnostic criteria of more than one syndrome (4,12,13). Although

BMI = body mass index, CFS = chronic fatigue syndrome, CP = chronic pain, FM = fibromyalgia, GI = gastrointestinal, IBS = irritable bowel syndrome, PSS = persistent somatic symptoms

these days most experts accept that there are common overarching factors and syndrome-specific factors (14,15), historically, etiological research focusing on PSS is heterogeneous in nature—that is, often directed at subcategories of PSS (11).

Deficient biomedical pathophysiological explanations for PSS have redirected attention to other health domains for astute identification and effective treatment (13,16,17). Many studies have shown that most somatic diseases result from a variety of factors, part of which are beyond the biomedical domain—thus, this is not only the case for PSS (18,19). In response to increasing knowledge that health and disease depend on more than biomedical pathology, the biopsychosocial model of health was introduced (20). Adoption and popularity of the model varies. Later, the biopsychosocial model has been expanded based on ecological/contextual models, the transactional model, and philosophical work on dynamic systems, into the recent dynamic biopsychosocial model (21). The dynamic biopsychosocial model construes that health is the consequence of reciprocal, time-dependent, influences of biological, psychological, interpersonal, and macrosystemic contextual factors. Furthermore, the dynamic biopsychosocial model includes the effects of health behaviors on health. Because of the complexity of PSS, fitting predictors to the dynamic model could contribute to elucidate the interplay between factors related to PSS onset.

In recent years, ample research has been directed at identifying predictors of PSS in a variety of health domains and across a multitude of PSS subcategories. The lack of an adequate or predominant explanation for PSS in a specific health domain requires an overview of which health domains are relevant for PSS diagnostics and treatment. Etiological research in PSS has predominantly focused on PSS subcategories, including recent reviews on risk factors (16,17). The present study aims to bridge the gap by focusing on the broad spectrum of PSS and identifying common overarching predictors of onset. To get more insight into what health domains are of clinical importance and to increase comprehensibility, the predictors will be categorized according to the dynamic biopsychosocial model of health.

METHODS

Search Strategy and Selection Criteria

Following the PRISMA 2020 statement (22), the present study is a systematic review of general population cohort or nested case-control studies on factors predicting PSS onset. We identified articles through a search of PubMed, Web of Science, PsychINFO, and Embase from inception to March 11, 2022. A search hedge of four parts was constructed: a) terms related to predictors, such as "risk factors" and "prediction model"; b) terms indicating any PSS, such as "medically unexplained (physical) symptoms," "somatization," and "fibromyalgia"; and c) terms related to study type, such as "cohort studies"

and "longitudinal" (see Appendix S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A879, for the full search hedge).

For inclusion, cohort studies or nested case-control studies had to investigate a) the general population, b) symptom and syndromes without well-known biomedical pathology with a duration of at least 3 months as an outcome, and c) possible predictors before PSS onset. A duration of 3 months was selected because this is the duration generally stated for chronicity of most PSS.

The search was performed by a medical librarian, and after the removal of duplicates, titles and abstracts were screened twice, once by a group of three graduate students and once by the first author (W.M.K.). W.M.K. and J.P. each screened half of full-text articles conservatively consistent with the inclusion and exclusion criteria. Any doubts were discussed in meetings between W.M.K., J.P., and R.v.d.V. In addition, a hand search of the reference list of included studies was performed. A meta-analysis on the included studies was not preformed. The main aim of this study was, namely, to provide a broad overview of predictors and their domains. In addition, a meta-analysis would not have been feasible because of the large heterogeneity of the predictor (i.e., >250 predictors and inconsistent use of measurement tools) and outcome variables (i.e., 27 PSS subcategories) and because our study aim was mostly directed at providing a broad overview of predictors and their domains. The study protocol was published on PROSPERO under CRD42018106628.

Data Synthesis

The data extracted include the first author, year of publication, study design, country, sample size, sex, age, outcome (including measurement type and definition), the length of follow-up, and measured predictors. To assess the risk of bias, a modified version of the Cochrane Collaboration–endorsed Newcastle-Ottawa Quality Assessment Scale for cohort studies was used (23), in which the threshold for length of follow-up was calculated based on the study type (i.e., birth cohorts, electronic medical record cohort studies, nested case-control studies, prospective studies, and retrospective studies).

The list of outcomes was devised counting all articles that observed a specific outcome. For providing an overview of specific PSS outcomes studied by included studies, outcomes were clustered into five main types of PSS: a) chronic pain (CP)–related PSS (e.g., regional pain or fibromyalgia [FM]), b) gastrointestinal (GI)-related PSS (e.g., IBS or functional dyspepsia), c) fatigue-related PSS, d) other specific PSS (e.g., tinnitus or benign paroxysmal vertigo), and e) unspecified PSS (containing umbrella terms like functional somatic symptoms and medically unexplained symptoms). All predictor variables were extracted and clustered into the five health domains in the dynamic biopsychosocial model of health (i.e., biological factors, psychological factors, interpersonal factors, contextual factors, and health behavior) in parallel by W.M.K., R.v.d.V., A.W.M.E., and M.E.N. For all predictors, significant association (including direction) with the outcome was extracted based on any test done in the article. Where possible and with constraint, similar factors for which different terms were used between articles (e.g., body weight–related metrics include body mass index [BMI], weight, obesity, waist-to-hip ratio, waist circumference) were merged based on expert knowledge from our interdisciplinary team and in collaboration between W.M.K., R.v.d.V., M.E.N., and A.W.M.E. To

TABLE 1. Levels of Evidence

Levels of Evidence	Criteria
Strong	• Investigated in at least 6 studies with >75% consistent findings
Moderate	• Investigated in 3–5 studies with at least >75% consistent finding, or • Investigated by at least 6 studies with >65% consistent findings
Limited	• Investigated in 2 studies with 100% consistency, or • Investigated in 3 to 5 studies with >65% consistent findings
Inconclusive	• Inconsistent findings (<65% consistency) in more than 6 studies, or • Found 100% predictive in < 2 studies

construe the levels of evidence, consistency of the association was determined by calculating the percentage of significant associations found in single studies (modified based on Ref. (24)). It should be noted that evidence levels depend on the number of studies, and a lower level of evidence does not necessarily indicate insufficient strength of association (we have not evaluated the effect size) but rather being less likely to be investigated. The level of evidence thus indicates how often a predictor is investigated and how often the association was found. For a detailed description of levels of evidence, see Table 1. This review reports about predictors at a symptom level and a clustered health domain level (i.e., according to the dynamic biopsychosocial model).

RESULTS

The initial search yielded 15,387 articles from four different databases and resulted in 9990 titles after removal of duplicates. The search and article screening resulted in a total inclusion of 154 articles (see Figure 1 for more details).

Of the 154 included studies, there were prospective cohorts ($n = 67$), cohort studies based on electronic medical record studies ($n = 52$), birth cohorts ($n = 22$), nested case-control studies ($n = 7$), and retrospective cohorts ($n = 6$). Study quality was high for 71 studies, moderate for 14 studies, and low for 67 studies (for more details, see Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A879). Limited time to follow-up, loss to follow-up, and type of assessment measures for predictors and outcome caused the largest discrepancies in study quality. Of all included studies, 46% defined one or multiple of their PSS-related outcome(s) as a CP-related PSS, 27.4% as a GI-related PSS, 14.0% as a fatigue-related PSS, 11.1% as another specific PSS, and 1.7% as an unspecified PSS (i.e., functional somatic symptoms and medically unexplained symptoms; for more details, see Table 2). Of these studies, $n = 17$ (11.3%) articles investigated multiple PSS subcategories as separate outcomes. The follow-up period varied between 6 months to 58 years between studies. The number of predictor variables investigated varied widely between studies as well, where 73 articles investigated only risk factors in a single domain and a limited number of studies investigated risk factors from all health domains ($n = 7$; Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A879).
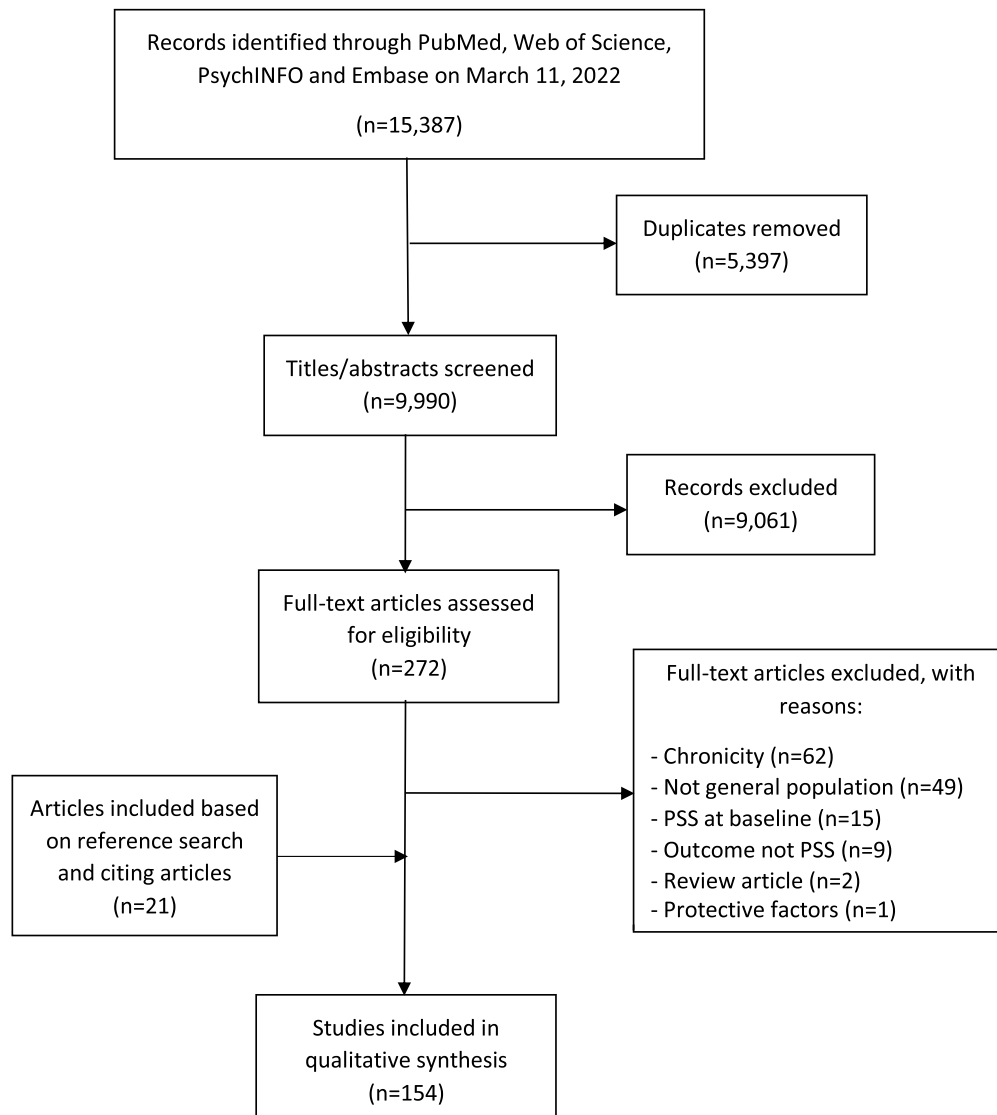

FIGURE 1. Flowchart study inclusion.

TABLE 2. Overview of PSS Definitions and Number of Articles Using the Definition as an Outcome

PSS Subcategory	No. Outcomes From 154 Articles ($n = 173$), n (%)[a]
Chronic pain-related PSS	
Fibromyalgia/chronic widespread pain	43 (25.0)
Low back pain	11 (6.4)
Chronic musculoskeletal complaints/pain	7 (4.1)
Chronic pain	7 (4.1)
Chronic back pain	5 (2.9)
Other chronic pain categories[b]	7 (4.1)
Gastrointestinal-related PSS	
Irritable bowel syndrome	40 (23.3)
Functional dyspepsia	6 (3.5)
Any functional gastrointestinal disorder	1 (0.6)
Fatigue-related PSS	
Chronic fatigue syndrome	18 (10.5)
Chronic fatigue	6 (3.5)
Other specific PSS	
Benign paroxysmal positional vertigo	8 (4.7)
Tinnitus	4 (2.3)
Interstitial cystitis/bladder pain syndrome	3 (1.7)
Vulvodynia	2 (1.2)
Chronic tension type headache	1 (0.6)
Chronic whiplash	1 (0.6)
Unspecified PSS	
Functional somatic symptoms	2 (1.2)
Medically unexplained symptoms	1 (0.6)

PSS = persistent somatic symptoms.

[a] n relates to number of outcomes. Several studies investigated multiple outcome categories.

[b] Neck, back, and shoulder pain; arm pain; orofacial pain; reginal pain; myofascial pain; and neck and low back pain.

The data synthesis identified 20 predictors with strong levels of evidence, 16 predictors with moderate certainty, and 10 predictors with limited certainty (for more details about the categories, see Table 1). Most factors were inconclusively related to PSS (~200), of which 8 factors were investigated frequently (by more than six studies) reporting mixed evidence.

The predictors were categorized according to health domain, in order of level of evidence (Table 3). In this section, we only describe the predictors with strong evidence in detail. For more detailed information about all predictors, see Appendix S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A879. Infections ($n = 33$) are mostly studied in GI- and fatigue-related PSS and found predictive in 87.9% of studies. The only study investigating another PSS subtype (*Helicobacter pylori* infection before FM onset) found no significant association. Sleep problems ($n = 28$) have a positive predictive value (92.6% consistency) predicting especially CP-related PSS conclusively ($n = 17$), but also GI-related PSS ($n = 3$), CF-related PSS ($n = 3$), tension-type headache ($n = 1$), and benign paroxysmal vertigo ($n = 1$). Anxiety ($n = 26$) predicts most subtypes of PSS with high consistency (92.0%). Depression ($n = 24$) was a consistent positive predictor in 92.0% of studies over different PSS subcategories. Body weight–related metrics ($n = 22$) predict PSS onset with a positive and U-shaped predictive value for CP ($n = 13$)

and GI ($n = 5$), except for fatigue-related PSS, which lacks significant results in four of five studies. Psychopathology ($n = 22$) is 81.0% positively related to CP-related PSS, GI-related PSS, and fatigue-related PSS. Somatic symptoms ($n = 12$) predict PSS onset with 90.9% consistency and are mostly investigated in CP-related PSS, but also for IBS ($n = 2$) and chronic fatigue syndrome (CFS; $n = 1$). Life events ($n = 11$), headache or migraine ($n = 10$), other general medical illnesses ($n = 9$), abdominal pain ($n = 9$), renal disease ($n = 7$), childhood adversity ($n = 7$), and interpersonal stress ($n = 7$) with high consistency (77.8%–88.9%) predict the onset of most types of PSS. Self-reported general health ($n = 10$), health care utilization ($n = 10$), and GI disorders ($n = 8$), all investigated in widely varying subtypes, and fatigue ($n = 7$), only investigated in CP-related PSS ($n = 5$) and CFS ($n = 2$), predict onset with 100% consistency. Employment type ($n = 7$) is related to PSS onset, although there is inconsistency whether the risk regards manual or office work. Lastly, allergies ($n = 6$) are investigated in FM, CFS, and IBS and predict onset with 83.3% consistency.

Less established factors for which no conclusive evidence was found were approximately 200 factors investigated only once or showing inconsistent findings in at least six studies (i.e., <65% consistent findings). Sex and age were investigated often ($n = 33$ and $n = 30$, respectively). There is moderate evidence (66.6% consistency) that age is predictive, with results indicating U-shaped relationship where young adults and older people tend to be more

TABLE 3. Predictors of PSS, by Health Domain and Level of Evidence

Health Domains	No. Articles (%[a])	Levels of Evidence[b]	Predictors of PSS[c]
Biological	122 (79.2)	Strong	Infections[d], body weight–related metrics[e], somatic symptoms, abdominal pain, other general medical illnesses, headaches or migraine, gastrointestinal disorders, renal disease, allergies[f]
		Moderate	Musculoskeletal conditions, rheumatological disorders, (TMJ) muscle tenderness on palpation, any type of chronic pain, genes, endometriosis, cardiovascular disease, skin disorders
		Limited	Low back pain, back/neck pain with neuropathy, cerebrovascular disease, dyslipidemia, injury, menstrual disorders, osteoporosis, vitamin D status
Psychological	61 (39.6)	Strong	Sleep problems[g], anxiety, depression[h], psychopathology/mental health, fatigue
		Moderate	Personality type[i], quality of life
		Limited	
Interpersonal	26 (16.9)	Strong	Life events, childhood adversity[j], interpersonal stress[k]
		Moderate	
		Limited	Social support
Contextual	64 (41.6)	Strong	Employment
		Moderate	Age, socioeconomic status
		Limited	Intelligence
Health behaviors	37 (24.0)	Strong	Health care utilization[l]
		Moderate	Physical activity, illness behavior, medications used, alcohol (use and abuse), pain medication use[m]
		Limited	

PSS = persistent somatic symptoms; TMJ = temporomandibular joint.

[a] Percentage of articles that investigated factors in the domain.

[b] Table only includes predictors that were investigated by more than one study.

[c] Ordered according to number of studies investigating the predictor.

[d] Including *Salmonella*, gastrointestinal, viral, nonspecific, *Giardia*, and urinary tract infections.

[e] Including body mass index, body weight, waist-to-hip ratio, and waist circumference.

[f] Including food allergies and allergic rhinitis.

[h] Including Hospital Anxiety and Depression Scale depression, major depression, bipolar disorder, and mood disorders.

[g] Excluding sleep apnea.

[i] Perfectionism, self-discipline, or conscientiousness.

[j] Including social and physical adversity, and physical and sexual abuse.

[k] Including intimate partner violence, discrimination, and (history of) physical or mental illness in the household.

[l] Including consultations, opioid use, emergency department visits, number of medications used, and referrals.

[m] Excluding opioids.

likely to develop PSS. Sex showed inconsistent results independent of study quality and outcome definition. Other inconsistent factors that were frequently investigated are diabetes ($n = 16$), smoking ($n = 14$), hypertension ($n = 13$), asthma ($n = 12$), education ($n = 10$), marital status ($n = 9$), and hyperlipidemia ($n = 7$). A full overview of factors identified in this research is available in Appendix S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A879.

At the level of the dynamic biopsychosocial domains, results showed that predictors categorized as biological factors are most likely to be investigated (79.2%), followed by contextual factors (41.6%) and psychological factors (39.6%), whereas health behavior and interpersonal factors are least likely to be investigated (24.0% and 16.9%, respectively) by studies included in the present review (Table 3). Moreover, $n = 7$ studies investigated factors from all domains, and contextual, interpersonal, and health behavior factors are least likely to be investigated unaccompanied by another factor ($n = 6$, $n = 5$, and $n = 2$, respectively).

DISCUSSION

To the best of our knowledge, the present systematic review is the first that provides a comprehensive overview of predictors for the onset of the broad spectrum of PSS as studied in prospective studies in all health domains. Research generally focuses on specific PSS syndromes or symptoms, such as FM or chronic low back pain. At the level of the dynamic biopsychosocial model, a wealth of evidence shows that all health domains are predictive of PSS onset. Strongest evidence is available for biological (e.g., infections, body weight–related metrics, many somatic symptoms/disorders) and psychological factors (e.g., sleep problems, anxiety, depression), followed by contextual factors (e.g., type of employment). Interpersonal stress–related factors and health behaviors, such as health care utilization, were less investigated but still consistently associated with PSS onset. We found no evidence that there was a difference between specific PSS complaints/conditions because predictors were generally investigated in multiple PSS

subcategories, suggesting that identified strong predictors are largely overarching. Evidence levels for predictors were construed based on the number of studies investigating the predictor and the percentage of consistent results among these studies. Therefore, the present study was unable to evaluate if predictors that were investigated a limited amount of times are PSS subtype specific or related to the broad spectrum of PSS.

The results of the systematic search show that extensive research has been directed at identification of predictors of PSS. Although included studies cover predictors in all health domains of the dynamic biopsychosocial model, the primary focus has been on biological factors. In total, more than 250 factors predicted PSS onset in the included literature, of which we found 46 that were supported by at least limited levels of evidence. However, some strong predictors (mainly infections) were primarily investigated in specific PSS subcategories. A detailed description of the predictors can be found in the next paragraphs, which are structured based on the domains of the dynamic biopsychosocial model of health in order of prevalence, as construed from the described analysis.

Results show that biological factors play a role in PSS onset. Remarkably, the predictor with strongest evidence—that is, infections—was investigated primarily in the specific PSS subtypes, namely, GI- and fatigue-related PSS. Nonetheless, other studies indicate that infections may play a role in FM and interstitial cystitis/bladder pain syndrome (25,26). Some biological predictors of PSS are easily measurable and controllable biometric predictors. These include body weight metrics, birth weight, hyperlipidemia, and vitamin D status. Although clear directionality of these factors was not evident from our findings, recent reviews indicate that BMI may have different predictive value from FM (17) and IBS (16). Although all these biometric factors may also be common in patients without PSS, future research should evaluate if routine measurements of these factors might aid in compiling a risk profile for patients at risk of PSS. At a symptomatic level, any type of somatic symptom or pain symptoms (such as, headaches, and [low] back pain) is predictive of PSS. Chronic medical conditions (e.g., cardiovascular, renal, skin, rheumatological disease) were predictive of PSS onset, which indicates that exclusion of patients with chronic medical conditions in studies investigating PSS, as done by some studies (27), is unwarranted. Lastly, in corroboration a systematic review on FM, we found evidence for a genetic predisposition in patients with PSS.

Psychological predictors were noticeably investigated unspecific to PSS subtype. Sleep problems and psychopathology (especially anxiety and depression) were one of the most investigated of all factors and relatively most consistently related to PSS onset. Furthermore, fatigue, personality types (e.g., perfectionist), and quality of life were conclusively related to PSS onset. This is in line with previous reviews that implicated all these parameters as important contributors to physical health (1,18,19), related to stress (1,19), and having (neuro)biological consequences (28). In all, results suggest that psychological factors are critical contributors to PSS onset.

Although interpersonal factors are least likely to be investigated, strong evidence suggests that stress-related factors such as life events, childhood adversity, and interpersonal stress are often associated with PSS onset, unrelated to PSS subtype. Although the present study finds this evidence mostly in cohort studies with

poor quality, results of high-quality systematic reviews/meta-analyses suggest that they may indeed be important for PSS onset (29,30). Future investigation of these factors in well-designed cohort studies is needed to confirm the nature of the relationship. Besides, our results indicate a relationship between a lack of social support and PSS onset, which is in line with studies proposing that social support mediate stress and health outcomes (31,32).

A moderately high number of studies (also) investigated contextual factors, which was largely due to this category also containing the age and sex. Age and sex are generally seen as important predictors of PSS, although previous systematic reviews and meta-analyses show mixed evidence (33–36). Several empirical studies (25,37), as well as systematic reviews, suggest that predictors may be age and sex specific and that this may be where the initial association stems from (34,38). The latter, in combination with the mixed findings in the present study, implies that, although sex and age may influence PSS onset, they are unlikely to be independent predictors. This is in line with previous systematic reviews showing limited consistency (34,39). Although there are only a few contextual factors sufficiently relatable to PSS onset, the evidence for socioeconomic position and related variables (employment, intelligence) indicates that social context should be taken into account in relation to risk of PSS onset.

Lastly, several studies indicated health behavioral predictors of PSS onset. Although some studies show discrepancies in the association with health care utilization between PSS subtypes (40,41), our results indicate that it is associated with PSS onset across subtypes. Physical activity was strongly related to PSS onset, although primarily investigated in CP and fatigue. Research in other PSS categories shows that physical activity is likely to be related to PSS in general (42,43). We found moderate evidence for alcohol use and illness behavior. Alcohol use was investigated in a variety of PSS subcategories. Illness behavior was notably investigated only by specific research groups (44–47). Nonetheless, illness behavior has been related to other PSS by many others (48).

In the context of the dynamic biopsychosocial model of health, studies investigating factors in all health domains imply that the origin of PSS cannot be attributed to a single domain. Many other studies suggest this (11,16,17,48–51); for instance, Klem et al. (50) found an increased risk of IBS after infection, especially in women, patients using antibiotics, and patients with depression, somatization, and anxiety. Similarly, Hulme et al. (51) indicate that an interplay between biopsychosocial factors increases the risk of going from acute to chronic fatigue. More recently, two expert population-based reviews show that risk factors from all domains predict FM and IBS onset (16,17). Because of the broadness and design of the present review, we are able to provide strong evidence to corroborate these findings. For all PSS subcategories, results suggest that onset cannot be exclusively attributed to specific factors, or even a specific health domain. Thus, to distil the cause of PSS, elaborate investigation of the interplay between specific factors within an individual is imperative. Longitudinal studies investigating factors from all domains are therefore needed. Based on our findings in relation to the dynamic biopsychosocial model (21), especially in the health behavioral, interpersonal, and contextual (e.g., age and sex) domains, we hypothesize that interaction effects may play a role and should not be overlooked (see Ref. (52) for recent publication regarding interaction of predictors for FM onset). Focusing on the moderating and mediating factors

may further help clarify which factors are predisposing and precipitating PSS onset.

The results of this review should be interpreted in the light of several strengths and limitations. First, approaching the broad spectrum of PSS and thus combining PSS subcategories are both a limitation and a strength of this study. Although the design limits our ability to differentiate between overarching predictors and subtype-specific predictors for less investigated factors, it does enable identifying commonly investigated overarching predictors. Another limitation is that the inclusion was restricted to cohort studies. Although we believe that cohort studies provide the best level of evidence for our purpose, because of the ecological validity, some risk factors that are less likely to be investigated in cohort studies (e.g., based on neuroimaging studies) may have been missed. Lastly, because the present study aimed to identify predictors of onset, as a result, implications for treatment drawn from the results are indirect and can only serve as recommendations for future research.

In conclusion, the present study shows that there is mounting evidence that a large number of risk factors, from all domains in the dynamic biopsychosocial model, predict PSS onset. We found no evidence that these factors are PSS complaint or condition specific. This corroborates conclusions from other research, which demonstrate that PSS requires a multidomain classification and treatment (48,49,53,54). Clinicians should therefore use a wide range of screening instruments in which all these domains are measured to identify patients at risk at an early stage. Future research should focus on a better and more complete measurement of all dimensions, especially related to behavior and social context, and measuring the broad spectrum of PSS. Such studies could help improve current, or aid the development of new, screening tools and prediction models for more astute identification and more holistic treatment of PSS. Because of the magnitude of the problem of PSS in society, development of tailored interventions, which map the factors and construe the interrelatedness of factors to find the best path toward health improvement, is much needed.

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