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# Promoting early recognition of persistent somatic symptoms in primary care

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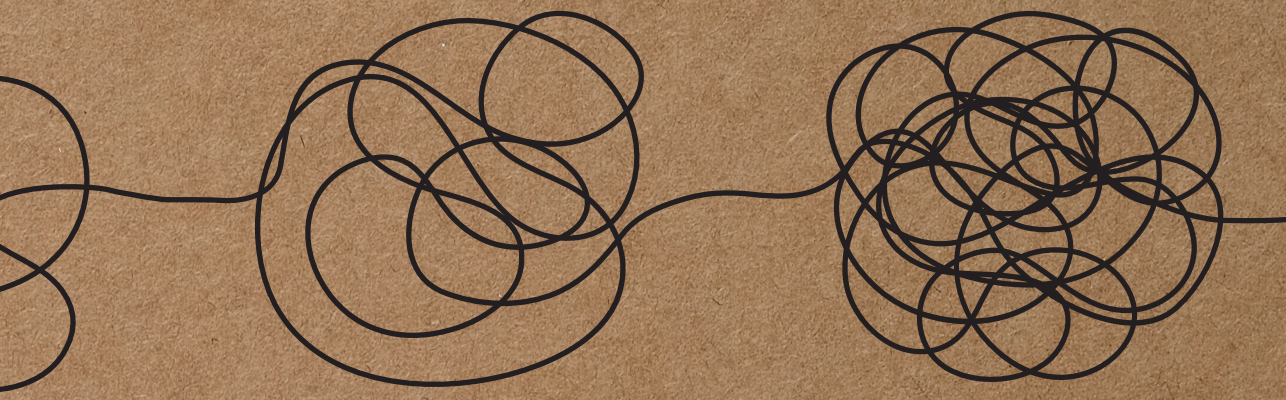
# PROMOTING **EARLY RECOGNITION OF PERSISTENT SOMATIC SYMPTOMS** IN PRIMARY CARE

*Willeke Kitselaar*



# Promoting early recognition of persistent somatic symptoms in primary care

Willeke Kitselaar

**Promoting early recognition of persistent somatic symptoms in primary care**
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# Promoting early recognition of persistent somatic symptoms in primary care

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I can of my own self

do nothing

**- John 5:30**

Of course, it is happening inside your head, […]
but why on earth should that mean
that it is not real?
**- Prof. Dumbledore**

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# Chapter 1

General introduction

## Persistent somatic symptoms in the general population

Experiencing somatic symptoms is common for most people in daily life. General population studies show that 80 to 95% of adults experience at least one somatic symptom at any given point in time.[1–3] Symptoms may vary widely, but are most commonly forms of pain, fatigue, gastrointestinal complaints, and dizziness. While most of these symptoms are self-limiting, approximately 20% of adults experience persistent or recurring disabling somatic symptoms.[1,4] It is commonly accepted that somatic symptoms are related to established physical disease, but it is also common knowledge that symptoms may also be present in individuals without such disease. Furthermore, research shows that most somatic symptoms are not fully explained by established biomedical pathophysiology and cannot be fully attributed to objectively determined disease severity.[5–7] Hence, both individuals with biomedical disorders, such as cardiovascular disease [8] and cancer,[9] as well as individuals without such a disorder may experience somatic symptoms that persist without clear biomedical pathophysiological explanation.[10–13] In all, up to 10% of the general population experience persistent somatic symptoms (PSS) that persist beyond biomedical expectation.[7,14–16]

## Distinguishing PSS from well-understood biomedical disorders

The distinction of PSS from well-established biomedical disorders can be challenging.[17] Historically, PSS classification was based on the exclusion of well-established physical conditions.[18,19] Challenges may, for instance, arise from similarities between symptoms of PSS and other conditions, potential comorbid biomedical disorders, the heterogeneity of symptoms, lack of universal guidelines, and the lack of biomarkers.[19–22] Moreover, in the biomedical model of health, which to date is still dominant in Western health care, the origin of symptoms is attributed to either biomedical or psychological factors. Especially in the case of PSS this model does not suffice, since studies have shown that the origin of PSS is related to factors from multiple domains – i.e., more consistent with the (dynamic) biopsychosocial model.[20,21,23,24] Physicians may be limited in investigating problems beyond the biomedical domain due to time constraints and high work pressure.[25] Studies show that GPs experience many other barriers towards classifying PSS.[26–28] For instance, due to cultural differences,[29] fear of missing a life-threatening

medical illness,[30,31] reluctance to link somatic symptoms to psychosocial problems,[32] or lacking training.[31,33] The latter may explain why identification is limited even though several validated screening tools for PSS have been developed (4DSQ, PHQ15, SSD-12).[3,12,34] Unsurprisingly, due to the complexity of the origin and the connected challenges, identification of PSS may be delayed for a long time. This is, for instance, seen in studies that show an average diagnostic delay of 6 years in patients with fibromyalgia (FM),[35] and 4.5 years for chronic fatigue syndrome (CFS).[36] Delayed diagnosis comes with delayed treatment and may result in higher burden of disease.

## The societal burden of PSS

Studies show that PSS are highly burdensome to patients, physicians, health care, and society in general.[21,37] Patients with PSS generally experience reduced health-related quality of life.[38–40] Moreover, symptoms can affect many aspects of life, including physical, psychological, and social functioning. For instance, the longer patients experience somatic symptoms, the more likely they will experience disability, work absenteeism,[41,42] and utilize health care resources.[40,43,44] Furthermore, research has shown that patients with PSS are generally less satisfied with the care they receive.[45] Challenges and delays in diagnostics put a strain on the patient, physician, and society. Health care and physician burden relate to the high healthcare utilization and accompanying time and costs.[37,40,46,47] For instance, up to 50% of GP consultations are related to symptoms without well-understood biomedical pathology. Similarly, 30-50% of symptoms in secondary care cannot be fully explained by well-established biomedical pathophysiology.[14,48,49] In addition, research shows that PSS are related to frustrations in GPs and patients due to diagnostic delays and mutual misunderstanding, which may result in disturbed doctor-patient relationships.[31–33,50–52]

## Etiology, terminology, and definitions of PSS

Complex etiology, inconsistent terminology, and ambiguous definitions characterize PSS. Long since, the etiology of PSS is under debate and differences within and between health care domains and disciplines exist.[21,53] As briefly mentioned previously, advances in the understanding of the etiology of PSS may be impeded by dualistic and reductionists views related to the biomedical view Western medicine presently

maintains.[54] These views require symptom attribution to a single cause which can be either physical (e.g., an infection) or psychological (e.g., stress). This view may be especially unhelpful for PSS, in which symptoms are related to factors from different health domains.[19–23,55] As for instance is seen in the PSS-subtype irritable bowel syndrome (IBS), in which symptoms are related to the complex interplay between stress and inflammatory and immune responses.[56]

Although there are some differences in exact definitions, umbrella terms such as medically unexplained (physical) symptoms (MUPS), functional somatic symptoms, and the psychiatric diagnosis 'somatic symptom disorder' (SSD) are used more or less interchangeably. Most recent definitions of PSS, such as SSD, focus on thoughts, behavior, and emotions regarding somatic symptoms and relinquished the distinction between patients with or without coexisting biomedical pathophysiology (APA, 2013). Patients with PSS related to specific symptom clusters may also be diagnosed with a PSS-related syndrome (e.g., common syndromes are fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome). The diagnostic distinctiveness of these syndromes in the context of PSS is debatable, since patients with syndromes which use bodily symptoms as diagnostic criteria, often fulfill the diagnostic criteria of more than one syndrome.[7,53,57] While these days most experts accept that there are common overarching factors as well as syndrome-specific factors,[58,59] historically, etiological research focusing on PSS is heterogeneous in nature – i.e., often directed at subcategories of PSS.[21] In general, patients with PSS are characterized by presenting different somatic symptoms, as well as symptoms beyond the biomedical domain.[20,60] In all, identifying patients with PSS is ambiguous and challenging in the current daily practice of GPs.[21,26,27]

This thesis primarily focuses on the common aspects of PSS, conform current international standards (i.e., persistent somatic symptomology with or without coexisting biomedical disease), and the re-use of anonymously extracted routine primary care data. Due to the great variety of definitions in the pre-existing literature and the limitations of the re-use of routine care data, the studies in this thesis aimed to define PSS based on the best fitting PSS classifications per data source. While most population selection methods of the included studies did not focus on patients with exacerbated

symptomology in biomedical diseases, patients with biomedical diseases were explicitly not excluded in any of the presented studies. Thereby the assumption was made that the included population would provide adequate proxies for the total population. This assumption was further investigated in chapter 4 and 5.

## The re-use of routine primary care data for PSS research

In countries such as the Netherlands, where GPs are the gatekeeper to specialist care, GPs are most likely to be the first to be consulted in case of somatic symptoms. Even so, in addition to identification problems described above, registrations of PSS in primary care are hampered, for example due to a lack of codes or consultation constrains such as overloaded surgery hours.[27,61] In electronic medical records (EMRs) of Dutch GPs, the international classification of primary care (ICPC) is used. The ICPC does not include a code for PSS, which may complicate registration of PSS. Although the ICPC does include options to register complaints beyond the biomedical domain, availability of such codes is limited compared to biomedical codes. In recent years, research has increasingly utilized routine primary care data for mental health [62] and PSS research.[63–70] Predictive modeling of the broad spectrum of PSS based on routine care data showed moderate success [63,64] and an EMR-based study on identification of patients with fibromyalgia showed promising results.[67] Even so, limitations of the re-use of EMR data should be heeded. For instance, the PSS index date (i.e., first date of PSS registration) may not represent the date of PSS-onset since diagnosis of PSS is often delayed.[35,36,71] In addition, since EMR data are not collected for research purposes and data is only registered when the patient visit the GP and the GP chooses to register, EMR data is characterized by high levels of (non-random) missing data.[72] Furthermore, as indicated above, registrations beyond the biomedical domain may be limited. Although disputed by some studies,[73,74] machine learning techniques and data mining may circumvent problems with missing data and increase performance of predictive models.[75,76] Furthermore, recent studies based on routine primary care data showed that theory driven and data driven machine learning approaches support early identification of patients at risk of non-biomedical problems.[75,77,78] Therefore, this thesis explores the use of theory driven, data driven, and

combined approaches to utilize EMR data from Dutch primary care for predictive modeling.

## Aim and outline of this thesis

The primary aim of this thesis is to promote early identification of PSS in primary care in order to reduce the burden of PSS on the patient, physician, and society. The theory and data driven approaches towards this aim are presented in this thesis as follows:
Firstly, **Chapter 2** presents an overview of predictors of PSS in the general population. The predictors are construed from a large systematic review of the state of evidence regarding predictors of PSS and its subtypes, based on longitudinal cohort studies. Predictors are categorized according to the dynamic biopsychosocial model and result in an overview of investigated domains and the importance of multidomain exploration in clinical practice.
In **Chapter 3**, results from a survey on GP's perspectives regarding the classification and registration of PSS in primary care is presented. Results provide insight in the methods of registration using ICPC coding and beyond, as well as GP's perspectives on their abilities and needs regarding PSS classification and registration. Subsequently, **Chapter 4** further explores how the broad spectrum of PSS can be identified in routine primary care data despite lacking unambiguous clinical coding. Subsequent exploration of the usability of routine primary care data and the differences and similarities of PSS-subtypes is presented in **Chapter 5**. Herein, the viability of psychological registration in primary care data and their predictive value were investigated in three most common PSS syndromes which have ICPC codes, namely irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS).The insights from all previously mentioned chapters come together in **Chapter 6**, in which theory and data driven approaches and a combination of both are utilized to identify patients at risk of the broad spectrum of PSS two years prior to their classification in primary care. Finally, **Chapter 7** presents a general discussion of all research presented in this thesis, including evaluations of the used methods and techniques, scientific and societal implications, and recommendations for future directions for research and clinical practice.

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# Chapter 2

## Predictors of Persistent Somatic Symptoms in the General Population: a systematic review of cohort studies

Willeke M. Kitselaar, Rosalie van der Vaart, Johanna Perschl, Mattijs E. Numans, Andrea W.M. Evers

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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 behavioural (health care utilization) predictors.

**Conclusions:** The results provide strong evidence for factors from all dynamic biopsychosocial domains, although interpersonal and health behavioural 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 is essential to improve the clinical course of PSS.

## 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, persistent somatic symptoms (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] While umbrella terms such as medically unexplained (physical) symptoms (MUPS), 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, or irritable bowel syndrome). The diagnostic distinctiveness of these syndromes in the context of PSS is debatable, since patients with syndromes which use bodily symptoms as diagnostic criteria, often fulfil the diagnostic criteria of more than one syndrome.[4,12,13] While these days most experts accept that there are common overarching factors as well as syndrome-specific factors,[14,15] historically, etiological research focusing on PSS is heterogeneous in nature – i.e., 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 behaviours on health. Due to 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 in 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

The present study is a systematic review, following PRISMA 2020 statement,[22] 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, 11th 2022. A search hedge of four parts was constructed: (1) terms related to predictors, such as “risk factors” and “prediction model”; (2) terms indicating any PSS, such as “medically unexplained (physical) symptoms”, “somatization” and, “fibromyalgia”; and (3) terms related to study type, such as “cohort studies” and “longitudinal” (see appendix A for the full search hedge).

For inclusion, cohort studies or nested-case control studies had to investigate (1) the general population; (2) symptom and syndromes without well-known biomedical pathology with a duration of at least 3 months as an outcome; and (3) 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, following the removal of duplicates titles and abstracts were screened twice, once by a group of three graduate students and once by the first author (WK). WK and JP each screened half of full-text articles conservatively consistent with the in- and exclusion criteria. Any doubts were discussed in meetings between WK, JP, and RV. Additionally, 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. Additionally, a meta-analysis would not have been feasible due to 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, gender, 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 (NOS) 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: (1) chronic pain-related PSS (e.g., regional pain or fibromyalgia); (2) gastrointestinal-related PSS (e.g., irritable bowel syndrome (IBS) or functional dyspepsia); (3) fatigue-related PSS; (4) other specific PSS (e.g., tinnitus or benign paroxysmal vertigo (BPPV)); and (5) 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 behaviour) in parallel by WK, RV, AE, and ME. 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 BMI, weight, obesity, waist-hip ratio, waist circumference) were merged based on expert knowledge from our interdisciplinary team and in collaboration between WK, RV, ME, and AE. To 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 [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).

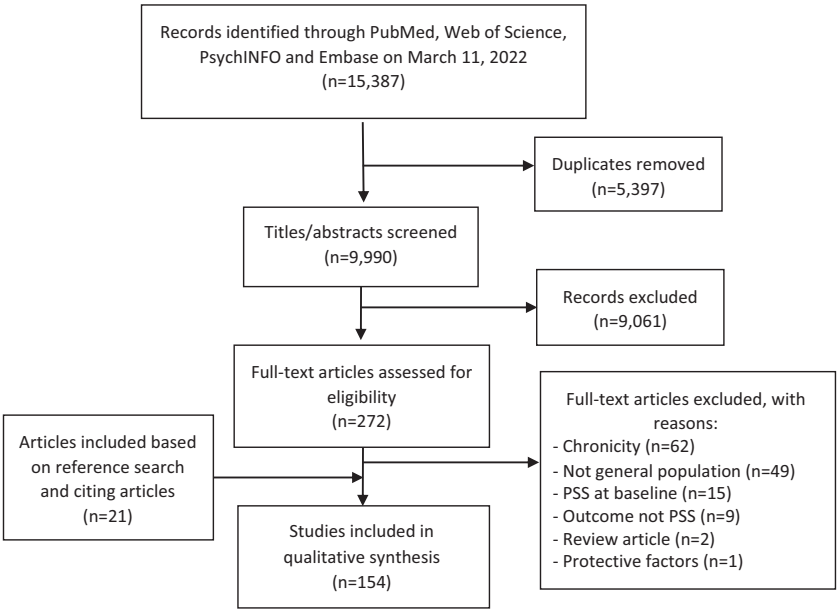
***Table 1.*** Levels of Evidence

| Levels of evidence | Criteria |
|---|---|
| **Strong** | • Investigated in at least 6 studies, of which >75% consistent findings |
| **Moderate** | • Investigated in 3 to 5 studies, with at least >75% consistent finding, or; |
| | • Investigated by at least 6 studies of which >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) more than 6 studies, or; |
| | • Found 100% predictive in < 2 studies. |

## 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).

***Figure 1.*** Flow chart study inclusion




Of the 154 included studies, there were prospective cohorts (n=67), cohort studies based on electronic medical record (EMR) 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 (more details, see appendix B). 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 chronic pain (CP)-related PSS, 27.4% as a gastrointestinal (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 (FSS) and medically unexplained symptoms (MUS); for more details, see Table 2). Of these studies, n=17 (11.3%) articles investigated multiple PSS-sub-

categories 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) (see appendix C).

***Table 2.*** Overview of PSS definitions and number of articles using the definition as an outcome

| **Persistent somatic symptoms (PSS) subcategory** | **Number of outcomes from 154 articles (n=173)** n (%)[†] |
|---|---|
| ***Chronic pain-related PSS*** | |
| Fibromyalgia (FM) / Chronic widespread pain (CWP) | 43 (25.0) |
| Low back pain (LBP) | 11 (6.4) |
| Chronic musculoskeletal complaints/pain | 7 (4.1) |
| Chronic pain | 7 (4.1) |
| Chronic back pain (CBP) | 5 (2.9) |
| Other chronic pain categories[*] | 7 (4.1) |
| ***Gastrointestinal-related PSS*** | |
| Irritable bowel syndrome (IBS) | 40 (23.3) |
| Functional dyspepsia | 6 (3.5) |
| Any functional gastrointestinal disorder | 1 (0.6) |
| ***Fatigue-related PSS*** | |
| Chronic fatigue syndrome (CFS/ME) | 18 (10.5) |
| Chronic fatigue | 6 (3.5) |
| ***Other specific PSS*** | |
| Benign paroxysmal positional vertigo (BPPV) | 8 (4.7) |
| Tinnitus | 4 (2.3) |
| Interstitial cystitis/bladder pain syndrome (IC/BPS) | 3 (1.7) |
| Vulvodynia | 2 (1.2) |
| Chronic tension type headache (TTH) | 1 (0.6) |
| Chronic whiplash | 1 (0.6) |
| ***Unspecified PSS*** | |
| Functional somatic symptoms (FSS) | 2 (1.2) |
| Medically unexplained symptoms (MUS) | 1 (0.6) |

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

[*] Neck, back and shoulder pain; arm pain; orofacial pain; reginal pain; myofascial pain; 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 6 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 B. **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 prior to 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 BPPV (n=1). **Anxiety** (n=26) predicts most sub-types 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), GI- (n=5), except for fatigue-related PSS which lacks significant results in 4 out of 5 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 CFS (n=1). **Life events** (n=11), **headache or migraine** (n=10), **other general medical illnesses** (n=9), **abdominal pain** (n=9), and **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), **gastrointestinal** 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.

***Table 3.*** Predictors of PSS, by health domain and level of evidence

| Health domains | Number of articles (%*) | Levels of evidence† | Predictors of PSS‡ |
|---|---|---|---|
| **Biological** | 122 (79.2) | *Strong* | Infections[a], body weight-related metrics[b], somatic symptoms, abdominal pain, other general medical illnesses, headaches or migraine, gastrointestinal disorders, renal disease, allergies[c]. |
| | | *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, dyslipidaemia, injury, menstrual disorders, osteoporosis, vitamin D status. |
| **Psychological** | 61 (39.6) | *Strong* | Sleep problems[e], anxiety, depression[d], psychopathology/mental health, fatigue. |
| | | *Moderate* | Personality type[f], quality of life. |
| | | *Limited* | |
| **Interpersonal** | 26 (16.9) | *Strong* | Life events, childhood adversity[g], interpersonal stress[h]. |
| | | *Moderate* | |
| | | *Limited* | Social support. |
| **Contextual** | 64 (41.6) | *Strong* | Employment. |
| | | *Moderate* | Age, socio-economic status. |
| | | *Limited* | Intelligence. |
| **Health behaviours** | 37 (24.0) | *Strong* | Health care utilization[k]. |
| | | *Moderate* | Physical activity, illness behaviour, medications used, alcohol (use and abuse), pain medication use[m]. |
| | | *Limited* | |

* Percentage of articles that investigated factors in the domain. † Table only includes predictors that were investigated by >1 study. ‡Ordered according to number of studies investigating the predictor.

[a] Including salmonella-, gastrointestinal-, viral-, non-specific-, giardia- and urinary tract infections; [b] including BMI, body weight, waist- to hip-ratio, and waist circumference; [c] including food allergies, and allergic rhinitis; [d] including HADS depression, major depression, bipolar disorder, and mood disorders; [e] excluding sleep apnoea; [f] perfectionism, self-discipline or conscientiousness; [g] including social and physical adversity, physical- and sexual abuse; [h] including intimate partner violence, discrimination, and (history of) physical or mental illness in the household ; [k] including consultations, opioid use, ER visits, number of medications used, and referrals; [m] excluding opioids.

Less established factors for which no conclusive evidence was found, were approximately 200 factors investigated only once or showing inconsistent findings in ≥6 studies (i.e., < 65% consistent findings). Gender and age were investigated often (n=33 and n=30, respectively). There is moderate evidence (66.6% consistency) that age is predictive,

results indicating U-shaped relationship where young adults and older people tend to be more likely to develop PSS. Gender 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 hyperlipidaemia (n=7). A full overview of factors identified in this research is available in appendix C.

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 behaviour and interpersonal factors are least likely to be investigated (24.0% and 16.9%, respectively) by studies included in the present review (see Table 3). Moreover, n=7 studies investigated factors from all domains and contextual, interpersonal, and health behaviour factors are least likely to be investigated unaccompanied by another factor (n=6, n=5, 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 fibromyalgia 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 behaviours, 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 since 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 amongst 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. While included studies cover predictors in all health domains of the dynamic biopsychosocial model, the primary focus has been on biological factors. In total, over 250 factors predicted PSS onset in the included literature, of which we found 46 which 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 – i.e., 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 IC/BPS.[25,26] Some biological predictors of PSS are easily measurable and controllable biometric predictors. These include body-weight metrics, birth weight, hyperlipidaemia, and vitamin D status. While clear directionality of these factors was not evident from our findings, recent reviews indicate 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 which 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. While 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 are 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 gender. Age and gender 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 gender 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 gender 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] While there are only a few contextual factors sufficiently relatable to PSS onset, the evidence for socioeconomic position and related variables (employment, intelligence) indicate that social context should be taken into account in relation to risk of PSS onset.

Lastly, several studies indicated **health behavioural** 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 chronic pain and fatigue. Research in other PSS-categories, show that physical activity is likely to be related to PSS in general.[42,43] We found moderate evidence for alcohol use and illness behaviour. Alcohol use was investigated in a variety of PSS-subcategories. Illness behaviour was notably investigated only by specific research groups.[44–47] Nonetheless, illness behaviour 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 increased risk of IBS after infection, especially in women, patients using antibiotics, as well as patients with depression, somatization, and anxiety. Similarly, Hulme [51] indicates 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 fibromyalgia and IBS onset.[16,17] Due to 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 behavioural, interpersonal, and contextual (e.g., age and gender) domains, we hypothesize that interaction effects may play a role, and should not be overlooked (see [52] for recent publication regarding interaction of predictors for fibromyalgia 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, is both a limitation and a strength of this study. While the design limits our ability to differentiate between overarching predictors and sub-type 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 cohort studies provide the best level of evidence for our purpose, due to the ecological validity, some risk factors which are less likely to be investigated in cohort studies (e.g., based on neuroimaging studies), may have been missed. Lastly, since 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 in order 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 behaviour 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. Due to the magnitude of the problem of PSS in society, development of tailored interventions, which map the factors and construes the interrelatedness of factors to find the best path towards health improvement, is much needed.

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# Appendixes

## ***Appendix A.*** Search hedge (PubMed)

**(((("Risk Factors"[majr] OR "risk factor"[ti] OR "risk factors"[ti] OR "Risk Assessment"[majr] OR "risk assessment"[ti] OR "Risk stratification"[ti] OR "prediction model"[ti] OR "prediction models"[ti] OR "predictive"[ti] OR "predicts"[ti] OR "predictor"[ti] OR "predictors"[ti] OR "predicted"[ti] OR "prediction"[ti]) AND (**"Medically Unexplained Symptoms"[majr] OR "medically unexplained symptom"[ti] OR "medically unexplained symptoms"[ti] OR "medically unexplained physical symptom"[ti] OR "medically unexplained physical symptoms"[ti] OR "Medically Unexplained Syndrome"[ti] OR "bodily distress syndrome"[ti] OR "wide spread pain"[ti] OR "widespread pain"[ti] OR "widespread pain"[ti] OR "widespread body pain"[ti] OR "musculoskeletal pain"[ti] OR "multisite pain"[ti] OR "functional somatic syndrome"[ti] OR "functional somatic syndromes"[ti] OR "functional syndrome"[ti] OR "functional somatic symptom"[ti] OR "functional somatic symptoms"[ti] OR "functional disorders"[ti] OR "central sensitivity syndrome"[ti] OR "central sensitivity syndromes"[ti] OR "central sensitization"[ti] OR "Central Nervous System Sensitization"[majr] OR "somatisation" OR "central sensitisation"[ti] OR "Myofascial Pain Syndromes"[majr] OR "myofascial pain syndrome"[ti] OR "chronic vulvar pain"[ti] OR "Vulvodynia"[majr] OR "vulvodynia"[ti] OR "Tension-type Headache"[majr] OR "tension-type headache"[ti] OR "tension headache"[ti] OR "stress headache"[ti] OR "idiopathic headache"[ti] OR "psychogenic headache"[ti] OR "Fibromyalgia"[majr] OR "fibromyalgia"[ti] OR "Fatigue Syndrome, Chronic"[majr] OR "chronic fatigue syndrome"[ti] OR "myalgic encephalomyelitis"[ti] OR "Irritable Bowel Syndrome"[majr] OR "irritable bowel syndrome"[ti] OR "Cystitis, Interstitial"[majr] OR "interstitial cystitis"[ti] OR "Restless Legs Syndrome"[majr] OR "restless legs syndrome"[ti] OR "restless legs syndrome"[ti] OR "restless-legs syndromes"[ti] OR "psychosomatic pain"[ti] OR "psychosomatic syndrome"[ti] OR "psychosomatic syndromes"[ti] OR "Somatoform Disorders"[majr] OR "somatoform disorder"[ti] OR "somatoform disorders"[ti] OR "somatoform pain disorder"[ti] OR "somatoform pain disorders"[ti] OR "somatization"[ti] OR "somatisation"[ti] OR "Back Pain"[majr] OR "back pain"[ti] OR "bladder pain syndrome"[ti] OR "Tinnitus"[majr] OR "tinnitus"[ti] OR "Vertigo"[majr] OR "vertigo"[ti] OR "vertigos"[ti] OR "Chronic primary pain"[ti] OR "complex regional pain syndrome 1"[ti] OR "complex regional pain syndrome i"[ti] OR "complex regional pain syndrome type 1"[ti] OR "complex regional pain syndrome type i"[ti] OR "pain disorder"[ti] OR "pain disorders"[ti] OR "Whiplash Injuries"[majr] OR "whiplash"[ti] OR "chronic pelvic pain"[ti] OR "chronic neck pain"[ti] OR "nonspecific chest pain"[ti] OR "non-specific chest pain"[ti] OR "non-cardiac chest pain"[ti] OR "chronic complainer"[ti] OR "Neurasthenia"[ti] OR "Neurasthenia"[majr] OR "psychophysiological disorder"[ti] OR "psychophysiological disorders"[ti] OR "psychophysiologic disorders"[majr])) **OR** (("Cohort Studies"[Mesh] OR "cohort study"[tw] OR "Follow-Up Studies"[mesh] OR "Longitudinal Studies"[mesh] OR "Prospective Studies"[mesh] OR "Retrospective Studies"[mesh] OR "Follow-Up Study"[tw] OR "Longitudinal Study"[tw] OR "Prospective Study"[tw] OR "Retrospective Study"[tw]) **AND ("Risk Factors"[mesh] OR "risk factor"[tw] OR "risk factors"[tw] OR "Risk Assessment"[mesh] OR "risk assessment"[tw] OR "Risk stratification"[tw] OR "prediction model"[tw] OR "prediction models"[tw] OR "predictive"[tw] OR "predicts"[tw] OR "predictor"[tw] OR "predictors"[tw] OR "predicted"[tw] OR "prediction"[tw]) AND (**"Medically Unexplained Symptoms"[majr] OR "medically unexplained symptom"[ti] OR "medically unexplained symptoms"[ti] OR "medically unexplained physical symptom"[ti] OR "medically unexplained physical symptoms"[ti] OR "Medically Unexplained Syndrome"[ti] OR "bodily distress syndrome"[ti] OR "wide spread pain"[ti] OR "widespread pain"[ti] OR "widespread pain"[ti] OR "widespread body pain"[ti] OR "musculoskeletal pain"[ti] OR "multisite pain"[ti] OR "functional somatic syndrome"[ti] OR "functional somatic syndromes"[ti] OR "functional syndrome"[ti] OR "functional somatic symptom"[ti] OR "functional somatic symptoms"[ti] OR "functional disorders"[ti] OR "central sensitivity syndrome"[ti] OR "central sensitivity syndromes"[ti] OR "central sensitization"[ti] OR "Central Nervous System Sensitization"[majr] OR "somatisation" OR "central sensitisation"[ti] OR "myofascial pain syndrome"[ti] OR "chronic vulvar pain"[ti] OR "Vulvodynia"[majr] OR "vulvodynia"[ti] OR "Tension-type Headache"[majr] OR "tension-type headache"[ti] OR "tension headache"[ti] OR "stress headache"[ti] OR "idiopathic headache"[ti] OR "psychogenic headache"[ti] OR "Fibromyalgia"[majr] OR "fibromyalgia"[ti] OR "Fatigue Syndrome, Chronic"[majr] OR "chronic fatigue syndrome"[ti] OR "myalgic encephalomyelitis"[ti] OR "Irritable Bowel Syndrome"[majr] OR "irritable bowel syndrome"[ti] OR "Cystitis, Interstitial"[majr] OR "interstitial cystitis"[ti] OR "Restless Legs Syndrome"[majr] OR "restless legs syndrome"[ti] OR "restless-legs syndromes"[ti] OR "restless legs syndrome"[ti] OR "restless-legs syndromes"[ti] OR "psychosomatic pain"[ti] OR "psychosomatic syndrome"[ti] OR "psychosomatic syndromes"[ti] OR "Somatoform Disorders"[majr] OR "somatoform disorder"[ti] OR "somatoform disorders"[ti] OR "somatoform pain disorder"[ti] OR "somatoform pain disorders"[ti] OR "somatization"[ti] OR "somatisation"[ti] OR "Back Pain"[majr] OR "back pain"[ti] OR "bladder pain syndrome"[ti] OR "Tinnitus"[majr] OR "tinnitus"[ti] OR "Vertigo"[majr] OR "vertigo"[ti] OR "vertigos"[ti] OR "Chronic primary pain"[ti] OR "complex regional pain syndrome 1"[ti] OR "complex regional pain syndrome i"[ti] OR "complex regional pain syndrome type 1"[ti] OR "complex regional pain syndrome type i"[ti] OR "pain disorder"[ti] OR "pain disorders"[ti] OR "Whiplash Injuries"[majr] OR "whiplash"[ti] OR "chronic pelvic pain"[ti] OR "chronic neck pain"[ti] OR "nonspecific chest pain"[ti] OR "non-specific chest pain"[ti] OR "non-cardiac chest pain"[ti] OR "chronic complainer"[ti] OR "Neurasthenia"[ti] OR "Neurasthenia"[majr] OR "psychophysiological disorder"[ti] OR "psychophysiological disorders"[ti] OR "psychophysiologic disorders"[majr]))) **AND** (english[la] OR dutch[la])

***Appendix B.*** Quality assessment

| Author, year published | Representativeness of exposed cohort | Non-exposed drawn from same community | Random/ consecutive selection of subjects | Risk factor assessment | Outcome not present at baseline | Adjusted for age+sex | Adjusted for most important confounders | Outcome assessment | Length follow-up (months) | Adequacy of follow-up | Assessment risk of bias (NOS) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aggarwal et al., 2010 | a | a | yes | b | yes | yes | no | c | 24 | b | poor quality |
| Ali et al., 2018 | a | a | yes | b | yes | yes | yes | b | 60 | b | good quality |
| Alli et al., 2021 | a | a | yes | c | yes | yes | no | b | 252 | c | good quality |
| Andorsen et al., 2017 | a | a | yes | c | yes | yes | no | b | 144 | c | good quality |
| Bergman et al., 2002 | a | a | yes | c | yes | yes | yes | b | 35 | c | poor quality |
| Bergman et al., 2004 | a | a | yes | b | yes | yes | no | b | 36 | b | good quality |
| Bernhardt et al., 2011 | a | a | yes | b | yes | yes | yes | a | 62 | a | poor quality |
| Bondesson et al., 2018 | a | a | yes | a | yes | yes | yes | b | 120 | a | good quality |
| Bonvanie et al., 2015 | b | a | yes | b | no | yes | no | b | 96 | c | poor quality |
| Bonvanie et al., 2017 | c | a | yes | b | no | no | yes | b | 96 | a | fair quality |
| Brown et al., 2018 | a | a | yes | c | no | yes | yes | c | 120 | a | poor quality |
| Brummond et al., 2015 | a | a | yes | a | yes | yes | no | b | 456 | c | good quality |
| Carrol et al., 2004 | a | a | yes | b | no | no | yes | b | 12 | c | poor quality |
| Carvalho et al., 2020 | a | a | yes | c | yes | yes | yes | c | 86 | c | poor quality |
| Chan et al., 2017 | b | a | yes | a | yes | yes | yes | a | 156 | a | good quality |
| Chandan et al., 2021 | c | a | yes | a | yes | yes | yes | b | 38 | a | good quality |
| Chang et al., 2015 | a | a | yes | a | yes | yes | yes | a | 96 | a | good quality |
| Chen CS et al., 2018 | b | a | yes | a | yes | yes | yes | b | 84 | a | good quality |
| Chen JH et al., 2018 | a | a | yes | a | yes | yes | yes | a | 144 | a | good quality |
| Chen ZJ et al., 2016 | a | a | yes | a | yes | yes | yes | a | 156 | a | good quality |
| Chu et al., 2015 | b | a | yes | a | yes | yes | yes | b | 76 | a | good quality |
| Chung et al., 2014 | a | a | yes | a | yes | yes | yes | a | 36 | a | good quality |
| Clark et al., 2011 | b | a | yes | c | no | yes | yes | c | 420 | c | poor quality |
| Collin et al., 2017 | d | a | yes | a | yes | no | no | b | 144 | a | poor quality |
| Creed, 2022 | d | a | yes | c | no | yes | yes | c | 36 | b | fair quality |
| Cremon et al., 2014 | a | a | yes | b | yes | yes | yes | b | 192 | b | good quality |
| Currie & Wang, 2005 | a | a | yes | b | yes | yes | yes | c | 24 | b | poor quality |
| Dai et al., 2022 | a | a | yes | a | yes | yes | yes | b | 104 | a | good quality |
| Davies et al., 2009 | a | a | yes | b | yes | yes | yes | b | 15 | c | poor quality |
| Donnachie et al., 2018 | a | a | yes | a | yes | no | no | b | 60 | a | poor quality |
| Duncan et al., 2019 | b | a | yes | c | yes | no | yes | b | 108 | d | fair quality |
| Elliot et al., 2002 | a | a | yes | c | yes | no | yes | b | 49 | b | good quality |
| Emir et al., 2015 | a | a | yes | a | yes | yes | yes | b | 12 | a | good quality |
| Ford et al., 2008 | b | a | yes | a | yes | no | no | b | 120 | c | poor quality |
| Gale et al., 2012 | b | a | yes | b | no | no | yes | b | 408 | c | fair quality |
| Goodwin et al., 2011 | b | a | yes | b | no | yes | yes | c | 372 | c | poor quality |
| Goodwin et al., 2013 | b | a | yes | b | no | yes | no | c | 420 | c | poor quality |
| Gupta et al., 2007 | a | a | yes | b | yes | no | no | b | 15 | c | poor quality |
| Hagen et al., 2012 | a | a | yes | c | yes | yes | yes | c | 132 | c | poor quality |
| Hamilton et al., 2009 | b | a | yes | a | yes | no | no | a | 36 | a | poor quality |
| Hanevik et al., 2014 | b | a | yes | a | yes | yes | yes | b | 72 | c | good quality |
| Harvey et al., 2008a | b | a | yes | b | no | yes | yes | b | 636 | c | fair quality |
| Harvey et al., 2008b | b | a | yes | b | no | yes | no | b | 480 | c | fair quality |
| Heuch et al., 2013 | a | a | yes | a | no | no | yes | c | 132 | b | good quality |
| Heuch et al., 2014a | a | a | yes | a | no | no | yes | c | 132 | b | good quality |
| Heuch et al., 2014b | a | a | yes | a | no | no | yes | c | 132 | c | poor quality |
| Heuch et al., 2015a | a | a | yes | a | no | no | yes | c | 132 | b | good quality |
| Heuch et al., 2015b | a | a | yes | a | no | no | yes | c | 132 | c | poor quality |
| Heuch et al., 2016 | a | a | yes | a | no | no | yes | c | 132 | c | poor quality |
| Heuch et al., 2017 | a | a | yes | a | no | yes | yes | c | 132 | a | good quality |
| Heuch et al., 2019 | a | a | yes | a | no | yes | yes | c | 132 | c | poor quality |

***Appendix B.*** Quality assessment (continued)

| Author, year published | Representativeness of exposed cohort | Non-exposed drawn from same community | Random/ consecutive selection of subjects | Risk factor assessment | Outcome not present at baseline | Adjusted for age+sex | Adjusted for most important confounders | Outcome assessment | Length follow-up (months) | Adequacy of follow-up | Assessment risk of bias (NOS) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heuch et al., 2022 | b | a | yes | c | yes | yes | yes | c | 132 | a | fair quality |
| Hocking et al., 2009 | b | a | yes | a | no | no | yes | b | 540 | c | fair quality |
| Holiday et al., 2009 | a | a | yes | a | yes | no | no | b | 48 | d | poor quality |
| Holiday et al., 2010 | a | a | yes | a | yes | no | no | b | 48 | d | poor quality |
| Hou et al., 2020 | a | a | yes | a | yes | yes | yes | c | 90 | d | poor quality |
| Howell et al., 2004 | b | a | yes | b | no | no | no | b | 312 | b | poor quality |
| Hsu et al., 2015 | b | a | yes | a | yes | yes | yes | a | 120 | a | good quality |
| Hsu et al., 2019 | a | a | yes | a | yes | yes | yes | a | 120 | a | good quality |
| Huerta et al., 2002 | d | a | yes | a | yes | yes | yes | b | 48 | a | good quality |
| Hunskar et al., 2012 | b | a | yes | c | no | yes | yes | b | 36 | a | poor quality |
| Iversen et al., 2017 | b | a | yes | a | no | yes | yes | c | 312 | c | poor quality |
| Jones et al., 2006 | b | a | yes | a | yes | no | yes | b | 24 | a | poor quality |
| Jones et al., 2007 | b | a | yes | c | no | yes | yes | b | 456 | b | poor quality |
| Jones et al., 2009 | b | a | yes | c | no | yes | yes | b | 456 | b | poor quality |
| Jones et al., 2011 | a | a | yes | b | yes | yes | yes | b | 48 | c | poor quality |
| Kang et al., 2013 | b | a | yes | a | yes | yes | yes | b | 36 | a | good quality |
| Kim et al., 2019 | b | a | yes | a | yes | yes | yes | b | 132 | a | good quality |
| Kim et al., 2020a | b | a | yes | a | yes | yes | yes | a | 150 | a | good quality |
| Kim et al., 2020b | b | a | yes | a | yes | yes | yes | a | 150 | a | good quality |
| Kingma et al., 2013 | b | a | yes | a | no | yes | yes | c | 372 | c | poor quality |
| Klooker et al., 2009 | b | a | yes | a | no | no | no | a | 696 | c | poor quality |
| Koloski et al., 2012 | a | a | yes | b | yes | yes | no | b | 144 | b | good quality |
| Koloski et al., 2015 | a | a | yes | c | yes | yes | no | b | 144 | b | good quality |
| Koloski et al., 2016 | a | a | yes | b | yes | no | no | b | 12 | c | poor quality |
| Kopec et al., 2004 | a | a | yes | c | yes | no | yes | c | 24 | c | poor quality |
| Kopec et al., 2005 | a | a | yes | c | yes | no | yes | c | 48 | b | poor quality |
| Kowalcyk et al., 2014 | a | a | yes | a | yes | yes | yes | b | 132 | a | good quality |
| Larrosa Pardo et al., 2019 | a | a | yes | a | yes | yes | yes | b | 120 | a | good quality |
| Lau et al., 2014 | a | a | yes | a | yes | yes | yes | c | 60 | b | poor quality |
| Lau et al., 2015 | b | a | yes | a | yes | yes | yes | b | 24 | a | good quality |
| Lei et al., 2016 | b | a | yes | a | yes | no | yes | a | 36 | b | good quality |
| Liang et al., 2020 | b | a | yes | a | yes | yes | yes | b | 168 | a | good quality |
| Lin WC et al., 2017 | b | a | yes | a | yes | yes | yes | a | 120 | a | good quality |
| Lin WT et al., 2017 | a | a | yes | a | yes | yes | yes | a | 120 | a | good quality |
| Litleskare et al., 2015 | b | a | yes | c | no | yes | no | b | 35 | c | poor quality |
| Litleskare et al., 2018 | b | a | yes | a | no | yes | no | b | 120 | c | fair quality |
| Littlejohn et al., 2012 | b | a | yes | a | no | yes | yes | b | 540 | b | fair quality |
| Liu et al., 2017 | b | a | yes | a | yes | no | no | a | 132 | a | poor quality |
| Macfarlane et al., 2009 | b | a | yes | b | no | no | yes | a | 540 | c | fair quality |
| Marrie et al., 2009 | d | a | yes | a | yes | no | no | b | 240 | a | poor quality |
| Marshall et al., 2006 | a | a | yes | a | no | no | no | b | 24 | a | poor quality |
| Marshall et al., 2010 | a | a | yes | a | no | no | no | b | 96 | b | poor quality |
| Masters et al., 2015 | b | a | yes | a | yes | no | no | a | 12 | a | poor quality |
| McBeth et al., 2001 | a | a | yes | b | yes | yes | no | b | 12 | b | good quality |
| McBeth et al., 2003 | a | a | yes | c | yes | yes | no | b | 36 | b | good quality |
| McBeth et al., 2019 | a | a | yes | b | yes | yes | yes | b | 12 | b | good quality |
| McCabe et al., 2016 | b | a | yes | a | yes | no | yes | b | 51 | c | poor quality |
| Monden at al., 2020 | a | a | yes | b | yes | yes | yes | c | 29 | b | good quality |
| Mork et al., 2010 | b | a | yes | a | yes | no | yes | c | 132 | c | poor quality |
| Mork et al., 2012 | b | a | yes | c | yes | no | yes | c | 132 | c | poor quality |

***Appendix B.*** Quality assessment (continued)

| Author, year published | Representativeness of exposed cohort | Non-exposed drawn from same community | Random/ consecutive selection of subjects | Risk factor assessment | Outcome not present at baseline | Adjusted for age+sex | Adjusted for most important confounders | Outcome assessment | Length follow-up (months) | Adequacy of follow-up | Assessment risk of bias (NOS) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mork et al., 2013 | a | a | yes | c | yes | yes | yes | c | 132 | c | poor quality |
| Mork et al., 2014 | a | a | yes | c | yes | no | yes | c | 132 | c | poor quality |
| Mundal et al., 2014 | a | a | yes | c | no | yes | yes | b | 132 | c | fair quality |
| Muthuri et al., 2018 | b | a | yes | c | no | yes | yes | c | 816 | c | poor quality |
| Myrtveit et al., 2013 | a | a | yes | c | yes | no | no | c | 132 | d | poor quality |
| Nakamura et al., 2014 | a | a | yes | c | yes | yes | yes | c | 12 | d | poor quality |
| Nicholl et al., 2010 | b | a | yes | a | no | no | no | b | 300 | a | poor quality |
| Nicholl et al., 2011 | b | a | yes | a | no | no | no | b | 300 | a | poor quality |
| Nilsen et al., 2011 | a | a | yes | b | yes | no | yes | b | 132 | c | good quality |
| Nitter et al., 2012 | b | a | yes | b | yes | no | no | b | 204 | c | poor quality |
| Odegard et al., 2011 | a | a | yes | c | yes | yes | yes | b | 132 | c | good quality |
| Olen et al., 2018 | b | a | yes | a | yes | no | yes | b | 216 | a | good quality |
| Pan et al., 2016 | a | a | yes | a | yes | yes | yes | b | 120 | a | good quality |
| Pang et al., 2010 | b | a | yes | c | no | no | no | b | 456 | d | poor quality |
| Persson et al., 2015 | b | a | yes | a | no | no | yes | b | 72 | c | fair quality |
| Picavet et al., 2002 | a | a | yes | b | yes | no | no | b | 6 | b | poor quality |
| Pico-Espinosa et al., 2017 | a | a | yes | c | yes | no | yes | c | 48 | c | poor quality |
| Puroila et al., 2015 | b | a | yes | c | yes | no | yes | c | 204 | b | poor quality |
| Raphael et al., 2002 | b | a | yes | a | yes | no | yes | b | 5 | c | poor quality |
| Raslau et al., 2016 | b | a | yes | a | yes | no | no | b | 576 | d | poor quality |
| Reed et al., 2013 | c | a | yes | c | yes | no | no | c | NA | b | poor quality |
| Reed et al., 2014 | c | a | yes | b | yes | no | yes | c | 72 | b | good quality |
| Rodriguez & Ruigomez, 1999 | a | a | yes | a | yes | yes | yes | a | 12 | a | good quality |
| Ruigomez et al., 2003 | c | a | yes | a | yes | yes | yes | b | 72 | b | good quality |
| Ruigomez et al., 2007 | b | a | yes | a | yes | yes | yes | b | 120 | a | good quality |
| Ruigomez et al., 2009 | b | a | yes | a | yes | yes | yes | b | 12 | a | good quality |
| Shen et al., 2016 | a | a | yes | b | yes | yes | yes | b | 120 | a | good quality |
| Shih et al., 2017 | a | a | yes | b | yes | yes | yes | b | 120 | a | good quality |
| Shih et al., 2018 | a | a | yes | a | yes | yes | yes | b | 168 | a | good quality |
| Sivertsen et al., 2014 | a | a | yes | a | yes | yes | yes | c | 132 | c | good quality |
| Skarpsno et al., 2019a | a | a | yes | c | yes | yes | yes | b | 96 | c | good quality |
| Skarpsno et al., 2019b | b | a | yes | c | yes | no | yes | c | 132 | b | fair quality |
| Skarpsno et al., 2020 | a | a | yes | a | yes | yes | yes | c | 132 | c | poor quality |
| Smith et al., 2004 | a | a | yes | b | yes | no | yes | b | 48 | b | good quality |
| Talley et al., 2001 | b | a | yes | b | no | no | no | c | 96 | b | good quality |
| Tsai et al., 2014 | a | a | yes | a | yes | yes | yes | a | 48 | a | good quality |
| Tsai et al., 2018 | a | a | yes | a | yes | yes | yes | a | 144 | a | good quality |
| Tsai et al., 2019 | a | a | yes | a | yes | yes | yes | a | 96 | a | good quality |
| Uhlig et al., 2018 | a | a | yes | b | yes | yes | yes | b | 132 | c | good quality |
| Vandenkerkhof et al., 2011 | a | a | yes | c | no | no | no | c | 144 | d | poor quality |
| Varinen et al., 2019 | b | a | yes | c | yes | yes | yes | c | 120 | c | poor quality |
| Viner et al., 2004 | b | a | yes | b | yes | yes | yes | c | 240 | b | good quality |
| Waehrens et al., 2018 | a | a | yes | a | yes | yes | yes | b | 240 | a | good quality |
| Wang et al., 2017 | a | a | yes | a | yes | no | yes | b | 144 | a | good quality |
| Wensaas et al., 2011 | b | a | yes | a | no | yes | yes | c | 36 | c | poor quality |
| Wensaas et al., 2016 | b | a | yes | c | no | yes | yes | c | 36 | c | poor quality |
| Wu CC et al., 2018 | c | a | yes | a | yes | yes | yes | b | 72 | a | good quality |
| Yang CY et al., 2020 | a | a | yes | a | yes | yes | yes | b | 120 | a | good quality |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Bergman et al., 2004**[c] | Prospective study<br><br>Sweden | 1852 | 52.7<br><br>20-64 | Chronic widespread pain & chronic regional pain (Self-report, ACR criteria for fibromyalgia) | 3.0 | **SF-36 (physical functioning+**, **role physical+**, **role emotional+** (only for regional pain), **bodily pain+**, **general health+**, **vitality+**, **social functioning+**, **mental health+** | Biological<br>Psychological<br>Interpersonal |
| **Bernhardt, et al., 2011** | Prospective study (Study of Health)<br><br>Germany | 3134 | non-cases: 52.3 - cases: 45.8<br><br>non-cases: 48.9 (15.4) - cases: 57.1 (12.6) | Tinnitus (Diagnosis by ENT specialist) | 5.2 | **Palpation pain in the temporomandibular joint (TMJ)+**, **age+**, gender, **education-**, muscle tenderness on palpation+, reported TMJ pain, headache+, depression. | Biological<br>Psychological<br>Contextual |
| **Bonvanie et al., 2015**[d] | Prospective study (TRAILS)<br><br>Netherlands | 2230 | 50.8<br><br>19.0 (0.6) | Functional Somatic Symptoms (Somatic Complaints subscale of the Adult Self-Report ASR) | 8.0 | **Perfectionism+** | Health behaviour |
| **Bonvanie et al., 2017**[d] | Prospective study (TRAILS)<br><br>Netherlands | 2230 | 55.0<br><br>19.0 (0.6) | Functional Somatic Symptoms (Somatic Complaints subscale of the Adult Self-Report ASR) | 8.0 | Life events (**non-illness-related+**, illness related, **severity+**). | Interpersonal |
| **Brown et al., 2018** | Prospective study (MIDUS)<br><br>USA | 1908 | 53.9<br><br>54 (30-84) | Chronic pain (self-report, ≥ few months & BPI) | 10.0 | **Discrimination+**, personality(ln(K6), neuroticism, **conscientiousness+,** agreeableness), gender- (female), **age+,** race (**black+,** other), education, **marital status-, income-,** religion, **past chronic pain+,** ADL, height, disabled, health insurance, **employed-.** | Biological<br>Interpersonal<br>Contextual |
| **Brummond et al., 2015** | Prospective study (Olmsted County population)<br><br>USA | 4893 | 53.0<br><br>58 (15) | IBS (Self-report, Rome III) | 2.0-95.0 | **Birth cohort 1913-1922+**, Birth cohort 1923-1932, Birth cohort 1933-1942, Birth cohort 1943-1952, Birth cohort 1953-1962, Birth cohort 1973-1983 | Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Carroll et al., 2004** | Prospective study (HIRF)<br><br>Canada | 218 | 49.4<br><br>44.5 (13.5)[b] | Neck and low back pain (Chronic Pain Questionnaire, ≥ 6 months) | 0.5, 1.0 | **Depression+**. | Psychological |
| **Carvalho et al., 2020** | EMR cohort (NHIRD)<br><br>Taiwan | 16875 | 52<br><br>61.6 (7.0) | Musculoskeletal pain (Self report, >3 months) | 7.2 | **Diabetes+**. | Biological |
| **Chan et al., 2017** | EMR cohort (NHIRD/ LHID2005)<br><br>Taiwan | 13358 | 88.4<br><br>NA | BPPV (ICD-9-CM: 386.11, by neurologist / otolaryngologist) | 13.0 | Age, gender, **urbanization+**, **income-**, **osteoporosis+**, **cardiovascular disease+**, **hypertension+**, diabetes, heart failure, chronic obstructive pulmonary disease, asthma, coronary artery disease, cerebrovascular disease, and migraine. | Biological Contextual |
| **Chandan et al., 2021** | EMR cohort (THIN cohort)<br><br>UK | 92835 | 100<br><br>36.9 (12.5) [b] | Fibromyalgia & CFS (N239, N248 & F286) | 3.2 | **Intimate partner violence+.** | Interpersonal |
| **Chang et al., 2015** | EMR cohort (NHIRD/ LHID2000)<br><br>Taiwan | 85710 | 60.7<br><br>39.4 (16.5)[b] | Fibromyalgia (ICD-9-CM: 729.1) | 8.0 | **Depression+**, **migraine+**, **low back pain**+, asthma+, **allergic rhinitis+**, **atopic dermatitis+**, **hypertension+**, **diabetes mellitus+**, **dyslipidaemia+.** | Biological Psychological |
| **Chen et al., 2016** | EMR cohort (NHIRD/ LHID2000)<br><br>Taiwan | 22795 | 58.3<br><br>43† | BPPV (ICD-9-CM: 386.11, by neurologist) | 13.0 | **Age+**, **gender+**, **hypertension+**, **diabetes mellitus+**, **chronic liver disease+**, autoimmune disease, **congestive heart failure+**, **anxiety disorders+**, **hyperlipidaemia+**, **nephropathy+**, **cerebrovascular disease+**, **COPD+.** | Biological Psychological Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % | Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|---|
| **Chen CS et al., 2018** | EMR cohort (NHIRD) | Taiwan | 4420 | 74.0 | Non exposed: 55.7 (16.3) Exposed: 55.8 (16.2) | CFS (ICD-9-CM: 780.71) | 7.0 | **Dry eye syndrome+.** | Biological |
| **Chen JH et al., 2018** | EMR cohort (NHIRD) | Taiwan | 22550 | 51.6 | cases: 47.0 (16.5) – n-cases: 46.8 (16.6) **b** | Fibromyalgia (ICD-9-CM: 729.1) | 12.0 | **Inflammatory bowel disease+.** | Biological |
| **Chu et al., 2015** | EMR cohort (NHIRD) | Taiwan | 16532 | 72 | < 40 (53.3%) - >40 (46.7%) [b] | BPPV (ICD-9-CM: 386.11) | 6.3 | **Migraine+.** | Biological |
| **Chung et al., 2014** | EMR cohort (NHIRD/ LHID2000) | Taiwan | 32340 | 39.0 | 47.1 (15.7)[b] | Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) (ICD-9-CM 327.23, 780.51, 780.53, or 780.57, at least 2x) | 3.0 | **Obstructive sleep apnoea+**, gender, age, income, geographic region**, diabetes+, hypertension+, coronary heart disease+, obesity+, hyperlipidaemia+, chronic pelvic pain+, IBS+, FM+, CFS+, depression+, panic disorder+, migraines+, sicca syndrome+, allergies+, endometriosis+, asthma**+, alcohol abuse, **tobacco use disorder+.** | Biological Contextual Health behaviour |
| **Clark et al., 2011** | Birth cohort (British Birth Cohort) | UK | 11419 | both | 42 | CFS (self-report) | 9.0 19.0 26.0 31.0 35.0 | Gender Childhood: illness in household, in care, divorce parents, neglect, maternal absence, paternal absence, in care, divorce, **paternal physical abuse+**, **paternal sexual abuse+**, **many colds+**, school absence, **gastrointestinal** | Biological Psychological Interpersonal Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|
| **Clark et al., 2011** (continued) | | | | | | | **symptoms+**, **chronic illness+**, **cumulative childhood adversity+.** Adulthood: **psychopathology+**. | |
| **Collin et al., 2017** | EMR cohort (Clinical Practice Research Datalink) | UK | 42316 | N/A | CFS & Fibromyalgia (Self-report) | 12 | Gender, age | Contextual |
| **Creed, 2022** | Prospective cohort (Lifelines) | Netherlands | 150714 | N/A | Fibromyalgia (Self-report) | 3 | **Female sex+, years of education+, low income, work>32h per week+, unable to work through illness+, BMI, <4 allergies+, >2 times per week alcohol+, no of analgesics+, chronic cystitis+, asthma/any inhaler+, osteoarthritis+, rheumatoid arthritis+, RSI+, IBS+, chronic inflammation of throat/nasal cavity+, migraine+, no of psychiatric disorders+, life events+, no of healthcare contact in 5 yrs.+, somatic symptom score+, sleep+.** | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| **Cremon et al., 2014** | Prospective study (Salmonella outbreak 1994) | Italy | 331 | 65.4<br>Non-exposed: 31.1 (16.3) – exposed: 33.6 (18) | IBS (Self-report, Rome III) | 16.0 | **Salmonella infection+**, age, **gender+** (female), **functional dyspepsia+, PCS-12+, MCS-12+, HADS anxiety+,** HADS depression. | Biological<br>Psychological<br>Contextual |
| **Collin et al., 2017** | EMR cohort (Clinical Practice Research Datalink) | UK | 42316 | N/A | CFS & Fibromyalgia (Self-report) | 12 | Gender, age | Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Creed, 2022** | Prospective cohort (Lifelines)<br><br>Netherlands | 150714 | N/A | Fibromyalgia (Self-report) | 3 | **Female sex+, years of education+, low income, work>32h per week+, unable to work through illness+, BMI, <4 allergies+, >2 times per week alcohol+, no of analgesics+, chronic cystitis+, asthma/any inhaler+, osteoarthritis+, rheumatoid arthritis+, RSI+, IBS+, chronic inflammation of throat/nasal cavity+, migraine+, no of psychiatric disorders+, life events+, no of healthcare contact in 5 yrs.+, somatic symptom score+, sleep+.** | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| **Cremon et al., 2014** | Prospective study (Salmonella outbreak 1994)<br><br>Italy | 331 | 65.4<br><br>Non-exposed: 31.1 (16.3) – exposed: 33.6 (18) | IBS (Self-report, Rome III) | 16.0 | **Salmonella infection+**, age, **gender+** (female), **functional dyspepsia+, PCS-12+, MCS-12+, HADS anxiety+,** HADS depression. | Biological<br>Psychological<br>Contextual |
| **Currie & Wang, 2005** | Prospective study (NPHS)<br><br>Canada | 9909 | 52.0<br><br>exposed: 36.2 - non-exposed: 43.1 [b] | Chronic back pain (self-report, ≥ 6 months) | 2.0 | **Major depression+, number chronic medical conditions+, back/neck injury in previous 12 months+**. | Biological<br>Psychological |
| **Davies et al., 2009[E]** | Prospective study (EPIFUND)<br><br>UK | 5190 | 56.4<br><br>cases: 46.4-48.8, non-cases: 45.9-46.8 | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 1.3 | **Area level SES-**, gender, age. | Contextual |
| **Dai et al., 2022** | EMR cohort (NHIRD)<br><br>Taiwan | 27230 | 49.5<br><br>34.1 (13.5) [b] | IBS (ICD-9: 564.1, at least 3x) | | **Alopecia areata+** | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Donnachie et al., 2018** | EMR cohort (85% of the population of Bavaria)<br><br>Germany | 1016556 | 50.7<br><br>35.1[b] | IBS & CFS (ICD-10: K58 or F45.32) | 5.0 | **Age+**, female gender, **gastrointestinal infections+** (salmonella, campylobacter, Escherichia coli, other bacterial infection, proto-zoan infection), **viral infection+**, **non-specific infection+**, **depression+, anxiety+, time of infection+** (only for CFS). | Biological Psychological Contextual |
| **Duncan et al., 2019** | Birth cohort (Christchurch Health and Development Study (CHDS))<br><br>New Zealand | 408 | 52.2<br><br>30-38 | Medically Unexplained Symptoms (medical records, referral to secondary care in 2 or more occasions, diagnosis of known MUPS, e.g. fibromyalgia, headaches) | 9.0 | Sexual abuse (age 0-16), abuse not involving penetration, **abuse involving sexual penetration+.** | Interpersonal |
| **Elliott et al., 2002** | Prospective study<br><br>Scotland | 852 | 51.7<br><br>≥ 25 yrs. | Chronic pain (Validated questionnaire, CPG) | 4.1 | Sex, age, education, housing tenure, **employment-**, **SF-36 health domains+**, **marital status-**. | Biological , Psycho-logical, Interper-sonal , Contextual, Health behaviour |
| **Emir et al., 2015** | EMR cohort (Humedica)<br><br>USA | 587961 | 48.6<br><br>cases: 53.3 (14.6) – Non-cases: 52.7 (16.3) | Fibromyalgia (ICD-9: 780.73, at least 2x) | 1.0 | **GP visits i.c.w. lab-test requested+, outpatient visits+, age+, office visits+, opioid administration+, medications prescribed during consultation+, pain medication (excl. opioids)+, medications administered/ordered +, ER visits+, musculoskeletal conditions**+. | Biological Health behaviour |
| **Ford et al., 2008** | Prospective study (Helicobacter pylori screening + treatment program)<br><br>UK | 3659 | 56.0<br><br>50-59 | IBS (questionnaire w/ Manning criteria) | 10.0 | Age, **gender+**, H.pylori status, marital status (single/married), smoking status, **alcohol use+**, coffee drinker, ethnicity (white/nonwhite**), SES-**, **NSAID use+**, **Aspirin use+**, **dyspepsia+**, **QoL-**. | Biological Psychological Interpersonal Contextual Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Gale et al., 2012** | Birth cohort (British Birth Cohort study / national child development study)<br><br>UK | 6902 | 50.8<br><br>45 yrs. | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 34.0 | **IQ at age 11+**, gender, **social class-**, **education-**, **smoking+**, **BMI+**, **GHQ-12 score+** | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| **Goodwin et al., 2011** | Birth cohort (British Birth Cohort study 1958)<br><br>UK | 17415 | both<br><br>34 (7) | CFS/ME<br>(self-report) | 9.0<br>19.0<br>26.0<br>31.0<br>35.0 | **Psychopathology+** (any externalizing/internalizing problems at age 23 and 33, multiple reports age 16-33), **malaise+**, energy levels, activity level. | Biological<br>Psychological |
| **Goodwin et al., 2013** | Birth cohort (British Birth Cohort study 1958)<br><br>UK | 17415 | both<br><br>median:<br>34 (28-38) | IBS<br>(self-report) | 26.0<br>31.0<br>35.0 | Childhood: **Parental sexual abuse+**, parental physical abuse, cumulative adversity, internalizing problems, maternal/paternal absence, in care, divorce parents, **physical symptoms+**, **gastrointestinal symptoms+**, gastrointestinal illness, chronic illness, atopy, **infectious illness+**, neglected/underfed appearance, many colds, gender, **throat infection+** (more than 3 at age 16), **headache/migraine+**, **school absence+**, **sleeping problems+**, atopy<br>Adulthood: **psychopathology+** (age 23 and 33), | Biological<br>Psychological<br>Interpersonal<br>Contextual |
| **Gupta et al., 2007[E]** | Prospective study (EPIFUND)<br><br>UK | 3171 | 56.5<br><br>25-65 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 1.3 | **Somatic symptoms+**, **illness behaviour+**, **health anxiety+**, **HADS anxiety+**, **HADS depression+**, **sleep problems+**, **life events+** (≥2), **number of psychological factors+**. | Biological<br>Psychological<br>Interpersonal<br>Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Hagen et al., 2012** | Prospective study (HUNT 2+3)<br><br>Norway | 13781 | 56.5<br><br>47.1 (13.2) [b] | Chronic musculoskeletal complaints (Self-report) | 11.0 | **Headache+, migraine+.** | Biological |
| **Hamilton et al., 2009** | EMR cohort (General Practice Research Database (GPRD))<br><br>UK | 13164 | 68.5<br><br>median: 41 (31-53) | Chronic fatigue (GPRD codes) | 3.0 | BMI, systolic blood pressure, **primary care utilization+** (consultations, prescriptions, antibiotics, sickness certificate, referral), **abdominal pain+, fatigue symptom+, dizziness+, other abdominal symptoms+, any infection+, depressive disorders+, functional disorder+, menstrual disorders+, child birth+, atopy+, immunization+**, **upper respiratory tract infection+**, influenza-like illness, **gastroenteritis+, immunization+,** fractures, **tonsillitis+, viral infection+.** | Biological<br>Health behaviour |
| **Hanevik et al., 2014[f]** | Prospective study<br><br>Norway | 1160 | 68.1<br><br>exposed: 39.2, non-exposed: 41.0 | IBS & chronic fatigue (Self-report, Rome III & Fatigue questionnaire, ≥ 6 months) | 6.0 | **Giardia infection+.** | Biological |
| **Harvey et al., 2008a[G]** | Birth cohort 1946 (Medical Research Council National Survey of Health and Development)<br><br>UK | 5362 | 50.9<br><br>53 | CFS/ME (semi-structured interview, trained nurses) | 10.0<br>17.0<br>22.0<br>38.0<br>40.0<br>47.0<br>53.0 | **Gender+** (female), weight at birth and age 7, **BMI at age 36+, 43+** and 53, father SES, education, SES. Childhood: cough, convulsions, abdominal pain, vomiting, chronic illness, school absence, family members frequent colds, heart murmur, asthma, atopic illness, **energy level+**, sports ability, ability to sport. Adulthood: hay fever, skin trouble, allergies, atopic illness, family atopy, fitness, **sports or keep fit activities ≥4 times a month+**, **sport at least once a week+.** | Biological<br>Contextual<br>Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Heuch et al., 2013**[h] | Prospective study (HUNT 2+3)<br>Norway | 18882 | 53.7<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **BMI+**. | Biological |
| **Heuch et al., 2014a**[h] | Prospective study (HUNT 2+3)<br>Norway | 17209 | 47.9<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **High blood pressure-** (systolic, diastolic and pulse pressure). | Biological |
| **Heuch et al., 2014b**[h] | Prospective study (HUNT 2+3)<br>Norway | 18882 | 53.8<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Serum lipid levels+** (only triglycerides). | Biological |
| **Heuch et al., 2015a**[h] | Prospective study (HUNT 2+3)<br>Norway | 18784 | 53.6<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Body height+** (only women: ≥ 170cm) | Biological |
| **Heuch et al., 2015b**[h] | Prospective study (HUNT 2+3)<br>Norway | 18784 | 53.6<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Body weight+**, **BMI+**, **waist circumference+**, **hip circumference+**, **waist-hip ratio+**. | Biological |
| **Heuch et al., 2016**[h] | Prospective study (HUNT 2+3)<br>Norway | 18068 | 53.2<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Physical activity in leisure time-** (≥50 years old, education, ≥1 hard activity) | Health behaviour |
| **Heuch et al., 2017**[h] | Prospective study (HUNT 2+3)<br>Norway | 4822 | 56.4<br>30-66 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Vitamin D status+** (inconclusive association in women during winter/spring time). | Biological |
| **Heuch et al., 2019**[h] | Prospective study (HUNT 2+3)<br>Norway | 18972 | 54.0<br>41-80 | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Diabetes+** (only men). | Biological |
| **Heuch et al., 2022** | Prospective study (HUNT 2+3)<br>Norway | 5394, 11659 | 100.0<br>40-69 [b], 20-69 [b] | Chronic LBP (Self-report, ≥ 3 months) | 11.0 | **Age of menarche+**, age of menopause. | Biological |
| **Hocking et al., 2009** | Birth cohort (British Birth cohort 1995)<br>UK | 8572 | 52.2<br>45 | Chronic pain (Self-report, partial ACR criteria for fibromyalgia) | 45.0 | **ADRB2 SNP variants+, haplotype combinations+**, COMT variants | Biological |
| **Holliday et al., 2009**[e] | NCC cohort (EPIFUND)<br>UK | 1189 | 58.0<br>50 (9.6) | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 4.0 | SNP variants: GCHI-CAT, OPRMI | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Holliday et al., 2010**[e] | NCC cohort (EPIFUND)<br>UK | 994 | 58.0<br>50.9 (49.8 to 52.0)[b] | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 4.0 | CRH, CRH receptor 1 (CRHR1), CRH binding protein (CRHBP), ACTH precursor pro-opiomelanocortin (POMC) and its receptor (**MC2R+**), the glucocorticoid receptor (NR3C1) and corticosteroid binding globulin (**SERPINA6+**) | Biological |
| **Hou et al., 2020** | EMR cohort (NHIRD)<br>Taiwan | 22575 | 60.3<br>≥20yrs[b] | Tinnitus (ICD-9-CM, specialist diagnosis) | 7.5 | **Anxiety disorder+.** | Psychological |
| **Howell et al., 2004** | Birth cohort (Dunedin)<br>New Zealand | 980 | 46.3<br>26 | IBS (Manning/Rome criteria) | | **Childhood SES+.** | Contextual |
| **Hsu et al., 2015** | EMR cohort (NHIRD)<br>Taiwan | 281775 | 19.9<br>35 to 65 years (69.9%)[b] | IBS (ICD-9: 564.1) | 2.0-10.0 | **Alcohol use disorder+** | Health behaviour |
| **Hsu et al., 2019** | EMR cohort (NHIRD/ LHID2000)<br>Taiwan | 51485 | 54.0<br>30-39† | BPPV (diagnosed by neurologists or otorhinolaryngologists) | 10.0 | **Depressive disorder+**, age, sex, **hypertension+**, diabetes, **dyslipidaemia+**, **coronary artery disease+**, **hyperthyroidism+**, hypothyroidism, **cerebrovascular disease+**, systemic lupus erythematosus, degree of urbanization, income. | Biological Psychological Contextual |
| **Huerta et al., 2002** | EMR cohort (General practice research database)<br>UK | 5371 | N/A | IBS (Specialist diagnosis) | 4.0 | **Asthma+.** | Biological |
| **Hunskar et al., 2012**[F] | Retrospective cohort (Bergen)<br>Norway | 1945 | 65.7<br>36.2 | IBS & Chronic fatigue (Self-report, Rome III & Chalder fatigue questionnaire, ≥ 6 months) | 3.0 | Giardiasis i.c.w. asthma, giardia i.c.w. allergy | Biological |
| **Iversen et al., 2017** | Prospective study (Trondheim)<br>Norway | 216 | 53.2<br>26 | Chronic pain (Self-report, SF-36, ≥ 6 months) | 26.0 | **Birth weight-**, small for gestational age. | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Jones et al., 2006** | EMR cohort (General practice research database)<br><br>UK | 5481 | 51.0<br><br>N/A | IBS<br>(Read code) | 2.0 | **Depression+, anxiety+, asthma+, UTI+, gall-bladder surgery+, hysterectomy+.** Referral to: **general surgery+, general medicine+, gynaecology+, psychiatry+.** | Biological<br>Psychological<br>Health behaviour |
| **Jones et al., 2007**[I] | Birth cohort (British Birth Cohort study 1985)<br><br>UK | 7470 | both<br><br>45 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 38.0 | **Number of symptoms** (vomiting/bilious attacks, abdominal pain, headache/migraine) **at 7 years+**, **11 years+** and **16 years+.** | Biological |
| **Jones et al., 2009**[I] | Birth cohort (British Birth Cohort study 1985)<br><br>UK | 7517 | both<br><br>45 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 38.0 | Childhood physical traumatic events (before age 7): surgical operations, **hospitalization after traffic accident+**, hospitalization after domestic accident/other. Childhood social/psychological adversity (before age 7): **maternal separation+** (only > 6 months), **institutional care+,** death father, **death mother+, divorce/separation/desertion+, family alcoholism+, family financial difficulties+**. | Biological<br>Interpersonal |
| **Jones et al., 2011**[E] | NCC cohort (EPIFUND)<br><br>UK | 7517 | 57.4<br><br>25-65 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 4.0 | Traumatic events: **road traffic accident+**, injury at work, fracture, surgery, hospitalization, childbirth. | Biological |
| **Kang et al., 2013** | EMR cohort (NHIRD/ LHID2000)<br><br>Taiwan | 53772 | 100<br><br>50.4 (16.4) | Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)<br>(ICD-9-CM 327.23, 780.51, 780.53, or 780.57) | 3.0 | **Reflux esophagitis+.** | Biological |
| **Kim et al., 2019** | EMR cohort (HIRA)<br><br>Korea | 203410 | 74.5<br><br>≥20 yrs. [b] | BPPV<br>(ICD-10: H81.1, at least 2x) | 11.0 | **Migraine+.** | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Kim et al., 2020a** | EMR cohort (HIRA-NSC)<br><br>Korea | 51833 | 65.6<br><br>20-60 [b] | BPPV (ICD-10: H81.1, at least 2x) | 12.5 | **Mood disorder+**. | Psychological |
| **Kim et al., 2020b** | EMR cohort (NHIS- HEALS)<br><br>Korea | 32772 | both<br><br>40-60 [b] | BPPV (ICD-10: H81.2, at least 2x) | 12.5 | **Osteoporosis+** (only for women). | Biological |
| **Kingma et al., 2013** | Birth cohort (British Birth Cohort study)<br><br>UK | 17638 | 48.7<br><br>42 | IBS & CFS (self-report) | 31.0 | Childhood cognitive ability. | |
| **Klooker et al., 2009** | Birth cohort (Dutch Famine Birth Cohort)<br><br>Netherlands | 1423 | 55.0<br><br>58 | IBS (Self-report, Rome II) | 58.0 | Historic time of birth: during/**shortly after world war II+**. | |
| **Koloski et al., 2012[k]** | Prospective study<br><br>Australia | 1002 | 52.1<br><br>45.1 | Any functional gastrointestinal disorder (FGID) & IBS & functional dyspepsia (FD) (Self-report, Rome II) | 12.0 | **Anxiety+** (only any FGID and IBS), **depression+** (only IBS and FD). | |
| **Koloski et al., 2015[k]** | Prospective study<br><br>Australia | 767 | 48.2<br><br>59.9 (11.5) | IBS & functional dyspepsia (FD) (Self-report, Rome III) | 12.0 | **Gastroenteritis+** (only IBS), **antibiotic use+** (only IBS), overseas travel, caesarean delivery, prematurity, breastfed, **duration of breastfeeding-**, pet exposure, **herbivore pet+**, **carnivore pet+** (only FD), omnivore pet, **sharing bedroom+**, **hygiene factors+** (only IBS). | |
| **Koloski et al., 2016[k]** | Prospective study<br><br>Australia | 1900 | 53.0<br><br>57 (14) | IBS & functional dyspepsia (FD) (Self-report, modified Rome III) | 1.0 | **Anxiety+**, **depression+**. | |
| **Kopec et al., 2004[m]** | Prospective study (Canadian National Population Health Survey)<br><br>Canada | 10007 | 54.3<br><br>18-65+ | Chronic back pain (self-report, ≥ 6 months) | 2.0 | Male: age, **height+**, **self-rated health-**, **usual daily activities+**, **gardening-**, **chronic stress index+**. Female: **activity restriction+**, **arthritis/rheumatism+**, **personal stress index+**, **psychological childhood trauma+** (only ≥ 2). Weight, BMI, smoke exposure, | Biological<br>Psychological<br>Interpersonal<br>Contextual<br>Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|
| **Kopec et al., 2004**[m] (continued) | | | | | | | Male: age, **height+**, **self-rated health-**, **usual daily activities+**, **gardening-**, **chronic stress index+**.<br>Female: **activity restriction+**, **arthritis/rheumatism+**, **personal stress index+**, **psychological childhood trauma+** (only ≥ 2).<br>Weight, BMI, smoke exposure, energy expenditure, smoking, alcohol use, physical activity, vision, hearing, speech, mobility, dexterity, emotional, cognitive problems, health status, activity limiting injury, pregnancy, allergy, asthma, high blood pressure, migraine, chronic bronchitis, sinusitis, diabetes, epilepsy, heart disease, cancer, stomach/intestinal ulcers, stroke, incontinence, Alzheimer's, cataracts, glaucoma, acne, long-term condition, environmental/financial/family health/ relationship/child-related stress, chronic stress, depression, social support, self-esteem, locus of control, mental health distress, sense of coherence, frequency of contact, social involvement, recent life events, immigrant, education, income adequacy, language, main activity, living arrangements, marital status, urbanization, working status, work-stress/status combination. | |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Kopec et al., 2005**[m] | Prospective study (Canadian National Population Health Survey (NPHS))<br><br>Canada | 9552 | 55.4<br><br>18-65+ | Chronic back pain (self-report, ≥ 6 months) | 2.0, 4.0 | **Two or more stressful events in childhood+, prolonged hospitalization+**, parental drug abuse, parental divorce, **parental unemployment+**, physical abuse, sent away from home, **very scared+**. | Psychological<br>Interpersonal<br>Contextual |
| **Kowalcyk et al., 2014** | EMR cohort (NHIRD/ LHID2000)<br><br>Taiwan | 4782 | Both<br><br>37.9 | IBS (ICPC-code) | 11.0 | **Acute gastroenteritis+,** age group, female gender, SES, practice, **consultation frequency+, multiple gastroenteritis+, concomitant cramps+,** weight loss, **dyspepsia+, psycho-social+, fear+.** | Biological<br>Psychological<br>Contextual<br>Health behavioural |
| **Larrosa Pardo et al., 2019** | EMR cohort (Skåne Healthcare Register)<br><br>Sweden | 419291, 803805 | 50-100<br><br>>21 yrs. [b] | Fibromyalgia (ICD-10: M797) | 10.0 | **Rheumatoid arthritis+, endometriosis+, inflammatory bowel disease+.** | Biological |
| **Lau et al., 2014** | Prospective study (Study of Health in Pomerania)<br><br>Germany | 3134 | 51.9<br><br>non-cases: 48.9 (15.4)<br>- cases: 57.1 (12.6) [b] | Tinnitus (self-report) | 5.0 | **Palpation pain in TMJ+, age+**, gender, **education-**, **muscle tenderness on palpation+**, reported TMJ pain, **headache+**, depression. | Biological<br>Psychological<br>Contextual |
| **Lau et al., 2015** | EMR cohort (NHIRD)<br><br>Taiwan | 34510 | 73.3<br><br>45.5 (15.1) | CFS (ICD-9-CM: 780.71) | 2.0 | **Migraine+, age+,** sex, **hypertension+, diabetes+, hyperlipidaemia+, anxiety+, depression+, coronary artery disease+.** | Biological<br>Psychological<br>Contextual |
| **Lei et al., 2016** | EMR cohort (NHIRD/ LHID2003)<br><br>Taiwan | 53016 | 30.2<br><br>exposed: 47.9 (14.8)<br>non-exposed: 49.1 (15.6) | IBS (ICD-9-CM: code 564.0) | 3.0 | **Urinary stone attack+**, **geographic regions-** (only eastern compared to northern), income level, urbanization, diabetes, hypertension, renal failure, **liver cirrhosis+**, **stroke+**, **osteoporosis+**, **fibromyalgia+**. | Biological<br>Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Liang et al., 2020** | EMR cohort (NHIRD)<br><br>Taiwan | 13345 | 34.1<br><br>57.5 (18.1) | IBS (ICD-9-CM: code 564.0) | 14.0 | **Helicobacter Pylori infection+,** age group, insurance, coronary artery disease, **cardiovascular disease+,** hypertension, hyperlipidaemia, diabetes, **asthma+, season+,** location, urbanization, level of care | Biological Contextual |
| **Lin WC et al., 2017** | EMR cohort (NHIRD/ LHID2005)<br><br>Taiwan | 3134 | 52.6<br><br>46.3 (34.2–56.9)[b] | Myofascial pain (ICD-9-CM: 729.0, at least 2x) | 10.0 | **Insomnia+**, age, **gender+**, **urbanization level+**, income, **hypertension+**, diabetes mellitus, dyslipidaemia, coronary artery disease, congestive heart failure, cirrhosis, cerebrovascular disease, **malignant neoplasms+.** | Biological Contextual |
| **Lin WT et al., 2017** | EMR cohort (NHIRD/LHID2000 0)<br><br>Taiwan | 98265 | 58.5<br><br>≥ 20 [b] | IBS (ICD-9-CM code: 564.1, ≥ 3 outpatient visits / ≥ 1 hospitalization) | 10.0 | **SSRIs+**, gender, **age+**, anti-psychotics, diabetes, hypertension, hyperlipidaemia, colorectal cancer, major depressive disorders, **anxiety disorder+**, bipolar disorder. | Biological Psychological Contextual |
| **Litleskare et al., 2015[n]** | Prospective study (Bergen)<br><br>Norway | 1945 | 65.7<br><br>36.1 (range: 0-99)[b] | IBS (Self-report, Rome III) | 3.0 | **Giardia+, giardia i.c.w. perceived food intolerance+**. | Biological |
| **Litleskare et al., 2018[n]** | Prospective study (Bergen)<br><br>Norway | 1289 | 66.0<br><br>43 | IBS & chronic fatigue (Self-report, Rome III & Fatigue questionnaire) | 10.0 | **Giardia+.** | Biological |
| **Littlejohn et al., 2012** | Birth cohort (British Birth Cohort study / national child development study)<br><br>UK | 9377 | both<br><br>45 | Chronic widespread pain (validated questionnaire) | 45.0 | Gestational age, **birthweight-** (only very low birth weight). | Biological |
| **Liu et al., 2017** | EMR cohort (NHIRD/ LHID2000)<br><br>Taiwan | 4,560 | 100.0<br><br>51.8 (16.1) | BPPV (ICD-9-CM: 386.11, at least 2x) | 11.0 | **Age+, urbanization-, health care utilization+, insurance wage+/-** (only for males), **oestrogen prescription+.** | Biological Contextual Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Macfarlane et al., 2009** | Birth cohort (British Birth Cohort study / national child development study)<br><br>UK | 9377 | 42.7<br><br>45 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 45.0 | **Adult social class-, childhood social class-, recent life events+, GHQ score-, mental health rCIS score+, BMI+,** regular exercise. | Biological<br>Psychological<br>Interpersonal<br>Contextual |
| **Marrie et al., 2009** | EMR cohort (Manitoba Health)<br><br>Canada | 25132 | Both<br><br>≥20 yrs. [b] | Fibromyalgia (ICD-9 or ICD-10) | 20.0 | **Multiple sclerosis+, age+.** | Biological<br>Contextual |
| **Marshall et al., 2006** | Prospective study (Walkerton Health Study)<br><br>USA | 2069 | 55.5<br><br>46.6 [b] | IBS (Self-report & clinical record, Rome I criteria) | 3.0 | **Acute gastroenteritis+** | Biological |
| **Marshall et al., 2010** | Prospective study (Walkerton Health Study)<br><br>USA | 3280 | 55.5<br><br>49.3 (15.5) | IBS (Self-report & clinical record, Rome I criteria) | 8.0 | **Acute gastroenteritis+** | Biological |
| **Masters et al., 2015** | EMR cohort (Humedica)<br><br>USA | 587961 | 64.6<br><br>53 [b] | Fibromyalgia (ICD-9:780.73, at least 2x) | 1.0 | Comorbid conditions: **any musculoskeletal pain condition+, lupus+, diffuse diseases of connective tissue+, arthritis/other arteriopathies+, rheumatoid arthritis+, osteoarthritis+, low-back pain+, back-neck pain+, rheumatism+, other musculoskeletal pain condition+, any neuropathic pain condition+,** postherpetic neuralgia, **carpal-tunnel syndrome+, causalgias+, neuritis radiculitis+, trigeminal neuralgia+, atypical facial pain+,** phantom-limp pain, autonomic neuropathies, **mononeuritis of lower limp+, other polyneuropathies+, back-neck pain with neuropathic involvement+, any sleep disorder+, insomnia/sleep disorder/ apnoea+, restless-leg syndrome+,** | Biological<br>Psychological<br>Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|
| **Masters et al., 2015** (continued) | | | | | | | **any mental disorder+, depression+ anxiety/generalized anxiety disorder+, bipolar disorder+, panic disorder+, PTSD+, fatigue+, headache/migraine+, dyspareunia+,** tinnitus, **chest pain+, TMJ disorder+, memory loss+, abnormal involuntary movements+, (morbid) obesity+, interstitial cystitis+, any gastrointestinal disorder+, IBS+, other gastrointestinal disorder+.** Charlson comorbidity: **any Charlson comorbidity+,** myocardial infarction, **congestive heart failure+, peripheral vascular disease+, cerebrovascular disease+, dementia+, COPD+, rheumatologic disease+, peptic ulcer disease+, mild liver disease, diabetes+, diabetes with chronic complications+,** hemiplegia/paraplegia, **renal disease+,** malignancy, liver disease, metastatic solid tumour, AIDS. Health care resources: **ER visits+, hospitalizations+, office visits+, outpatient visits+, prescriptions+, prescription pain medication+, opioid prescriptions+, visits in which diagnostics/tests were ordered+,** visits in which imaging was ordered. | |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|
| **McBeth et al., 2001**[p] | Prospective study | UK | 1404 | 56.7<br>18-64 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 1.0 | **Illness behaviour+, somatic symptoms+, GHQ+, fatigue+**, health anxiety. | Biological<br>Psycholog.<br>Health behaviour |
| **McBeth et al., 2003**[p] | Prospective study | UK | 1403 | both<br>18-65 | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 3.0 | Work-related manual handling (lifting/carrying 25kg, **pushing/pulling 25kg+**) and posture (typing ≥ 30min, standing still ≥ 30 min, sitting ≥ 30 min**, kneeling+, repetitive movements of wrists/arms+**), workplace environment (job satisfaction, successful work, boring work, fast work, social support, ability to make own decisions, learning new things), GHQ, **illness behaviour+,** health anxiety, **somatic symptoms+, fatigue+**), pain status (**any pain+, low back+**, knee, **wrist/forearm+, shoulder+**). | Biological , Psychological, Interpersonal , Contextual, Health behaviour |
| **McBeth et al., 2019** | Prospective study (PAALS) | UK | 1162 | 57.1<br>non-cases: 61 (53-67)<br>- cases: 62 (54-67) [b] | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 1.0 | **Neuropathic pain+, pain characteristics+** (burning, painful cold, electric shock, tingling, pins and needles, itching, numbness), **number of pain sites+, number of pain medications+**, age**, gender+** (female), occupational status, deprivation, **HADS depression+, HADS anxiety+, sleep problems+.** | Biological<br>Psychological<br>Interpersonal<br>Contextual, Health behaviour |
| **McCabe et al., 2016** | Prospective study (EMAS) | Europe | 2313 | 0.0<br>58.8 (10.6) [b] | Chronic widespread pain<br>(Self-report, ACR criteria for fibromyalgia) | 4.3 | **Vitamin D status-,** age, **BMI+, sit-to-stand-time+, time-to-walk-50-feet+,** PASE score, alcohol consumption, smoking, **depression+, number of comorbidities+**, walking/cycling ≥ 30min a day. | Biological<br>Psychological<br>Contextual<br>Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % | Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|---|
| **Monden et al., 2020** | Prospective study (Lifelines) | Netherlands | 135862 | 55.0 | 48.8 (13.1) [b] | IBS & CFS & fibromyalgia (Self-report) | 1.4, 2.4 | **Gender+** (female), age, race, living style, lower education level, lower income, **work status-,** duration of searching job, diabetes, cancer, hypertension, stroke, asthma/COPD, health-related disorder, **gastrointestinal disorders+,** neurological disorder, blood related disorder, skin related disorders, no listed disorder, **IBS+, FM+, kidney disease+, musculoskeletal disorders+, psychiatric disorders+, high cholesterol+, allergy+, BMI+/-, medications+** (ATC -codes: A02B, A03A, A03F, A06A, G03A-, G03H, H03A, M01A, R01A, R03A, S01X), **health care utilization+, physical activity, smoking-, sleep disturbance+, alcohol consumption-, work absence due to illness, serious illness+,** injury, assault in past year (LTE), **serious life-events in past year (LTE)+, experience difficulties and stress related to health (LDI)+, long-term difficulties (LDI)+,** NEO personality inventory (only **self-discipline+),** somatization scale sum score (SCL-90)+, health-related of life scores (RAND; **bodily pain-, general health-, vitality-**), depression diagnosis, anxiety. | Biological<br>Psychological<br>Interpersonal<br>Contextual , Health behaviour |
| **Mork et al., 2010[R]** | Prospective study (HUNT1+2) | Norway | 15990 | 100.0 | ≥ 20 [b] | Fibromyalgia (Self-report) | 11.0 | **Exercise per week, exercise sessions per week, usual intensity of exercise, BMI+/-.** | Biological<br>Health behav. |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Mork et al., 2012[R]** | Prospective study (HUNT1+2)<br>Norway | 12350 | 100.0<br>≥ 20 [b] | Fibromyalgia (self-report) | 11.0 | **Sleep problems+.** | Biological |
| **Mork et al., 2013** | Prospective study (HUNT)<br>Norway | 27715 | 57.5<br>≥ 20 [b] | Chronic arm pain (self-report, ≥ 3 months) | 11.0 | **Exercise per week-, exercise sessions per week-, usual intensity of exercise-, BMI+/-.** | Biological Health behav |
| **Mork et al., 2014** | Prospective study (HUNT1+2)<br>Norway | 26896 | both<br>≥ 20 [b] | Chronic back pain (self-report, ≥ 3 months) | 11.0 | **Sleep problems+**. | Biological |
| **Mundal et al., 2014** | Prospective study (HUNT2+3)<br>Norway | 19192 | 53.8<br>44.5 [b] | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 11.0 | **Anxiety+, depression+, alcohol use-, sleep problems+, BMI+/-, smoking status+.** | Biological Psychological Health behaviour |
| **Muthuri et al., 2018** | Birth cohort (British Birth cohort (MRC NSHD))<br>UK | 2453 | both<br>31-69 | Chronic back pain (self-report, recurring) | 68.0 | Childhood: **height+** (only female), BMI, **abdominal pain+,** serious illness, emotional problems, **conduct problems+,** care responsi, parental divorce, **parental health-, father's occupation-**, father's education, **mother's education-, house-.** | Biological Psychological Contextual |
| **Myrtveit et al., 2013** | Prospective study (HUNT 2+3)<br>Norway | 20799 | 54.4<br>44.4 (11.9) [b] | Chronic whiplash (self-report) | 11.0 | Gender, **age+, marital status-**, **benefits+**, smoking, alcohol, **physical activity-**, **use of health-services+ (GP+,** company doc, **hospital doc+,** other doc, **physio+,** chiropr, homeopath, **different healer/doctor+, hospital stay+, number of different health-services visited+), use of meds+** (liver, **allergy+, analgesics+, asthma+**, cardiac, anti- depress, iron-pills, **sedative+**, sleep, vitamin D, **quantity+**), **self-rated health-, musculo-skeletal symp+, ≥2 diffuse complaints+, pain-relat sickleave+, comorbid somatic diagnoses+, anxiety+**, depression, **anxiety & depression+.** | Biological Psychological Contextual Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % | Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|---|
| **Mundal et al., 2014** | Prospective study (HUNT2+3) | Norway | 19192 | 53.8 | 44.5 [b] | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 11.0 | **Anxiety+, depression+, alcohol use-, sleep problems+, BMI+/-, smoking status+.** | Biological Psychological Health behaviour |
| **Muthuri et al., 2018** | Birth cohort (British Birth cohort (MRC NSHD)) | UK | 2453 | both | 31-69 | Chronic back pain (self-report, recurring) | 68.0 | Childhood: **height+** (only female), BMI, **abdominal pain+,** serious illness, emotional problems, **conduct problems+,** care of house and child, parental divorce, **parental health-, father's occupational class-**, father's education, **mother's education-, house-.** | Biological Psychological Contextual |
| **Myrtveit et al., 2013** | Prospective study (HUNT 2+3) | Norway | 20799 | 54.4 | 44.4 (11.9) [b] | Chronic whiplash (self-report) | 11.0 | Gender, **age+, marital status-, receipt of benefits+**, smoking, alcohol consumption, **physical activity-, use of health-services+ (general practitioner+,** company doctor, **hospital doctor+,** other doctor, **physiotherapist+,** chiropractor, homeopath, **different healer/doctor+, hospital stay+, number of different health-services visited+), use of medications+** (cod liver, **allergy medication+, analgesics+, asthma medications+**, cardiac medications, anti-depressants, iron-pills, **sedative+**, sleep medication, vitamin D, other, **number of medications used+), self-rated health-, musculoskeletal symptoms+, ≥2 diffuse complaints+, kept from working due to pain+, comorbid somatic diagnoses+, HADS anxiety+**, HADS depression, **anxiety and depression+.** | Biological Psychological Contextual Health behaviour |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|
| **Nakamura et al., 2014** | Prospective study | Japan | 4797 | 56.0<br>≥20 yrs. [b] | Chronic pain (Self-report, >6 months) | 1.0 | **Female gender+,** age group, area, **urbanization+, occupation+,** marital status, living condition, **BMI+, alcohol+, smoking+, education+,** income. | Biological<br>Contextual<br>Health behaviour |
| **Nicholl et al., 2010[T]** | NCC cohort (EPIFUND & EMAS) | UK | 994 | 66.0<br>non-cases: 48.5 – cases: 52.6 [b] | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 25.0 | Single nucleotide polymorphisms (SNP): COMT, rs4680. | Biological |
| **Nicholl et al., 2011[T]** | NCC cohort (EPIFUND & EMAS) | UK & Europe | | 36.6<br>48.5 - 59.5 (medians of 4 groups) [b] | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 25.0 | Single nucleotide polymorphisms (SNP): **rs12584920+**. | Biological |
| **Nilsen et al., 2011** | Prospective study (HUNT 1+2) | Norway | 32417 | 51.5<br>43-45 | Musculoskeletal pain in the low back or neck/shoulders (self-report, standardized Nordic Questionnaire) | 11.0 | **Weight+, activity level-**. | Biological<br>Health behaviour |
| **Nitter et al., 2012** | Prospective study | Norway | 577 | 100.0<br>20-49† | Chronic pain (Self-report + validation interview, ≥ 3 months) | 17.0 | **Disrupted sleep+, fatigue+, non-restorative sleep+, anxious/frightened/nervous+, regular headache+, rumbling stomach+**, stool, numbness/tingling, joints feel swollen, **non-specific health complaints+**, age. | Biological<br>Psychological<br>Contextual |
| **Odegard et al., 2011** | Prospective study (HUNT 2+3) | Norway | 14042 | non-exposed: 48.4 - with exposed: 53.4<br>non-exposed: 48.1 - with exposed: 55.2 [b] | Chronic tension type headache (Self-report, IICDH-2 criteria) | 11.0 | **Insomnia+/-.** | Psychological |
| **Olen et al., 2018** | Birth cohort | Sweden | | 18-37 | IBS (ICD-codes K58.0, K58.9) | 18.0 | **Birth weight for gestational age+, gestational age+/-, mode of deliver-,** Apgar score at 5 min, neonatal distress, **neonatal respiratory distress+.** | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Pan et al., 2016** | EMR cohort (NHIRD/ LHID2010)<br><br>Taiwan | 7634281 | Both<br><br>≥20 yrs[b] | IBS (ICD-9-CM: code 564.0) | | **Age+, female sex+.** | Contextual |
| **Pang et al., 2010**[I] | Birth cohort (1958 British Birth Cohort)<br><br>UK | 8572 | both<br><br>45 | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 38.0 | Parent and teacher reported: **maladaptive childhood behaviour age 7+, age 11+, 16+.** | Inter-personal |
| **Persson et al., 2015**[F] | Retrospective study (Bergen)<br><br>Norway | 1571 | 67.3<br><br>≥18 | IBS, functional dyspepsia, chronic fatigue, overactive bladder syndrome (Self-report, Rome III) | 6.0 | **Giardia+**. | Biological |
| **Picavet et al., 2002** | Prospective study (DMC3)<br><br>Netherlands | 1161 | 57.3<br><br>25-64 | Chronic LBP (validated questionnaire) | 0.5 | **Pain catastrophizing+**, kinesiophobia. | Biological Psychological |
| **Pico-Espinosa et al., 2017** | Prospective study (Stockholm Public Health Cohort)<br><br>Sweden | 10044 | 49.4<br><br>45-84 | Back, neck and shoulder pain (BNSP) (self-report) | 4.0 | **Diabetes+** (only male), **hyperlipidaemia+.** | Biological |
| **Puroila et al., 2015** | Birth cohort (1966 NFBC)<br><br>Finland | 5466 | 52.2<br><br>31 | Musculoskeletal pain (self-report, at least 2 sites, quite often during 12 months) | 17.0 | **Physical activity+** (only female), sports club membership, **body weight+, smoking+, alcohol consumption+.** | Biological Health behaviour |
| **Raphael et al., 2002** | Retrospective study<br><br>USA | 1312 | 100.0<br><br>38.6 (1.3) | Chronic fatigue (Interview, ≥ 6 months) | 0.4 | 9/11 terrorist attack. | Inter-personal |
| **Raslau et al., 2016** | NCC (Olmsted County)<br><br>USA | 178 | 61.0<br><br>median 48 (range: 25–70) | IBS (Self-report, Rome III) | 48.0 | **Birth weight-**, maternal age, gestational age, delivery method, peri-partum complications, epidural/spinal anastatic used, Apgar score, peri-partum length/hospital stay, serious medical condition at birth, jaundice, peri-partum ICU admission, nasogastric tube placed, serious medical condition in first year of life, post birth hospitalization in 1 year, post birth ER, antibiotic exposure, feeding method/durat. | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Reed et al., 2013** | Retrospective study<br><br>USA | 906 | 100.0<br><br>36.9 (8.6) | Vulvodynia (Self-report, ≥ 3 months) | 36.9 | Oral contraceptives. | Biological |
| **Reed et al., 2014** | Prospective study<br><br>USA | 1786 | 100.0<br><br>cases: 45.6 (14.4) – non-cases: 51.0 (16.7) [b] | Vulvodynia (Self-report, ≥ 3 months) | 6.0 | **Age-,** ethnicity, **marital status+, sleep dysfunction+, any chronic pain+/-, pain with intercourse+, vulvar symptoms (in past)+, sleep dysfunction+, psychological distress+** (PTSD, depression), **other chronic comorbid pain conditions+** (FM, interstitial cystitis, IBS) | Biological<br>Psychological<br>Contextual |
| **Rodriguez & Ruigomez, 1999** | EMR cohort (General Practice Research Database)<br><br>UK | 584626 | 47.9<br><br>25-74 [b] | IBS (Doctor diagnosed, random sample for confirmation) | 1.0 | **Gastroenteritis+**. | Biological |
| **Ruigomez et al., 2003** | EMR cohort (General Practice Research Database)<br><br>UK | 90119 | 100<br><br>50-69 [b] | IBS (Doctor diagnosed, random sample for confirmation) | 6.0 | **Hormonal replacement therapy+,** age, **consultation frequency+, mental- and CNS-disorders+, pain related disorders+, gastroenteritis+,** hysterectomy. | Biological<br>Psychological Contextual<br>Health behaviour |
| **Ruigomez et al., 2007** | EMR cohort (General Practice Research Database)<br><br>UK | 6105 | Both<br><br>≥20 yrs. [b] | IBS (Doctor diagnosed, random sample for confirmation) | 10.0 | **Gastroenteritis (bacterial)+, gastroesophageal reflux+, dyspepsia+,** peptic ulcer, appendicitis, **diarrhea+, depression+, anxiety+, stress+, sleep disorders+,** asthma, COPD, ischemic heart disease**, diabetes+,** smoking, **BMI+, alcohol consumption+.** | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| **Ruigomez et al., 2009** | EMR cohort (General Practice Research Database)<br><br>UK | 6421 | Both<br><br>≥20 yrs. [b] | IBS (Doctor diagnosed, random sample for confirmation) | 1.0 | **Gastroesophageal reflux disease+.** | Biological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Shen et al., 2016** | EMR cohort (NHIRD)<br><br>Taiwan | 148239 | 53.9<br><br>54 (18.1) [b] | IBS<br>(ICD-9 564.1) | 10.0 | **Asthma+,** gender, **age+, COPD+, GERD+, allergic rhinitis+, chronic sinusitis+, atopic dermatitis+, anxiety+, depression+, obesity+, follow-up year+.** | Biological<br>Psychological<br>Contextual |
| **Shih et al., 2017** | EMR cohort (NHIRD)<br><br>Taiwan | 741720 | 45.7<br><br>≥ 18 [b] | Tinnitus (ICD-9 388.3, ≥3 by otolaryngologists, intersperse by a min. 4 weeks) | 10.0 | **Chronic kidney disease+,** gender, age, hypertension, **diabetes+, heart failure+,** stroke, COPD, liver cirrhosis, **Meniere's disease+, traumatic brain injury+, Charlson comorbidity+,** aminoglycosides, macrolides, loop diuretics, antineoplastic agents, aspirin, NSAIDSs, **geographic location+** (northern is reference), **urbanization level+, insured premium+/-.** | Biological<br>Contextual |
| **Shih et al., 2018** | EMR cohort (NHIRD)<br><br>Taiwan | 123120 | 48.2<br><br>56.4 (17.5) [b] | BPPV (ICD-9-CM: 386.11) | 14.0 | **Non-apnoea sleep disorders+,** gender, age group, **hypertension+,** diabetes, **congestive heart failure+,** stroke, COPD, **liver cirrhosis+, chronic kidney disease+,** migraine, osteoporosis, hyperlipidaemia, **charlson comorbidity index+.** | Biological<br>Contextual. |
| **Sivertsen et al., 2014** | Prospective study (HUNT 2+3)<br><br>Norway | 24715 | 56.9<br><br>45.3 (19-67) | Fibromyalgia (Self-report) | 11.0 | **Insomnia+.** | Psycho-logical |
| **Skarpsno et al., 2019a** | Prospective study (Tromsø study)<br><br>Norway | 6356 | 50.6<br><br>53.5 (11.2) - 59.7 (10.3)) [b] | Chronic musculoskeletal pain & Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 8.0 | **Sleeplessness+,** high sensitivity C-reactive protein (only joint effect with sleeplessness). | Biological<br>Psychological |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % | Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|---|
| **Skarpsno et al., 2019b** | Prospective study (HUNT 2+3) | Norway | 14793 | 100.0 | exposed: 43.5 (12) – non-exposed: 47 (11.8) [b] | Fibromyalgia (self-report) | 11.0 | **Insomnia+**. | Psychological |
| **Skarpsno et al., 2020** | Prospective study (HUNT 3+4) | Norway | 10847 | 53.8 | 50.3 (13.7) - 46.0 (14.3) | Chronic widespread pain (Self-report) | 11.0 | **Insomnia+.** | Psycho-logical |
| **Smith et al., 2004** | Prospective study | Scotland | 1431 | both | ≥25 | Chronic back pain (self-report, ≥ 3 months) | 4.0 | **Female gender+, age+,** employment, **unable to work due to illness+,** living situation, education, housing tenure, marital status, **any chronic pain at baseline+, SF-36+** (general health, physical functioning, social functioning, role physical, role emotional, energy & vitality, bodily pain) | Biological Psychological Interpersonal Contextual Health behaviour |
| **Talley et al., 2001** | Birth cohort (Dunedin) | New Zealand | 890 | 49.2 | 26 | IBS (Questionnaire DSM-III criteria) | 8.0 | Mental health, anxiety, depression, substance dependence. | Psycho-logical Health behav |
| **Tsai et al., 2014** | EMR cohort (NHIRD/ LHID2005) | Taiwan | 46025 | 53.3 | 56 [b] | CFS (ICD-9: 780.71) | 4.0 | **Herpes zoster infection+.** | Biological |
| **Tsai et al., 2018[$]** | EMR cohort (NHIRD/ LHID2000) | Taiwan | 86016 | 52.2 | 45.5 (17.2) | CFS (ICD-9: 780.71) | 12.0 | **Burn injury+, gender+** (female), **age+, comorbidities+** (**diabetes+,** obesity, renal disease, rheumatoid arthritis, HIV, malignancy, **depression+, anxiety+, sleep disorder+,** and irritable bowel syndrome) | Biological Psychological Contextual |
| **Tsai et al., 2019[$]** | EMR cohort (NHIRD/ LHID2000) | Taiwan | 13080 | 48.0 | ≥ 20 [b] | CFS (ICD-9: 780.71) | 8.0 | **Psoriasis+** (only mild psoriasis), gender, **age+,** diabetes, **depression+, anxiety+, sleep disorder+, renal disease+.** | Biological Psychological Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) Country | sample size, n | Female gender, % Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|
| **Uhlig et al., 2018** | Prospective study (HUNT)<br><br>Norway | 13429 | 59.3<br><br>Non-exposed: 43.4 (12.2), exposed: 44.5 (12.2) [b] | Chronic (widespread) musculoskeletal complaints (Self-report, partial ACR criteria for fibromyalgia) | 11.0 | **Insomnia+.** | Psychological |
| **Vandenkerkhof et al., 2011** | Birth cohort (British birth cohort)<br><br>UK | 8572 | 50.9<br><br>45 | Chronic widespread pain (Self-report) | 12.0 | **Fruit/vegetable consumption+, fatty food+, chips+, alcohol+, physical activity+, employment+, physical exertion at work+, smoking+, BMI+, marital status+, social class+.** | Biological<br>Contextual<br>Health behaviour |
| **Varinen et al., 2019** | Retrospective study (HeSSup)<br><br>Finland | 11409 | 65.7<br><br>20-54 [b] | Fibromyalgia (self-report) | 10.0 | **Bullying+** (only severe bullying), **age+, gender+** (female), **education-, marital status-, depression+.** | Psycho-logical<br>Inter-personal |
| **Viner et al., 2004** | Birth cohort (BGS70)<br><br>UK | 11266 | 62.8<br><br>30 | CFS/ME (self-report) | 20.0<br>36.0 | Gender+ (female), Childhood: **father professional occupation+,** mother education, ethnicity, birth weight, birth order, **longstanding medical condition+,** atopy, obesity**, leisure time sports-,** school sports, school missed due to health, high abilities, illness in parent, behavioural problems, malaise, self-esteem, GHQ, Adulthood: **malaise+,** professional/managerial occupation. | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| **Waehrens et al., 2018** | EMR cohort<br><br>Sweden | 1963685 | 48.6<br><br>18-38 | IBS (ICD-8 564.19, ICD-9 564B, ICD-10 K57) | 20.0 | **Gender+** (female), **birth year-, fetal growth-, gestational age-, birthweight-, birth length-,** multiple birth, **birth order+, mat. age at delivery+/-, maternal marital status-, maternal/paternal educat-, caesarean+, parental history: IBS+, anxiety+, depression+.** | Biological<br>Interpersonal<br>Contextual |

***Appendix C.*** Description of studies included in systematic data synthesis (continued)

| Author, year published | Study type (cohort) | Country | sample size, n | Female gender, % | Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors | Investigated domains |
|---|---|---|---|---|---|---|---|---|---|
| **Wang et al., 2017** | NCC cohort (NHIRD/LHID2000) | Taiwan | 173150 | 51.7 | 52.3 (15.8) - 52.5 (15.6) (non-GERD - GERD)[b] | Fibromyalgia (FM ICD-9 729.0, 3x within 3 months) | 12.0 | **Gastroesophageal reflux disorder+,** gender, **age+, diabetes+, hyperten+, hyperlip.+,** depressi, **anxiety+, sleep disorder+,** alcohol-related illness, **stroke+, peptic ulcer+,** liver cirrhosis, H. pylori, **NSAIDs+,** proton inhib. | Biological Psychological Contextual |
| **Wensaas et al., 2011**[F] | Retrospective study (Bergen) | Norway | 1875 (IBS), 1912 (CF) | 65.7 | 36.1 | IBS & chronic fatigue (Self-report, Rome III & self-report, ≥ 6 months) | 3.0 | **Giardia+**. | Biological |
| **Wensaas et al., 2016** | Retrospective study (Bergen) | Norway | 4564 | 66.4 | 37.4 (19-94) | IBS & functional dyspepsia (Self-report, Rome II criteria) | 2.0 | **Giardia+**. | Biological |
| **Wu et al., 2015** | EMR cohort (NHIRD) | Taiwan | 36456 | 100.0 | 25-54[b] | IBS (ICD-9 564.1, at least 2x) | 5.0 | **Endometriosis+**. | Biological |
| **Wu CC et al., 2018** | EMR cohort (NHIRD/LHID2000) | Taiwan | 26764 | 100 | 34.8 (8.5) | Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) | 6.0 | **Endometriosis+**. | Biological |
| **Yang et al., 2015** | EMR cohort (NHIRD) | Taiwan | 212790 | 56.5 | 47 | CFS (ICD-9: 780.71) | 5.3 | **Atopy+**. | Biological |
| **Yang CY et al., 2020** | EMR cohort (NHIRD/LHID) | Taiwan | 18472 | 48.3 | >20 yrs. [b] | IBS (ICD-9-CM: code 564.0) | 10.0 | **Appendectomy+, gender+, age group+, diabetes+, hypertension+, hyperlipidaemia+, obesity+, interstitial cystitis+, fibromyalgia+, gastroesophageal reflux disease+, diarrhea+, urinary stones+, asthma+.** | Biological Contextual |
| **Yang TY et al., 2022** | EMR cohort (NHIRD/LHID2000) | Taiwan | 38329 | 32.1 | 60.5 (18.3) | CFS (ICD-9-CM: 780.71) | 12.0 | **Mycobac.infect+, age+,** sex, **diabetes+,** obesity, **renal disease+,** arthritis, HIV, malignancy, **IBD+.** | Biological Contextual. |

[a] Risk assessment score rang, poor, fair, good; [b] Age at baseline (age at outcome unknown); + Significant at < .05, positive relation; - Significant at < .05, negative relation; +/- Significant at < .05, U-curve relation.

# Chapter 3

## The General Practitioners' Perspective Regarding Registration of Persistent Somatic Symptoms in Primary Care: a survey

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## Abstract

**Background:** Persistent somatic symptoms (PSS) are common in primary care and often accompanied by an increasing disease burden for both the patient and healthcare. In medical practice, PSS is historically considered a diagnosis by exclusion or primarily seen as psychological. Besides, registration of PSS in electronic health records (EHR) is ambiguous and possibly does not reflect classification adequately. The present study explores how general practitioners (GPs) currently register PSS, and their view regarding the need for improvements in classification, registration, and consultations.

**Method:** Dutch GPs were invited by email to participate in a national cross-sectional online survey. The survey addressed ICPC-codes used by GPs to register PSS, PSS-related terminology added to free text areas, usage of PSS-related syndrome codes, and GPs' need for improvement of PSS classification, registration and care.

**Results:** GPs (n = 259) were most likely to use codes specific to the symptom presented (89.3%). PSS-related terminology in free-text areas was used sparsely. PSS-related syndrome codes were reportedly used by 91.5% of GPs, but this was primarily the case for the code for irritable bowel syndrome. The ambiguous registration of PSS is reported as problematic by 47.9% of GPs. Over 56.7% of GPs reported needing additional training, tools or other support for PSS classification and consultation. GPs also reported needing other referral options and better guidelines.

**Conclusions:** Registration of PSS in primary care is currently ambiguous. Approximately half of GPs felt a need for more options for registration of PSS and reported a need for further support. In order to improve classification, registration and care for patients with PSS, there is a need for a more appropriate coding scheme and additional training.

## Introduction

Up to 50% of primary care visits in Western societies are related to symptoms that cannot be fully explained by well-known biomedical pathology.[1-4] While most of these symptoms are self-limiting, 2.5-10% of cases persist without clear medical explanation.[5-9] These persistent somatic symptoms (PSS) are accompanied by increasing disease burden for both the patient and the healthcare system.[10] Differentiation from well-known chronic medical conditions and classification of symptoms as PSS is challenging.[11] Challenges arise from similarities between symptoms of PSS and other conditions, possible co-existence with a well-documented medical disorder, the heterogeneity of symptoms, lack of universal guidelines and the lack of biomarkers.[3, 12-14] Delayed identification of PSS impedes early management of symptoms, which in turn can result in inappropriate healthcare utilization and high costs.[15-17] Additionally, it may hinder reusability of electronic health records (EHR) for research, quality monitoring and proactive population health management.[17-20]

Across medical and psychological specialties, a variety of terminology and aetiology is reflected in different concepts of PSS. While some countries have specific guidelines for PSS, widely accepted guidelines for classifying (and treating) PSS are missing.[3] PSS is currently diagnosed as either a somatic disease or a mental disorder, since diagnostic classifications are inherently dualistic in nature.[21] In the medical field, patients may be classified under umbrella terms such as 'medically unexplained physical symptoms' (MUPS), 'functional somatic symptoms', and 'somatically fixed',[9, 22] which indicate a negative symptomology – i.e. a lack of medical pathology.[23] PSS may also be classified as syndromes such as irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS) or fibromyalgia (FM). Ongoing debate about terminology has redirected the most recent versions of the diagnostic and statistical manual of mental disorders (DSM-5)[24] and the international classification of disease (ICD-11)[25] towards no longer requiring the explicit exclusion of any underlying medical condition (this only applies to PSS-related classifications in the mental health chapter). Both focus on positive symptomology, such as maladaptive cognitions, emotions and/or behaviours related to the somatic symptoms,[3, 13] as described in the DSM-5 as the so-called B-criteria of somatic symptom

disorder (SSD).[24, 26] Still, consensus on labelling and addressing these symptoms is limited. In this paper, the term 'persistent somatic symptoms' (PSS) is used since the descriptive nature of the term transcends the problem of dualism. Moreover, recent research has found that this term is generally preferred over other terms.[27]

In the Dutch health care system, as well as in many (Western) countries, the GP serves as a gatekeeper for health care in general. The classification of symptoms and illnesses in EHRs by Dutch GPs is based on the International Classification of Primary Care (ICPC) system.[28] Since medical practice historically operates according to mind-body dualism, physicians are required to locate complaints either in the body or the mind.[21] Accordingly, most symptoms and disorders – physical and psychological – have a domain specific diagnostic code in the ICPC. Nonetheless, the current ICPC lacks a specific and clearly defined code for PSS and the ICPC system instructs to register symptoms not fulfilling the criteria for a diagnosis on a symptom level.[29, 30] Arguably, registration of cases with PSS is less straight forward due to the multi-domain nature of PSS even though the ICPC does contain a chapter with multi-domain codes (A-chapter). Nonetheless, there are international codes available for some PSS-related syndromes (such as, IBS), and the Dutch ICPC also contains codes for FM and CFS.[30]

While several studies have documented ample diagnostic variation regarding patients with PSS in general practice,[31, 32] it is not well documented which codes or other methods GPs use for registration of PSS and if they find their current approach to registration satisfactory. The primary aim of the present study was, therefore, to explore how GPs currently register PSS. The secondary aim was to gauge GPs' perspective on their needs to improve classification, registration and care for PSS.

## Methods

### Study design

A cross-sectional online survey was developed to reach our aims. The survey questions were developed in collaboration with experts in general practice, medical psychology and PSS. The survey was set up in Qualtrics.[33] This paper focuses on GPs' registration behaviour and needs, using the STROBE cross sectional reporting guidelines.[34] Prior to distribution, the survey was pilot tested among four GPs and modified based on their feedback. Informed consent was included at the start of the survey. The ethics committee of Leiden University Medical Centre supplied a waiver of ethical approval (C1O8.045/DJ/gk).

### Procedure

The survey was sent out via e-mail between June and September 2018 to mailing lists of Dutch GPs who consented to be approached anonymously for research purposes, and to email addresses obtained through an overarching Dutch healthcare website (www.zorgkaartnederland.nl). This method ensured optimal distribution over all regions of the Netherlands in order to obtain a representative and generalizable sample. Reminders were sent two weeks after first distribution. Ten gift cards of 25 euro were allotted to GPs who participated and provided us with their email address. The email addresses were not linked to the survey responses.

### Measures

To adhere to the term currently used in guidelines for PSS-related complaints, the Dutch term for MUPS ('SOLK') was used to indicate PSS in the survey. Somatisch onvoldoende verklaarde lichamelijke klachten (SOLK) is literally translated as somatic insufficiently explained physical complaints. In the introduction of the survey, a description of the definition of SOLK was presented: 'We speak of SOLK when regular medical care cannot find an adequate explanation for the complaints with which the patient presents him/herself. Patients with a well-known somatic condition can also have SOLK, either presenting with a totally different complaint or presenting with more severe complaints than is expected.' Distinction and explanation about self-limiting and persistent symptoms were provided. To address conceptual differences between GPs regarding PSS

and to ensure that both the medical and psychological domain of PSS was captured, separate questions were added which specifically addressed PSS in patients with a(n explained) chronic medical condition (i.e., 'patients presenting with more or more severe symptoms than you would expect') and/or the B-criteria of SSD (i.e., 'patients who have maladaptive cognitions, emotions and/or behaviours related to the somatic symptoms'). At the start of the survey, GPs were asked to fill in non-identifying demographic questions. All questions required at least one response to continue to the next question, except comment sections. Below you find a description of the survey questions (for an exact outline of the survey, see appendix A).

*Primary aim ('registration of PSS')* – The following four items were constructed to reach the primary aim: (1) First a description of a hypothetical patient was given as follows: 'Imagine a patient visiting your office who has consulted you frequently in the previous 6 months with the same or differing complaints. Extensive research has excluded a medical explanation for the complaint(s). For each complaint presented, choose the ICPC-code which you would use most often. You can choose a maximum of three ICPC-codes per complaint.' Then followed 4 complaints on different pages: bowel problems, fatigue, neck and back pain, and shortness of breath. A drop-down menu contained all codes related to the complaint in the thesaurus menu from ICPC-online,[30] which reflects the presentation in GPs' EHR. This list was supplemented with suitable codes based on a PSS-expert panel of GPs (see appendix B for the full list of ICPC-codes from which GPs could choose). The four separate complaints were offered in random order to minimize bias due to presentation order. Next, (2) GPs were asked whether they use the PSS-related syndrome codes A04.01 (CFS), D93 (IBS) and/or L18.01 (FM). Respondents selected one or more of five options: 'Yes, I diagnose the syndromes myself sometimes', 'Yes, I use this code when the syndrome is diagnosed by a medical specialist', 'No, I think these complaints should be reported on a symptom level', 'No, I am not convinced these are distinguishable syndromes', and 'Other, namely…' (with an additional comment section). This question was added to the survey in a later stage and was therefore only presented to 73% (n=189) of the GPs.

Subsequently, (3) GPs were asked whether they mention PSS-related terminology in the (3a) episode name or (3b) free text area (two 4-point scale items (ranging from 'never' to 'always')). Lastly, (4) a description of a hypothetical consultation with a patient with a diagnosed medical condition was given, whereby the patient presented with specific cognitive, emotional and behavioural problems (conforming to the B-criteria of SSD).[24] GPs were asked if they would mention this in their EHR (yes/no, and a comment section).

*Secondary aim ('GPs needs')* – The following four items were constructed to reach the secondary aim: First, (1) GPs were asked if the lack of an unambiguous way of classifying or coding PSS was problematic for them (yes/no, and a comment section). Next, (2) GPs were asked if they had a need for a code which captures the specific cognitions, emotions and behaviour conforming to the B-criteria of SSD (yes/no, and a comment section). Subsequently, an open-ended question was presented where GPs were asked (3) what they need to be able to improve registration and classification of PSS; and, in order to ensure not missing any needs, this was followed by three specific semi-open-ended questions – (4) if they have needs regarding training, (online) tools or other support, to improve consultations and classification of PSS (response options were: 'no' and 'yes, namely…').

### Data analysis

All results are based on descriptive statistics. Survey responses were summarized as is, using sample sizes and percentages, unless otherwise specified above. For the first hypothetical consultation, codes were first categorized into four groups: symptom-specific codes (e.g., A04-fatigue), general codes – i.e., non-specific codes (e.g., P28-limited function/disability(p)), somatization (P75-somatization disorder) and syndromes (A04.01-CFS, D93-IBS and L18.01-FM) (see appendix B). The responses on the four single complaints were analysed both combined and as separate complaints. For the question regarding the use of PSS-related syndrome codes, the two 'Yes, …' answering options were combined and the two 'No, …' answering options were combined to construct total scores.

## Results

Of the approximately 12,000 active GPs in the Netherlands, an estimated 2,000 GPs were reached through our distribution method. In total, 259 GPs (13%) fully completed the survey, with exception to the fourth item (4) which was completed by 189 GPs. Table 1 displays the characteristics of the total sample. Of the GPs who filled out the survey, 60.2% were female, which reflects the current trend towards increasing numbers of female GPs in the Netherlands.[35] GPs from all regions in the Netherlands completed the survey. GPs years since graduation is reasonably evenly distributed over 5-year periods, varying between the smallest group of GPs graduating between 26 to 30 years since participating in the survey (8.5%) and the largest group of GPs graduating between 6 to 10 years before participation (17.8%).

***Table 1.*** Characteristics of the 259 Dutch GPs participating in the study

| **General practitioners** | **n=259 (%)** |
|---|---|
| **Gender (female)** | 156 (60.2) |
| **Years since graduation** | |
| ***< 5*** | 41 (15.8) |
| ***6 - 10*** | 46 (17.8) |
| ***11 - 15*** | 44 (14.0) |
| ***16 - 20*** | 39 (15.1) |
| ***21 - 25*** | 31 (12.0) |
| ***26 - 30*** | 22 (8.5) |
| ***> 30*** | 36 (13.9) |
| **Location of practice** | |
| ***Urban (Randstad)*** | 81 (31.0) |
| ***North*** | 62 (23.8) |
| ***Middle*** | 102 (35.6) |
| ***South*** | 23 (8.8) |

## Registration of PSS

As shown in Figure 1, GPs vary in their way of reporting PSS. Combining the preferred first choices of code for the four PSS case examples, the general trend indicates that GPs were most likely to register PSS on a symptom-specific level (89.3%). The frequency of choosing general codes increased from 6.9% as a first choice to 31.1% for the second and

45.5% for the third choice. The choice for ICPC code P75 (somatization disorder) increased from 1% as a first choice, to 5.1% and 8.0% for the second and third choice respectively. When presented with fatigue complaints, more than 35.7% chose to report the complaint with P75 (as a second or third choice). Looking at the number of times a syndrome code (IBS, CFS or FM) was generally chosen either as a first, second or third choice, 144 chose D93 (IBS) in case of bowel complaints, 69 GPs chose A04.01 (CFS) in case of fatigue complaints, and 6 chose L18.01 (FM) in case of neck and back pain. For a more detailed description of the choices of ICPC codes per presented symptom, see appendix C.

***Figure 1.*** Visualizations of general practitioners' order of choosing ICPC-codes for specified persistent somatic symptoms (PSS).

Table 2 shows the reported likelihood that GPs mention PSS-related terminology and cognitions, emotions or behaviour related to PSS in their EHR. Some GPs mentioned in the comment section that a fear of stigmatization was the reason for avoiding PSS-related terms.

***Table 2.*** GPs (n=259) mentioning PSS-related terminology in their EHR

| **Do you mention PSS in the episode name?** | **n (%)** |
|---|---|
| *never* | 79 (30.5) |
| *occasionally* | 146 (56.4) |
| *often* | 28 (10.8) |
| *always* | 6 (2.3) |
| **Do you mention PSS in the free-text area?** | |
| *never* | 29 (11.2) |
| *occasionally* | 156 (60.2) |
| *often* | 64 (24.7) |
| *always* | 10 (3.9) |
| **Do you mention components [a] of PSS in the free-text area?** | |
| *Yes* | 204 (78.8) |

[a] Specific thoughts, feelings and behaviour conforming to the B-criteria of SSD

Of all GPs who answered the question regarding ICPC-codes for recognized PSS-syndromes (n=189), 91.5% indicated that they use the codes for IBS (D93), CVS (A04.01) and FM (L18.01) (not shown in Table). The answering options given in the survey are depicted in Table 3. While 68.3% of GPs reported diagnosing the syndrome themselves, several GPs commented that this was only the case for IBS (which was also the case in most GPs who selected the answer 'Other, namely…').

***Table 3.*** GPs (n=189) use of PSS-related syndrome codes

| **Do you use the PSS-syndrome ICPC codes?** [a,b] | n = 189 |
|---|---|
| *Yes, I diagnose the syndromes myself sometimes* | 129 (68.3) |
| *Yes, I use this code when the syndrome is diagnosed by a medical specialist* | 74 (39.2) |
| *No, I think these complaints should be reported on a symptom level* | 25 (12.2) |
| *No, I am not convinced these are distinguishable syndromes* | 9 (4.8) |
| *Other, namely…* | 19 (10.1) |

[a] A04.01 – CFS; D93 – IBS; L18.01 - FM

[b] Multiple answers possible per GP

## GPs needs

Table 4 shows the results relating to the second aim of this study. Approximately half of GPs (47.9%) reported that the lack of an unambiguous way of classifying or coding PSS is a problem for them. Many GPs commented that a specific code for PSS would be helpful, and some suggested that PSS-codes per tract or a specific code with different severity levels would be helpful. GPs commented requiring widely accepted guidelines in combination with a new PSS-code. Of those who did not see the lack of a specific PSS code as a problem (52.1%), many commented they sometimes describe PSS in the available free text area when registering the patient's somatic complaint. Others felt there is still too much uncertainty regarding PSS to code it, felt unwilling to apply "that label" to a patient, or commented that registration at a symptom level was sufficient. Of all GPs, 32.8% reported that they would like to be able to express PSS-related components – i.e., specific thoughts, feelings and behaviour conforming to the B-criteria of SSD – in a code. Although some of these GPs commented that they found it difficult to specify the components. Additionally, GPs indicated a need for training (56.7%) and/or an – (online) classification and/or risk assessment – tool (58.3%) and/or other support (69.7%). Other PSS-related needs mentioned by GPs in the elective comment sections regarded clearer or more referral options, more time and financial compensation for consultations and better guidelines (although others explicitly mentioned that they found the current guidelines adequate).

***Table 4.*** GPs' needs for improving registration and classification of persistent somatic symptoms in EHR

| **There is no ICPC code for PSS; is this a problem for you?** | **n=259 (%)** |
|---|---|
| *Yes* | 127 (47.9) |
| **Would you like to express components [a] of PSS in an ICPC code?** | **n=259 (%)** |
| *Yes* | 85 (32.8) |
| **Do you have a need for … to improve consultations/classification for PSS?** | **n=254 (%)** |
| *…training… (yes)* | 144 (56.7) |
| *…an (online) tool… (yes)* | 148 (58.3) |
| *…other support… (yes)* | 177 (69.7) |

[a] Specific thoughts, feelings and behaviour conforming to the B-criteria of SSD

## Discussion and conclusion

The results of this survey indicate that codes used for registration of PSS in primary care varies widely among GPs. PSS are primarily coded at a specific somatic symptom level and GPs often avoid using terminology related to PSS in their EHR. In addition, GPs indicate they us the codes for well-known PSS-syndromes as IBS, CFS, or FM, although IBS is coded more often than CFS and FM. Besides, the cognitive, emotional, or behavioural components of PSS are sparsely reported in EHRs. Some GPs indicated that they have difficulties in specifying these components. Overall, half of GPs are unsatisfied with current registration options for PSS. Many GPs have a need for additional tools, training or support regarding PSS registration and classification. Still, while GPs provide several suggestions for improvements of the classification system, there is little consensus on this matter.

Looking more specifically at the first aim of this study, many GPs are struggling with registration of PSS and are hesitant to use codes beyond the somatic complaints they objectively observe. This is in line with instructions of the ICPC [13, 30] and previous research findings, reporting that GPs' fear of stigmatization may lead them to avoid codes related to social and psychological problems.[29, 37, 39] On the other hand, respondents did indicate more frequently diagnosing the PSS-related syndrome IBS, compared to CFS and FM, which is in line with previous research indicating that GPs are more proficient in diagnosing IBS.[11] This suggests that registration behaviour may be more depended upon the GP's confidence in classifying PSS than upon fear of stigmatization.

Regarding the second aim of this study, our results show that the current registration and classification options for PSS are insufficient for a substantial number of GPs. These GPs reportedly require a specific code for PSS, in combination with training, tools, a widely accepted guideline, and referral options. In contrast, the literature shows that there are a variety of training options,[40] concise and validated screening questionnaires,[26, 38, 41] and referral options [3, 13, 42] available to GPs. Besides, the Dutch GP association has an elaborate PSS guideline.[13] In line with this guideline, some GPs suggested coding of PSS should be done by severity, which is also in line with studies

which propose the introduction of codes that specify severity to improve documentation of mild PSS.[8, 9, 29] Interestingly, research demonstrated that the GPs' use of subcategories directed at classifying severity is challenged by the GPs' conceptual understanding of PSS.[8] It is therefore conceivable that GPs do indeed need training, and knowledge of the availability of training, to increase their understanding of PSS.

### Strengths and limitations

To the best of our knowledge, this study is the first to capture an overview of GPs' perspectives regarding registration and classification of PSS through exploration of their specific ICPC-registration behaviour. Our data sheds light on GPs' reasoning regarding PSS, confirms the lack of consensus on registration and classification and offers guidance for improvements in registration and classification based on the GPs' reported needs. Nonetheless, some limitations should be noted. First, in order to distribute the survey as broadly as we have, we involved third parties (i.e. regional GP-networks) to promote distribution. This resulted in a limited overview of the number of GPs reached, leading to a rough estimate of the response rate. Second, responses may have been biased by elective participation. Still, although adequate reference data is limited, responses appear fairly representative for the population of GPs in the Netherlands.[36, 43] Regarding the content of the survey, a strength is that face valid answers were facilitated for the choice in ICPC codes by presenting GPs with codes in a drop-down menu, similar to their EHRs' set-up. Nonetheless, this came with the limitation that it is unclear if the more frequently coded 'P75-somatization disorder' in case of fatigue compared to other complaints is a true finding, or whether it demonstrates the limitations of the ICPC coding system itself to facilitate classification of PSS, or if it is related to a lack of potential alternative codes (see appendix B). Lastly, generalisation of the findings should be done with caution, since many questions were based on hypothetical situations.

### Practical implications

The great variance in responses and methods for registration of PSS found in our research suggests that clinical practice may be improved by better registration of PSS. Improving classification and providing adequate registration options may support GPs in the overall care for PSS. To improve registration, a clear definition with a specific code for

PSS should be implemented in the ICPC system. Introduction of such a code should be combined with (communication on) training options for GPs, which also broadens the GPs' knowledge on currently available diagnostic tools, guidelines, and referral options. Besides providing more accessible coding and training options, research could support the GP further by developing a data-based screening tool for early identification of patients at risk for PSS. This could be another way to support the GP with their challenges in conceptualizing PSS. Besides, this may promote timely treatment of the cognitive, emotional, and behavioural components of PSS, which, in turn, may decrease the burden of PSS and reduce the risk of iatrogenic harm.

### Conclusion

Registration of PSS in primary care is currently ambiguous. Specific complaints presented by patients with PSS are primarily coded on a symptom-specific level. Approximately half of GPs expressed a need for more coding options for PSS and over half of GPs reported a need for further training, tools or other support regarding PSS. Since many of the latter already exist, improvements should be directed at new options for registration, specifically coding, and increasing and spreading knowledge about PSS, guidelines, available tools, and referral options.

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# Appendixes

## ***Appendix A.*** Survey translation: SOLK in general practice, a general practitioners' perspective

This file contains SOLK-related definitions and questions outlined in the measures section of the article are presented below.

**Definition of 'somatisch onvoldoende verklaarde lichamelijke klachten' (SOLK):**

We speak of SOLK when regular medical care cannot find an adequate explanation for the complaints with which the patient presents him/herself. Patients with a well-known somatic condition can also have SOLK, either presenting with a totally different complaint or presenting with more severe complaints regarding their diagnosed condition than would be expected.

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**Part 1:** *Imagine a patient visiting your office who has consulted you frequently in the precious 6 months with the same or differing complaints. Extensive research has excluded a medical explanation for the complaint(s).*

For each complaint presented, choose the ICPC-code which you would use most often. You can choose a maximum of three ICPC-codes per complaint.

a) Bowel problems

*Three drop-down menus (see appendix B for list of ICPC codes)*

b) Fatigue

*Three drop-down menus (see appendix B for list of ICPC codes)*

c) Neck and back pain

*Three drop-down menus (see appendix B for list of ICPC codes)*

d) Shortness of breath

*Three drop-down menus (see appendix B for list of ICPC codes)*

*(Each complaint was presented on a new page with the description of the hypothetical patients at the top of the page)*

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**Part 2:** Do you use the ICPC-codes for fibromyalgia (L18.01), chronic fatigue syndrome (A04.01) and/or irritable bowel syndrome (D93)? (multiple answers possible)

☐ Yes, I diagnose these syndromes myself sometimes

☐ Yes, I use these codes when the diagnosis is made by a medical specialist

☐ No, I prefer reporting these complaints at a symptom level

☐ No, I am not convinced that these are discernable syndromes

☐ Other, namely…

Comments: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

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**Part 3:** The next questions are about if or how you report SOLK in your electronic health record (EHR) when you have enough reasons to assume that the complaints are SOLK.

| | never | now and then | often | always |
|---|---|---|---|---|
| a) Do you write SOLK in the episode name? | ○ | ○ | ○ | ○ |

b) Do you write SOLK in the free text area of the EHR?

Comments: _ _ _

***Appendix B.*** Overview of items, ICPC codes and categorization

| | | Type of complaint | | | | |
|---|---|---|---|---|---|---|
| **ICPC** | **Name** | **Neck & back** | **Bowel** | **Shortness of breath** | **Fatigue** | **Category** |
| A01 | Pain general/multiple sites | X | X | | | General |
| A04 | Weakness/tiredness general | | | X | X | Symptom-specific |
| A04.01 | Chronic fatigue syndrome | | | X | X | Syndrome |
| A28 | Limited function/disability NOS | X | X | X | X | General |
| A97 | No disease | X | X | X | X | General |
| A99 | General disease NOS | X | X | X | X | General |
| D01 | Abdominal pain/cramps general | | X | | | Symptom-specific |
| D02 | Abdominal pain epigastric | | X | | | Symptom-specific |
| D06 | Abdominal pain localized other | | X | | | Symptom-specific |
| D20 | Mouth/tongue/lip symptom/complt. | | | X | | Symptom-specific |
| D28 | Limited function/disability (d) | | X | | | General |
| D29 | Digestive symptom/complaint other | | X | | | General |
| D93 | Irritable bowel syndrome | | X | | | Syndrome |
| K02 | Pressure/tightness of heart | | | X | | Symptom-specific |
| K03 | Cardiovascular pain NOS | | | X | | General |
| K04 | Palpitations/awareness of heart | | | X | | Symptom-specific |
| K05 | Irregular heartbeat other | | | X | | Symptom-specific |
| L01 | Neck symptom/complain | X | | | | Symptom-specific |
| L02 | Back symptom/complaint | X | | | | Symptom-specific |
| L03 | Low back symptom/complaint | X | | | | Symptom-specific |
| L18 | Muscle pain | X | | | | Symptom-specific |
| L18.01 | Fibromyalgia | X | | | | Syndrome |
| L27 | Fear musculoskeletal disease other | X | | | | General |
| L28 | Limited function/disability (l) | X | | | | General |
| L29 | Sympt/com. musculoskeletal other | X | | | | General |
| L79 | Sprain/strain of joint NOS | X | | | | Symptom-specific |
| L79.01 | Whiplashtrauma cervical spine | X | | | | Symptom-specific |
| L83 | Neck syndrome | X | | | | Symptom-specific |
| L86 | Back syndrome with radiating pain | X | | | | Symptom-specific |
| L86.01 | Spinal disc hernia (thoracic/lumbar) | X | | | | Symptom-specific |
| N01 | Headache | X | | | | Symptom-specific |
| N28 | Limited function/diability (n) | X | X | | | General |
| N29 | Neurological symptom/com other | X | X | X | | General |
| P28 | Limited function/disability (p) | X | X | X | X | General |
| P29 | Psychological symptom/com other | X | X | X | X | General |
| P75 | Somatization disorder | X | X | X | X | Somatization |
| P99 | Psychological disorders, other | X | X | X | X | General |
| R01 | Pain respiratory system | | | X | | Symptom-specific |
| R02 | Shortness of breath/dyspnoea | | | X | | Symptom-specific |
| R04 | Breathing problem, other | | | X | | General |
| R28 | Limited function/disability (r) | | | x | | General |
| U13 | Bladder symptom/complaint other | | X | | | General |
| U28 | Limited function/disability urinary | | X | | | General |

***Appendix C.*** Registration of PSS-related complaints using ICPC (n = 259)

| Registration method | First choice [a] | Second choice [a] | Third choice [a] |
|---|---|---|---|
| **Combination** [b] | **n = 1035** | **n = 791** | **n = 500** |
| *Symptom-specific* [c] | 924 (89.3) | 377 (47.7) | 172 (34.4) |
| *General* [d] | 71 (6.9) | 246 (31.1) | 227 (45.5) |
| *Somatization* [e] | 10 (1.0) | 40 (5.1) | 40 (8.0) |
| *Syndrome* [f] | 30 (2.9) | 128 (16.1) | 61 (12.2) |
| **Fatigue** | **n = 259** | **n = 154** | **n = 88** |
| *Symptom-specific* [c] | 252 (97.3) | 14 (9.1) | 11 (12.5) |
| *General* [d] | 2 (0.8) | 61 (39.6) | 47 (53.4) |
| *Somatization* [e] | 3 (1.2) | 24 (15.6) | 18 (20.5) |
| *Syndrome* [f] | 2 (0.8) | 55 (35.7) | 12 (13.6) |
| **Bowel problems** | **n = 259** | **n = 216** | **n = 139** |
| *Symptom-specific* [c] | 218 (84.2) | 104 (48.1) | 46 (33.1) |
| *General* [d] | 11 (4.2) | 37 (17.1) | 38 (27.3) |
| *Somatization* [e] | 2 (0.8) | 4 (1.9) | 10 (7.2) |
| *Syndrome* [f] | 28 (10.8) | 71 (32.9) | 45 (32.4) |
| **Shortness of Breath** | **n = 259** | **n = 190** | **n = 107** |
| *Symptom-specific* [c] | 210 (81.1) | 67 (35.3) | 30 (28.0) |
| *General* [d] | 45 (17.4) | 114 (60.0) | 70 (65.4) |
| *Somatization* [e] | 4 (1.5) | 9 (4.7) | 7 (6.5) |
| *Syndrome* [f] | 0 (0) | 0 (0) | 0 (0) |
| **Neck and back pain** | **n = 258** | **n = 231** | **n = 166** |
| *Symptom-specific* [c] | 244 (94.6) | 192 (83.1) | 85 (51.2) |
| *General* [d] | 13 (5.0) | 34 (14.7) | 72 (43.4) |
| *Somatization* [e] | 1 (0.4) | 3 (1.3) | 5 (3.0) |
| *Syndrome* [f] | 0 (0) | 2 (0.9) | 4 (2.4) |

[a] Top three ICPC codes (by category) GPs most likely choose for PSS-related complaints (second and third choice elective).
[b] Combination of all responses for the four complaints (fatigue, bowel problems, shortness of breath, and neck and back pain).
[c] Includes range of (mainly symptomatic) ICPC codes.
[d] Includes range of more general ICPC codes without specified location or diagnosis.
[e] P75 – somatization disorder.
[f] Fatigue: A04.01 – CFS; bowel problems: D93 – IBS; shortness of breath: no code available; neck and back pain: L18.01 - FM.

# Chapter 4

## Identifying Persistent Somatic Symptoms in Electronic Health Records: exploring multiple theory-driven methods of identification

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## Abstract

**Objective:** Persistent somatic symptoms (PSSs) are defined as symptoms not fully explained by well-established pathophysiological mechanisms and are prevalent in up to 10% of patients in primary care. The present study aimed to explore methods to identify patients with a recognisable risk of having PSS in routine primary care data.

**Design:** A cross-sectional study to explore four identification methods that each cover part of the broad spectrum of PSS was performed. Cases were selected based on (1) PSS-related syndrome codes, (2) PSS-related symptom codes, (3) PSS-related terminology and (4) Four-Dimensional Symptom Questionnaire scores and all methods combined.

**Setting:** Coded electronic health record data were extracted from 76 general practices in the Netherlands.

**Participants:** Patients who were registered for at least 1 year during 2014–2018, were included (n=169,138).

**Outcome measures:** Identification methods were explored based on (1) PSS sample sizes and demographics, (2) presence of chronic conditions and (3) healthcare utilisation (HCU) variables. Overlap between methods and practice specific differences were examined.

**Results:** The percentage of cases identified varied between 0.3% and 7.0% across the methods. Over 58.1% of cases had chronic physical condition(s) and over 33.8% had chronic mental condition(s). HCU was generally higher for cases selected by any method compared with the total cohort. HCU was higher for method B compared with the other methods. In 26.7% of cases, cases were selected by multiple methods. Overlap between methods was low.

**Conclusions:** Different methods yielded different patient samples which were general practice specific. Therefore, for the most comprehensive data-based selection of PSS cases, a combination of methods A, C and D would be recommended. Advanced (data-driven) methods are needed to create a more sensitive algorithm for identifying the full spectrum of PSS. For clinical purposes, method B could possibly support screening of patients who are currently missed in daily practice.

## Introduction

In the general population, approximately 20% of adults experience persistent or recurring disabling physical symptoms.[1–4] These physical symptoms are generally not fully explained by established biomedical pathology, and cannot be fully attributed to objectively determined anatomical or functional disease severity.[4–7] This is often the case for both patients with well-documented diseases such as cancer[8,9] and cardiovascular disease,[10,11] as well as for patients with so-called medically 'unexplained' physical symptoms.[12–15] 'Unexplained' symptoms account for up to 50% of all primary care consultations in western populations.[16–18] While most of these symptoms are self-limiting, they persist in 2.5%–10% of cases.[12,13,15] Due to conceptual and domain specific differences, these conditions have been described using a wide range of labels, including medically unexplained physical symptoms, functional disorders, somatization, and somatic symptom disorder (SSD).[15,19,20] Alternatively, patients with a specific set of symptoms are classified as having a syndrome (e.g., chronic fatigue syndrome (CFS), fibromyalgia (FM) or irritable bowel syndrome (IBS)). In general, symptoms are often classified into one of the 'unexplained' categories, based on exclusion of physical conditions with well-documented biomedical pathology.[21] In this paper, the term 'persistent somatic symptoms' (PSS) is used, since recent research has found that this term is generally preferred over other terms.[22] Moreover, the term PSS is in line with recent advances in the field, specifically related DSM and ICD classifications, which no longer require exclusion based on the presence of a medical condition but instead focus on positive symptomology (e.g., the presence and burden of symptoms).[20]

This broad spectrum of PSS, whether or not accompanied by a physical condition, either directly or indirectly affect a major part of the population and are generally accompanied by an increasing burden of disease for both the patient and healthcare systems.[23] Although widely discussed, consensus on classification, diagnostic procedure and treatment approaches is still lacking.[24–27] This impedes early recognition and proactive clinical intervention of patients at risk of developing persistent problems, resulting in inappropriate and relatively high healthcare utilisation (HCU) and costs.[28,29] Particularly in primary care, which serves as a gatekeeper for healthcare in

many (western) countries,[30–32] earlier recognition is desirable as it could help to prevent unnecessary referrals and could enable the initiation of proactive interventions, aiming to avoid problems becoming permanent or other adverse health consequences.

Recent advancements in data science have shown that routine primary care data can be responsibly used for epidemiological research,[33,34] predictive modelling [35] and population health management purposes.[36] The use of routine primary care data for research on PSS, however, is currently hampered by ambiguous registration of diagnoses in the domain of PSS,[37–40] which has led to individual general practitioner (GP) and/or general practices recording PSS differently. Nonetheless, several methods for identifying patients with PSS in the electronic medical records (EMR) of patients in primary care have been explored in previous research.[26,39,40] Yet, none of those seem fully satisfactory due to the need for additional diagnostics, limited sensitivity, and exclusion of patients with mental or physical conditions.

This study aims to gain better insight into the most comprehensive data-based options for identifying the full spectrum of patients carrying the risk of having PSS in routine primary care data. A more comprehensive method of data-based identification of patients with PSS will make it possible to feedback an individual risk score to physicians that might help to increase awareness of PSS, but it might also improve future research on specific interventions. We explored the differences between previously used identification methods, focusing on (A) PSS-related syndromes [26,41] and (B) PSS-related symptomology [26,39,40] and adding new options. First, findings from a recent survey among GPs undertaken by our group,[27] indicated the use of (C) PSS-related terminology in free-text areas. Second, we found results from the validated Four-Dimensional Symptom Questionnaire (4DSQ), which screens for PSS,[42] to be registered in Dutch primary care health records. The 4DSQ is most likely to be administered by the mental health nurse practitioner, when patients are referred by their GP for psychological complaints. Recorded results of the (D) somatic symptoms subscale of the 4DSQ were included as another method for identifying PSS. Lastly, all methods (A–D) were combined. For all methods, outcomes relating to sample characteristics, presence of diagnosed chronic conditions and HCU were assessed.[43–45]

## Method

### Study design

In the Netherlands, all residents are enlisted with a GP in their neighbourhood and general practice care is covered by the mandatory health insurance. In the Dutch healthcare system, the GP acts as the gatekeeper to hospital services. Routine EMR data from primary care are a valuable source of information for research, healthcare organisation and population health as well as quality management.

For this study, we reused anonymously extracted routine care data[46] from 76 general practice centres that were affiliated with the Extramural Leiden University Medical Center Academic Network (ELAN) primary care network, the Netherlands. All practices were located in the greater Leiden and The Hague area.

For the current study, coded EMR patient data were used, including demographics, enrolment information, consultation types and dates, symptoms and diagnoses coded according to the International Classification of Primary Care (ICPC)[47] in the episode and contact registration (in the Netherlands, ICPC-1 is used with nationally relevant adjustments[48]); textual episode descriptions; coded information of laboratory tests, dates and results; Anatomical Therapeutic Chemical (ATC) classification[49] of medications and prescription dates; and coded correspondence with other healthcare professionals and dates. For this paper, the Strengthening the Reporting of Observational Studies in Epidemiology cross sectional reporting guidelines was used.[50]

### Study population

All patients enrolled for at least 1 year with one of the affiliated general practices between January 2014 and December 2018, who were born before 1989 (25 years of age) and born after 1914 (100 years of age) were included in the study. Length of enrolment was primarily determined on quarterly payment data. When payment data were unavailable or enrolment and unenrolment dates indicated that the patient was enrolled for a longer period, the enrolment and unenrolment dates were used.

### Identification methods

While data-driven research may circumvent healthcare professionals' difficulties with identifying patients at risk of PSS, the debate on definitions and terminology remains.[6] While some earlier developed definitions required physicians to classify patients primarily on the basis of exclusion of any medical explanation for the symptoms, recently developed classifications favour focusing on common behavioural similarities related to PSS instead.[6 20 51] The latter explicitly do not exclude patients with known medical illnesses. In line with these recent developments, our patient group is defined as having PSS when their complaints are not fully explained by established biomedical pathology. However, these symptoms and the accompanying behaviour, can also exist alongside other chronic physical conditions that are explained by established biomedical pathology. To reach the aim of our study, four methods were included (see table 1). Two methods (A and B) were based on identification methods used in previous studies, one was derived from these two existing methods (C), and one was based on expert knowledge about the available data in the ELAN-database (D). Method A identifies patients with CFS, FM and IBS based on their available ICPC codes (codes for CFS and FM are specific to the Dutch ICPC system)[26 41]; method B identifies patients with PSS-related symptoms which were extracted from a latent class analysis on symptoms highly prevalent in patients with PSS and has been previously used in research[39 40 52]; method C identifies patients based on PSS-related terminology in the episode description (the episode description is adjustable for GPs; that is, in case a GP registers A04.01, this automatically gives the description 'CFS', but the description can be adjusted to any term the GP prefers. Our available data were systematically searched by cross-checking ICPC codes and related descriptions),[27] and, method D identifies patients based on recorded results of the somatic symptoms subscale of the 4DSQ.[42] Additionally, besides exploring overlap between methods, all four methods were integrated, selecting all patients identified by any of the methods.

***Table 1.*** Description of methods for PSS identification.

| | Method A | Method B | Method C | Method D |
|---|---|---|---|---|
| **General PSS-related criteria** | Irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. | Frequent consultation for multiple PSS-related symptoms. | Reported PSS-related terminology.[a] | Somatic symptom subscale of the 4DSQ.[b] |
| **Criteria translated to EMR data** | ICPC codes for chronic fatigue syndrome (A04.01), fibromyalgia (L18.01), and irritable bowel syndrome (D93). | Symptoms based on the 'Robbins list'.[c] The symptoms have been linked to ICPC-codes. | Terminology is based on a cross-search of the data with ICPC codes from methods A and B. | The 4DSQ is a validated questionnaire available in EMRs of Dutch GPs. |
| **Duration/ cut-off** | At least 6 months, or at least 2 contact registrations. | At least 6 registrations with one or more relevant ICPC codes within a 6-month period. | At least 6 months. | A score of ≥ 20 on the somatic symptom subscale of the 4DSQ. |
| **Registration type** | Based on episode and contact registration. | Based on contact registration. | Based on description in the episode registration. | Laboratory test results. |

[a] Examples of included terms: somatization, psychosomatic, central sensitization, atypical low back pain, stress related pain, interstitial cystitis, extreme fatigue, tension headache: good CT, functional.
[b] Four-dimensional symptom questionnaire.[42]
[c] Robbins list: Back pain, joint pain, extremity pain, headaches, fatigue/weakness, sleep disturbance, difficulty concentrating, loss of appetite, weight change, restlessness, thoughts slower, chest pain, shortness of breath, palpations, dizziness, lump in throat, numbness, nausea, loose bowels, gas/bloating, constipation, abdominal pain.[52]

## Outcomes

For all methods we calculated the following outcomes: (1) number of patients with PSS and their demographics, (2) presence of chronic physical and mental illness, and (3) HCU. Demographic variables consist of gender and age in 2014. Presence of chronic physical or mental illness was defined based on the list of ICPC codes for chronic conditions, by the Dutch institute of research in primary care (Nederlands Instituut Voor onderzoek van de EersteLijnsgezondheidszorg).[53] HCU was operationalised using consult frequency, number of lab tests, number of prescribed medications and number of referrals.[43–45]

For all HCU frequencies, mean 1-year frequencies were calculated based on the total frequency during the study period, divided by the length of enrolment of the patient.

Mean consultation frequency was calculated based on the type of registration in the contact registration per patient, with the exclusion of administrative contacts (such as making appointments). Lab tests was calculated based on the number of referrals registered for each patient to a laboratory test centre. For the mean number of medications, ATC codes were reduced to four characters which specify up to the pharmacological group a medication belongs to.[49] Each unique pharmacological group registered in the patients EMR was recoded as one medication. Referrals are divided into primary care and secondary care referrals and each unique referral was recorded as one referral per patient.

### Data analysis

Statistical analyses were carried out using R (V.4.0.2).[54] First, patients were selected based on each unique identification method. Descriptive statistics were reported on gender, age, chronic mental and physical conditions, and HCU variables for each method. Second, in order to identify overlap between methods, the percentage of patients being selected by a combination of methods was explored and depicted in a Venn diagram. A graphical display of the number of patients selected by each method per general practice was produced and depicted in a histogram with reported skewness and kurtosis. patient and public involvement GPs were consulted during the development phase of the research design.

## Results

### Number of patients with PSS and their demographics per identification method

Table 2 shows an overview of the complete cohort which includes 168 682 primary care patients with a mean age of 51.4 (SD=16.4), of whom 52.9% are female. Patients were enlisted in their general practice for an average of 4.6 years (SD=1.0) between January 2014 and December 2018. The 4DSQ, used for identifying patients (method D), was administered and registered for 1102 (0.7%) patients of the total cohort from 2017 to 2019. The number of cases identified with each method separately varied between 482 (0.3%) for method D and 11 893 (7.0%) for method B. Integrating all methods identified 20 855 cases (12.3%).

***Table 2.*** Number of patients with PSS and their demographics per identification method

| | **Total cohort** | **Method A** | **Method B** | **Method C** | **Method D** | **All methods combined** |
|---|---|---|---|---|---|---|
| | **n (%) or Mean ± s.d.** | **n (%) or Mean ± s.d.** | **n (%) or Mean ± s.d.** | **n (%) or Mean ± s.d.** | **n (%) or Mean ± s.d.** | **n (%) or Mean ± s.d.** |
| **Patients** | 169,138 (100.0) | 8,407 (5.0) | 11,893 (7.0) | 5,574 (3.3) | 482 (0.3) | 20,855 (12.3) |
| **Female** | 89,432 (52.9) | 6,276 (74.7) | 8,020 (67.4) | 4,164 (74.7) | 340 (70.5) | 14,490 (69.5) |
| **Age** | 51.4 ± 16.4 | 48.6 ± 15.0 | 57.6 ± 18.2 | 49.6 ± 14.6 | 42.6 ± 12.0 | 53.6 ± 17.4 |
| **Years enrolled** | 4.6 ± 1.0 | 4.6 ± 0.9 | 4.5 ± 1.0 | 4.6 ± 0.9 | 4.7 ± 0.8 | 4.6 ± 1.0 |

Method A: patients with recorded FM, IBS, and/or CFS based on ICPC-codes;
Method B: patients with at least six ICPC codes that correspond to the Robbins list in any six-month period;
Method C: patients with reported PSS-related terminology;
Method D: patients with ≥ 20 points on the somatization subscale of the 4DSQ.

### Presence of chronic physical and mental illness per identification method

Cases selected by methods A, B and C are more likely to have a chronic physical condition than the total cohort (60.2% vs ≥66.9%). Cases selected by method B are most likely to have a chronic physical condition (79.4%). Cases selected by all four methods are more likely to have a chronic mental condition compared with the total cohort (18.2% vs ≥33.8%). Cases selected by method D are most likely to have a chronic mental condition (60.0%) (table 3).

***Table 3.*** Presence of chronic physical and mental conditions per identification method

| | Total cohort n (%) | Method A n (%) | Method B n (%) | Method C n (%) | Method D n (%) | All methods combined n (%) |
|---|---|---|---|---|---|---|
| **Chronic physical condition** | 101,868 (60.2) | 5,624 (66.9) | 9,446 (79.4) | 3,957 (70.0) | 280 (58.1) | 15,313 (73.4) |
| **Chronic mental condition** | 30,750 (18.2) | 2,838 (33.8) | 4188 (35.2) | 2020 (36.2) | 289 (60.0) | 7,080 (33.9) |

Method A: patients with recorded FM, IBS, and/or CFS based on ICPC-codes;
Method B: patients with at least six ICPC codes that correspond to the Robbins list in any six-month period;
Method C: patients with reported PSS-related terminology;
Method D: patients with ≥ 20 points on the somatization subscale of the 4DSQ.

## Health care utilization (HCU) per identification method

HCU is generally higher among cases selected by any of the methods, compared with the total cohort. Cases selected by method A, C and D show similar patterns regarding most of the HCU variables. Cases selected by method B show higher average frequencies on the HCU variables compared with cases selected by the other methods, except for primary care referrals, which are similar to cases selected by method D (0.17±0.21 and 0.17±0.19, respectively) (table 4).

***Table 4.*** Health care utilization per identification method

| | Total cohort Mean ± s.d. | Method A Mean ± s.d. | Method B Mean ± s.d. | Method C Mean ± s.d. | Method D Mean ± s.d. | All methods combined Mean ± s.d. |
|---|---|---|---|---|---|---|
| **Consult frequency (per year)** | 4.75 ± 5.43 | 7.74 ± 7.32 | 11.70± 9.47 | 8.21 ± 8.30 | 8.39 ± 5.89 | 9.42 ± 8.47 |
| **Lab tests (per year)** | 0.28 ± 0.50 | 0.50 (0.56 | 0.69 ± 0.88 | 0.51 ± 0.68 | 0.43 ± 0.56 | 0.57 ± 0.75 |
| **Medications (per year)** | 1.82 ± 1.88 | 2.65 ± 2.12 | 3.64 ± 2.70 | 2.81 ± 2.17 | 2.62 ± 1.78 | 3.10 ± 2.48 |
| **Primary care referrals (per year)** | 0.09 ± 0.15 | 0.14 ± 0.19 | 0.17 ± 0.21 | 0.15 ± 0.20 | 0.17 ± 0.19 | 0.15 ± 0.20 |
| **Secondary care referrals (per year)** | 0.30 ± 0.42 | 0.46 ± 0.54 | 0.62 ± 0.61 | 0.50 ± 0.57 | 0.48 ± 0.45 | 0.53 ± 0.57 |

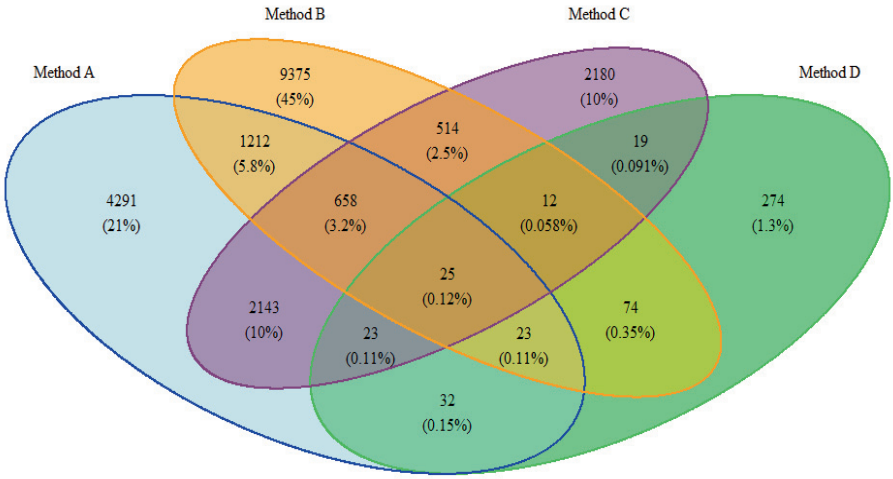
Method A: patients with recorded FM, IBS, and/or CFS based on ICPC-codes;
Method B: patients with at least six ICPC codes that correspond to the Robbins list in any six-month period;
Method C: patients with reported PSS-related terminology;
Method D: patients with ≥ 20 points on the somatization subscale of the 4DSQ.

## Overlap on outcomes between identification methods

In all, 12.3% of patients are selected by all methods combined, which is less than the cumulative percentage (15.6%) of patients selected by method A, B, C and D separately

(see table 2). Thus, 3.3% of the total cohort is selected by more than one method—which is a total of 26.8% of all selected patients. Relative to other methods (all ≤11.6%), patients are selected by method A and C are most likely to be selected by both methods (34.4%). The likelihood that patients selected by method D are also selected by any other methods is lowest (≤1.3%) (see figure 1 for an elaborate overview of overlap between all the methods).

***Figure 1***. Overlap between selected patient samples per identification method

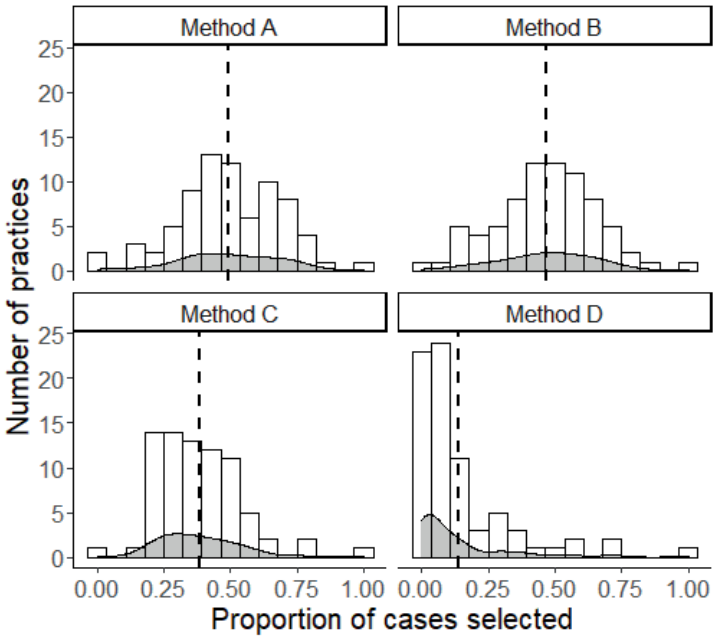



Method A: patients with recorded FM, IBS, and/or CFS based on ICPC-codes;
Method B: patients with at least six ICPC codes that correspond to the Robbins list in any six-month period;
Method C: patients with reported PSS-related terminology;
Method D: patients with ≥ 20 points on the somatization subscale of the 4DSQ.

## Overlap between practices for selecting patients with PSS

We also explored the proportion of cases selected by each general practice (n=76). Case selection based on method A and B is most evenly distributed between practices (skewness=−0.17 and −0.10, and kurtosis=3.01 and 3.06, respectively). For method C, a moderate left skewed distribution (skewness=0.99 and kurtosis=5.21) shows that many practices contribute a small number of cases and some practices contribute a moderately large number of cases. Method D is highly left skewed (skewness=2.22 and kurtosis=8.29), indicating that many practices contribute no cases or a limited number of cases, while few practices contribute a large number of cases (figure 2).

***Figure 2.*** Variation between practices in applying methods of registration




Method A: patients with recorded FM, IBS, and/or CFS based on ICPC-codes;
Method B: patients with at least six ICPC codes that correspond to the Robbins list in any six-month period;
Method C: patients with reported PSS-related terminology;
Method D: patients with ≥ 20 points on the somatization subscale of the 4DSQ.

## Discussion

### Statement of principal findings

This paper describes a comprehensive study on identifying patients with PSS in routine primary care data, in which four different identification methods are explored. The different methods identify a wide range in proportions of cases: from 0.3% selected by method D (ie, recoded 4DSQ assessments), to 7.0% selected by method B (ie, based on PSS-related ICPC codes and consult frequency). When all separate identification methods are combined, a total of 12.3% of the complete cohort is selected, of which 26.8% is selected by multiple methods. In line with findings from previous studies on PSS, selected cases are more often female (in all methods) and younger (in three out of four methods) compared with the total cohort (which approximates the general population). This study shows that the use of any single method will inevitably lead to underestimation of the number of patients with recognisable risk of PSS recognised.

Detailed analysis of the selected samples reveals some notable results. First, patients selected by any of the methods are generally more likely to have a chronic physical or mental condition, compared with the total cohort. These findings corroborate previous observations that PSS are highly prevalent in patients with chronic physical conditions and emphasises the undesirability of classifying PSS based on exclusion of a chronic physical condition.[14] Furthermore, in line with recommended practice to administer the 4DSQ among patients with psychological complaints,[42] cases selected by method D have a markedly high likelihood of having a chronic mental condition. Cases selected by method B are most likely to have a chronic physical condition, which indicates that differentiating which complaints are PSS and which complaints are strictly related to a physical condition may be most challenging for cases selected by method B.

Second, HCU is higher for all samples compared with the total cohort. However, HCU spikes and deviates for cases selected by method B, compared with all other cases. Several reasons for this could be plausible. Most notably, that high HCU is expected in this selected group since consultation frequency is part of the inclusion criteria for this method and increased consultation frequency implies higher frequencies for all HCU variables. The higher HCU is also presumed to be related to the heightened likelihood of

these cases to have a chronic physical condition. Finally, one could theorise that these patients seek healthcare more frequently because their PSS is not yet recognised. Remarkably, cases selected by method D, among whom chronic mental conditions spike, HCU is not much different from cases selected by method A (ie, CFS, FM and IBS) and C (ie, PSS-related terminology in episode description). Thus, even though cases selected by method D are more likely to have a chronic mental condition, HCU indicates that healthcare seeking behaviour in cases selected by methods A, C and D is more similar than in cases selected by method B.

Finally, our results show a relatively low likelihood that patients are selected by multiple methods. High variance between general practices in using one of the registration methods, especially method D, indicates that the limited overlap is explained by GPs not applying all methods equally. This is consistent with previous research which demonstrated high degrees of discordance between healthcare professionals regarding defining and classifying patients with PSS[27] and an ambiguous coding scheme for PSS.[27 37] From this finding we can conclude that the need for using either a single or multiple methods to identify PSS cases may depend on the aim of the identification. For instance, when calculating exact prevalence rates, using a single method will not be sufficient, since prevalence rates of PSS in the general Dutch population most likely range from 10% to 15%.[55] However, using a single method (eg, method C) may be sufficient to identify risk factors for persistence of PSS, although this should be confirmed by further research.

### Strengths and limitations

The results of this study should be viewed in context of several strengths and limitations. Using multiple methods to identify the PSS patient group, exploring their outcomes on a variety of clinically relevant variables, and exploration of general practice specific variations, results in a very comprehensive review. The use of a large set of routine EMR data from multiple general practices in a highly versatile area of the Netherlands increases ecological validity and generalisability to other populations. Additionally, the inclusion of patients with chronic conditions provides insight in PSS in the general population and gauges the immensity of the problem for healthcare. Nonetheless, the use of routine care data comes with challenges and limitations. While registration quality

is increasingly promoted and improved, it is reliant on many factors specific to the healthcare provider and general practice. Another limitation of this study is the lack of an external validation of the patient group. This seems primarily problematic for method B, which relies on ICPC codes which—while empirically related to PSS [52]—can also be fully explained by biomedical pathology. Notably, the small number of registrations of the 4DSQ in the EMRs reduces the usability of method D. Besides, since some ICPC codes (method A; A04.01 and L18.01), specific (Dutch) terminology (method C), and incorporation of questionnaires evaluating PSS-related problems (method D) are specific to Dutch EMRs, tailored solutions are needed to generalise the results to other countries.

### Implications for clinicians and future research

The current study provides unique insight into the complexity of identifying patients with PSS in routine care data. While the results indicate that current classification and coding of PSS is highly scattered, it shows that a data-based screening of patients with PSS in routine care data is possible. Depending on the desirable goal, single or multiple methods can be used for identification.

From a research perspective, in the first place, replicability of the methods to non-Dutch EMRs should be examined. Second, although the combination of method A, C and D improved earlier approaches towards accurate prevalence rate based on routine primary care data,[43] some steps still need to be taken to get accurate prevalence rates. Nonetheless, combining method A, C and D decreases the portion of patients with PSS that are misclassified as non-PSS, which may enhance the possibilities for data-driven predictive modelling of patients at risk of the broad spectrum of PSS. Finally, while it was beyond the scope of this study to investigate this further, our results regarding practice specific differences in registration may be specifically relevant for identifying GPs who need support for PSS consultations. Especially because previous research shows that a large group of GPs require additional support.[27] Future research should investigate whether the need for support can be linked or tailored to GPs with specific registration methods.

While the present study was primarily methodological, some clinical implications may be relevant to discuss which could enable data-based support for PSS identification (which

could promote awareness among GPs regarding PSS-risk). First, clinicians may need to improve registration of the 4DSQ, because this—per suggestion by our expert panel of GPs—is the most likely cause of the limited usability of the method for data-based identification. Alternatively, in line with the implications for research, since patients identified with method A, C and D are most likely on the clinicians' 'radar'—that is, they have a clear PSS-related indicator recorded, patients that are currently missed can be screened by method B. Method B is supported by previous studies which successfully used a similar method for screening routine care data for patients with PSS.[26,39,40] Subsequently, validated questionnaires such as the 4DSQ[42] or the SSD B-criteria scale (SSD-12)[4] can be used to identify those patients selected by method B who need additional attention/proactive intervention. Future research should be aimed at monitoring patients selected based on method B—both towards verifying the effectiveness of this method and whether merely identifying these patients influences the health trajectory of the patients, or gauging if other interventions are needed. Ultimately, all the above could encourage the use of advanced computer systems to support the diagnostic process and subsequent decision making in practice.[56]

## Conclusion

In all, the results indicate that the theory-driven methods identify different samples of patients with PSS. A combination of methods A, C and D can form a basis for identifying the full spectrum of patients with PSS, for example, for calculating prevalence rates. Henceforth, additional advanced (data-driven) methods and validation may help to create more sensitive algorithms. These algorithms might be used in clinical practice to increase awareness of physicians on the risk of PSS, thus potentially opening possibilities to proactive interventions. For method B, the relatively high number of cases with chronic physical conditions and HCU indicates the need for additional diagnostics. Further research should focus on investigating whether method B combined with subsequent screening can be a way to identify patients with unidentified PSS who are not yet on the GPs radar.

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# Chapter 5

## Predicting Persistent Somatic Symptom Onset with Mental Health-related Registrations in Primary Care

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## Abstract

**Background:** Somatic symptoms of common syndromes like irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), and fibromyalgia (FM) cannot be fully attributed to well-established biomedical pathology. General practitioners (GPs) experience difficulties in recognizing these syndromes and diagnosis is often delayed. This study assessed if routinely registered mental health registrations can predict IBS, CFS, and FM diagnoses, and whether the similar factors predict diagnosis of either syndrome.

**Method:** A longitudinal cohort design was employed using anonymously extracted registrations of 11,409 primary care patients in the Netherlands. Cases were allocated to syndrome related subsamples with 1:2 age and sex-matched non-cases. Potential predictors were available mental health-related registrations in the dataset (i.e., mental health-related ICPC-codes, referrals, and psychopharmaceuticals) registered prior to diagnosis. For predictive modelling, logistic LASSO regressions were applied.

**Results:** Classification performance of the models was fair ($AUC_{IBS}$ = .77) to good ($AUC_{CFS}$ = .82, $AUC_{FM}$ = .88). LASSO logistic regression retained 24, 10, and 20 predictors for IBS, CFS, and FM, respectively. Of the 25 predictors derived from the models, five were shared between all syndromes (i.e., anxiety, psychosis, addiction behaviour, and concentration disorders had positive predictive value and mental health-related referrals has negative predictive value).

**Conclusions:** Findings indicate that mental health-related registrations in primary care can accurately predict IBS, CFS, and/or FM diagnoses. Prediction rules derived from mental health-related registrations might be able to support GPs in identifying patients with PSS. Future studies should investigate whether distinct decision rules are needed for the different syndromes.

## Introduction

Persistent somatic symptoms (PSS) affect an estimate of 20.4 million people in Europe.[1] PSS is an umbrella term for specific or nonspecific somatic symptoms that cause distress or other serious disruptions in the patients' life.[2] These symptoms cannot be (fully) attributed to biomedical pathophysiology.[3–6] Although definitions may vary somewhat according to their historic timing or related discipline, the term PSS is often used interchangeably with other terms such as medically unexplained (physical) symptoms, or the psychiatric diagnosis of somatic symptom disorder (SSD),[2] or symptom clusters may be diagnosed in PSS subtypes. Common PSS subtypes are irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS) and fibromyalgia (FM) and have a prevalence of 11.2%,[7] 1%,[8] and up to 6.6%,[9] respectively. The origin of these syndromes is often attributed to a complex interplay between factors belonging to multiple domains of the biopsychosocial model.[10,11]

The three syndromes are related to a reduced quality of life due to the bothersome symptomology.[12–14] IBS affects the gastrointestinal system, causing pain in the abdominal area and altering bowel functioning.[12] CFS is sometimes related to a sequel of a viral infection[15] and is marked by intense fatigue that is not alleviated by rest.[13] FM is characterized by widespread musculoskeletal pain related to rheumatic disease and is historically diagnosed by exclusion of any other cause by rheumatologists.[9] All three syndromes affect patients' lives greatly. Patients may suffer from suicidal ideation,[12] or may for instance receive invasive treatments,[16] experience severe physical and economic disability,[17] and social and occupational lives may be impacted.[18] IBS, CFS, and FM have been associated with a variety of mental health problems.[13,14,19] For instance, Monden et al.[20] identified anxiety and depression as risk factors for IBS, CFS, and FM onset. Furthermore, research indicates that mental health problems not only predict the syndromes but that the syndromes and mental health problems exacerbate each other.[21–23] Overall, the nature of associations between PSS and mental health problems is manifold.

Recognition and diagnosis of PSS and PSS-related syndromes such as IBS, CFS, and FM is often delayed for a long time.[24–26] Research found that in primary care, which is generally

the first contact of patients with somatic complaints, GPs experience difficulties with identifying PSS due to a great number of barriers.[3,27,28] To date, GPs are trained according to the biomedical model of disease and may consider diagnosing and treating biomedical disease as their fundamental task.[29] Furthermore, the biomedical model requires GPs to either find a physical or psychological origin of symptoms. Due to the multidomain complexity of its origin this may be especially problematic for PSS and be part of the reason why early recognition is hampered. Additionally, biomedical focus, high workload amongst GPs, and reluctance of patients to discuss,[30] may result in under-recognition and -registration of mental health problems in primary care.[31]

As follows, the primary aim of this study is to examine whether mental health registrations in primary care are sufficiently registered to predict the common PSS syndromes with clinical codes in primary care (i.e., IBS, CFS, and FM). If this is possible, the models could possibly be used to produce a clinical decision rule, or an algorithm to be used in daily practice, that may support GPs with early identification and timely treatment of PSS. This is especially desirable because delayed identification may not only increase healthcare utilization and costs, but may also hamper treatment.[32] Secondarily, this study investigated the three syndromes in parallel to explore the overarching and distinct factors associated with syndrome onset. This is especially interesting in light of the ongoing debate on the distinctness of the syndromes,[4,10,20,33–36] and give insight in the necessity of separate prediction rules for each syndrome or possible common factors that can be targeted by corresponding treatments.

## Methods

### Study design and participants

A population-based cohort study was conducted based on routinely collected primary care data from the Extramural LUMC academic network (ELAN), of Leiden University Medical Center (LUMC) in the Netherlands. As part of Dutch mandatory insurance for each citizen, primary care is free of charge for inhabitants of the Netherlands. The ELAN-data warehouse enables access to anonymized and coded electronic medical record (EMR) data of an increasing number of general practices centres located in the Leiden and The Hague area. For the present study, we were able to access anonymized data from 76 practice centres. We reused coded demographical data (age and sex), contact registrations, coded symptomatology, and diagnoses (according to the international classification of primary care ICPC, developed for the World academic organization of primary care (WONCA)), coded prescriptions (based on anatomical therapeutic chemical (ATC) codes developed for the world health organization (WHO), and quarterly payment data.

The data contained 306,859 Dutch primary care patients aged 48 years (*SD* = 17.9) on average during 2010. Patients with IBS, CFS, and FM represent the PSS cohorts. Patients with more than one of these syndromes were excluded. The screening of cases was conducted in accordance with findings by Kitselaar et al.[37]: a combination of WONCA ICPC codes and terminology related to IBS, CFS, and FM in an episode (i.e., general disease registration) description (i.e., a combination of methods A and C from Kitselaar et al.[37], with primary focus on IBS, CFS, and FM). To enhance the reliability of a patient having received a diagnosis, only patients with at least two registrations of each syndrome were included. Furthermore, to be included, patients had to be registered with their GP for at least five years (for PSS cohorts prior to first PSS registration). Length of registration was determined based on quarterly payment data. Finally, three PSS subgroups were constructed according to each of the syndromes. The non-PSS cohorts were created with two age and sex-matched patients without IBS, CFS, or FM registrations per PSS patient.

Thereafter, the predictive values of mental health problem indicators for each PSS cohort were determined. Then, the similarities and differences of the resulting prediction models were explored regarding shared and syndrome-specific predictors. Since the goal of the resulting model was to predict PSS, indicators of mental health problems were only included in the analyses if they were registered before the first PSS registration.

## Measures

### *Predictors*

Three methods were used to identify mental health problems. Firstly, mental health problems were identified based on the Dutch version of the WONCA ICPC codes (i.e., most codes under P, all codes under T06 and Z29.01) and terminology (e.g., depression, dysthymia, depressed, etc.) in the episode registrations (see appendix A).[38] Secondly, presence of mental health problems was determined via referral to mental health specialists. Thirdly, the use of psychopharmaceuticals was determined via registrations of their corresponding ATC codes (i.e., N06, A08A, N05; see appendix B for more details). To increase the accuracy in parameter estimation, certain registrations of mental health problems were merged before conducting the analyses. The merging decisions were based on topical similarity (e.g., depressiveness, depression, post-partum depression, bipolar depression and dysthymia formed the candidate predictor 'depression').

### *Outcomes*

IBS, CFS, and FM patients were be identified via WONCA ICPC code registrations (D93, A04.01, and L18.01, respectively) and corresponding terminology (e.g., Dutch versions of IBS: spastic colon, irritable bowel; CFS: chronic fatigue, persistent fatigue, FM: fibromyalgia, widespread pain) in free text descriptions of the episode registrations.

## Statistical analyses

R version 4.0.1 (R Core Team, 2020) was used for pre-processing and analyses. Separate prediction models were constructed for IBS, CFS, and FM with least absolute shrinkage and selection operator (LASSO) logistic regression. The penalty term (L1 regularization) in this type of modelling helps to find the best possible balance between bias and variance of a prediction model.[39] It avoids overfitting by shrinking regression coefficients which works especially well if the effect is small, if there are many predictors,[39] and if

multicollinearity is to be expected.[40] Splitting the data into training and test sets preserves generalizability to other samples.[39]

The data of each sub-sample was split: 80% of the data formed the training sets, and 20% formed the test sets. The training sets were used to fit the regression models, providing estimated regression coefficients. To select the available predictor variables and their regression coefficients (Odds Ratio (*OR*)), lambda was determined via 10-fold cross-validation on the training data. To provide insights into the stability of the model's predictors we constructed 100 bootstrap samples per PSS sub-type and determined the rate at which each predictor was retained. After constructing the prediction models on the training data, the models were tested on the test data for their classification performance. Receiver operating curves (ROCs) were plotted to examine the area under the curve (AUC).

## Results

The three samples consisted of an IBS cohort (3,059 cases), a CFS cohort (114 cases), and an FM cohort (630 cases), which were sex and age-matched with non-PSS patients (1:2 ratio). The majority of IBS, CFS, and FM samples consisted of 70.9%, 74.6%, and 89.2% female patients, respectively. Mean ages were relatively similar across samples (IBS=46.1±15.2; CFS=44.7±13.1; FM=47.0±13.6). The baseline characteristics are displayed across the training and test sets for all samples, tested with Chi-square and a t-test, do not show differences (Table 1). Frequencies of each candidate predictor per sample have been checked (Appendix C).

***Table 1.*** Baseline Characteristics

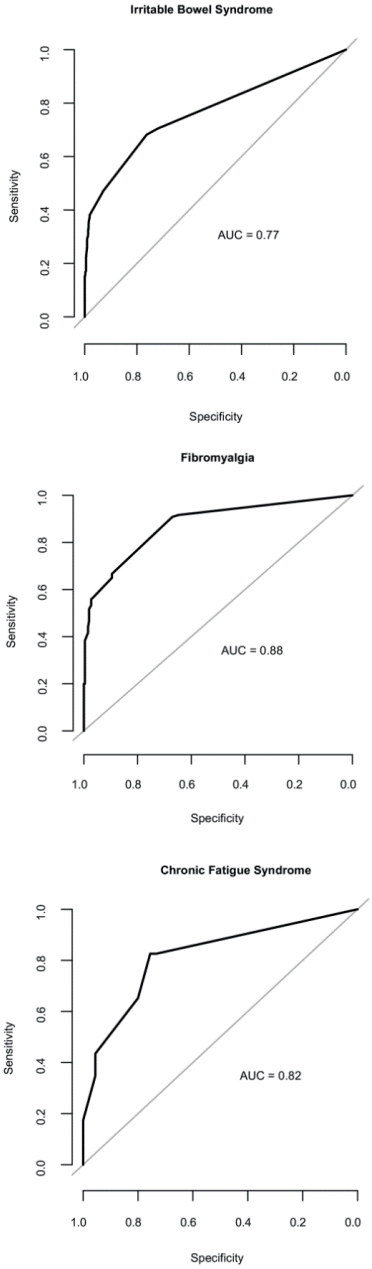
| | **IBS study** | | **CFS study** | | **FM study** | |
|---|---|---|---|---|---|---|
| | **Train** | **Test** | **Train** | **Test** | **Train** | **Test** |
| ***n*** | **7341** | **1836** | **274** | **68** | **1512** | **378** |
| **PSS frequency *n* (%)** | 2447 (33.3) | 613 (33.4) | 91 (33.2) | 23 (33.8) | 510 (33.7) | 120 (31.7) |
| **Mean age in years (*SD*)** | 46.1 (15.2) | 45.4 (15.4) | 44.7 (13.2) | 46.8 (12.5) | 47.0 (13.5) | 46.1 (13.7) |
| **Female *n* (%)** | 5196 (70.8) | 1308 (71.2) | 201 (73.4) | 54 (79.4) | 1344 (88.9) | 342 (90.5) |

*Note*. Characteristics are displayed separately for training and test datasets.
IBS = Irritable bowel syndrome, CFS = chronic fatigue syndrome, FM = fibromyalgia

## Model performance

When testing the prediction models on the test sets, the classification performance was fair for IBS ($AUC_{IBS}$ = .77), and good for CFS and FM ($AUC_{CFS}$ = .82; $AUC_{FM}$ = .88,) (see Figure 1 for ROCs). The misclassification rate of patients as having or not having IBS, CFS, or FM reached 26%, 24%, and 25%, respectively.

***Figure 1.*** Receiver Operating Curves (ROC) of Prediction Model's Classification Performance




*Note.* Figure depicts how the predictive models performed on the test dataset

### Predictive Models for PSS

In total, the predictive models retained 27, 12, and 22 predictors after L1 regularization for IBS, CFS, and FM, respectively. The five strongest predictors for IBS were registrations of sexual dysfunction (OR = 4.0), irritability (OR = 3.7), posttraumatic stress disorder (PTSD) (OR = 3.7), feeling old (OR = 3.5), and adult life stage problem (OR = 3.3). The five strongest predictors for CFS were registrations of concentration disorders (OR = 2.9), not-specified psychological symptoms (OR = 2.4), functional disability due to mental illness (OR = 2.2), psychoses (OR = 2.0), and anxiety (OR = 1.8). The five strongest predictors for FM were registrations of neurasthenia (OR = 3.1), depression (OR = 2.6), psychoses (OR = 2.5), concentration disorders (OR = 2.0), and sexual dysfunction (OR = 1.9) (Table 2).

### Explorative Comparison of predictive models for IBS, CFS, and FM

Nine predictors were relevant for predicting all syndromes. Out of these nine, four predictors increased the likelihood of all PSS subtypes: anxiety, psychoses, addiction (excl. alcohol), concentration disorders, and referrals to mental health care decreased the likelihood of all PSS subtypes. The remaining four predictors were inconsistent across models. Of these, registrations of personality disorders and not specified psychological symptoms increased the likelihood of IBS but decreased the likelihood of CFS and FM. Psychopharmaceutical prescription decreased the likelihood of IBS while increasing the likelihood of CFS and FM. Lastly, depression increased the likelihood of IBS and FM, and decreased the likelihood of CFS.

The models for IBS and FM had a further nine predictors in common. Four of these increased the likelihood of IBS and FM: registrations of suicidality, PTSD, burn-out, sexual dysfunction, not specified mental disorder. Three decreased the likelihood of IBS and FM: senile dementia/Alzheimer's, neurasthenia, and fear of mental illness. Finally, alcohol abuse showed contradictory results, by increasing the likelihood of IBS and decreasing the likelihood of FM. IBS has the highest number of unique predictors (*n*=6). Registrations of eating disorders, stuttering, irritability, feeling old, and adult life stage problems increased the likelihood of IBS while mental disability decreased this likelihood. Unique predictors for FM (*n*=2) were registrations of delirium and developmental issues

increasing the likelihood of FM. CFS had one unique predictor: registration of functional disability due to mental illness increased the likelihood of CFS.

***Table 2.*** Odds Ratio of Coefficients per Prediction Model determined via LASSO regression

| **Predictors** | **IBS [a]** | **CFS [b]** | **FM [c]** |
|---|---|---|---|
| **Total *n*** | **24** | **10** | **20** |
| Intercept | -1.5 | -1.5 | -2.0 |
| **Mental health referral [d] (%*)** | 0.6 (100) | 0.9 (95) | 0.8 (100) |
| **Psychopharmaceuticals [e] (%*)** | 0.8 (100) | 1.1 (100) | 1.3 (100) |
| **Depression [f] (%*)** | 2.5 (100) | 0.9 (96) | 2.6 (100) |
| **Suicidality [g] (%*)** | 2.1 (100) | (48) | 1.4 (100) |
| **Anxiety [h] (%*)** | 2.8 (100) | 1.8 (97) | 2.5 (100) |
| **Posttraumatic stress disorder [i] (%*)** | 3.7 (100) | (9) | 2.1 (100) |
| **Burn-out [j] (%*)** | 2.3 (100) | (24) | 1.1 (75) |
| **Psychoses [k] (%*)** | 2.0 (100) | 2.0 (91) | 1.2 (94) |
| **Addiction (excl. alcohol) [l] (%*)** | 2.2 (100) | 1.2 (89) | 1.6 (100) |
| **Alcohol abuse [m] (%*)** | 1.6 (100) | (0) | 0.7 (70) |
| **Eating disorders [n] (%*)** | 1.4 (91) | (0) | (2) |
| **Sexual dysfunction [o] (%*)** | 4.0 (100) | (0) | 1.9 (88) |
| **Concentration disorders [p] (%*)** | 2.3 (100) | 2.9 (98) | 2.0 (100) |
| **Senile dementia/Alzheimer's [q] (%*)** | 0.01 (75) | (0) | 0.4 (65) |
| **Delirium [r] (%*)** | (0) | (0) | 1.2 (65) |
| **Developmental issues [s] (%*)** | (51) | (0) | 1.2 (73) |
| **Mental disability [t] (%*)** | 0.2 (47) | (0) | (0) |
| **Functional disability due to mental illness [u] (%*)** | (24) | 2.2 (61) | (31) |
| **Stuttering [v] (%*)** | 2.8 (69) | (0) | (0) |
| **Neurasthenia [w] (%*)** | 2.6 (100) | (59) | 3.1 (100) |
| **Personality disorders [x] (%*)** | 1.2 (100) | 0.6 (65) | 0.2 (58) |
| **Irritability [y] (%*)** | 3.7 (100) | (0) | (2) |
| **Feeling old [z] (%*)** | 3.5 (60) | (0) | (0) |
| **Adult life stage problem [aa] (%*)** | 3.3 (74) | (0) | (0) |
| **Not specified mental disorder [ab] (%*)** | 2.6 (100) | (0) | 1.6 (95) |
| **Not specified psychological symptoms [ac] (%*)** | 2.3 (100) | 2.4 (66) | 0.6 (75) |
| **Fear of mental illness [ad] (%*)** | 0.1 (64) | (0) | 0.01 (41) |

*Note.* Textual episode descriptions according to ICPC codes of predictors can be found in appendix A.

*Percentage of bootstrap samples that resulted in the coefficient being included in the model

[a] Irritable bowel syndrome; [b] chronic fatigue syndrome; [c] fibromyalgia; [d] correspondence with mental health professional; [e] anti-depressants, psychostimulants, psycholeptics and psychoanaleptics, anti-dementia drugs, phentermine, anti-psychotics, anxiolytics, hypnotics and sedatives (ATC codes: N06, A08A, N05); [f] ICPC: P03, P73.02, P76, P76.01, P73.02; [g] ICPC: P02, P77, P77.01; [h] ICPC: P01, P74, P74.01, P74.02, P79, P79.01, P79.02; [i] ICPC: P02.01; [j] ICPC: Z29.01; [k] ICPC: P71, P72, P73, P98; [l] ICPC: P17, P18, P19, P19.01, P19.02, P80.02; [m] ICPC: P15, P15.01, P15.02, P15.05, P15.06, P16; [n] ICPC: T06, T06.01, T06.02; [o] ICPC: P07, P08; [p] ICPC: P20, P21; [q] ICPC: P70, P70.01, P70.02; [r] ICPC: P71.04; [s] ICPC: P23, P24, P24.01, P24.02, P24.03; [t] ICPC: P85, P99.01; [u] ICPC: P28; [v] ICPC: P10, P10.01, P10.02; [w] ICPC: P78; [x] ICPC: P80, P80.01; [y] ICPC: P04; [z] ICPC: P05; [aa] ICPC: P25; [ab] ICPC: P99.; [ac] ICPC: P29; [ad] ICPC: P27

## Discussion

This study provides valuable insight into the usability and predictive value of mental health-related registration in primary care for the common PSS (i.e., IBS, CFS, and FM). Findings show that registrations such as mental health-related symptoms (e.g., registrations of depression and anxiety), referrals to mental health specialists, and psychopharmaceutical prescription, are predictive of IBS, CFS, and/or FM. Some predictors are shared by all models (e.g., anxiety, psychoses, addiction, concentration disorders); others were unique to a single model (e.g., eating disorders for IBS, functional mental disability for CFS, and delirium for FM). Based on shared predictors, IBS and FM had the most similar prediction models. While most of the shared predictors are the same across models, some predictors increase the likelihood of one PSS subtype while decreasing the likelihood of another subtype (e.g., depression increased the chance of IBS and FM but decreases the chance of CFS). Though they did not focus on mental health problems alone, Monden et al.'s[20] findings support predictors being only partly shared across syndromes. Interestingly, despite the distinctions in IBS and FM symptomology, their study corroborates our finding that IBS and FM show the most similar predictors and point towards some shared aetiology. Overall, this study shows that mental health registrations in primary care data can predict IBS, CFS, and FM with clinically relevant accuracy.

While other studies have successfully predicted IBS, CFS, and/or FM,[41-43] this is, to our knowledge, the first study on PSS using EMR data and have a primary focus on mental health registrations. Generally, our findings that registrations of mental health problems are predictive of IBS, CFS, and FM onset is in line with associative (see for example [44-46]) and prediction studies (see for example [20,47]) based on non-EMR data. For instance: Ju et al.,[48] and Ciccone et al.,[49] who showed that PTSD predicted FM and IBS onset; Hod et al.[50] found burnout to be associated with IBS; Raphael et al.[45] found an association between depression and anxiety and FM; and Daniels et al.[51] found CFS to be associated with anxiety. In contrast, Bhui et al.[52] identified depression as a risk factor for CFS while the *OR*s in our CFS model indicates a lower likelihood of CFS in case of a depression registration. Similarly, while previous studies found either positive [53] or no association

between CFS and personality disorders,[54,55] our study suggests a negative predictive effect of personality disorders on CFS. Furthermore, our results show that registration of personality disorders is a positive predictor for IBS but a negative predictor for FM. Although these were association studies that did not focus on predicting onset, their findings may imply that registrations in primary care EMR data are suboptimal to investigate PSS aetiology. This could be related to the proposed under-registration of mental health problems in primary care. Finally, while psychopharmaceuticals and referrals to mental health care indicate mental health treatment and thus mental health problems in a patient, both only increased the likelihood of CFS and FM but not IBS. Research has shown that mental health treatments are effective for PSS [56-58] and the findings for IBS may therefore indicate a potential preventative or protective effect for developing PSS. However, the results for CFS and FM may dispute this argument so this discrepancy should be further investigated.

The study findings are highly valuable considering its various strengths. Firstly, the sample size (n=11,409) and temporal nature of the data increased the possibility of discovering relevant candidate predictors. Secondly, exploring the differences between models of each subtype gives insight into overarching and distinct aetiology of PSS subtypes. Finally, the design of the study gives insight into mental health-related registrations in primary care and their general usability for EMR research. Additionally, certain limitations must be considered. Firstly, within primary care, the precision of the predictive models may be impacted by differences in registration behaviour of GPs.[27,59] Second, since diagnosing PSS is often delayed,[24,25] we cannot ascertain prediction of PSS onset, but rather of PSS registration/identification by GPs. However, this limitation stipulates the high relevance of this study since results might assist in earlier identification by GPs.

This study has implications for future research and for interventions in clinical practice. Future research should investigate the feasibility of implementing the prediction models into clinical decision rules. Such rules would be especially relevant to GPs and ideally contribute to earlier identification of syndromes. In addition, while findings add to the knowledge on distinct and overarching aetiology of the syndromes, a study comparing

(high quality) empirical data with EMR data from routine clinical practice is needed to understand the validity of the findings regarding individual predictors. Moreover, lower performance of the IBS model could be investigated by evaluating the relationship between length of diagnostic delay between the syndromes.[60] This may be especially relevant due to the nature of the data. For instance, patients with IBS may have fewer consultations and therefore show fewer data to draw predictors from.

To conclude, non-supplemented primary care registrations of certain mental health problems are suitable for predicting the diagnosis of IBS, CFS, and/or FM. Registration-based predictors of the PSS syndromes show that there are distinct and overarching aspects. Furthermore, based on shared predictors IBS and FM had the closest prediction models while IBS and CFS models were the most dissimilar. Future research should examine how a clinical decision rule using mental health-related registrations can assist GPs in identifying patients sooner and whether distinct decision rules are needed for the different syndromes.

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## Appendixes

***Appendix A.*** *Candidate predictors and ICPC codes and textual (episode) descriptors used for identification*

| Psychological symptoms [a] | ICPC codes [b] | Episode description [c] |
|---|---|---|
| **Nervous feeling** | P01 | Anxious, nervous, tense |
| **Crisis** | P02 | Crisis, stress |
| **Posttraumatic stress disorder** | P02.01 | Posttraumatic stress, posttraumatic stress disorder |
| **Depressive feeling** | P03 | Down, depressive |
| **Irritability** | P04 | irritable, irritability, angry |
| **Feeling old** | P05 | Feeling old, behaving old |
| **Libido reduction** | P07 | Libido loss, libido reduction |
| **Sexual satisfaction reduction** | P08 | Sexual satisfaction loss, sexual satisfaction loss |
| **Sexual preference concerns** | P09 | Concerns sexual preference, concerns sexuality |
| **Gender incongruity** | P09.01 | Gender incongruity, gender dysphoria |
| **Stuttering** | P10(.01,.02) | Stutter, tics, stereotype |
| **Chronic alcohol abuse** | P15 | Chronic alcohol abuse |
| **Alcoholism** | P15.01 | Alcoholism |
| **Delirium tremens** | P15.02 | Delirium tremens |
| **Problematic alcohol use** | P15.05 | Problematic alcohol use |
| **Binge drinking** | P15.06 | Binge drinking |
| **Acute alcohol abuse** | P16 | Acute alcohol abuse, intoxication |
| **Tobacco use** | P17 | Tobacco use |
| **Medication abuse** | P18 | Medication abuse |
| **Drug abuse** | P19 | Drug abuse |
| **Abuse soft drugs** | P19.01 | Abuse soft drugs |
| **Abuse hard drugs** | P19.02 | Abuse hard drugs |
| **Concentration disorders** | P20 | Memory-, concentration-, orientation problem |
| **Attention deficit hyperactivity disorder** | P21 | Overactive, overactive syndrome |
| **Other concerns adolescent's behavior** | P23 | Concerns adolescent's behavior |
| **Specific learning problem** | P24 | Specific learning problem |
| **Dyslexia** | P24.01 | Dyslexia, dyslexic |
| **Specific developmental disorder** | P24.02 | Speech development disorder |
| **Motor development disorder** | P24.03 | Motor development problem |
| **Adult life stage problem** | P25 | Adult life stage problem |
| **Fear of mental illness** | P27 | Fear of mental illness |
| **Disability** | P28 | Functional disability, handicap |
| **Other psychological symptoms** | P29 | psychological symptoms/complaints |

***Appendix A.*** Candidate predictors and ICPC codes and textual (episode) descriptors used for identification (continued)

| Psychological symptoms [a] | ICPC codes [b] | Episode description [c] |
|---|---|---|
| **Senile dementia/Alzheimer's** | P70 | Senile dementia, Alzheimer |
| **Alzheimer's disease** | P70.01 | Alzheimer's disease |
| **Multi-infarct dementia** | P70.02 | Multi-infarct dementia |
| **Other organic psychoses** | P71 | Organic psychoses |
| **Delirium** | P71.04 | Delirium |
| **Schizophrenia** | P72 | Schizophrenia |
| **Affective psychosis** | P73 | Affective psychosis |
| **Bipolar disorder** | P73.02 | Bipolar, bipolar depression |
| **Anxiety disorder** | P74 | Anxiety disorder, anxiety state |
| **Panic disorder** | P74.01 | Panic disorder, panic attacks |
| **Generalized anxiety** | P74.02 | Generalized anxiety |
| **Depression** | P76 | Depression |
| **Postpartum depression** | P76.01 | Postpartum depression |
| **Dysthymia** | P76.02 | Dysthymia, dysthymic |
| **Suicide attempt** | P77(.01) | Suicide attempt, suicidality |
| **Neurasthenia** | P78 | Neurasthenia |
| **Other neuroses** | P79 | Neuroses, other neuroses |
| **Phobia** | P79.01 | Phobia |
| **Obsessive compulsive disorder** | P79.02 | Compulsive neuroses |
| **Personality disorder** | P80 | Personality disorder |
| **Borderline personality disorder** | P80.01 | Borderline personality disorder, borderline |
| **Gambling addiction** | P80.02 | Gambling addiction |
| **Mental disability** | P85 | Mental handicap, intellectual handicap |
| **not specified psychoses** | P98 | Other psychoses, not specified psychoses, psychoses |
| **Other mental disorders** | P99 | Other psychological disorder |
| **Autism** | P99.01 | Autism, autism spectrum |
| **Adjustment disorder** | P99.02 | Adjustment disorder |
| **Anorexia nervosa, bulimia** | T06 | Anorexia nervosa, bulimia |
| **Anorexia nervosa** | T06.0 | Anorexia nervosa |
| **Bulimia** | T06.02 | Bulimia |
| **Burn-out** | Z29.01 | Burn-out |

*Note.* In cases where the data entries of classification of primary care codes did not correspond to the textual episode descriptions, the textual episode entry was the deciding factor for the variable identification.

[a] Candidate predictors resembling psychological symptoms; [b] ICPC codes corresponding to the candidate predictors and were used for screening the data set; [c] the textual episode descriptions that correspond to the candidate predictors and were used for screening the data set, since the data stems from Dutch general practitioners all terms are translated to Dutch.

***Appendix B.*** Psychopharmaceuticals and respective codes included in the variable

| Psychopharmaceutical drug | Third level ATC code |
|---|---|
| **Anti-depressants** | N06A |
| **Psychostimulants, agents for ADHD treatment, and nootropics** | N06B |
| **Psycholeptics and psychoanaleptics in combination** | N06C |
| **Anti-dementia drugs** | N06D |
| **Phentermine** | A08A |
| **Anti-psychotics** | N05A |
| **Anxiolytics** | N05B |
| **Hypnotics and sedatives** | N05C |

*Note*. Adapted from https://www.whocc.no/atc_ddd_index/

***Appendix C.*** Frequencies of predictors per sample

| | IBS [a] | CFS [b] | FM [c] |
|---|---|---|---|
| **Psychopharmaceuticals [d]** | 3356 (36.6%) | 110 (32.2%) | 874 (46.2%) |
| **Mental health referral [e]** | 1589 (17.3%) | 61 (17.8%) | 373 (19.7%) |
| **Anxiety [f]** | 497 (5.4%) | 17 (5.0%) | 134 (7.1%) |
| **Eating disorders [g]** | 9 (0.1%) | 0 (0%) | 1 (0.1%) |
| **Depression [h]** | 417 (4.5%) | 14 (4.1%) | 154 (8.1%) |
| **Suicidality [i]** | 116 (1.3%) | 5 (1.5%) | 45 (2.4%) |
| **personality disorders [j]** | 59 (0.6%) | 2 (0.6%) | 21 (1.1%) |
| **Alcohol abuse [k]** | 51 (0.6%) | 1 (0.3%) | 6 (0.3%) |
| **Addiction [l]** | 225 (2.5%) | 7 (2.0%) | 64 (3.4%) |
| **Senile dementia/Alzheimer's [m]** | 14 (0.2%) | 0 (0%) | 2 (0.1%) |
| **Sexual dysfunction [n]** | 23 (0.3%) | 1 (0.3%) | 7 (0.4%) |
| **Psychoses [o]** | 28 (0.3%) | 2 (0.6%) | 10 (0.5%) |
| **Developmental issues [p]** | 8 (0.1%) | 0 (0%) | 3 (0.2%) |
| **Gender/sexuality concerns [q]** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Concentration disorders [r]** | 99 (1.1%) | 5 (1.5%) | 25 (1.3%) |
| **Disability due to mental illness [s]** | 5 (0.1%) | 1 (0.3%) | 1 (0.05%) |
| **Mental disability [t]** | 10 (0.1%) | 0 (0%) | 2 (0.1%) |
| **Burn-out [u]** | 32 (0.3%) | 3 (0.9%) | 8 (1.3%) |
| **Adjustment disorder [v]** | 1 (0.01%) | 0 (0%) | 0 (0%) |
| **Posttraumatic stress disorder [w]** | 42 (0.5%) | 2 (0.6%) | 23 (1.2%) |
| **Irritability [x]** | 28 (0.3%) | 2 (0.6%) | 2 (0.1%) |
| **Feeling old [y]** | 2 (0.02%) | 0 (0%) | 0 (0%) |

***Appendix C.*** Frequencies of predictors per sample (continued)

| | IBS [a] | CFS [b] | FM [c] |
|---|---|---|---|
| **Stuttering [z]** | 5 (0.1%) | 0 (0%) | 0 (0%) |
| **Adult life stage problem [aa]** | 4 (0.04%) | 0 (0%) | 0 (0%) |
| **Fear of mental illness [ab]** | 4 (0.04%) | 0 (0%) | 3 (0.2%) |
| **Other psychological symptoms [ac]** | 51 (0.6%) | 4 (1.2%) | 14 (0.7%) |
| **Delirium [ad]** | 2 (0.02%) | 0 (0%) | 1 (0.05%) |
| **Neurasthenia [ae]** | 192 (2.1%) | 12 (3.5%) | 50 (2.6%) |
| **Other mental disorder [af]** | 41 (0.4%) | 2 (0.6%) | 8 (0.4%) |

*Note.* Textual episode descriptions according to ICPC codes of predictors can be found in appendix A.

[a] Irritable bowel syndrome; [b] chronic fatigue syndrome; [c] fibromyalgia; [d] anti-depressants, psychostimulants, psycholeptics and psychoanaleptics, anti-dementia drugs, phentermine, anti-psychotics, anxiolytics, hypnotics and sedatives (respective ATC codes: N06, A08A, N05); [e] correspondence with mental health professional; [f] ICPC: P01, P74, P74.01, P74.02, P79, P79.01, P79.02; [g] ICPC: T06, T06.01, T06.02; [h] ICPC: P74.01; [i] ICPC: P02, P77, P77.01; [j] ICPC: P80, P80.01; [k] ICPC: P15, P15.01, P15.02, P15.05, P15.06, P16; [l] ICPC: P17, P18, P19, P19.01, P19.02, P80.02; [m] ICPC: P70, P70.01, P70.02: [n] ICPC: P07, P08; [o] ICPC: P71, P72, P73, P98; [p] ICPC: P23, P24, P24.01, P24.02, P24.03; [q] ICPC: P09, P09.01; [r] ICPC: P20, P21; [s] ICPC: P28; [t] ICPC: P85, P99.01; [u] ICPC: Z29.01; [v] ICPC: P99.02; [w] ICPC: P02.01; [x] ICPC: P04; [y] ICPC: P05; [z] ICPC: PP10, P10.01, P10.02; [aa] ICPC: P25; [ab] ICPC: P27; [ac] ICPC: P29; [ad] ICPC: P71.04; [ae] ICPC: P78; [af] ICPC: P99.

The best way to take care of the future,
is to take care of
the present moment.
**- Thich Nhat Hanh**

# Chapter 6

## Early Identification of Persistent Somatic Symptoms in Primary Care: data- and theory-driven predictive modelling based on electronic medical records of Dutch general practices

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## Abstract

**Objective:** The present study aimed to early identify patients with persistent somatic symptoms (PSS) in primary care by exploring data-based approaches.

**Design/setting:** A cohort study based on routine primary care data, from 76 general practices in the Netherlands was executed for predictive modelling.

**Participants:** Inclusion of 94,440 adult patients was based on: at least 7-year general practice enrolment, having more than one symptom/disease registration, and >10 consultations.

**Methods:** Cases were selected based on a first PSS registration in 2017-2018. Candidate predictors were selected 2-5 years prior to first registration of PSS and categorized into data-driven approaches: symptoms/diseases, medications, referrals, sequential patterns, and changing lab results; and theory-driven approaches: constructed factors based on literature and terminology in free text. Of these, 12 candidate predictor categories were formed and used to develop prediction models by cross-validated LASSO regression on 80% of the dataset. Derived models were internally validated on the remaining 20% of the dataset.

**Results:** All models had comparable predictive value (AUCs=.70-.72). Predictors are related to genital complaints, specific symptoms (e.g., digestive, fatigue, mood), health care utilization, and number of complaints. Most fruitful predictor categories are literature-based and medications. Predictors often had overlapping constructs, such as, digestive symptoms (symptom/disease codes) and drugs for anti-constipation (medication codes), indicating that registration is inconsistent between general practitioners.

**Conclusions:** This study shows that a simple clinical decision rule based on structured symptom/disease- or medication codes could possibly be an efficient way to support GPs in identifying patients in need of a different diagnostic or care approach. A fully data-based prediction currently appears to be hampered by inconsistent and missing registrations. Future research on predictive modelling of PSS using routine care data, should focus on data enrichment or free text mining, to overcome inconsistent registrations and improve predictive accuracy.

## Introduction

In the general population, up to 10% of adults experience persistent somatic symptoms (PSS) that cannot be fully attributed to established biomedical pathological mechanisms.[1-4] PSS are present in both patients with well-established diseases such as cancer [5] and cardiovascular disease,[6] as well as in patients with symptoms without well-established biomedical pathology.[1] PSS are not only burdensome to the patient,[7] but also greatly impact health care.[8] For instance, in general practice up to 50% of consultations are related to symptoms which are not clearly relatable to biomedical pathology.[9] Most of these symptoms are self-limiting and do not need further investigation or treatment. However, identifying patients at risk of developing persistent symptoms is generally challenging.[10]

Definitions of PSS are ever changing. Historically PSS classification was based on the exclusion of well-established physical conditions.[11] Recent developments lack such a distinction and focus on more positive definitions (including dysfunctional symptom perceptions).[12,13] Moreover, PSS may be defined under broad 'umbrella' terms or based on specific syndromes such as irritable bowel syndrome (IBS), fibromyalgia (FM), or chronic fatigue syndrome (CFS). Previous research debated the distinctness of specific syndromes.[14] However, nowadays most experts accept accumulating evidence that there are both overarching common factors as well as syndrome-specific aspects to PSS.[15,16] Similarly, differing terminology is used between health care professionals. For instance, in psychiatry the umbrella term 'somatic symptom disorder' may be used, whereas in general medicine the term 'functional somatic symptoms' is used.[13,17,18] Lastly, some physicians refrain from using terms beyond well-established biomedical disorders for somatic symptoms.[19,20] In this paper we use the term PSS, since we aim to approach identifying the broad spectrum of patients with persistent symptoms without well-established pathophysiology, and since recent research indicates that this term is generally preferred over other umbrella terms.[21]

Ambiguity in definitions and terminology has contributed to hampered (early) identification and proactive clinical intervention of patients at risk of developing PSS.[22-24] For instance, research shows that patients with fibromyalgia are diagnosed around 6

years after symptom onset.[25] Consequently, PSS are related to inappropriate and relatively high healthcare utilization and costs.[26-28] Especially in many western countries, where general practitioners (GPs) serve as a gatekeeper for specialist health care.[29,30] To prevent unnecessary referrals and medicalization, with potential risk of iatrogenic harm, and to enable the initiation of proactive interventions, early identification is necessary.[31,32] However, there are many barriers towards identification of PSS in primary care.[10,19] For example, diagnosis may be difficult due to predominance of the biomedical disease model, fear of missing malignancy or other life threatening conditions, the GP's experience and knowledge relating to PSS, and consultation constraints like overloaded surgery hours. Research from a European network of experts in the field stresses the need for a systemic change to overcome these challenges.[33] Furthermore, research shows that an integrative care approach (with attention for psychological, social, interpersonal, and contextual factors, in addition to keeping track of any biomedical deterioration) is needed to improve care for PSS.[34,35]

Over the years, several screening tools for patients with PSS-related issues were developed for clinical use.[1,36-38] While diagnostic accuracy and validity have been demonstrated, wide-spread use is not forthcoming. A survey of Dutch GPs showed that GPs are still in need of tools for PSS related diagnostics.[20] Studies have shown that routine care data can be responsibly used for predictive modelling.[39,40] The development of prediction models based on routine primary care data may enable screening based on readily available clinical information and support GPs in their practice. Recent studies reveal the multi-applicability of routine care data, since it can be used in several different ways. Approaches range from the more classic theory-driven approaches, simple data-driven approaches,[41] and more complex temporal data-mining techniques.[39,40]

This paper represents a first attempt to develop a clinical decision rule for PSS-onset based on routine primary care data. The study aims to predict what patients are at risk of developing PSS two-years prior to onset and explores different candidate predictor selection approaches. While a theory-driven approach is well established and has a long history in science, especially in cohort studies, the use of routine care data potentially provides an approach that is more generalizable to clinical practice. Moreover, since we

cannot control variable collection, we are interested in how theory-driven variable selection performs compared to non-routinely collected studies. Therefore, the present study, explores different theory and data-driven approaches of variable selection, and their combinations, to identify the best approach for predictive modelling of PSS.

## Methods

### Study design

A population-based retrospective cohort study was performed using data from 76 primary care practices affiliated with the extramural Leiden academic network (ELAN) of the Leiden University Medical Center (LUMC), the Netherlands. First, onset date of PSS was determined according to the approach described below (see 'Outcome' section) within the period 1st of January 2017 until 31st of December 2018 (random 'onset' dates were selected for patients without PSS). Thereafter, candidate predictors were selected 2 to 7 years prior to the onset date (i.e., for each patient 5 years of data was used to select candidate predictors). The ELAN data consists of several subsets, including demographic data (gender, year of birth), consultations (dates, coded symptomology and diagnoses according to the Dutch version of the WONCA International Classification of Primary Care (ICPC [42]), prescribed medication (dates and coded WHO anatomical therapeutic chemical (ATC) classification [43]), laboratory test (dates and results), and correspondence data (dates and type of healthcare professionals (e.g. profession/specialty of the other professional).[44] Part of the consultation registration is the ICPC-coded episode registration, where chronic disorders are registered. The episode data may be available up to the date of birth.

### Study population

Patients aged 25-100 years from the ELAN datawarehouse were used for this study. Participating practices were located in the greater Leiden and The Hague area. In general, all Dutch residents are enlisted and registered at a general practice in their neighbourhood. Primary care is included in the mandatory Dutch insurance and free of additional charge for insured citizens. The ELAN data warehouse consists of pseudonymized routine healthcare data extracted from the electronic medical records (EMRs).[45] Inclusion criteria were: registered at the general practice for at least 7 years, having at least 10 contacts and 1 ICPC code. These criteria were used to ensure availability of enough registrations per patient to enable candidate predictor construction. Furthermore, due to higher likelihood of registration errors, patients who were over 100 years of age on December 31st of 2018, were excluded from the study.

Because we were interested in PSS onset prediction, patients who were registered with PSS before the 1st of January 2017 were excluded from the analysis.

### Outcome

The definition of PSS is based on an earlier analysis by our research group, for which the same ELAN database was used.[32] Three approaches towards PSS identification were applied. Patients were identified as having PSS based on either having (1) ICPC-codes for PSS-syndromes (A04.01; chronic fatigue syndrome, D93; irritable bowel syndrome, and L18.01; fibromyalgia); (2) PSS-umbrella terms, PSS-syndrome, or PSS-complaint in the episode description; and /or (3) a score of ≥ 20 on the somatization subscale of the four-dimensional symptom questionnaire (4DSQ), registered in the lab-results. For a more detailed description of the selection criteria see [32].

### Candidate predictors

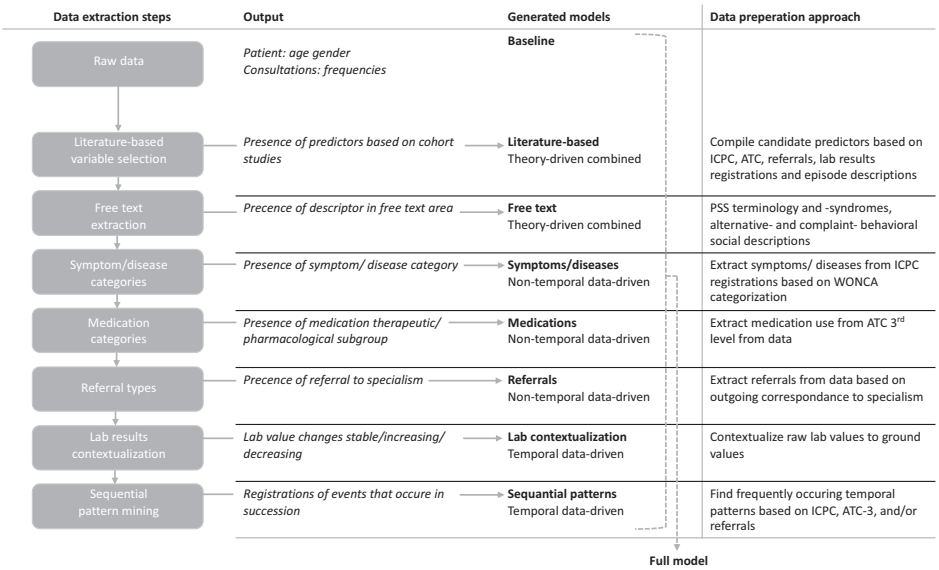
Different datasets were constructed with specific theory and data-driven candidate predictors of PSS in the ELAN data. Below a brief description of the predictor categories related to each dataset-based model will be given, see figure 1 for an overview of the data extraction steps and appendix A for a detailed overview of candidate predictors. Two distinct theory-driven datasets were operationalized; (1) literature-based risk factors of PSS, (see [35] for more detail) and; (2) frequencies of specific PSS-related terms and words in the free text with limited structured registration options (see appendix A). Data-driven datasets were divided into non-temporal and temporal data-driven datasets. The non-temporal datasets consist of dichotomized medical coding data (symptom/disease codes, medication codes, and referrals). The coded symptom/disease dataset was based on ICPC codes categorized into WONCA chapters and code categories.[46] The coded medication dataset was based on ATC codes reduced to 3rd level (to therapeutic/pharmacological subgroup).[47] The referral dataset was based on correspondences GPs have with other health care professionals.

The temporal approach consists of contextualized lab results and sequential patterns in medical coding data. Due to the high number of different lab results and inconsistent availability, using reference values for this study was not feasible. Contextualization of

lab results provide a solution to enable interpretability of lab results for individual patients. In relative grounding, a lab value is comparted to its previous value to deter whether values are decreasing, increasing, or have remained stable.[39] To avoid relatively small fluctuations in lab values as decreases or increases, variables were scaled and a minimum of 5% difference between values was required to count as a change. After relative grounding the number of stable, decreased, and increased values per lab measure were used as candidate predictors.

Sequential pattern identification of medical coding data was detected using the Sequential PAttern Discovery using Equivalence classes (SPADE) algorithm.[48] The SPADE algorithm is an efficient way to find statistically significant patterns in temporal data. To identify patterns with the SPADE algorithm, sequences of registrations (ICPC, ATC, and referrals) are ordered by date and subsequent registrations are associated to each object in which it occurs.[48] Thus, when patient has multiple registrations on one day these will be separated and combined with possible subsequent registrations (e.g., patient X has the following registrations on date Y: fatigue, abdominal pain, anti-constipation drug and date Z: physiotherapy, this will result in 3 patterns for patient X: (1) fatigue → physiotherapy; (2) abdominal pain → physiotherapy; (3) anti-constipation drug → physiotherapy). We selected frequent patterns as candidate predictors based on having at least 1% difference between patients with PSS and patients without PSS in the support value (i.e., prevalence of the pattern in de dataset). Please see [48] for a more detailed description of the SPADE algorithm.

***Figure 1.*** Diagram showing the data extraction steps for each constructed model.




## Predictive modelling

For predictive modelling a machine learning approach by means of least absolute shrinkage and selection operator (LASSO) logistic regression was used. Relating to our dataset and aim, LASSO logistic regression has several advantages over other methods. LASSO is especially suitable for unbalanced datasets, in which the outcome classification groups differ greatly in size. Moreover, LASSO avoids overfitting in in case of a great number of candidate predictors [49] and when multicollinearity is expected.[50] Regression was chosen because of its general comprehensibility and because previous studies in EMR-data have shown this generally preforms all popular methods.[39,51]

The combined dataset was stratified into a training set (80%) and test set (20%). For training, a 5-fold cross-validation, with hyperparameter tuning, was performed on the training set. For each unique model (i.e., literature-review, free text, coded symptom/diseases, coded medications, referrals, contextualization of lab results, and sequential patterns) and all combined models (i.e., theory-driven, data-driven nontemporal, data-driven temporal, and full model), near zero-variance candidate

predictors were removed (see appendix B for total number of candidate predictors in the model and data sources). To evaluate the predictive value of each model, a sensitivity analysis was performed and the area under the ROC curve (AUC) was calculated. All data was prepared and analysed using R version 4.0. For the final modelling, the caret-package was used.

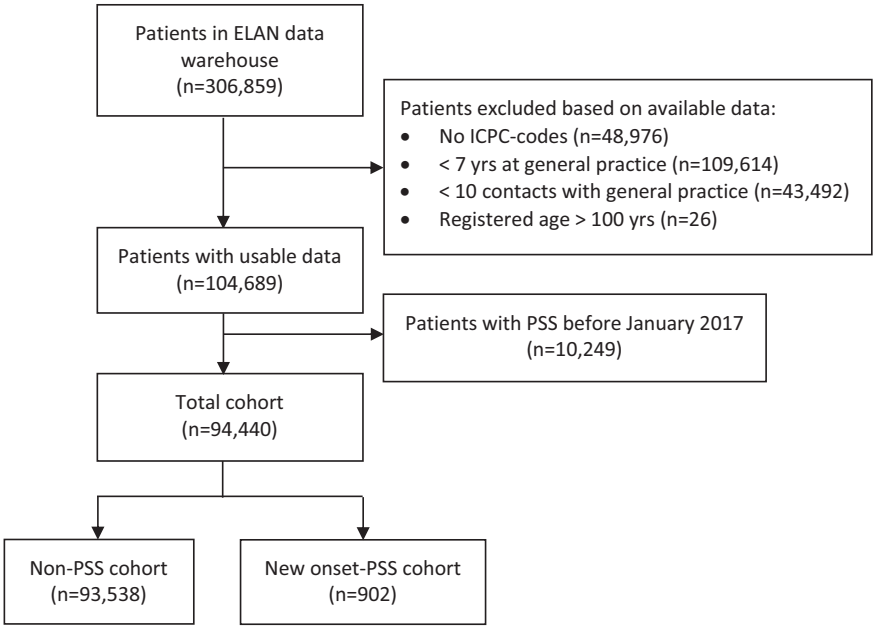
### Final model evaluation

To evaluate the models obtained using from model training (using the training dataset) and ensure there was no overfitting of the models, the models were internally validated on the test dataset for their classification performance. Finally, predictors of the final full model were evaluated. Estimated coefficients of predictors included in the final model were presented as odds ratios (ORs). To verify the stability of the predictor estimates, frequencies of estimates receiving non-zero values were calculated across 1000 bootstrap samples.

## Results

The total number of patients in the ELAN database we used for our research contained 306,859 patients, of which a total of 202,168 patients were excluded based on available data. A total of 10,249 patients were classified as having PSS before January 1st and therefore also excluded from the study. As a result, 94,440 patients were included in the final analysis (figure 2).

***Figure 2.*** flow chart patient inclusion ELAN study cohort




As shown in table 1, 0.9% (n=902) of patients in the ELAN cohort had new-onset PSS. Compared to the total cohort, patients with PSS are more likely to be female (69.0% vs. 52.9%), are generally younger (52.6±14.4 vs. 57.2±15.4) and have higher consultation frequency (8.7±7.3 vs. 6.3±5.8). Moreover, patients with PSS are more likely to have a mental health disorder (60.3% vs. 46.8%) while the likelihood of a physical disorder does not differ (64.6% vs. 63.6%, $p$ = .87). The patients with new-onset PSS in the training and test set differ on baseline variable female (68.3% vs. 72.2%). Post-hoc evaluation revealed that patients with PSS in the training and test set also differ regarding the

prevalence of mental comorbidities (59.6% vs 63.3%, respectively) and physical comorbidities (65.1% vs. 62.8%) (not depicted in table).

***Table 1.*** Patient characteristics

| | Total cohort | PSS | | |
|---|---|---|---|---|
| | **Full dataset** | **Full dataset** | **Training** | **Test** |
| **n (%)** | 94440 (100.00) | 902 (0.9) | 772 (0.9) | 180 (0.9) |
| **Female, n (%)** | 49998 (52.9) | 623 (69.0) | 493 (68.3) | 130 (72.2) |
| **Age, mean (s.d.)** | 57.2 (15.4) | 52.6 (14.4) | 52.9 (14.5) | 51.3 (13.7) |
| **Consultations, mean (s.d.)** | 6.3 (5.8) | 8.7 (7.3) | 7.44 (6.3) | 7.2 (5.5) |
| **Urbanization level, n (%)** | | | | |
| **Urban area** | 45567 (48.2) | 404 (44.8) | 326 (45.2) | 78 (43.3) |
| **Sub-urban area** | 43296 (45.8) | 448 (49.7) | 358 (49.6) | 90 (50.0) |
| **Rural** | 2711 (2.9) | 9 (1.0) | 7 (1.0) | 2 (1.1) |
| **Disadvantage neighbourhood** | 67215 (71.2) | 622 (69.0) | 494 (68.4) | 128 (71.1) |
| **Physical comorbidity, n (%)** | 60019 (63.6) | 583 (64.6) | 470 (65.1) | 113 (62.8) |
| **Mental comorbidity, n (%)** | 44292 (46.9) | 544 (60.3) | 430 (59.6) | 114 (63.3) |

In Table 2 the predictive value based on sensitivity, specificity and the AUCs of each unique and combined model is depicted. The AUCs of the validated models varied from .68 for the baseline model to .72 for the full model. From the separate models, all models preformed equally well, based on an approximate AUC .70. Using the optimal cut-off selection (i.e., highest number of cases selected accurately), the present model would, with 72.2% sensitivity detect patients at-risk of PSS onset within 2 years (see table 2 for AUC's and sensitivity analyses, and the appendixes A-C for more details on the model contents).

***Table 2.*** Prediction models based on LASSO logistic regression analysis

| | | | TRAINING | | TEST | |
|---|---|---|---|---|---|---|
| | | | **AUC** | **Sensitivity** | **Specificity** | **AUC** |
| **Theory-driven** | | **Baseline model** [a] | **.66** | **.73** | **.54** | **.68** |
| | | Literature-based [b, c] | .70 | .61 | .68 | .71 |
| | | Free text [b, d] | .68 | .70 | .56 | .71 |
| | | **Combined** [a] | **.69** | **.73** | **.60** | **.71** |
| **Non-temporal** | **Data-driven** | Symptoms/diseases [b, e] | .68 | .72 | .57 | .70 |
| | | Medications [b, f] | .69 | .76 | .58 | .70 |
| | | Referrals [b, g] | .66 | .71 | .55 | .69 |
| | | **Combined** [b] | **.70** | **.57** | **.72** | **.71** |
| **Temporal** | **Data-** | Lab contextualization [b, h] | .67 | .73 | .58 | .70 |
| | | Sequential patterns [b, i] | .66 | .83 | .43 | .69 |
| | | **Combined** [b] | **.68** | **.73** | **.58** | **.70** |
| | | **Full model** [b, j] | **.70** | **.72** | **.60** | **.72** |

[a] Gender, age, consultation frequency; [b] includes baseline model; [c] Variables selected based on literature search of risk factors in the general population; [d] Word search through free journal text; [e] ICPC-codes categorized according to the WONCA categorization (dichotomized); [f] ATC-3: therapeutic/pharmacological subgroup (dichotomized); [g] Outgoing correspondence to medical specialists (dichotomized); [h] Relative grounded lab-results (stable, increase, decrease; dichotomized); [i] Order of ICPC, ATC and referrals over time, patterns identified with the SPADE algorithm (see appendix C); [j] All available candidate predictors combined; For a detailed description of the models, see appendix A

Final predictors were derived from the full model. From all candidate predictors used for the full model (n=545), 29 of the variables contributed to the prediction of PSS onset. Predictors stemmed from all predictor type categories, baseline (n=2), literature review (n=8), ATC (n=8), ICPC (n=3), free text (n=2), referrals (n=1), lab contextualization (n=3), and sequential patterns (n=1). From the baseline predictors, age decreased (OR=0.82) and female gender increased (OR=1.13) the likelihood of PSS-onset. Baseline variable consultation frequency was not a relevant predictor in the full model, but it was an important predictor in all other models, except for the theory driven combined model. Some other highly stable predictors: using PSS-related complaint description in the free text (OR=1.12) are; having stable lymphocyte counts based on lab tests (OR=84.2); using PSS-related terminology in free text (OR=83.6%); the number of referrals for imaging (OR=1.10); number of medications (OR=1.12), and; having a neurological disorder (OR=1.10) (see table 3 for the complete list of predictors and ORs). Frequencies of

estimates having non-zero values across 1000 bootstrap samples indicate the level of interchangeability of predictors for other predictors (high percentage indicating higher importance of the predictor for predicting PSS onset).

***Table 3.*** Predictors of PSS obtained from full model LASSO logistic regression analysis

| Predictors | Total cohort % or mean (s.d.) | PSS-cohort % or mean (s.d.) | Odds ratio | %[a] |
|---|---|---|---|---|
| ***Baseline*** | | | | |
| Age | 57.2 (15.4) | 52.6 (14.4) | 0.82 | 99.5 |
| Female gender | 52.9 | 69.0 | 1.13 | 78.1 |
| ***Literature based (theory-driven)*** | | | | |
| Painful intercourse (female) [b] | 1.1 | 3.1 | 1.17 | 60.8 |
| Medications [c] | 2.0 (1.4) | 2.5 (1.6) | 1.12 | 94.7 |
| Number of imaging referrals [d] | 0.09 (0.09) | 0.1 (0.1) | 1.10 | 96.1 |
| Fatigue [e] | 20.5 | 31.2 | 1.04 | 47.5 |
| Mood disorder [f] | 14.6 | 23.6 | 1.03 | 47.7 |
| Number of pain sites [g] | 0.3 (0.6) | 0.5 (0.7) | 1.02 | 63.7 |
| Headache [h] | 19.8 | 32.6 | 1.02 | 44.8 |
| Number of ICPC-codes [i] | 2.6 (1.5) | 3.3 (1.7) | 1.004 | 13.5 |
| ***Free text (theory driven)*** | | | | |
| Complaint description [j] | 0.7 (1.0) | 1.3 (1.6) | 1.12 | 99.3 |
| PSS terminology [k] | 0.06 (0.15) | 0.11 (0.21) | 1.04 | 83.6 |
| ***Symptom/disease codes (non-temporal data-driven)*** | | | | |
| Neurological disorder [l] | 18.1 | 27.3 | 1.11 | 77.9 |
| Digestive symptoms [m] | 50.4 | 65.5 | 1.07 | 66.7 |
| Female genital symptoms [n] | 28.8 | 46.6 | 1.07 | 53.0 |
| Female genital infection [o] | 8.3 | 15.9 | 1.04 | 48.9 |
| ***Medication codes (non-temporal data-driven)*** | | | | |
| Capillary stabilizers [p] | 0.1 | 0.7 | 1.47 | 57.6 |
| Selective CA+ blockers [q] | 10.6 | 6.3 | 0.93 | 58.0 |
| Topical contraceptives [r] | 5.5 | 10.5 | 1.06 | 58.8 |
| Lipid modifier [s] | 21.4 | 15.6 | 0.95 | 54.2 |
| Nasal spray, topical [t] | 40.1 | 51.7 | 1.02 | 51.1 |
| Anti-constipation drug [u] | 28.4 | 40.1 | 1.02 | 52.1 |
| Eyedrops, topical [v] | 16.2 | 22.3 | 1.01 | 47.3 |
| Anti-thrombotic agents [w] | 20.8 | 16.0 | 0.999 | 41.0 |

***Table 3.*** Predictors of PSS obtained from full model LASSO logistic regression analysis (continued)

| Predictors | Total cohort % or mean (s.d.) | PSS-cohort % or mean (s.d.) | Odds ratio | %[a] |
|---|---|---|---|---|
| ***Referrals (non-temporal data-driven)*** | | | | |
| Physiotherapy [x] | 30.2 | 39.5 | 1.01 | 43.6 |
| ***Lab contextualization (temporal data-driven)*** | | | | |
| Lymphocytes, stable | 0.3 (0.5) | 0.4 (0.5) | 1.06 | 84.2 |
| Thyroid, stable | 0.5 (1.1) | 0.8 (1.4) | 1.04 | 70.3 |
| Systolic blood pressure, stable | 1.8 (3.2) | 1.5 (2.8) | 0.999 | 39.0 |
| *Sequential patterns (temporal data-driven)* | | | | |
| Referral to Rontgen | 3.1 | 7.1 | 1.10 | 57.6 |

[a] Frequency of estimates having non-zero values across 1000 bootstrap samples; [b] ICPC-codes: X04, P08.02; [c] Frequency based on full ATC codes; [d] Rontgen or echography; [e] ICPC-code: A04; [f] ICPC codes: P03, P73, P73.02, P76 and ATC codes: N06A, N05AN, D11AX04; [g] Number of pain-related ICPC codes; [h] ICPC codes: N01, N02, N89, N90, R09; [i] all unique ICPC codes; [j] fatigue, dizziness, back pain (see appendix A for full list); [k] e.g., somatization or a-specific symptoms (see appendix A for full list); [l] ICPC: N86-99; [m] ICPC codes: D01-29; [n] ICPC codes: X01-29; [o] ICPC codes: X70-74 and X90-92; [p] ATC4-codes: C05C; [q] ATC4 codes: C08C; [r] ATC4 codes: G02B; [s] ATC4 codes: C10A; [t] ATC4 codes: R01A; [u] ATC4 codes: A06A; [v] ATC4 codes: S01X; [w] ATC4 codes: B01A; [x] Correspondence with physiotherapy.

Several of the predictors may have overlapping aetiology or overlapping variable constructs but differ in their data-source. This is for instance seen in: (1) female genital symptoms (ICPC), painful intercourse (literature review), both contain ICPC code X04; (2) ‘headache’ (literature review) and neurological disorders (ICPC), both containing ICPC codes N89 and N90; (3) digestive symptoms (ICPC) and drugs for anti-constipation (ATC); and (4) ‘fatigue’ (ICPC) and ‘complaint description’ (free text descriptors, which contains the term fatigue).

## Discussion

This study provides a comprehensive overview of the effectiveness of different approaches towards predicting PSS based on routine primary care data two years prior to index date. Model performance based on specific predictor generation approaches do not differ greatly. Therefore, the use of the simplest approach may be most desirable. Based on the full model (including all candidate predictors), predictors associated with PSS onset stem from all predictor categories, although theory-driven and medication types (ATC) predictors were most prevalent. In line with previous literature, important predictors are related to being female (including, painful intercourse, genital infections/symptoms, and contraceptives), specific symptoms (e.g., digestive issues, fatigue, mood disorders, and headache), health care utilization (e.g., number of medications or imaging, referrals, or physiotherapy), and number of complaints (e.g., number of pain sites or ICPC-codes). Consistent with knowledge that PSS is unrelated to established biomedical pathology, results show that stable lab results (especially lymphocytes and thyroid) are important indicators of PSS. Notably, constructs of some predictors contain overlapping variables (such as: 'neurological disorder' and 'headache', and; 'fatigue' and 'complaint description'). This indicates that ambiguous registration may result in scattered predictors, which may have contributed to the limited predictive accuracy of the models.

Several strengths and limitations apply to this study. A major strength is the population-based cohort, with high ecological validity, with a large sample size and at least 7 years of data. Second, inclusion in our PSS cohort is based on a previously published approach which has enabled us to select patients beyond the poorly reported ICPC codes for the syndromes,[32] and not limited to commonly investigated IBS, FM, and CFS.[52] To our knowledge, we included a wider range of predictors than previous studies, and these are clinically relevant and generalizable to general practice. Moreover, the models were compared based on predictor categories which provides important evidence for more efficient future analyses. Lastly, we have used sophisticated machine learning techniques (temporal pattern mining and relative grounding) and analysis (LASSO regression). This allowed for optimal use of temporal data and enabled us to use all available candidate

predictors in one final model. Finally, although the machine learning techniques did not improve the performance of the full model, some novel predictors were identified (i.e., stable lab results: lymphocytes and thyroid). On the other hand, the use of routine care data may also limit the generalizability of the predictors to the general population since registration depend on the decision of patients to contact the physician and on the decision of physician/staff what to register. Furthermore, interpretation of predictors should be done with caution since the present analysis is directed at finding the optimal model performance, rather than explaining the outcome. For example, registration of social and psychological predictors may frequently be missing, since medical priorities might be estimated as the more important issues to code and register.[32,41,53] Finally, the selection of patients with PSS was based on previous research on the same dataset.[32] This approach enabled conservative selection of patients with PSS, but may have missed some cases. The aim was to enable data-driven selection and not rely on GP diagnosis, since research indicates that PSS are often missed by physicians.[54] Data-driven selection would enhance re-usability of routine care data.

To our knowledge this is the first cohort study to predict PSS two years prior to onset. However, previous predictive EMR studies on PSS or PSS-subgroups show better model performance. This may be due to the 2-year prediction gap, which was not applied in previous studies or because their use of questionnaires or physician dependent diagnoses.[55-57] A recent study based on the ELAN datawarehouse with a non-biomedical outcome showed similar predictive value,[41] which could mean that routine primary care data has limited capacity for non-biomedical outcome measures. However, this study also did not apply a 2-year prediction gap. Prediction models based on other types of large cohort studies, have primarily focused on PSS sub-types.[52,57] Monden et al.,[54] reported notably higher odds ratios, which may be related to less available confounding variables and/or to active data collection resulting in access to multidomain (i.e., more complete social and psychological) data. This is in line with studies showing that GPs are less likely to report social and psychological factors [19,20,58] and a recent systematic review demonstrating the importance of using multidomain data.[45] Lastly, in contrast to a body of evidence,[57,59,60] our LASSO regression of the full model did not indicate that

consultation frequency predicts PSS. Since consultation frequency was predictive in most sub-models, findings imply that factors latent to consultation (such as number of imaging referrals or number of ICPC-codes) may be more precise predictors of PSS onset than consultation frequency.

Our study shows how routine primary care data can be used as a source that supports early prediction of PSS, although predictive accuracy indicates that it cannot be used without additional screening. Relatively simple ICPC/ATC-based models can assist in distinguishing between PSS and well-established biomedical problems. Predictive value of free text 'complaint description' and 'PSS terminology' indicate that clinical evaluation and registration of PSS-related psychological and social constructs is important for early identification of PSS. Thus, in combination with the simple ICPC/ATC-based models, available validated screening tools such as the 4DSQ and SSD-12 might further facilitate early identification of PSS. Moreover, the overlapping constructs of several predictors which do not correlate highly, indicate a difference in registration behaviour between GPs practices, which may have limited the predictive value of the data. Although sequential patterns and lab contextualization did not enhance model performance, the former implies that other machine learning techniques (e.g., text mining) should be further explored. Especially because of the fair performance of the free text-based model, for which in the present study only limited free text is utilized.

Results provide clear directions for both clinical and EMR research. Clinical research should be directed at the feasibility of the ICPC/ATC-based models for clinical implementation in combination with additional screening with a validated screening tool (e.g., 4DSQ or SSD-12). The screening tools would provide a proxy for the difficulty to systematically register PSS-related aspects captured in the free text. Future research should evaluate criterium validity of the present outcome by selecting the outcome (i.e., PSS) using validated screening tools (e.g., 4DSQ, SSD-12), and further evaluate if this could enhance accuracy of routine primary care data-based predictions. Furthermore, EMR research should further develop the theory-driven and data-driven approaches. The theory-driven approach could thus be improved by more elaborate candidate predictor construction, combing variables with similar constructs more thoroughly, and patient

reported outcome measures. The data-driven approach could possibly be improved using data enrichment techniques or by developing models based on more advanced approaches for free text analysis.

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## Appendixes

***Appendix A.*** Predictors derived from models based on LASSO regression

| **Baseline model** | Gender, age, consultation frequency | | | | |
|---|---|---|---|---|---|
| **Literature-based*** | Urbanization, deprived neighbourhood, frequency of referral to imaging, frequency of referral to psychology, frequency of referral to alternative medicine, frequency of referral to ER, frequency of referral for secondary care, frequency of referral to primary care, frequency of referral for laboratory tests, variation in medication prescription (full length ATC), variation in ICPC codes, anxiety, number of pain symptoms, arterial pathology, asthma, atopy, burn injury, BMI, burn, CTS, birth, cholesterol, chronic illness, chronic kidney disease, chronic sinus, chronic stress, conduct problems, COPD, coronary artery disease, dementia, diabetes, diffuse pain, dizziness, dyslipidaemia, dyspareunia, dyspepsia, employment, family history of disease, fatigue, gastrointestinal symptoms, headache, health anxiety, heart failure, hormonal medication, hypertension, hyperthyroidism, vaccinations, infections, life events, liver disease, malignant neoplasm, marital status, memory problems, mental health, menstrual disorders, Meniere disease, mood disorders, musculoskeletal disease, neuritis, neuropathic pain, non-specific complaints, osteoporosis, pain medications, psoriasis, restless-leg syndrome, rheumatism, SES, abuse, sleep apnoea, sleep disorder, smoking, somatic symptoms, specific pain, stroke, teeth grinding, traffic accident, traumatic brain injury. | | | | |
| **Free text*** | **PSS TERMINOLOGY:** MUPS, somatization, psychosomatic, unexplained, functional complaints, central sensitization, somatization disorder, somatically unexplained, complaints, somatoform, misunderstood, complaints, neurasthenia functional, barriers, vague complaints, vague pain, non-specific, | **PSS SYNDROMES:** Fibromyalgia, spastic colon, irritable bowel, gut syndrome, IBS, CFS, chronic fatigue, ME/CFS, tinnitus, facial pain, vulvodynia, restless legs syndrome, bladder syndrome, bladder pain syndrome, interstitial cystitis, unstable bladder, tension headache, | **ALTERNATIVE DESCRIPTION**: Stagnant, recovery, persistent, working hypothesis, no abnormalities, impediments, meaningless, pain experience, illness anxiety, negative thoughts, fear of movement, experiences, to experience, complaint-contingent approach, sensitive, load capacity, explanatory model. | **COMPLAINT DESCRIPTION**: Dizziness, fatigue, concentration, tension, stress-related, generalized/staggering pain, hypermobile, low back, SI pain, lumbago, backpain, pseudo-radicular, tendinosis, muscle-joint pain, musculoskeletal system, memory problems, headache, tingling, dispirited, rebellious, | **BEHAVIOR-SOCIAL:** Avoidance behaviour, absenteeism, surroundings, social problems, functioning, culture, tensions, traumatic event, abuse, addiction, violence, domestic. |

***Appendix A.*** Predictors derived from models based on LASSO regression (continued)

| **Free text*** (continued) | **PSS TERMINOLOGY:** reactive complaints, unexplained complaints, stress complaints, stress complaints. | **PSS SYNDROMES:** pain syndrome. | **ALTERNATIVE DESCRIPTION**: | **COMPLAINT DESCRIPTION**: desperate, depressed, sleep, nauseous, shiver, anxiety symptoms, angry, anxious, emotional, dejected, worry, listless, upset stomach, on chest, neck pain, itch, sad, gloom | **BEHAVIOR-SOCIAL:** |
|---|---|---|---|---|---|
| **Symptoms/diseases*** | WONCA categorized ICPC-codes: general/unspecified congenital anomalies (A90), general/unspecified infections (A70-78), general/unspecified injuries (A80-89), general/unspecified other diagnoses (A91-99), general/unspecified non-specific symptoms (A01, A05, A20, A28-29), general/unspecified specific symptoms (A02-06, A08-09, A12), blood/immune Infections (B70-71), blood/immune other diagnoses (B80-99), blood/immune symptoms (B02-29), digestive infections (D70-73), digestive neoplasms (D74-78), digestive other diagnoses (D82-99), digestive symptoms (D01-29), eye infections (F70-73), eye injuries (F75-79), eye other diagnoses (F82-99), eye symptoms (F01-29), ear infections (H70-74), ear injuries (76-79), ear other diagnoses (H81-99), ear symptoms(H01-29), cardiovascular congenital (K73), cardiovascular other diagnoses (K74-99), cardiovascular symptoms (K01-29) musculoskeletal injuries (L72-81), musculoskeletal other diagnoses (L83-95), musculoskeletal non-specific symptoms (L18-20, L28-29), musculoskeletal specific symptoms (L01-17), neurological neoplasms (N74-76), neurological other diagnoses (N86-99), neurological symptoms (N04, N06-08), psychological other diagnoses (P70-99, T06), psychological symptoms (P01-29), respiratory infections (R70-83), respiratory injuries (R87-88), respiratory neoplasms (R84-86), respiratory other diagnoses (R90-99), respiratory symptoms (R01-29), skin congenital (S81-83), skin infections (S03, S09-11, S84, S95), skin injuries (S12-19), skin neoplasms (S77-80), skin other diagnoses (S84-94, S96-99), skin symptoms (S01-29), endocrine/metabolic other diagnoses (T81-99), endocrine/metabolic symptoms (T01-29), urological other diagnoses (U88-99), urological symptoms (U01-29), family planning other diagnoses (W77-99), family planning symptoms (W01-29), female genital infections (X70-74, X90-91), female genital neoplasms (X75-81), female genital other diagnoses (X84-89, X99), female genital symptoms (X01-29), male genital congenital (Y81-84), male genital infections (Y70-76), male genital other diagnoses (Y85-99), male genital symptoms (Y01-29), social symptoms (Z01-29). | | | | |
| **Medications*** | ATC 3rd level: therapeutic/pharmacological subgroup | | | | |

***Appendix A.*** Predictors derived from models based on LASSO regression (continued)

| | |
|---|---|
| **Referrals*** | Acupuncture, allergology, anaesthetics, autography, cardiology, surgery, cytology, dermatology, dietarian, primary care psychologist, endocrinology, physiotherapy, mental health care, gynaecology, haptomology, internal medicine, ear-nose-throat specialist, laboratory testing, pneumology, gastroenterology, medical microbiology, neurology, optomologist, orthopedy, plastic surgery, pain relief centre, podiatry, psychology, psychotherapy, radio therapy, rheumatology, rehabilitation centre, Rontgen, emergency care, urologist. |
| **Lab contextualization*** | Bilirubin, cholesterol, creatine, CRP/BSE, glucose, granulocyte, HbA1c, haemoglobin, minerals, monocytes, neutrophiles, PH (urine), systolic blood pressure, thyroid function, transaminase, vitamin B (excl. B12), vitamin B12, vitamin D, weight/BMI |
| **Sequential patterns*** | *3-level patterns*: Antibacterial drugs (systemic; ATC-code: J01) >> secondary care referrals, analgesic drugs (ATC-code: N02) >> secondary care referral<br>*2-level patterns*: hypertensive heart disease >> secondary care referral, specific musculoskeletal symptoms (ICPC-codes: L01-17) >> secondary care referral, Rontgen referral >> secondary care referral, hypertensive heart disease >> Rontgen referral, specific musculoskeletal symptoms (ICPC-codes: L01-17) >> Rontgen referral, antibacterial drugs (systemic; ATC: J01) >> specific musculoskeletal symptoms (ICPC-codes: L01-17), hypertensive heart disease >> specific musculoskeletal symptoms (ICPC-codes: L01-17), Rontgen referral >> specific musculoskeletal symptoms (ICPC-codes: L01-17), secondary care referral >> musculoskeletal disease (ICPC-codes: L83-95, L98-99), specific musculoskeletal symptoms (ICPC-codes: L01-17) > analgesic drugs (ATC-code: N02).<br>*1-level patterns*: General and unspecified disease (ICPC-codes: A91-99), fatigue (ICPC-code: A04), no disease (ICPC-code: A97), abdominal symptoms (ICPC-codes: D01-29), peripheral osteoarthritis (ICPC-codes: L89-91), drugs for acid related disorders (ATC-code: A02), drugs for constipation (ATC-code: A06), vitamin preparations (ATC-code: A11), antithrombotic agents (ATC-code: B01), dermatological corticosteroids (ATC-codes: D07), antibacterial drugs (systemic; ATC: J01), analgesic drugs (ATC-code: N02), drugs for obstructive airway diseases (ATC-codes: R03), cough and cold preparations (ATC-codes: R05), ophthalmological drugs (ATC-codes: S01), acute unitary infection (ICPC-codes: U70-72), cancer (ICPC-codes: A79, B72-73, D74-77, L71, N74, R84-85, S77, T71, U75-77, W72, X75-77, Y77-78), chronic abdominal pain (ICPC-codes: D01-02, D04, D06, Y02) dizziness (ICPC-codes: H82, N17), eye symptoms, eye diseases (ICPC-codes: F83-84, F92-94), hypertensive heart disease (ICPC-codes: K86-87), cardiovascular other diagnoses (ICPC-codes: K74-99), cardiovascular symptoms (ICPC-codes: K01-29), musculoskeletal injuries (ICPC-codes: L72-81), musculoskeletal other diagnoses (ICPC-codes: L83-95, L98-99), specific musculoskeletal symptoms (ICPC-codes: L01-17), neck and shoulder symptoms (ICPC-codes: L01, L08), psychological symptoms (ICPC-codes: P01-29), respiratory symptoms (ICPC-codes: R01-29), Rontgen referral, skin other diagnoses (ICPC-codes:), skin symptoms (ICPC-codes: S01-29), secondary care referral, vitamin deficiency (ICPC-codes: T91), infections upper respiratory tract (ICPC-codes: A77, R72, R74-76), urological symptoms (ICPC-codes: U01-29), female genital symptoms (ICPC-codes: X01-29). |

* Near zero variance and high-correlating variables removed

***Appendix B.*** Number of variables by dataset and source table

| Datasets | Source table(s) | n |
|---|---|---|
| Baseline | Patient | 3 |
| Symptoms/diseases | Journal and episode | 96 |
| Medications | Medication | 176 |
| Referrals | Correspondence | 51 |
| Literature review | Patient, journal, episode, lab, correspondence, medication | 92 |
| Free text | Journal | 8 |
| Lab contextualization | Lab results | 76 |
| Sequential patterns | Journal, episode, lab, correspondence, medication | 57 |
| Full model | Patient, journal, episode, lab, correspondence, medication | 545 |

***Appendix C.*** Patterns derived from the SPADE algorithm and subsequent LASSO regression for the sequential patterns model

| Sequences | support (difference) | Odds ratio |
|---|---|---|
| Rontgen referral | 0.077 | 1.08 |
| Female genital symptom [a] | 0.043 | 1.03 |
| Hypertension [b] | 0.036 | 0.97 |
| Fatigue[c] | 0.025 | 1.02 |
| Antibacterials for systemic use >> specialist care referral | 0.012 | 1.02 |
| Antibacterials for systemic use >> specific musculoskeletal symptoms [d] | 0.011 | 0.98 |
| Drugs for constipation (A06) | 0.274 | 1.00 |
| Cardiovascular diagnosis [e] | 0.031 | 1.00 |
| Neck and back complaints [f] | 0.036 | 1.00 |

[a] ICPC-codes X01-X29; [b] ICPC-codes K86 or K87; [c] ICPC-code A04; [d] ICPC-codes L01, L02, L03, L04, L05, L06, L07, L08, L09, L10, L11, L12, L13, L14, L15, L16, L17, L17.01; [e] ICPC codes K74-K99 (excl. K86 and K87); [f] ICPC codes L01, L02, L03, L83, L84, or L86

# Chapter 7

## General discussion

# General discussion

The studies presented in this thesis intend to provide comprehensive insight into possibilities to predict persistent somatic symptoms (PSS) and how to reuse routine primary care data extracted from electronic medical records (EMR) for this purpose. The included studies are aimed at supporting and promoting early identification of patients with PSS and facilitate early intervention. Based on the findings presented in this thesis it is possible to identify patients with PSS with moderate to high accuracy at least two years prior to diagnosis. Moreover, the compiled studies provide direction for more precise data-based prediction. In the current chapter, the study findings are outlined and discussed in relation to each other. First, the main findings of the studies in this thesis will be listed, to form an overview of key messages. Thereafter, the main issues regarding early identification of PSS based on routine primary care data are discussed.

## Main findings

1. Predictors of PSS onset are multifold and cannot be reduced to a single domain of the dynamic biopsychosocial model (**chapter 2**). Exploring complaints from different domains is therefore paramount to improve care for patients with PSS.
2. The majority of general practitioners (GPs) reports to require additional tools or other support for classification of PSS and consultation with patients at risk of PSS (**chapter 3**).
3. GPs use a wide range of methods for registration of PSS in their electronic medical records (EMRs; self-reported results from **chapter 3** are supported by observation in **chapter 4**). These registration methods can differ greatly between GPs.
4. Identifying patients within the broad spectrum of PSS in routine primary care data (**chapter 4**) is possible by using a combination of methods (including clinical codes of PSS-syndromes, episode descriptions, and recorded outcomes of screening tools).
5. Mental health-related registrations in routine primary care data, such as psychological ICPC-codes, referrals to mental health care, and psychopharmacological prescriptions, can be adequately re-used to predict diagnosis of common PSS syndromes (IBS, FM, and CFS) (**chapter 5**).

6. There are both overarching and distinct mental health registrations for PSS syndromes (IBS, CFS, and FM) in routine primary care data (**chapter 5**).
7. Patients with medium to high risk of PSS can be identified in routine primary care data two to seven years prior to diagnosis (**chapter 6**). Highly accurate recognition of risk of PSS appears to be impeded by general registration irregularities and missing data.
8. Theory- and data-driven methods show similar performance in the ability to predict PSS diagnosis based on extracted and anonymized routine primary care data (**chapter 6**). Benefits of using more complex, time-consuming methods may therefore be limited.

## Selecting patients with PSS in routine primary care data

The primary challenge towards predictive modeling of PSS based on routine care data is the lack of a gold standard method of classifying PSS. As demonstrated in **chapter 3**, GPs reportedly use a variety of methods to register PSS and an unambiguous clinical code for PSS is not available. This does not only limit the reusability of routine primary care data for PSS research purposes but is also problematic for many GPs in daily clinical practice. Moreover, besides the problematic lack of a clinical code, GPs report to have difficulties in classifying and identifying PSS, which is further corroborated by other studies [1-3] and studies showing a significant diagnostic delay in PSS-syndromes.[4-6] Consequently, it would be undesirable to solely rely on GPs or the clinical codes they use for selecting patients with PSS in the routine care data. Previous EMR studies used a variety of approaches to select patients with PSS, including inquiring GPs about specific patients and a combination of clinical (symptom) codes with exclusion of comorbid mental or medical conditions.[7-11] Since research shows that patients with PSS often have comorbid conditions [12,13] (see also, **chapter 4**) the latter is undesirable. Based on this knowledge the studies in **chapter 3** and **chapter 4** were directed at developing a data-based classifier for PSS.

In **chapter 3** registration behavior was gathered via a survey that included ecologically valid methods of inquiry. Based on the findings, the most viable methods were selected and effectiveness was explored in **chapter 4.** This resulted in a combination of methods

that identifies a group of patients that approaches the prevalence rate of PSS in the general population. The identification consists of clinical coding of PSS-syndromes, unstructured episode descriptions of PSS, and recorded outcomes of screening questionnaires. Results show that the use of a combination of these methods is crucial, since GPs vary in their approach towards registration of complaints and disorders. In all, because the use of additional screening questionnaires or the exclusion of comorbid chronic medical and mental conditions are not required, a data-based classifier of PSS can facilitate the use of large routine primary care databases for research on the broad spectrum of PSS. Still, this approach towards identification of PSS in routine care data is cumbersome and reusability of EMR data can be facilitated by incorporating a single general code for PSS in classification systems such as the ICPC or ICD. Such a code could also benefit GPs, since they report that the lack of a single unambiguous code is problematic for them (**chapter 3**). However, such a code should be accompanied with adequate universally accepted guidelines and definitions, which has been proven to be a large challenge in the international field of PSS.[14]

### The challenge of creating a multidomain risk profile using routine primary care data

In **chapter 2**, an extensive review of cohort studies is presented mapping multidomain predictors of PSS. This was executed in order to evaluate which data in primary care EMRs would be relevant to include in our predictive model. This review shows that although risk factors from the biomedical domain are currently dominant in the literature, factors from all domains of the dynamic biopsychosocial model (i.e., biological, psychological, interpersonal, contextual, and health behavior) have shown to be significant predictors of PSS-onset. Still, investigations of routine care data showed a predominance of biomedical registrations and predictors, which impedes the creation of a fully multidomain risk profile using currently available routine primary care data. This is especially evident in the prediction model presented in **chapter 6** in which all available primary care data was utilized (i.e., the full model) and PSS was predicted at least two years prior to diagnosis. Based on LASSO regression (a machine learning technique that is able to handle large amounts of data and incorporates predictor reduction), the EMR-based predictors mainly consist of biomedical variables, with limited representation of

psychosocial factors. However, in contrast, the prediction models presented in **chapter 5** based on the same data and similar analysis shows that PSS syndrome (i.e., IBS, CFS, and FM) diagnosis can be predicted with high accuracy based on mental health-related registrations. In contrast to **chapter 6**, this study only investigated mental health-related registrations and candidate predictors were constructed based on registration directly prior to PSS diagnosis. Based on these findings it is hypothesized that psychosocial problems are under registered and/or recognized by GPs, unless the patient presents with persistent problems. This may also be related to findings from other studies that indicate that patients may not readily visit their GP with mental health problems (for instance because of cultural reasons).[15-19] Thus, arguably, in routine primary care data registrations of psychosocial problems that are present prior to (severe or recurring) somatic symptom onset could be missing in the data. Consequently, the somewhat limited performance of the models in **chapter 6** could be related to high levels of missing data in the psychological and social domains or limited consultations prior to PSS diagnosis.

### Further considerations for a data-based early classification of PSS

Although lacking registrations of mental health and psychosocial problems seems a plausible explanation for the differences in performance of the models presented in **chapter 5** and **chapter 6**, there are some other explanations that should be considered. First, the use of a 2-year prediction gap in **chapter 6**, compared to no prediction gap in **chapter 5** (i.e., gathering candidate predictors directly before PSS index date) is likely to affect the results. EMRs may contain limited relevant data, because data is dependent of patients visiting the GP and GP's registration behavior. On the other hand, since PSS is often accompanied by an accumulation of recurring complaints, the repeated out-patient visits or number of symptoms should be indicative of emerging PSS. In **chapter 6**, where LASSO regression indicated that consultation frequency may be explained by other variables, valuable evidence is given to explain the relationship between consultation frequency and PSS, as indicated by a large body of research. That is, factors such as repeated imaging referrals, and multiple pain sites and symptoms, are predictors that may explain increased consultation frequency. This sheds light on the importance of

correctly interpreting some of these behavior- or context-related predictors (such as, HCU and unemployment). Thus, while these are also found in the large body of literature on predictors of PSS (**chapter 2)**, it should be noted that these predictors are rather a consequence of the accumulated disease burden than an actual predictor leading to PSS. Specification of predictors that may lead to undesirable contextual or behavioral aberration may be especially useful to distinguish PSS from other disorders that are accompanied by high consultation frequency. Thus, focusing primarily on consultation frequency may limit specificity of PSS prediction and identifying related latent factors may be necessary to increase predictive accuracy. Second, the broader definition of PSS in **chapter 6** (investigating the broad spectrum of PSS) compared to **chapter 5** (having unique PSS-syndrome classifications as outcomes) may affect predictive accuracy, because of increasing heterogeneity between patients. For instance, patients with IBS and FM display distinct somatic symptom presentations (bowel problems and widespread musculoskeletal pain, respectively). Furthermore, research indicates that the duration of diagnostic delays may be different between PSS subtypes.[4-6] This is further corroborated by findings from **chapter 3**, where GPs report more competency and willingness to diagnose IBS compared to CFS and FM (for which they are more likely to refer to specialist care). Different durations in diagnostic delay may also affect heterogeneity between patients with PSS. **Chapter 5** corroborates this finding by identifying a difference in predictive accuracy between the three prediction models for IBS, FM, and CFS, and some discrepancies in predictors (although the latter is mainly the case for CFS). Since diagnostic delays can cause a large number of problems, including inducing psychological problems [20] and complicating the physician-patient relationship,[16,21,22] it is likely this also affects EMR registrations.

## Promoting integrative care for patients with PSS

The limited registration of factors beyond the biomedical domain appears to have a twofold effect on PSS classification, both affecting physician-based classification and data driven classification. While research clearly indicates that the origin of PSS is multidomain in nature (**chapter 2**), the predictors derived from the early prediction model in **chapter 6** indicate that GPs do not make use of an integrative understanding of

the patients' problems (i.e., relating combined biological, behavioral, psychological, interpersonal, and contextual factors to the health of the patient). On the other hand, the lack of information also limits the performance of the early prediction model. Although, based on these findings, it could be argued that routine primary care data is not suitable for predictive modeling of PSS, the moderate accuracy of the model may have potential to break the cycle of under-recognition by physician and algorithm. Especially because overloaded work hours and prioritization of potential life-threatening diseases, limits the options of GPs to inquire about psychosocial factors – irrespective of having the appropriate training or not. Therefore, a simple data-based clinical decision rule may have the potential to sift or identify patients that require and may benefit from an integrative approach. This is in line, with the current trend towards proactive population health management: identify patients at risk for adverse health events like ineffective and counterproductive specialist referrals and expose them to less invasive interventions.[23,24] The implementation of a clinical decision rule into EMR software, flagging patients with increased risk of developing PSS, would enable (earlier) referral to interdisciplinary health care resources for further assessment. For GPs, earlier referral could reduce time investment and refocusing on the exclusion of possible life-threatening pathophysiology.

## The contributions of machine learning techniques

In this thesis, a variety of statistical methods were used, including machine learning techniques (**chapter 6**). Previous research has shown that temporal pattern mining and relative grounding of lab results of structured data could be effectively employed to improve model performance and reconfirm and identify new predictors.[25,26] Therefore, to increase the likelihood of finding predictors that were thus far unidentified, both techniques were employed. Although the machine learning techniques did not improve the performance of the model, it did identify some known (i.e., referral to radiology) and novel plausible predictors (i.e., stable lab results for lymphocytes, thyroid, and systolic blood pressure), which validates the effectivity of the methods. Finally, the predictions were modeled using logistic LASSO regression as a form of supervised machine learning. While studies show that LASSO logistic regression generally performs well for predictive

modeling,[26,27] recent studies show that more advanced machine learning techniques may result in better performing models.[28] However, compared to more advanced machine learning algorithms in which logical explanations of models are often lost due to the black box phenomenon (i.e., lack of interpretability), regression is generally seen as more comprehensible. Although research has been directed at improving the interpretability of more advance machine learning techniques,(see for example [29]) regression is generally deemed more suitable for the use in clinical populations.[30-34]

## Methodological considerations

The results and the implications of this thesis should be viewed in the light of several strengths and limitations. With the use of routine primary care data come both great opportunities and challenges. In recent years the increased quality of routine primary care data (i.e., both registration quality and technical advances) has provided many opportunities for scientific research. The data is generally low-cost and provides relatively easy access to rich, ecologically valid, longitudinal data from large populations.[35] On the other hand, registration of (especially) non-biomedical health information may be inconsistent (**chapter 3-6**) and depends highly on the patient's decision to visit the GP with a particular problem and the GP's or practice personnel's registration behavior. One of the major challenges of reusing routine care data is the methodological handling of missing data.[36-38] While data collected in a standardized way is generally missing at random and imputation techniques may be safely used, imputation for routine care data is less straightforward. In routine care data, it is common practice to assume that "missing data" means a factor is not present.[37,39] However, this is disputed by findings from **chapter 3-6**, that imply that especially data beyond the biomedical domain is likely to be sparsely recorded. Due to these considerations, imputation was not used for the reported studies.

A major strength of this thesis is the extensive research towards the aim of early identification of patients with PSS based on routine primary care data. The steps taken in this process highlights several factors that should be considered for future studies. First, **chapter 5** shows that there may be differences in predictors for PSS-subtypes and that the performance of all models in **chapter 6** (which includes a broad spectrum of PSS) is

markedly lower than the models in **chapter 5**. This could indicate that subtype-specific differences in predictors or registrations may impact the performance of the models. Second, although the survey in GPs (**chapter 3**) provided elaborate insight into registration behavior of Dutch GPs regarding PSS as an outcome, the survey lacked information on other outcomes (e.g., the registration of possible psychosocial predictors) that may be relevant to PSS. It should however be noted that, the results of the survey may be quite generalizable, even to countries using other classification systems, such as the ICD-11. This is indicated by studies that show that German GPs, who operate an ICD coded system, also have difficulties in registration and classification of PSS.[2,3,40] Finally, in hindsight, preliminary investigations should also have included investigations of differences in diagnostic delays between PSS-subtypes. The current literature does not contain information on syndrome specific diagnostic delays in primary care, which would be needed to evaluate how this may affect looking at the broad spectrum of PSS.

In all, the investigations in this thesis increased the validity of the defined candidate predictors and the outcome employed for the final modeling (**chapter 6**). Even so, due to the nature of the data, misclassification is inevitable and a major limitation to this research. Firstly, the outcome was not externally validated, and the prevalence rate was somewhat lower than prevalence in the general population. Second, candidate predictors in all models were compiled based on data with high levels of (nonrandom) missings. Although the applied design aimed to control for registration irregularities by compiling candidate predictors based on a variety of sources (such as ICPC, ATC, referrals, and lab results), success was limited for the desired early prediction model. Nonetheless, these results do reflect best the current clinical practice, since the data available is the data available to the GP, which increases the generalizability of the results.

## Clinical and societal implications

As described above, the implication of the clinical decision rule that can be derived from **chapter 6** has the potential to promote proactive population health management. Patients at risk for adverse health events (e.g., ineffective and counterproductive specialist referrals) are identified and exposed to less invasive investigations and

interventions). As such, the clinical decision rule indicates which patients require and would potentially benefit from an integrative care approach. Due to the multidomain origin of PSS, the implementation of an integrative approach is expected to result in early identification of PSS. Furthermore, the implementation of an integrative approach for the at-risk population could potentially impact the way physicians perceive PSS, improve consultations, and improve understanding between physician and patient. Studies have shown that an integrated approach to health has many benefits for patients, physicians, and society, for instance by increasing perceived quality of care and increasing survival rates in cancer.[41-43]

**Chapter 3** shows that many GPs report a need for more support in the diagnosis and classification of PSS. This indicates that GP training should be improved with more attention to consultations and classifications related to PSS. Improvements in GP training should for instance include training in communication skills that facilitate a broader integrative inquiry of problems.[21,22,44,45] Additionally, since PSS have a problematic history of being burdensome to clinical care, reframing of PSS is desirable. Johansen et al., 2017 makes a strong case for reframing using experience-based knowledge from senior GPs and integrate models from different disciplines.[1]

**Chapter 3-6** show a reported and observed lack of an unambiguous coding scheme for PSS. The simplest example to this ambiguity is the lack of a singular accepted clinical code for PSS. To optimize the utility of EMR data for clinical practice and research, PSS requires more globally accepted uniform coding schemes (that will increase interrater reliability). While a simple way towards the development of such a scheme has proven difficult in the past, the collaboration between groups of experts such as EURONET-SOMA, ICPC and ICD workgroups may be necessary.

In **chapter 5** (i.e., prediction of the three common PSS syndromes IBS, FM, and CFS, shortly prior to diagnosis) the algorithm's performance is sufficient for clinical implementation. Implementation of the algorithm in the GP's EMR software could support the GP in more prompt classification and treatment. Especially for FM, which has marked long diagnostic delays,[4] implementation could impact patients greatly, possibly

leading to more proactive intervention and consequential lessening of the disease burden.

In sum, the implementation of integrated care, an unambiguous coding scheme, and support for GPs (including but not limited to a clinical decision rule) is needed to improve care for patients with PSS and decrease the burden of PSS on the health care system.

## Future directions for data-based early recognition of PSS in primary care

The findings of this thesis provide a road map towards early identification of patients with PSS in primary care using data from EMRs. While the findings are promising, at present concise data-based identification of PSS diagnoses is limited. To improve predictive modeling for PSS with the current state of data, some promising approaches remain. Firstly, optimal utilization of unstructured (i.e., free text) data could possibly improve existing models. For the present study there was only limited accessibility and since GPs may be more prone to unstructured registration of factors beyond the medical domain (**chapter 3**). Natural language processing may assist in changing such data in quantifiable factors.[46] Second, although previous efforts showed limited success,[47] advances in the field of semantic enrichment (i.e., targeting irregularities in registrations), may improve future models. Finally, since different PSS syndromes have unique lengths of diagnostic delay, using different timelines for candidate predictor selection may enhance heterogeneity of predictor data. Future research could also employ simple data-based methods to identify patients at medium to high risk of PSS and test whether this, in combination with widely available screening questionnaires (i.e., 4DSQ, SSD-12, PHQ-15) can support the GP in early recognition of high PSS risk. Such a wide classification could be beneficial for the current trend towards more preventative health care and proactive population health management,[48,49] since measurable and controllable problems may be especially prevalent in patients with an elevated risk of PSS. Ultimately, the goal would be to improve the GPs understanding of the patient from different perspectives – even beyond the better known two-track policy (i.e., exploring both physical and mental health problems), rather towards a multi-track policy of integrated care (i.e., exploring problems from a biopsychosocial perspective and beyond). Thus, based on a simple algorithm implemented in the GP's EMR, the GP would

have a clearer direction for what patients the integrated approach may be most important. As a results, this may alleviate both the burden on the patient as well as increasing long-term time efficiency for primary care.

## In conclusion

Patients with somatic symptoms generally visit their GP to find a cause and treatment for their symptoms. Most GPs consider identifying a biomedical cause, an appropriate treatment, and if needed adequate referral of patients to secondary health care as their primary job. However, some somatic symptoms may be caused by a complex interplay between multidomain factors through which it is not possible to find a single biomedical cause for symptoms. Problems arise when symptoms persist or are aggravated without a well understood biomedical cause in line with the presentation (i.e., in the case of PSS). Besides obvious burden of disease on patient and health care costs related to repeated consultations and testing, this also puts a strain on GPs who reportedly do not have adequate training and tools to specifically identify patients with PSS early. Identifying early on whose somatic symptoms may not be explainable by a biomedical pathology but by problems from multiple biopsychosocial domains is key to improve care for patients with PSS. These patients may benefit from an integrated treatment approach (i.e., targeting a combination of biological, psychological, social, interpersonal, and contextual factors that influence the patients' health), also if they have identifiable comorbidity. This thesis shows that relatively simple data-based algorithms may help to identify patients at risk of PSS at an earlier stage. This suggests that a data-based clinical decision algorithm can provide support for GPs in early identification of PSS. With early identification, GPs can possibly direct patients at risk of PSS on track for an integrated treatment approach that may reduce the disease burden of both patient and the health care system.

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# Chapter 8

## Summary

## Summary

It is estimated that up to 10% of the general population experiences persistent somatic symptoms (PSS). PSS are symptoms that cannot be fully attributed to well-established biomedical pathology or to objectively determined anatomical or functional disease severity. The disease burden of PSS is often high for patients, physicians, and society. General practitioners (GPs) regularly experience difficulties in recognizing PSS and may search for a primary biomedical or psychological origin of the complaints for a long time. This approach may largely be unsuccessful due to the multidomain origin of PSS. Diagnostic difficulties are further complicated due to ambiguity in definitions and terminology of PSS. This complexity of diagnostics contributes to diagnostic delays and increases the burden of PSS, for instance by affecting the doctor-patient relationship, but also because it hampers timely and appropriate intervention. The main objective of this thesis was to promote early recognition of PSS in primary care. Due to the time constraints in primary care, the high health care utilization of patients with PSS, and the availability of large electronic medical record (EMR) datasets, the viability of a data-based approach towards predictive modeling of PSS was explored. A stepwise construction of the studies in this thesis leads to a comprehensive overview of the data available and needed to enable early data-based identification of PSS.

One of the preliminary steps towards predictive modeling of PSS was to map predictors of PSS from scientific literature. The goal of this step was to provide strong underpinning for theory-based predictive modeling using routine care data. Furthermore, this would provide insight into the availability of relevant data in GPs EMRs. Findings from the systematic review in **chapter 2** show that risk factors from the biomedical domain are currently dominant in scientific research on predictors of PSS. However, >250 predictors from all domains of the dynamic biopsychosocial model (i.e., biological, psychological, interpersonal, contextual, and health behavior) were identified. Of those, 46 were identified with adequate consistency in multiple studies. Overall, the review provides strong evidence that factors from all domains of the dynamic biopsychosocial model are important for PSS-onset. This suggests that a broad view on all possible related factors would enhance diagnostic accuracy in PSS.

Further preliminary investigations towards predictive modeling of PSS were related to determining an PSS outcome classifier and explore the GPs needs regarding PSS. The main obstacles towards developing a clinical prediction rule for PSS based on routine primary care data is the lack of a gold standard for PSS diagnosis and a data-based outcome classifier. To get insight in registration behavior and needs of GPs, a survey was distributed amongst Dutch GPs. The results of this survey shown in **chapter 3** demonstrate that the lack of an unambiguous method of identifying PSS is not only problematic from a research perspective, but also a problem for approximately half of GPs. Results show that GPs are likely to use a variety of structured (i.e., symptom-, diagnostic-, or generic-codes) and unstructured (i.e., free text) methods to register PSS. In addition to providing insight into registration practices of GPs, results from the survey confirmed that many GPs need more support or additional tools for consultations with patients (at risk of) PSS or PSS classification.

To select the most viable method for data-based identification of PSS, four methods were derived from the survey, in combination with clinical and literature-based knowledge. In **chapter 4**, the four methods were analyzed and evaluated. Results showed that a combination of three methods would enable the most accurate data-based identification of PSS. The final identification method consist of a combination of (1) clinical coding of PSS-syndromes, (2) unstructured episode descriptions of PSS, and (3) recorded outcomes of screening questionnaires. PSS-syndromes with clinical codes in Dutch EMRs are irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS). Unstructured episode descriptions can include a term synonymous to the aforementioned syndromes, but also include other PSS-syndromes (e.g., interstitial cystitis, vulvodynia, and tension headache), or be synonymous to PSS (e.g., functional complaints, somatoform, and unspecific pain). Finally, screening questionnaires include the 4-dimensional symptom questionnaire (4DSQ) which is regularly recorded in Dutch routine primary care data. A score of >20 on the somatic symptom subscale indicates PSS. With a total prevalence PSS of 8.6% in the study population, the combination of these three methods would approach general population prevalence of PSS.

Due to the knowledge that PSS has a multidomain origin and to overcome the overall predominance of biomedical structured data in routine primary care data, the viability of mental health registrations of predicting PSS diagnosis was tested in **chapter 5**. The prediction model in this chapter used mental health-related registrations from the five years directly prior to the PSS index date. In addition, it focused on the most common PSS syndromes with active ICPC codes in Dutch GP EMRs, namely IBS, FM, and CFS. This enabled further insight into similarities and differences between PSS-subtypes. The results showed that mental health registrations can predict PSS diagnosis with high accuracy. Model performance was different between PSS subtypes, with models for FM and CFS having the highest prediction value (AUC= .88 and AUC= .82, respectively) and the model for IBS being least predictive (AUC= .76). Although quantity of predictors was markedly lower for CFS, predictors generally overlap between PSS-subtypes (especially anxiety, psychosis, concentration disorders, addiction, and mental health-related referrals), while some factors may be unique to a specific syndrome, for example irritability and feeling old in IBS, delirium and developmental issues for FM, and disability due to mental illness for CFS.

Finally in **chapter 6**, results from all previous chapters are brought together to explore the optimal model for early prediction of PSS. For this study, routine care data from 76 general practices in the Netherlands were used, with an inclusion of 94,440 patients for the analyses. Candidate predictors were identified 2 to 7 years prior to PSS index date. The outcome was determined by combining the three data-based methods derived from **chapter 4**. To make optimal use of the large body of data and possibility to derive multidomain predictors, seven approaches were used to construct candidate predictors. First, two theory-driven approaches were used to extract candidate predictors. For this approach a combination of structured data was used to construct candidate predictors based on the systematic literature review in **chapter 2**. In addition, based on the knowledge derived from **chapter 3** that GPs psychosocial and behavioral indicators of PSS are most likely to be reported in the journal text, free text descriptions were extracted to form candidate predictors. Second, three non-temporal data-driven approaches were used to construct candidate predictors. Structured multidomain data from the EMRs, including symptom- and disease-codes (i.e., based ICPC-codes), medication prescriptions

(i.e., based on ATC-codes), and referrals, were dichotomized. Third, utilizing machine learning techniques, two temporal data-driven approaches were used to construct candidate predictors. The same structured multidomain data used in the non-temporal data driven approaches were used to find relevant temporal patterns. In addition, lab results were contextualized using relative grounding (i.e., indicating stable, increased, or decreased values of a particular lab test). Finally, LASSO logistic regression was applied to build 12 prediction models using a variety of combinations of 545 candidate predictors derived from the methods described above. This resulted in one baseline model, seven models based on each unique extraction approach described above, three models containing predictors from each extraction subcategory (i.e., theory-driven, and temporal and non-temporal data-driven models), and one model for which all candidate predictors were utilized (i.e., the full model). The full model showed that there is an underrepresentation of psychosocial predictors compared to what is expected based on the literature. Nonetheless, the used approaches were able to predict PSS registration with moderate certainty (AUC= .72). Despite the variety of candidate predictor extraction approaches, performance was fairly equal between the models (AUC's between .70 and .71). The performance of these models are markedly lower than the models presented in **chapter 5**. Although further research is needed to confirm this, the most notable differences are the lack of a prediction gap and the focus on specific PSS-syndromes in **chapter 5** compared to **chapter 6**.

In conclusion, this thesis provides comprehensive evidence that the multidomain nature of PSS makes the identification of PSS highly complex. The lack of an unambiguous system to diagnose and classify PSS is problematic from both a clinical as well as a research perspective, and GPs report a need for support to improve the care for patients with PSS. Despite registration difficulties, the results of this thesis show that analysis of routine primary care data can be used to develop tools to promote early recognition of PSS. Findings from this thesis indicate that the registrations of psychosocial factors should be improved to promote the reusability of data and to improve early recognition of PSS. Finally, for clinical purposes, the early prediction of PSS can be promoted based on this thesis by implementing a relatively simple non-temporal data-driven model based on ATC (medication) or ICPC (symptom and disease) codes. Such a clinical decision rule

should be implemented into the GPs EMR and flag patients at risk of PSS. Flagged patients would ideally receive multidomain care using an integrative (multi-track) approach, in which there is attention for psychological, social, interpersonal, and contextual factors, in addition to keeping track of any biomedical deterioration. In primary care this could result in (earlier) referral to interdisciplinary health care resources who may screen the patient for PSS and other multidomain problems such as mental health problems or problems in the social realm. If this results in earlier detection of PSS or other problems beyond the biomedical domain, this could enable earlier intervention which may limit deterioration of or even lead to recovery from symptoms. This will eventually result in lower health care utilization and cost, less pressure on GPs and lower disease burden for patients.

# Appendices

Nederlandse samenvatting (Dutch summary)

Acknowledgments (dankwoord)

Curriculum vitea

# Nederlandse samenvatting (Dutch summary)

Geschat wordt dat tot 10% van de bevolking aanhoudende lichamelijke klachten (ALK) ervaart. De lichamelijke klachten die we nu als ALK omschrijven zijn klachten waarvoor artsen geen duidelijke (medische) verklaring kunnen vinden. Er zijn verschillende termen en definities voor ALK, welke vaak afhankelijk zijn van het gezondheidszorg domein. Zo werd ALK eerder in de (huisarts)geneeskunde omschreven als (ernstige) “somatisch onvoldoende verklaarde lichamelijke klachten” (SOLK) en zijn termen als “somatoforme stoornis” of “somatische symptoomstoornis” gebruikelijker in de geestelijke gezondheidszorg. De klachten die mensen met ALK ervaren zijn langdurig en patiënten ondervinden er veel last van. Naast voor de patiënten, zijn de klachten ook ingewikkeld voor artsen. Zo vinden (huis)artsen het vaak moeilijk om deze klachten te onderscheiden van klachten die wel verband hebben met een herkenbare medische oorzaak. Huisartsen besteden vaak veel tijd aan het vinden van een medische of psychologische oorzaak van de klachten, terwijl ALK meestal veroorzaakt wordt door een complexe samenkomst van problemen in meerdere domeinen (bijvoorbeeld zowel biologische, psychologische als sociale problemen). Het stellen van een ALK diagnose is bovendien vaak ingewikkeld omdat er veel verschillende definities en termen door elkaar worden gebruikt. Al met al is er dus vaak vertraging in de herkenning van ALK. Dit kan grote gevolgen hebben voor de patiënt en de zorg. Zo is bekend dat hierdoor de arts-patiëntrelatie kan verslechteren. Daarnaast kan het gebrek aan adequaat ingrijpen op klachten deze in stand doen houden of verergeren. Daarom is het hoofddoel van dit proefschrift om een manier te vinden om (huis-)artsen te ondersteunen in de vroege herkenning van ALK. Omdat er veel gegevens beschikbaar zijn in de elektronische patiëntendossiers van huisartsen en analyse en terugkoppeling uit die dossiers mogelijk een efficiënte oplossing zou kunnen zijn voor de al zo drukke huisarts, hebben we ons als doel gesteld om te kijken hoe we deze gegevens kunnen gebruiken om ALK vroegtijdig te voorspellen. De onderzoeken in dit proefschrift zijn stapsgewijs opgebouwd om de beschikbare en benodigde gegevens voor vroege herkenning van ALK op basis van patiëntdossiergegevens in kaart te brengen.

Om het voorspellen van ALK op basis van patiëntdossiergegevens mogelijk te maken hebben we eerst een overzicht gemaakt van alle problemen die ten grondslag kunnen

liggen aan ALK. Hiervoor hebben we een groot overzicht gemaakt op basis van beschikbare wetenschappelijke artikelen. Bevindingen uit deze systematische literatuurstudie, beschreven in **hoofdstuk 2,** laten zien dat problemen uit het biomedische domein het meeste onderzocht zijn en veel hiervan (bijv. infecties en het hebben van veel verschillende klachten) voorspellen ook het ontstaan van ALK. Echter, uit de resultaten van het onderzoek bleek ook dat er meer dan 250 problemen zijn ontdekt die voorspellend zijn voor ALK. Deze voorspellers komen uit alle biopsychosociale domeinen (biologisch, psychologisch, interpersoonlijk, contextueel en gezondheidsgedrag). Van deze ruim 250 voorspellers bleek er voor 46 voorspellers veel bewijs te zijn dat ze ten grondslag liggen aan het ontstaan van ALK (er zijn meerdere onderzoeken van goede kwaliteit die deze klachten aanmerken als voorspellers). Concluderend toont deze literatuurstudie aan dat problemen uit alle biopsychosociale domeinen belangrijk kunnen zijn bij het ontstaan van ALK. Dit wijst erop dat een brede kijk op problemen in al deze domeinen van belang is om de vroege herkenning van ALK te verbeteren.

Een ingewikkeld obstakel voor het maken van een voorspelmodel voor ALK op basis van patiëntdossiergegevens is het ontbreken van een eenduidige manier om ALK te diagnosticeren en registreren. Het selecteren van patiënten met ALK is namelijk de eerste stap in het maken van een voorspelmodel. Om inzicht te krijgen in hoe ALK dan wel wordt geregistreerd en hoe huisartsen dit ervaren en waar hun behoeften liggen omtrent ALK registratie en zorg, hebben we een enquête onderzoek gedaan onder Nederlandse huisartsen. De resultaten van dit onderzoek, weergegeven in **hoofdstuk 3**, laten zien dat het ontbreken van een eenduidige methode om ALK te registreren niet alleen een probleem is vanuit onderzoeksperspectief, maar ook voor ongeveer de helft van de huisartsen een praktisch probleem is. De resultaten laten ook zien dat huisartsen veel verschillende manieren gebruiken om ALK te registreren in het patiëntdossier. Deze manieren verschillen zowel tussen huisartsen, maar ook kan een huisarts zelf verschillende manieren gebruiken die verschillen per klacht of patiënt. Huisartsen gebruiken in de registratie niet alleen vaak verschillende codes (symptoom-, diagnostische of generieke codes), maar omschrijven de klachten ook vaak verschillend

in de journaaltekst. Ten slotte laten de resultaten zien dat veel huisartsen behoefte hebben aan meer ondersteuning of aanvullende hulpmiddelen (zoals diagnostische vragenlijsten) voor de consultvoering met patiënten met ALK.

Om patiënten met ALK te kunnen selecteren in de elektronische patiëntdossiers van huisartsen, hebben we vier methoden onderscheden, die zijn afgeleid uit eerder wetenschappelijk onderzoek en de resultaten van bovenbeschreven enquête-onderzoek. In **hoofdstuk 4** zijn de vier methoden geanalyseerd en geëvalueerd. De resultaten laten zien dat een combinatie van drie van de onderzochte methoden de meest nauwkeurige manier is om ALK te selecteren. De selectiemethode bestaat uit een combinatie van (1) klinische codering van ALK-syndromen, (2) ongestructureerde episodebeschrijvingen van ALK en (3) geregistreerde uitkomsten van screeningvragenlijsten. ALK-syndromen (1) met klinische codes in huisarts-patiëntdossiers zijn prikkelbare darmsyndroom, fibromyalgie en chronisch vermoeidheidssyndroom. Ongestructureerde episodebeschrijvingen (een korte omschrijving van de klacht door de huisarts) (2) zijn geselecteerd wanneer deze een term bevatten die synoniem is voor de bovengenoemde of andere ALK-syndromen omvatten (bijvoorbeeld blaaspijnsyndroom, tinnitus of spanningshoofdpijn), of synoniem zijn voor ALK (bijvoorbeeld functionele klachten, somatoforme en niet-specifieke pijn). Tot de screeningsvragenlijsten (3) behoort de 4-dimensionale symptoomvragenlijst die regelmatig wordt vastgelegd in de Nederlandse reguliere eerstelijnszorggegevens. Een score van >20 op de subschaal “somatische symptomen” wijst op ALK. In totaal bleek op basis hiervan 8,6% in de patiënten in de bruikbare dossiers ALK te hebben.

Zoals eerder onderzoek heeft laten zien, heeft ALK een multidomein oorsprong. Verder is er bekend dat huisartsen hoofdzakelijk biomedische klachten gestructureerd (door middel van codes) registreren. Om na te gaan in hoeverre dit een probleem is, hebben we in het onderzoek omschreven in **hoofdstuk 5** onderzocht of registraties gerelateerd aan psychische gezondheid voldoende beschikbaar zijn om te voorspellen welke patiënten ALK-syndromen ontwikkelen. Het onderzoek richtte zich op de meest voorkomende ALK-syndromen (prikkelbare darmsyndroom, fibromyalgie en chronisch vermoeidheidssyndroom). Dit zijn de enige ALK-syndromen die een registratiecode hebben in Nederlandse huisarts-patiëntdossiers. Door aparte voorspelmodellen voor

ieder syndroom te maken is het bovendien mogelijk om overeenkomsten en verschillen tussen ALK-subtypes in kaart te brengen. Huisartsregistraties in de patiëntdossiers vijf jaar direct voorafgaande aan de ALK-subtype diagnose zijn gebruikt als voorspellers (het betreft hier dus niet zozeer een vroege voorspelling). De resultaten laten zien dat de diagnose van een ALK-subtype op basis van de registraties van psychische klachten goed voorspeld kan worden. Daarbij waren fibromyalgie en chronisch vermoeidheidssyndroom het beste te voorspellen (respectievelijk, 88% en 82% zekerheid) en het prikkelbare darmsyndroom iets minder goed (76%). Hoewel de hoeveelheid voorspellers aanzienlijk lager was voor chronisch vermoeidheidssyndroom, overlappen voorspellers tussen ALK-subtypes over het algemeen (vooral angst, psychose, concentratiestoornissen, verslaving en verwijzingen naar geestelijke gezondheidszorg). Echter, sommige factoren bleken uniek voor een specifiek syndroom, bijvoorbeeld prikkelbaarheid en zich oud voelen bij prikkelbare darmsyndroom, delirium en ontwikkelingsproblemen bij fibromyalgie, en invaliditeit als gevolg van psychische aandoeningen bij chronisch vermoeidheidssyndroom.

Ten slotte zijn in **hoofdstuk 6** de resultaten van alle voorgaande hoofstukken gebruikt om te onderzoeken hoe we ALK het beste vroegtijdig kunnen voorspellen. Voor dit onderzoek zijn gegevens uit de reguliere zorg van 76 huisartspraktijken in Nederland toegankelijk gemaakt, waarbij gegevens van 94.440 patiënten konden worden gebruikt voor de analyses. Registraties van twee tot zeven jaar voorafgaand aan de eerste ALK-registratie werden gebruikt om mogelijke voorspellers te bepalen. Een combinatie van de drie selectiemethodes uit hoofdstuk 4 werd gebruikt voor de uitkomstmaat (de eerste ALK-registratie). Om optimaal gebruik te maken van de grote hoeveelheid gegevens en de mogelijkheid om multidomein voorspellers te vinden, werden zeven benaderingen gebruikt om mogelijke voorspellers te bepalen. Er werden *twee theorie-gedreven benaderingen* gebruikt om mogelijke voorspellers te bepalen. Een van de theorie-gedreven methoden was het construeren van voorspellers op basis van voorspellers gevonden in het systematische literatuuronderzoek in hoofdstuk 2. Zo werden variabelen geconstrueerd op basis van een combinatie van gestructureerde gegevens (bijvoorbeeld zowel een symptoomcode voor depressie als een medicatiecode voor antidepressiva werden als ‘depressie’ aangemerkt). De tweede theorie-gedreven methode kwam tot

stand op basis van de kennis uit hoofdstuk 3 dat huisartsen psychosociale en gedragsindicatoren doorgaans in het journaaltekst rapporteren. Zo werden vrije-tekstbeschrijvingen die gerelateerd zijn aan ALK geëxtraheerd om mogelijke voorspellers te construeren. Verder werden *drie niet-temporele data-gedreven benaderingen* gebruikt om mogelijke voorspellers te construeren. De aan- of afwezigheid van gestructureerde multidomein-gegevens van de elektronische patiëntdossiers, waaronder symptoom- en ziektecodes, medicatievoorschriften en verwijzingen, werden genoteerd. Ten slotte werden met behulp van machine learning-technieken *twee temporele data-gedreven benaderingen* (patronen van gegevens over de tijd) toegepast om mogelijke voorspellers te construeren. Dezelfde gestructureerde multidomein-gegevens die worden gebruikt in de niet-temporele data-gedreven benaderingen, werden gebruikt om relevante temporele patronen te vinden (bijv. opeenvolgende registratie van buikpijn, verwijzing naar fysiotherapie en voorschrift van maagzuurremmer). Tevens werden op basis van de registratie van laboratoriumuitslagen bepaald of er verhoging, verlaging of stabiel blijvende lab-uitslagen waren. Ten slotte werd LASSO-logistische regressie toegepast om twaalf voorspellingsmodellen te ontwikkelen met behulp van verschillende combinaties van de 545 mogelijke voorspellers die uit de hierboven beschreven benaderingen zijn afgeleid. Dit resulteerde in één basismodel, zeven modellen gebaseerd op elke hierboven beschreven unieke extractiebenadering, drie modellen met voorspellers uit elke extractiesubcategorie (theorie-gestuurde en temporele en niet-temporele data-gedreven modellen), en één model waarvoor alle mogelijke voorspellers werden gebruikt (het volledige model). Uit het volledige model blijkt een ondervertegenwoordiging van psychosociale voorspellers in vergelijking met wat op basis van de literatuur kan worden verwacht. Desalniettemin waren de gebruikte benaderingen in staat om ALK-registratie met matige zekerheid te voorspellen (72%). Ondanks de verschillende benaderingen om voorspellers te construeren, waren de prestaties van alle modellen redelijk gelijk (70-71%). De prestaties van deze modellen zijn echter aanzienlijk lager dan die van de modellen gepresenteerd in hoofdstuk 5. Hoewel verder onderzoek nodig is om te bevestigen of het de werkelijke oorzaken van de verschillen zijn, zijn de meest opvallende verschillen het ontbreken van een voorspellingskloof (data direct voorafgaande aan ALK-registratie ten opzichte van data vanaf twee tot vijf jaar

voorafgaande aan ALK-registratie) en de focus op specifieke ALK-syndromen in hoofdstuk 5 in vergelijking met hoofdstuk 6.

Concluderend levert dit proefschrift uitgebreid bewijs dat de multidomein oorsprong van ALK de selectie en herkenning van ALK zeer complex maakt. Het ontbreken van een eenduidige methode om ALK te diagnosticeren en registreren is zowel voor onderzoek als de (huisarts)praktijk problematisch. Daarnaast geven huisartsen aan behoefte te hebben aan ondersteuning om de zorg voor patiënten met ALK te verbeteren. Ondanks registratieproblemen laten de resultaten van dit proefschrift zien dat analyse van huisarts dossiergegevens mogelijk gebruikt kan worden om hulpmiddelen te ontwikkelen die vroege herkenning van ALK ondersteunen. Bevindingen uit dit proefschrift geven aan dat de registratie van psychosociale factoren moet worden verbeterd om de herbruikbaarheid van patiëntdossier gegevens te bevorderen en de vroege herkenning van ALK te verbeteren. Ten slotte kan de vroege voorspelling van ALK voor klinische doeleinden worden bevorderd op basis van dit proefschrift door een relatief eenvoudig (niet-temporeel) data-gedreven model (op basis van medicatie- of symptoom-codes) te gebruiken. Een dergelijke klinische beslisregel zou kunnen worden geïmplementeerd in het elektronische patiëntdossier van huisartsen, waarbij patiënten die risico lopen op ALK worden gemarkeerd. Idealiter ontvangen gesignaleerde patiënten interdisciplinaire zorg volgens een integratieve (meer-sporen) benadering, waarbij naast het bijhouden van eventuele biomedische achteruitgang ook aandacht is voor psychologische, sociale, interpersoonlijke en contextuele factoren. In de eerste lijn zou de implementatie van een klinische beslisregel mogelijk kunnen leiden tot eerdere en meer gerichte doorverwijzing naar interdisciplinaire zorg voor problemen waar dat relevant voor is. Hier zou de patiënt dan uitgebreider gescreend kunnen worden op ALK en andere multidomein problematiek zoals psychische problematiek of problemen op sociaal gebied, met een relatief grotere kans op het vinden van behandelbare aanknopingspunten. Als hierdoor ALK of andere problemen buiten het biomedische domein eerder worden gesignaleerd, kan eerder worden ingegrepen om zo te voorkomen dat klachten verergeren of om herstel mogelijk te maken. Dit zal uiteindelijk leiden tot lager zorggebruik en -kosten, minder druk op de huisarts en een lagere ziektelast voor de patiënt.

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# Curriculum Vitae

Willeke Kitselaar was born in Waalwijk, the Netherlands in 1985. For admission to the bachelors' program psychology at Tilburg University she completed a colloquium doctum (i.e., VWO level math, biology, and English) in 2009. She completed the bachelors' in health psychology at Tilburg University in 2013. Her bachelors' thesis on the neurobiology of chronic pain, marked her interest in research and the field of persistent somatic symptoms. Subsequently, she continued with the two-year masters' program in Medical Psychology at Tilburg University, completing the research track 'Biological Psychology' in 2015. During her masters' she did research on fatigue in patients who underwent craniotomy for tumor resection and completed her master thesis on stress responses in patients with coronary artery disease.

After completion of her masters, she continued at Tilburg University to complete her research on fatigue. After a period of traveling and working as a research assistant at the University of South Australia, where she contributed to a project on motor consolidation after mindfulness meditation, she started her PhD research in 2017. The PhD project was part of the profile area 'health prevention and the human life cycle' which marked the collaboration between the department of Medical, Health, and Neuropsychology of Leiden University and the Health Campus The Hague of the LUMC. During her PhD she co-founded the interdisciplinary European PSS early career researchers' network.

In 2021 she started working for NeurolabNL as a researcher investigating the mental health impact of the COVID pandemic and became involved in the EMOVERE citizen science project focusing on recovery from persistent somatic symptoms (PSS) whilst finishing her PhD thesis. Since April 2023, she works as a postdoctoral researcher at the Biological Psychology department of VU Amsterdam as part of the consortium project Stress in Action. In this project her main mission is to harmonize data from Dutch cohorts with ambulatory stress-related data and to investigate how daily life stress impacts health. Besides her work as a researcher, since 2014, Willeke is an active facilitator of mindfulness groups and has organized several mindfulness retreats for young people.

Als je het gewoon doet,

gebeurt het gewoon.