Promoting early recognition of persistent somatic symptoms in primary care

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Chapter 2

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

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Abstract

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

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

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

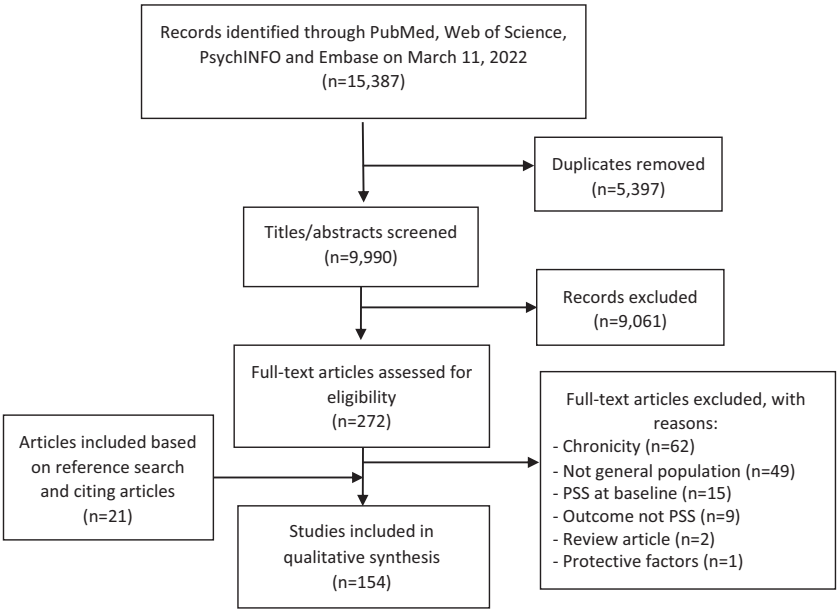
Table 1. Levels of Evidence

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 Sweden	1852	52.7 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 Psychological Interpersonal
Bernhardt, et al., 2011	Prospective study (Study of Health) Germany	3134	non-cases: 52.3 - cases: 45.8 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 Psychological Contextual
Bonvanie et al., 2015[d]	Prospective study (TRAILS) Netherlands	2230	50.8 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) Netherlands	2230	55.0 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) USA	1908	53.9 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 Interpersonal Contextual
Brummond et al., 2015	Prospective study (Olmsted County population) USA	4893	53.0 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) Canada	218	49.4 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) Taiwan	16875	52 61.6 (7.0)	Musculoskeletal pain (Self report, >3 months)	7.2	**Diabetes+**.	Biological
Chan et al., 2017	EMR cohort (NHIRD/ LHID2005) Taiwan	13358	88.4 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) UK	92835	100 36.9 (12.5) [b]	Fibromyalgia & CFS (N239, N248 & F286)	3.2	**Intimate partner violence+.**	Interpersonal
Chang et al., 2015	EMR cohort (NHIRD/ LHID2000) Taiwan	85710	60.7 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) Taiwan	22795	58.3 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 Psychological Contextual Health behaviour
Cremon et al., 2014	Prospective study (Salmonella outbreak 1994) Italy	331	65.4 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 Psychological 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) 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 Psychological Contextual Health behaviour
Cremon et al., 2014	Prospective study (Salmonella outbreak 1994) Italy	331	65.4 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 Psychological Contextual
Currie & Wang, 2005	Prospective study (NPHS) Canada	9909	52.0 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 Psychological
Davies et al., 2009[E]	Prospective study (EPIFUND) UK	5190	56.4 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) Taiwan	27230	49.5 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) Germany	1016556	50.7 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)) New Zealand	408	52.2 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 Scotland	852	51.7 ≥ 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) USA	587961	48.6 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) UK	3659	56.0 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) UK	6902	50.8 45 yrs.	Chronic widespread pain (Self-report, ACR criteria for fibromyalgia)	34.0	**IQ at age 11+**, gender, **social class-**, **education-**, **smoking+**, **BMI+**, **GHQ-12 score+**	Biological Psychological Contextual Health behaviour
Goodwin et al., 2011	Birth cohort (British Birth Cohort study 1958) UK	17415	both 34 (7)	CFS/ME (self-report)	9.0 19.0 26.0 31.0 35.0	**Psychopathology+** (any externalizing/internalizing problems at age 23 and 33, multiple reports age 16-33), **malaise+**, energy levels, activity level.	Biological Psychological
Goodwin et al., 2013	Birth cohort (British Birth Cohort study 1958) UK	17415	both median: 34 (28-38)	IBS (self-report)	26.0 31.0 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 Adulthood: **psychopathology+** (age 23 and 33),	Biological Psychological Interpersonal Contextual
Gupta et al., 2007[E]	Prospective study (EPIFUND) UK	3171	56.5 25-65	Chronic widespread pain (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 Psychological Interpersonal 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) Norway	13781	56.5 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)) UK	13164	68.5 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 Health behaviour
Hanevik et al., 2014[f]	Prospective study Norway	1160	68.1 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) UK	5362	50.9 53	CFS/ME (semi-structured interview, trained nurses)	10.0 17.0 22.0 38.0 40.0 47.0 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 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
Heuch et al., 2013[h]	Prospective study (HUNT 2+3) Norway	18882	53.7 41-80	Chronic LBP (Self-report, ≥ 3 months)	11.0	**BMI+**.	Biological
Heuch et al., 2014a[h]	Prospective study (HUNT 2+3) Norway	17209	47.9 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) Norway	18882	53.8 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) Norway	18784	53.6 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) Norway	18784	53.6 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) Norway	18068	53.2 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) Norway	4822	56.4 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) Norway	18972	54.0 41-80	Chronic LBP (Self-report, ≥ 3 months)	11.0	**Diabetes+** (only men).	Biological
Heuch et al., 2022	Prospective study (HUNT 2+3) Norway	5394, 11659	100.0 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) UK	8572	52.2 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) UK	1189	58.0 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) UK	994	58.0 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) Taiwan	22575	60.3 ≥20yrs [b]	Tinnitus (ICD-9-CM, specialist diagnosis)	7.5	**Anxiety disorder+.**	Psychological
Howell et al., 2004	Birth cohort (Dunedin) New Zealand	980	46.3 26	IBS (Manning/Rome criteria)		**Childhood SES+.**	Contextual
Hsu et al., 2015	EMR cohort (NHIRD) Taiwan	281775	19.9 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) Taiwan	51485	54.0 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) UK	5371	N/A	IBS (Specialist diagnosis)	4.0	**Asthma+.**	Biological
Hunskar et al., 2012[F]	Retrospective cohort (Bergen) Norway	1945	65.7 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) Norway	216	53.2 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) UK	5481	51.0 N/A	IBS (Read code)	2.0	**Depression+, anxiety+, asthma+, UTI+, gall-bladder surgery+, hysterectomy+.** Referral to: **general surgery+, general medicine+, gynaecology+, psychiatry+.**	Biological Psychological Health behaviour
Jones et al., 2007[I]	Birth cohort (British Birth Cohort study 1985) UK	7470	both 45	Chronic widespread pain (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) UK	7517	both 45	Chronic widespread pain (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 Interpersonal
Jones et al., 2011[E]	NCC cohort (EPIFUND) UK	7517	57.4 25-65	Chronic widespread pain (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) Taiwan	53772	100 50.4 (16.4)	Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) (ICD-9-CM 327.23, 780.51, 780.53, or 780.57)	3.0	**Reflux esophagitis+.**	Biological
Kim et al., 2019	EMR cohort (HIRA) Korea	203410	74.5 ≥20 yrs. [b]	BPPV (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) Korea	51833	65.6 20-60 [b]	BPPV (ICD-10: H81.1, at least 2x)	12.5	**Mood disorder+**.	Psychological
Kim et al., 2020b	EMR cohort (NHIS- HEALS) Korea	32772	both 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) UK	17638	48.7 42	IBS & CFS (self-report)	31.0	Childhood cognitive ability.	
Klooker et al., 2009	Birth cohort (Dutch Famine Birth Cohort) Netherlands	1423	55.0 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 Australia	1002	52.1 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 Australia	767	48.2 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 Australia	1900	53.0 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) Canada	10007	54.3 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 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
Kopec et al., 2004[m] (continued)							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, 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)) Canada	9552	55.4 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 Interpersonal Contextual
Kowalcyk et al., 2014	EMR cohort (NHIRD/ LHID2000) Taiwan	4782	Both 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 Psychological Contextual Health behavioural
Larrosa Pardo et al., 2019	EMR cohort (Skåne Healthcare Register) Sweden	419291, 803805	50-100 >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) Germany	3134	51.9 non-cases: 48.9 (15.4) - 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 Psychological Contextual
Lau et al., 2015	EMR cohort (NHIRD) Taiwan	34510	73.3 45.5 (15.1)	CFS (ICD-9-CM: 780.71)	2.0	**Migraine+, age+,** sex, **hypertension+, diabetes+, hyperlipidaemia+, anxiety+, depression+, coronary artery disease+.**	Biological Psychological Contextual
Lei et al., 2016	EMR cohort (NHIRD/ LHID2003) Taiwan	53016	30.2 exposed: 47.9 (14.8) 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 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) Taiwan	13345	34.1 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) Taiwan	3134	52.6 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) Taiwan	98265	58.5 ≥ 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) Norway	1945	65.7 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) Norway	1289	66.0 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) UK	9377	both 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) Taiwan	4,560	100.0 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) UK	9377	42.7 45	Chronic widespread pain (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 Psychological Interpersonal Contextual
Marrie et al., 2009	EMR cohort (Manitoba Health) Canada	25132	Both ≥20 yrs. [b]	Fibromyalgia (ICD-9 or ICD-10)	20.0	**Multiple sclerosis+, age+.**	Biological Contextual
Marshall et al., 2006	Prospective study (Walkerton Health Study) USA	2069	55.5 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) USA	3280	55.5 49.3 (15.5)	IBS (Self-report & clinical record, Rome I criteria)	8.0	**Acute gastroenteritis+**	Biological
Masters et al., 2015	EMR cohort (Humedica) USA	587961	64.6 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 Psychological 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 18-64	Chronic widespread pain (Self-report, ACR criteria for fibromyalgia)	1.0	**Illness behaviour+, somatic symptoms+, GHQ+, fatigue+**, health anxiety.	Biological Psycholog. Health behaviour
McBeth et al., 2003[p]	Prospective study UK	1403	both 18-65	Chronic widespread pain (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 non-cases: 61 (53-67) - cases: 62 (54-67) [b]	Chronic widespread pain (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 Psychological Interpersonal Contextual, Health behaviour
McCabe et al., 2016	Prospective study (EMAS) Europe	2313	0.0 58.8 (10.6) [b]	Chronic widespread pain (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 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
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 Psychological Interpersonal 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 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) Norway	12350	100.0 ≥ 20 [b]	Fibromyalgia (self-report)	11.0	**Sleep problems+.**	Biological
Mork et al., 2013	Prospective study (HUNT) Norway	27715	57.5 ≥ 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) Norway	26896	both ≥ 20 [b]	Chronic back pain (self-report, ≥ 3 months)	11.0	**Sleep problems+**.	Biological
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 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) Norway	20799	54.4 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 ≥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 Contextual Health behaviour
Nicholl et al., 2010[T]	NCC cohort (EPIFUND & EMAS) UK	994	66.0 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 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 43-45	Musculoskeletal pain in the low back or neck/shoulders (self-report, standardized Nordic Questionnaire)	11.0	**Weight+, activity level-**.	Biological Health behaviour
Nitter et al., 2012	Prospective study Norway	577	100.0 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 Psychological Contextual
Odegard et al., 2011	Prospective study (HUNT 2+3) Norway	14042	non-exposed: 48.4 - with exposed: 53.4 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) Taiwan	7634281	Both ≥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) UK	8572	both 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) Norway	1571	67.3 ≥18	IBS, functional dyspepsia, chronic fatigue, overactive bladder syndrome (Self-report, Rome III)	6.0	**Giardia+**.	Biological
Picavet et al., 2002	Prospective study (DMC3) Netherlands	1161	57.3 25-64	Chronic LBP (validated questionnaire)	0.5	**Pain catastrophizing+**, kinesiophobia.	Biological Psychological
Pico-Espinosa et al., 2017	Prospective study (Stockholm Public Health Cohort) Sweden	10044	49.4 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) Finland	5466	52.2 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 USA	1312	100.0 38.6 (1.3)	Chronic fatigue (Interview, ≥ 6 months)	0.4	9/11 terrorist attack.	Inter-personal
Raslau et al., 2016	NCC (Olmsted County) USA	178	61.0 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 USA	906	100.0 36.9 (8.6)	Vulvodynia (Self-report, ≥ 3 months)	36.9	Oral contraceptives.	Biological
Reed et al., 2014	Prospective study USA	1786	100.0 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 Psychological Contextual
Rodriguez & Ruigomez, 1999	EMR cohort (General Practice Research Database) UK	584626	47.9 25-74 [b]	IBS (Doctor diagnosed, random sample for confirmation)	1.0	**Gastroenteritis+**.	Biological
Ruigomez et al., 2003	EMR cohort (General Practice Research Database) UK	90119	100 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 Psychological Contextual Health behaviour
Ruigomez et al., 2007	EMR cohort (General Practice Research Database) UK	6105	Both ≥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 Psychological Contextual Health behaviour
Ruigomez et al., 2009	EMR cohort (General Practice Research Database) UK	6421	Both ≥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) Taiwan	148239	53.9 54 (18.1) [b]	IBS (ICD-9 564.1)	10.0	**Asthma+,** gender**, age+, COPD+, GERD+, allergic rhinitis+, chronic sinusitis+, atopic dermatitis+, anxiety+, depression+, obesity+, follow-up year+.**	Biological Psychological Contextual
Shih et al., 2017	EMR cohort (NHIRD) Taiwan	741720	45.7 ≥ 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 Contextual
Shih et al., 2018	EMR cohort (NHIRD) Taiwan	123120	48.2 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 Contextual.
Sivertsen et al., 2014	Prospective study (HUNT 2+3) Norway	24715	56.9 45.3 (19-67)	Fibromyalgia (Self-report)	11.0	**Insomnia+.**	Psycho-logical
Skarpsno et al., 2019a	Prospective study (Tromsø study) Norway	6356	50.6 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 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[s]	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[s]	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) Norway	13429	59.3 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) UK	8572	50.9 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 Contextual Health behaviour
Varinen et al., 2019	Retrospective study (HeSSup) Finland	11409	65.7 20-54 [b]	Fibromyalgia (self-report)	10.0	**Bullying+** (only severe bullying), **age+, gender+** (female), **education-, marital status-, depression+.**	Psychological Interpersonal
Viner et al., 2004	Birth cohort (BGS70) UK	11266	62.8 30	CFS/ME (self-report)	20.0 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 Psychological Contextual Health behaviour
Waehrens et al., 2018	EMR cohort Sweden	1963685	48.6 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 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
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.