



Universiteit  
Leiden  
The Netherlands

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

Kitselaar, W.M.

### Citation

Kitselaar, W. M. (2023, June 27). *Promoting early recognition of persistent somatic symptoms in primary care*. Retrieved from <https://hdl.handle.net/1887/3628068>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3628068>

**Note:** To cite this publication please use the final published version (if applicable).

# Chapter 2

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

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

Based on: Kitselaar WM, van der Vaart R, Perschl J, Numans ME, Evers AWM. Predictors of Persistent Somatic Symptoms in the General Population: A Systematic Review of Cohort Studies. *Psychosomatic Medicine* 85(1):p 71-78, January 2023.  
DOI: 10.1097/PSY.0000000000001145

## 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.<sup>1–4</sup> So-called, persistent somatic symptoms (PSS) – symptoms without identified biomedical pathophysiology – are prevalent in both patients with well-understood disorders, such as cancer<sup>5</sup> and cardiovascular disease,<sup>6</sup> as well as in patients without well-understood disorders.<sup>7–9</sup> 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.<sup>10</sup> Terminology and classification for PSS vary widely across and within health care domains and disciplines.<sup>11</sup> 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.<sup>4,12,13</sup> While these days most experts accept that there are common overarching factors as well as syndrome-specific factors,<sup>14,15</sup> historically, etiological research focusing on PSS is heterogeneous in nature – i.e., often directed at subcategories of PSS.<sup>11</sup>

Deficient biomedical pathophysiological explanations for PSS have redirected attention to other health domains for astute identification and effective treatment.<sup>13,16,17</sup> 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.<sup>18,19</sup> In response to increasing knowledge that health and disease depend on more than biomedical pathology, the biopsychosocial model of health was introduced.<sup>20</sup> 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.<sup>21</sup> 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.<sup>16,17</sup> 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,<sup>22</sup> 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,<sup>23</sup> 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 <sup>24</sup>). 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).

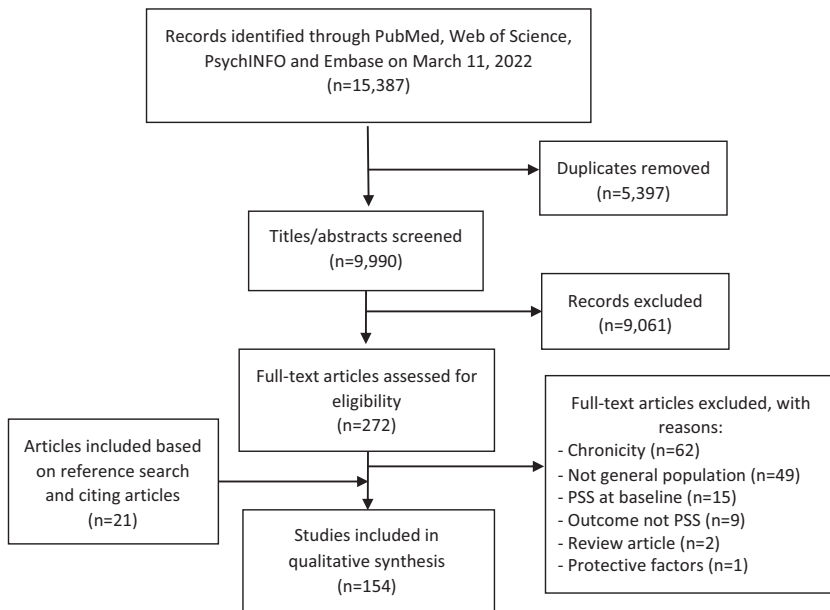
**Table 1.** Levels of Evidence

| Levels of evidence  | Criteria                                                                                                                                                                                                         |
|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Strong</b>       | <ul style="list-style-type: none"> <li>Investigated in at least 6 studies, of which &gt;75% consistent findings</li> </ul>                                                                                       |
| <b>Moderate</b>     | <ul style="list-style-type: none"> <li>Investigated in 3 to 5 studies, with at least &gt;75% consistent finding, or;</li> <li>Investigated by at least 6 studies of which &gt;65% consistent findings</li> </ul> |
| <b>Limited</b>      | <ul style="list-style-type: none"> <li>Investigated in 2 studies with 100% consistency, or;</li> <li>Investigated in 3 to 5 studies with &gt;65% consistent findings</li> </ul>                                  |
| <b>Inconclusive</b> | <ul style="list-style-type: none"> <li>Inconsistent findings (&lt;65% consistency) more than 6 studies, or;</li> <li>Found 100% predictive in &lt; 2 studies.</li> </ul>                                         |

## 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<br>154 articles (n=173)<br>n (%) <sup>†</sup> |
|------------------------------------------------------|-----------------------------------------------------------------------|
| <b><i>Chronic pain-related PSS</i></b>               |                                                                       |
| 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)                                                               |
| <b><i>Gastrointestinal-related PSS</i></b>           |                                                                       |
| Irritable bowel syndrome (IBS)                       | 40 (23.3)                                                             |
| Functional dyspepsia                                 | 6 (3.5)                                                               |
| Any functional gastrointestinal disorder             | 1 (0.6)                                                               |
| <b><i>Fatigue-related PSS</i></b>                    |                                                                       |
| Chronic fatigue syndrome (CFS/ME)                    | 18 (10.5)                                                             |
| Chronic fatigue                                      | 6 (3.5)                                                               |
| <b><i>Other specific PSS</i></b>                     |                                                                       |
| 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)                                                               |
| <b><i>Unspecified PSS</i></b>                        |                                                                       |
| Functional somatic symptoms (FSS)                    | 2 (1.2)                                                               |
| Medically unexplained symptoms (MUS)                 | 1 (0.6)                                                               |

<sup>†</sup> 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 <sup>†</sup> | Predictors of PSS <sup>‡</sup>                                                                                                                                                                                                     |
|----------------------|-------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Biological</b>    | 122 (79.2)              | <i>Strong</i>                   | Infections <sup>a</sup> , body weight-related metrics <sup>b</sup> , somatic symptoms, abdominal pain, other general medical illnesses, headaches or migraine, gastrointestinal disorders, renal disease, allergies <sup>c</sup> . |
|                      |                         | <i>Moderate</i>                 | Musculoskeletal conditions, rheumatological disorders, (TMJ) muscle tenderness on palpation, any type of chronic pain, genes, endometriosis, cardiovascular disease, skin disorders.                                               |
|                      |                         | <i>Limited</i>                  | Low back pain, back/neck pain with neuropathy, cerebrovascular disease, dyslipidaemia, injury, menstrual disorders, osteoporosis, vitamin D status.                                                                                |
| <b>Psychological</b> | 61 (39.6)               | <i>Strong</i>                   | Sleep problems <sup>e</sup> , anxiety, depression <sup>d</sup> , psychopathology/mental health, fatigue.                                                                                                                           |
|                      |                         | <i>Moderate</i>                 | Personality type <sup>f</sup> , quality of life.                                                                                                                                                                                   |
|                      |                         | <i>Limited</i>                  |                                                                                                                                                                                                                                    |
| <b>Interpersonal</b> | 26 (16.9)               | <i>Strong</i>                   | Life events, childhood adversity <sup>g</sup> , interpersonal stress <sup>h</sup> .                                                                                                                                                |
|                      |                         | <i>Moderate</i>                 |                                                                                                                                                                                                                                    |
|                      |                         | <i>Limited</i>                  | Social support.                                                                                                                                                                                                                    |
| <b>Contextual</b>    | 64 (41.6)               | <i>Strong</i>                   | Employment.                                                                                                                                                                                                                        |
|                      |                         | <i>Moderate</i>                 | Age, socio-economic status.                                                                                                                                                                                                        |
|                      |                         | <i>Limited</i>                  | Intelligence.                                                                                                                                                                                                                      |
| <b>Health</b>        | 37                      | <i>Strong</i>                   | Health care utilization <sup>k</sup> .                                                                                                                                                                                             |
| <b>behaviours</b>    | (24.0)                  | <i>Moderate</i>                 | Physical activity, illness behaviour, medications used, alcohol (use and abuse), pain medication use <sup>m</sup> .                                                                                                                |
|                      |                         | <i>Limited</i>                  |                                                                                                                                                                                                                                    |

\* 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.

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

Less established factors for which no conclusive evidence was found, were approximately 200 factors investigated only once or showing inconsistent findings in  $\geq 6$  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.<sup>25,26</sup> 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<sup>17</sup> and IBS.<sup>16</sup> 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,<sup>27</sup> 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,<sup>1,18,19</sup> related to stress,<sup>1,19</sup> and having (neuro)biological consequences.<sup>28</sup> 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.<sup>29,30</sup> 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.<sup>31,32</sup>

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.<sup>33–36</sup> Several empirical studies,<sup>25,37</sup> 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.<sup>34,38</sup> 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.<sup>34,39</sup> 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,<sup>40,41</sup> 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.<sup>42,43</sup> 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.<sup>44–47</sup> Nonetheless, illness behaviour has been related to other PSS by many others.<sup>48</sup>

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,<sup>11,16,17,48–51</sup> for instance Klem et al.<sup>50</sup> found increased risk of IBS after infection, especially in women, patients using antibiotics, as well as patients with depression, somatization, and anxiety. Similarly, Hulme<sup>51</sup> 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.<sup>16,17</sup> 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,<sup>21</sup> 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<sup>52</sup> 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.<sup>48,49,53,54</sup> 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.

### **Acknowledgments**

This study was funded by the Executive Board of Leiden University through the profile area “Health, Prevention and the Human Life Cycle” and hosted by the Faculty of Social and Behavioural Sciences of Leiden University and Leiden University Medical Centre at Campus The Hague. With gratitude we thank Jan Schoones for his help with executing the search and Esmeralda Harris-Mostert, and Clariska H. van Biessum-Smit for the time and effort they put into the screening of articles.

## References

- 1 Katon W, Lin EHB, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007; 29: 147–55.
- 2 Rief W, Burton C, Frostholm L, et al. Core Outcome Domains for Clinical Trials on Somatic Symptom Disorder, Bodily Distress Disorder, and Functional Somatic Syndromes: European Network on Somatic Symptom Disorders Recommendations. *Psychosom Med* 2017; 79: 1008–15.
- 3 Kroenke K. A practical and evidence-based approach to common symptoms: A narrative review. *Ann Intern Med*. 2014; 161: 579–86.
- 4 Petersen MW, Schröder A, Jørgensen T, et al. Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD. *Sci Rep* 2020; 10.
- 5 Grassi L, Caruso R, Nanni MG. Somatization and somatic symptom presentation in cancer: A neglected area. *International Review of Psychiatry* 2013; 25: 41–51.
- 6 Kohlmann S, Gierk B, Hummelgen M, Blankenberg S, Lowe B. Somatic Symptoms in Patients With Coronary Heart Disease: Prevalence, Risk Factors, and Quality of Life. *JAMA Intern Med* 2013; 173: 1469–71.
- 7 Toft T, Fink P, Oernboel E, Christensen K, Frostholm L, Olesen F. Mental disorders in primary care: prevalence and co-morbidity among disorders. Results from the functional illness in primary care (FIP) study. *Psychol Med* 2005; 35: 1175–84.
- 8 Verhaak PFM. Persistent presentation of medically unexplained symptoms in general practice. *Fam Pract* 2006; 23: 414–20.
- 9 Kop WJ, Toussaint A, Mols F, Löwe B. Somatic symptom disorder in the general population: Associations with medical status and health care utilization using the SSD-12. *Gen Hosp Psychiatry* 2019; 56: 36–41.
- 10 Sirri L, Grandi S, Tossani E. Medically unexplained symptoms and general practitioners: a comprehensive survey about their attitudes, experiences and management strategies. *Fam Pract* 2017; 34: 201–5.
- 11 Henningsen P, Gündel H, Kop WJ, et al. Persistent Physical Symptoms as Perceptual Dysregulation. *Psychosom Med* 2018; 80: 422–31.
- 12 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *The Lancet* 1999; 354: 936–9.
- 13 Chalder T, Willis C. “Lumping” and “splitting” medically unexplained symptoms: is there a role for a transdiagnostic approach? *Journal of Mental Health*. 2017; 26: 187–91.
- 14 Cano-García FJ, Muñoz-Navarro R, Sesé Abad A, et al. Latent structure and factor invariance of somatic symptoms in the patient health questionnaire (PHQ-15). *J Affect Disord* 2020; 261: 21–9.

- 15 Withthöft M, Fischer S, Jasper F, Rist F, Nater UM. Clarifying the latent structure and correlates of somatic symptom distress: A bifactor model approach. *Psychol Assess* 2016; 28: 109–15.
- 16 Creed F. Review article: the incidence and risk factors for irritable bowel syndrome in population-based studies. *Aliment Pharmacol Ther* 2019; 50: 507–16.
- 17 Creed F. A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. *Pain* 2020; 161: 1169–76.
- 18 Kop WJ, Synowski SJ, Gottlieb SS. Depression in Heart Failure: Biobehavioral Mechanisms. *Heart Fail Clin*. 2011; 7: 23–38.
- 19 Prince M, Patel V, Saxena S, et al. No health without mental health. *The Lancet* 2007; 370: 859–77.
- 20 Engel GL. The clinical application of the biopsychosocial model. *Journal of Medicine and Philosophy (United Kingdom)* 1981; 6: 101–23.
- 21 Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. *Soc Personal Psychol Compass* 2017; 11.
- 22 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372.
- 23 Wells G, Shea B, O’Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute. 2000.
- 24 Traa MJ, De Vries J, Roukema JA, Den Ouden BL. Sexual (dys)function and the quality of sexual life in patients with colorectal cancer: A systematic review. *Annals of Oncology* 2012; 23: 19–27.
- 25 He Q, Yang Y, Xia M, et al. Sex differences in risk factors for interstitial cystitis/painful bladder syndrome in patients with lower urinary tract symptoms in China. *Surg Pract* 2015; 19: 69–74.
- 26 Buskila D, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: The possible role of infection and vaccination. *Autoimmun Rev* 2008; 8: 41–3.
- 27 Den Boeft M, Van Der Wouden JC, Rydell-Lexmond TR, De Wit NJ, Van Der Horst HE, Numans ME. Identifying patients with medically unexplained physical symptoms in electronic medical records in primary care: A validation study. *BMC Fam Pract* 2014; 15: 109.
- 28 Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron* 2002; 34: 13–25.
- 29 Low EXS, Mandhari MNK AI, Herndon CC, Loo EXL, Tham EH, Siah KTH. Parental, Perinatal, and Childhood Risk Factors for Development of Irritable Bowel Syndrome: A Systematic Review. *J Neurogastroenterol Motil* 2020; 26: 437–46.
- 30 Kaleycheva N, Cullen AE, Evans R, Harris T, Nicholson T, Chalder T. The role of lifetime stressors in adult fibromyalgia: Systematic review and meta-analysis of case-control studies. *Psychol Med* 2021; 51: 177–93.
- 31 Fritz J, de Graaff AM, Caisley H, van Harmelen AL, Wilkinson PO. A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry* 2018; 9.

- 32 Ogbe E, Harmon S, van den Bergh R, Degomme O. A systematic review of intimate partner violence interventions focused on improving social support and/ mental health outcomes of survivors. *PLoS One* 2020; 15.
- 33 Walton DM, Pretty J, MacDermid JC, Teasel RW. Risk Factors for Persistent Problems Following Whiplash Injury: Results of a Systematic Review and Meta-analysis. *Journal of Orthopaedic & Sports Physical Therapy* 2009; 39: 334–50.
- 34 Lovell RM, Ford AC. Effect of gender on prevalence of irritable bowel syndrome in the community: Systematic review and meta-analysis. *American Journal of Gastroenterology*. 2012; 107: 991–1000.
- 35 Parreira P, Maher CG, Steffens D, Hancock MJ, Ferreira ML. Risk factors for low back pain and sciatica: an umbrella review. *The Spine Journal* 2018; 18: 1715–21.
- 36 Nondahl DM, Cruickshanks KJ, Huang GH, et al. Tinnitus and its risk factors in the Beaver Dam Offspring Study. *Int J Audiol* 2011; 50: 313–20.
- 37 Hooftman WE, van Poppel MNM, van der Beek AJ, Bongers PM, van Mechelen W. Gender differences in the relations between work-related physical and psychosocial risk factors and musculoskeletal complaints. *Scand J Work Environ Health*. 2004; 30: 261–78.
- 38 Walton DM, MacDermid JC, Giorgianni AA, Mascarenhas JC, West SC, Zammit CA. Risk Factors for Persistent Problems Following Acute Whiplash Injury: Update of a Systematic Review and Meta-analysis. *Journal of Orthopaedic & Sports Physical Therapy* 2013; 43: 31–43.
- 39 Larsson B, Björk J, Börsbo B, Gerdle B. A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. *European Journal of Pain (United Kingdom)*. 2012; 16: 1084–93.
- 40 Jeffery DD, Bulathsinhala L, Kroc M, Dorris J. Prevalence, health care utilization, and costs of fibromyalgia, irritable bowel, and chronic fatigue syndromes in the military health system, 2006–2010. *Mil Med* 2014; 179: 1021–9.
- 41 Monden R, Rosmalen JGM, Wardenaar KJ, Creed F. Predictors of new onsets of irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia: The lifelines study. *Psychol Med* 2020; 1–9.
- 42 Sadeghian M, Sadeghi O, Hassanzadeh Keshteli A, Daghighzadeh H, Esmailzadeh A, Adibi P. Physical activity in relation to irritable bowel syndrome among Iranian adults. *PLoS One* 2018; 13: e0205806.
- 43 Hennings A, Schwarz MJ, Riemer S, Stapf TM, Selberdinger VB, Rief W. Exercise affects symptom severity but not biological measures in depression and somatization – results on IL-6, neopterin, tryptophan, kynurenine and 5-HIAA. *Psychiatry Res* 2013; 210: 925–33.
- 44 McBeth J, Harkness EF, Silman AJ, Macfarlane GJ. The role of workplace low-level mechanical trauma, posture and environment in the onset of chronic widespread pain. *Rheumatology (Oxford)* 2003; 42: 1486–94.
- 45 Gupta A, Silman AJ, Ray D, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology* 2007; 46: 666–71.

- 46 McBeth J, Macfarlane GJ, Benjamin S, Silman AJ. Features of somatization predict the onset of chronic widespread pain: Results of a large population-based study. *Arthritis Rheum* 2001; 44: 940–6.
- 47 Mcbeth J, Mulvey MR, Rashid A, Anderson J, Druce K. The relationship between regional pain with or without neuropathic symptoms and chronic widespread pain. 2019.
- 48 Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet*. 2007; 369: 946–55.
- 49 Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: Systematic review. *Br Med J* 2001; 322: 1511–6.
- 50 Klem F, Wadhwa A, Prokop LJ, et al. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; 152: 1042-1054.e1.
- 51 Hulme K, Hudson JL, Rojczyk P, Little P, Moss-Morris R. Biopsychosocial risk factors of persistent fatigue after acute infection: A systematic review to inform interventions. *J Psychosom Res*. 2017; 99: 120–9.
- 52 Creed F. The risk factors for self-reported fibromyalgia with and without multiple somatic symptoms: The Lifelines cohort study. *J Psychosom Res* 2022; 155: 110745.
- 53 Burton C, Fink P, Henningsen P, Löwe B, Rief W. Functional somatic disorders: Discussion paper for a new common classification for research and clinical use. *BMC Med* 2020; 18: 1–7.
- 54 van der Feltz-Cornelis CM, Elfeddali I, Werneke U, et al. A European research agenda for somatic symptom disorders, bodily distress disorders, and functional disorders: Results of an estimate-talk-estimate Delphi expert study. *Front Psychol* 2018; 9: 151.

## 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 "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,<br>year published | Representativeness of<br>exposed cohort | Non-exposed drawn from<br>same community | Random/ consecutive<br>selection of subjects | Risk factor assessment | Outcome not present at<br>baseline | Adjusted for age+sex | Adjusted for most<br>important confounders | Outcome assessment | Length follow-up (months) | Adequacy of<br>follow-up | Assessment risk of bias<br>(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 ZI 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,<br>year published  | Representativeness of<br>exposed cohort | Non-exposed drawn from<br>same community | Random/ consecutive<br>selection of subjects | Risk factor assessment | Outcome not present at<br>baseline | Adjusted for age+sex | Adjusted for most<br>important confounders | Outcome assessment | Length follow-up (months) | Adequacy of<br>follow-up | Assessment risk of bias<br>(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                     |
| Kopeck et al., 2004        | a                                       | a                                        | yes                                          | c                      | yes                                | no                   | yes                                        | c                  | 24                        | c                        | poor quality                     |
| Kopeck et al., 2005        | a                                       | a                                        | yes                                          | c                      | yes                                | no                   | yes                                        | c                  | 48                        | b                        | poor quality                     |
| Kowalczyk 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 et 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,<br>year published  | Representativeness of<br>exposed cohort | Non-exposed drawn from<br>same community | Random/ consecutive<br>selection of subjects | Risk factor assessment | Outcome not present at<br>baseline | Adjusted for age+sex | Adjusted for most<br>important confounders | Outcome assessment | Length follow-up (months) | Adequacy of<br>follow-up | Assessment risk of bias<br>(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, %<br>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 <sup>c</sup>  | Prospective study                             |         | 1852           | 52.7                                                     | Chronic widespread pain & chronic regional pain (Self-report, ACR criteria for fibromyalgia) | 3.0                         | <b>SF-36 (physical functioning+, role physical+, role emotional+ (only for regional pain), bodily pain+, general health+, vitality+, social functioning+, mental health+</b>                                                                                                                                                | Biological<br>Psychological<br>Interpersonal |
|                                    | Sweden                                        |         |                | 20-64                                                    |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |
| Bernhardt, et al., 2011            | Prospective study (Study of Health)           |         | 3134           | non-cases: 52.3 - cases: 45.8                            | Tinnitus (Diagnosis by ENT specialist)                                                       | 5.2                         | <b>Palpation pain in the temporomandibular joint (TMJ)+, age+, gender, education-, muscle tenderness on palpation+, reported TMJ pain, headache+, depression.</b>                                                                                                                                                           | Biological<br>Psychological<br>Contextual    |
|                                    | Germany                                       |         |                | non-cases: 48.9 (15.4) - cases: 57.1 (12.6)              |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |
| Bonvanie et al., 2015 <sup>d</sup> | Prospective study (TRAILS)                    |         | 2230           | 50.8                                                     | Functional Somatic Symptoms (Somatic Complaints subscale of the Adult Self-Report ASR)       | 8.0                         | <b>Perfectionism+</b>                                                                                                                                                                                                                                                                                                       | Health behaviour                             |
|                                    | Netherlands                                   |         |                | 19.0 (0.6)                                               |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |
| Bonvanie et al., 2017 <sup>d</sup> | Prospective study (TRAILS)                    |         | 2230           | 55.0                                                     | Functional Somatic Symptoms (Somatic Complaints subscale of the Adult Self-Report ASR)       | 8.0                         | Life events ( <b>non-illness-related+</b> , illness related, <b>severity+</b> ).                                                                                                                                                                                                                                            | Interpersonal                                |
|                                    | Netherlands                                   |         |                | 19.0 (0.6)                                               |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |
| Brown et al., 2018                 | Prospective study (MIDUS)                     |         | 1908           | 53.9                                                     | Chronic pain (self-report, $\geq$ few months & BPI)                                          | 10.0                        | <b>Discrimination+</b> , personality(In(K6), neuroticism, <b>conscientiousness+</b> , agreeableness), gender- (female), <b>age+</b> , race ( <b>black+</b> , other), education, <b>marital status-</b> , <b>income-</b> , religion, <b>past chronic pain+</b> , ADL, height, disabled, health insurance, <b>employed-</b> . | Biological<br>Interpersonal<br>Contextual    |
|                                    | USA                                           |         |                | 54 (30-84)                                               |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |
| Brummond et al., 2015              | Prospective study (Olmsted County population) |         | 4893           | 53.0                                                     | IBS (Self-report, Rome III)                                                                  | 2.0-95.0                    | <b>Birth cohort 1913-1922+</b> , Birth cohort 1923-1932, Birth cohort 1933-1942, Birth cohort 1943-1952, Birth cohort 1953-1962, Birth cohort 1973-1983                                                                                                                                                                     | Contextual                                   |
|                                    | USA                                           |         |                | 58 (15)                                                  |                                                                                              |                             |                                                                                                                                                                                                                                                                                                                             |                                              |

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

| Author, year published | Study type (cohort)          | Country | sample size, n | Female gender, %<br>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)     |         | 218            | 49.4                                                     | Neck and low back pain                                     | 0.5, 1.0                    | Depression+.                                                                                                                                                                                                                        | Psychological                       |
|                        | Canada                       |         |                | 44.5 (13.5) <sup>b</sup>                                 | (Chronic Pain Questionnaire, ≥ 6 months)                   |                             |                                                                                                                                                                                                                                     |                                     |
| Carvalho et al., 2020  | EMR cohort (NHIRD)           |         | 16875          | 52                                                       | Musculoskeletal pain (Self report, >3 months)              | 7.2                         | Diabetes+.                                                                                                                                                                                                                          | Biological                          |
|                        | Taiwan                       |         |                | 61.6 (7.0)                                               |                                                            |                             |                                                                                                                                                                                                                                     |                                     |
| Chan et al., 2017      | EMR cohort (NHIRD/ LHID2005) |         | 13358          | 88.4                                                     | 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               |
|                        | Taiwan                       |         |                | NA                                                       |                                                            |                             |                                                                                                                                                                                                                                     |                                     |
| Chandan et al., 2021   | EMR cohort (THIN cohort)     |         | 92835          | 100                                                      | Fibromyalgia & CFS (N239, N248 & F286)                     | 3.2                         | Intimate partner violence+.                                                                                                                                                                                                         | Interpersonal                       |
|                        | UK                           |         |                | 36.9 (12.5) <sup>b</sup>                                 |                                                            |                             |                                                                                                                                                                                                                                     |                                     |
| Chang et al., 2015     | EMR cohort (NHIRD/ LHID2000) |         | 85710          | 60.7                                                     | Fibromyalgia (ICD-9-CM: 729.1)                             | 8.0                         | Depression+, migraine+, low back pain+, asthma+, allergic rhinitis+, atopic dermatitis+, hypertension+, diabetes mellitus+, dyslipidaemia+.                                                                                         | Biological Psychological            |
|                        | Taiwan                       |         |                | 39.4 (16.5) <sup>b</sup>                                 |                                                            |                             |                                                                                                                                                                                                                                     |                                     |
| Chen et al., 2016      | EMR cohort (NHIRD/ LHID2000) |         | 22795          | 58.3                                                     | 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 |
|                        | Taiwan                       |         |                | 43 <sup>†</sup>                                          |                                                            |                             |                                                                                                                                                                                                                                     |                                     |

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

| Author, year published | Study type (cohort)                 | Country | sample size, n | Female gender, %<br>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<br><br>Non exposed: 55.7 (16.3)<br>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<br><br>cases: 47.0 (16.5) –<br>n-cases: 46.8 (16.6) <sup>b</sup> | Fibromyalgia (ICD-9-CM: 729.1)                                                                                 | 12.0                                | Inflammatory bowel disease+.                                                                                                                                                                                                                                                                                                   | Biological                                                 |
| Chu et al., 2015       | EMR cohort (NHIRD)                  | Taiwan  | 16532          | 72<br><br>< 40 (53.3%) -<br>>40 (46.7%) <sup>b</sup>                  | BPPV (ICD-9-CM: 386.11)                                                                                        | 6.3                                 | Migraine+.                                                                                                                                                                                                                                                                                                                     | Biological                                                 |
| Chung et al., 2014     | EMR cohort (NHIRD/LHID2000)         | Taiwan  | 32340          | 39.0<br><br>47.1 (15.7) <sup>b</sup>                                  | 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<br>Contextual<br>Health behaviour               |
| Clark et al., 2011     | Birth cohort (British Birth Cohort) | UK      | 11419          | both<br><br>42                                                        | CFS (self-report)                                                                                              | 9.0<br>19.0<br>26.0<br>31.0<br>35.0 | Gender<br>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<br>Psychological<br>Interpersonal<br>Contextual |

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

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

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

| Author, year published                 | Study type (cohort)                          | Country     | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.)     | Outcome (measurement type, definition)                               | Length of follow-up (years) | Measured factors                                                                                                                                                                                                                                                                                                                                                                                                                            | Investigated domains                                          |
|----------------------------------------|----------------------------------------------|-------------|----------------|--------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| <b>Creed, 2022</b>                     | Prospective cohort (Lifelines)               | Netherlands | 150714         | N/A                                                          | Fibromyalgia (Self-report)                                           | 3                           | Female sex+, years of education+, low income, work>32h per week+, unable to work through illness+, BMI, <4 allergies+, >2 times per week alcohol+, no of analgesics+, chronic cystitis+, asthma/any inhaler+, osteoarthritis+, rheumatoid arthritis+, RSI+, IBS+, chronic inflammation of throat/nasal cavity+, migraine+, no of psychiatric disorders+, life events+, no of healthcare contact in 5 yrs.+, somatic symptom score+, sleep+. | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| <b>Cremon et al., 2014</b>             | Prospective study (Salmonella outbreak 1994) | Italy       | 331            | 65.4<br><br>Non-exposed: 31.1 (16.3)<br>– exposed: 33.6 (18) | IBS (Self-report, Rome III)                                          | 16.0                        | Salmonella infection+, age, gender+ (female), functional dyspepsia+, PCS-12+, MCS-12+, HADS anxiety+, HADS depression.                                                                                                                                                                                                                                                                                                                      | Biological<br>Psychological<br>Contextual                     |
| <b>Currie &amp; Wang, 2005</b>         | Prospective study (NPHS)                     | Canada      | 9909           | 52.0<br><br>exposed: 36.2 - non-exposed: 43.1 <sup>b</sup>   | Chronic back pain (self-report, ≥ 6 months)                          | 2.0                         | Major depression+, number chronic medical conditions+, back/neck injury in previous 12 months+.                                                                                                                                                                                                                                                                                                                                             | Biological<br>Psychological                                   |
| <b>Davies et al., 2009<sup>e</sup></b> | Prospective study (EPIFUND)                  | UK          | 5190           | 56.4<br><br>cases: 46.4-48.8, non-cases: 45.9-46.8           | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 1.3                         | Area level SES-, gender, age.                                                                                                                                                                                                                                                                                                                                                                                                               | Contextual                                                    |
| <b>Dai et al., 2022</b>                | EMR cohort (NHIRD)                           | Taiwan      | 27230          | 49.5<br><br>34.1 (13.5)<br><sup>b</sup>                      | 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, %<br>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     | 101655<br>6    | 50.7<br>35.1 <sup>b</sup>                                | IBS & CFS (ICD-10: K58 or F45.32)                                                                                                                          | 5.0                         | Age+, female gender, <b>gastrointestinal infections+</b> (salmonella, campylobacter, Escherichia coli, other bacterial infection, proto-zoon infection), <b>viral infection+, non-specific infection+, depression+, anxiety+, time of infection+</b> (only for CFS).        | Biological<br>Psychological<br>Contextual                                      |
| Duncan et al., 2019    | Birth cohort (Christchurch Health and Development Study (CHDS))       | New Zealand | 408            | 52.2<br>30-38                                            | Medically Unexplained Symptoms (medical records, referral to secondary care in 2 or more occasions, diagnosis of known MUPS, e.g. fibromyalgia, headaches) | 9.0                         | Sexual abuse (age 0-16), abuse not involving penetration, <b>abuse involving sexual penetration+</b> .                                                                                                                                                                      | Interpersonal                                                                  |
| Elliott et al., 2002   | Prospective study                                                     | Scotland    | 852            | 51.7<br>≥ 25 yrs.                                        | Chronic pain (Validated questionnaire, CPG)                                                                                                                | 4.1                         | Sex, age, education, housing tenure, <b>employment-, SF-36 health domains+, marital status-</b> .                                                                                                                                                                           | Biological, Psychological, Interpersonal, Contextual, Health behaviour         |
| Emir et al., 2015      | EMR cohort (Humedica)                                                 | USA         | 587961         | 48.6<br>cases: 53.3 (14.6)<br>– Non-cases: 52.7 (16.3)   | Fibromyalgia (ICD-9: 780.73, at least 2x)                                                                                                                  | 1.0                         | <b>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+</b> . | Biological<br>Health behaviour                                                 |
| Ford et al., 2008      | Prospective study (Helicobacter pylori screening + treatment program) | UK          | 3659           | 56.0<br>50-59                                            | IBS (questionnaire w/ Manning criteria)                                                                                                                    | 10.0                        | Age, <b>gender+</b> , H.pylori status, marital status (single/married), smoking status, <b>alcohol use+</b> , coffee drinker, ethnicity (white/nonwhite), <b>SES-, NSAID use+, Aspirin use+, dyspepsia+, QoL-</b> .                                                         | Biological<br>Psychological<br>Interpersonal<br>Contextual<br>Health behaviour |

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

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

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

| Author, year published            | Study type (cohort)                                                                    | Country | sample size, n | Female gender, %<br>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<br>47.1 (13.2) <sup>b</sup>                         | 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<br>median: 41 (31-53)                               | Chronic fatigue (GPRD codes)                                                      | 3.0                                                  | BMI, systolic blood pressure, <b>primary care utilization+</b> (consultations, prescriptions, antibiotics, sickness certificate, referral), <b>abdominal pain+</b> , <b>fatigue symptom+</b> , <b>dizziness+</b> , <b>other abdominal symptoms+</b> , <b>any infection+</b> , <b>depressive disorders+</b> , <b>functional disorder+</b> , <b>menstrual disorders+</b> , <b>child birth+</b> , <b>atopy+</b> , <b>immunization+</b> , <b>upper respiratory tract infection+</b> , influenza-like illness, <b>gastroenteritis+</b> , <b>immunization+</b> , <b>fractures</b> , <b>tonsillitis+</b> , <b>viral infection+</b> . | Biological<br>Health behaviour               |
| Hanevik et al., 2014 <sup>f</sup> | Prospective study                                                                      | Norway  | 1160           | 68.1<br>exposed: 39.2, non-exposed: 41.0                 | IBS & chronic fatigue (Self-report, Rome III & Fatigue questionnaire, ≥ 6 months) | 6.0                                                  | <b>Giardia infection+</b> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Biological                                   |
| Harvey et al., 2008a <sup>g</sup> | Birth cohort 1946 (Medical Research Council National Survey of Health and Development) | UK      | 5362           | 50.9<br>53                                               | CFS/ME (semi-structured interview, trained nurses)                                | 10.0<br>17.0<br>22.0<br>38.0<br>40.0<br>47.0<br>53.0 | <b>Gender+</b> (female), weight at birth and age 7, <b>BMI at age 36+, 43+</b> 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, <b>energy level+</b> , sports ability, ability to sport. Adulthood: hay fever, skin trouble, allergies, atopic illness, family atopy, fitness, <b>sports or keep fit activities ≥4 times a month+</b> , <b>sport at least once a week+</b> .                                                                                                | Biological<br>Contextual<br>Health behaviour |

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

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

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

| Author, year published             | Study type (cohort)                             | Country     | sample size, n | Female gender, %<br>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 <sup>e</sup> | NCC cohort (EPIFUND)                            | UK          | 994            | 58.0<br>50.9 (49.8 to 52.0) <sup>b</sup>                 | 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<br>≥20yrs <sup>b</sup>                              | Tinnitus (ICD-9-CM, specialist diagnosis)                                                 | 7.5                         | Anxiety disorder+                                                                                                                                                                                                            | Psychological                             |
| Howell et al., 2004                | Birth cohort (Dunedin)                          | New Zealand | 980            | 46.3<br>26                                               | IBS (Manning/Rome criteria)                                                               |                             | Childhood SES+                                                                                                                                                                                                               | Contextual                                |
| Hsu et al., 2015                   | EMR cohort (NHIRD)                              | Taiwan      | 281775         | 19.9<br>35 to 65 years (69.9%) <sup>b</sup>              | 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<br>30-39†                                           | BPPV (diagnosed by neurologists or otorhinolaryngologists)                                | 10.0                        | Depressive disorder+, age, sex, hypertension+, diabetes, dyslipidaemia+, coronary artery disease+, hyperthyroidism+, hypothyroidism, cerebrovascular disease+, systemic lupus erythematosus, degree of urbanization, income. | Biological<br>Psychological<br>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 <sup>f</sup>  | Retrospective cohort (Bergen)                   | Norway      | 1945           | 65.7<br>36.2                                             | IBS & Chronic fatigue (Self-report, Rome III & Chalder fatigue questionnaire, ≥ 6 months) | 3.0                         | Giardiasis i.c.w. asthma, giardia i.c.w. allergy                                                                                                                                                                             | Biological                                |
| Iversen et al., 2017               | Prospective study (Trondheim)                   | Norway      | 216            | 53.2<br>26                                               | Chronic pain (Self-report, SF-36, ≥ 6 months)                                             | 26.0                        | Birth weight-, small for gestational age.                                                                                                                                                                                    | Biological                                |

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

| Author, year published          | Study type (cohort)                             | Country | sample size, n | Female gender, %<br>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<br>N/A                                              | IBS (Read code)                                                                                   | 2.0                         | Depression+, anxiety+, asthma+, UTI+, gall-bladder surgery+, hysterectomy+. Referral to: general surgery+, general medicine+, gynaecology+, psychiatry+.                                                                                                                                                                                                                                                | Biological<br>Psychological<br>Health behaviour |
| Jones et al., 2007 <sup>i</sup> | Birth cohort (British Birth Cohort study 1985)  | UK      | 7470           | both<br>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 <sup>i</sup> | Birth cohort (British Birth Cohort study 1985)  | UK      | 7517           | both<br>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<br>Interpersonal                     |
| Jones et al., 2011 <sup>e</sup> | NCC cohort (EPIFUND)                            | UK      | 7517           | 57.4<br>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<br>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<br>≥20 yrs. <sup>b</sup>                            | 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, %<br>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<br>20-60 <sup>b</sup>                               | BPPV (ICD-10: H81.1, at least 2x)                                                                        | 12.5                        | Mood disorder+.                                                                                                                                                                                                                                                        | Psychological                                                               |
| Kim et al., 2020b                 | EMR cohort (NHIS- HEALS)                                       | Korea       | 32772          | both<br>40-60 <sup>b</sup>                               | 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<br>42                                               | IBS & CFS (self-report)                                                                                  | 31.0                        | Childhood cognitive ability.                                                                                                                                                                                                                                           |                                                                             |
| Klooker et al., 2009              | Birth cohort (Dutch Famine Birth Cohort)                       | Netherlands | 1423           | 55.0<br>58                                               | IBS (Self-report, Rome II)                                                                               | 58.0                        | Historic time of birth: during/shortly after world war II+.                                                                                                                                                                                                            |                                                                             |
| Koloski et al., 2012 <sup>k</sup> | Prospective study                                              | Australia   | 1002           | 52.1<br>45.1                                             | Any functional gastrointestinal disorder (FGID) & IBS & functional dyspepsia (FD) (Self-report, Rome II) | 12.0                        | Anxiety+ (only any FGID and IBS), depression+ (only IBS and FD).                                                                                                                                                                                                       |                                                                             |
| Koloski et al., 2015 <sup>k</sup> | Prospective study                                              | Australia   | 767            | 48.2<br>59.9 (11.5)                                      | IBS & functional dyspepsia (FD) (Self-report, Rome III)                                                  | 12.0                        | Gastroenteritis+ (only IBS), antibiotic use+ (only IBS), overseas travel, caesarean delivery, prematurity, breastfed, duration of breastfeeding-, pet exposure, herbivore pet+, carnivore pet+ (only FD), omnivore pet, sharing bedroom+, hygiene factors+ (only IBS). |                                                                             |
| Koloski et al., 2016 <sup>k</sup> | Prospective study                                              | Australia   | 1900           | 53.0<br>57 (14)                                          | IBS & functional dyspepsia (FD) (Self-report, modified Rome III)                                         | 1.0                         | Anxiety+, depression+.                                                                                                                                                                                                                                                 |                                                                             |
| Kopeck et al., 2004 <sup>m</sup>  | Prospective study (Canadian National Population Health Survey) | Canada      | 10007          | 54.3<br>18-65+                                           | Chronic back pain (self-report, ≥ 6 months)                                                              | 2.0                         | Male: age, height+, self-rated health-, usual daily activities+, gardening-, chronic stress index+.<br>Female: activity restriction+, arthritis/rheumatism+, personal stress index+, psychological childhood trauma+ (only ≥ 2). Weight, BMI, smoke exposure,          | Biological<br>Psychological<br>Interpersonal<br>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, %<br>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 <sup>m</sup><br>(continued) |                     |         |                |                                                          |                                        |                             | Male: age, height+, self-rated health-, usual daily activities+, gardening-, chronic stress index+.<br>Female: activity restriction+, arthritis/rheumatism+, personal stress index+, psychological childhood trauma+ (only ≥ 2).<br>Weight, BMI, smoke exposure, energy expenditure, smoking, alcohol use, physical activity, vision, hearing, speech, mobility, dexterity, emotional, cognitive problems, health status, activity limiting injury, pregnancy, allergy, asthma, high blood pressure, migraine, chronic bronchitis, sinusitis, diabetes, epilepsy, heart disease, cancer, stomach/intestinal ulcers, stroke, incontinence, Alzheimer's, cataracts, glaucoma, acne, long-term condition, environmental/financial/family health/relationship/child-related stress, chronic stress, depression, social support, self-esteem, locus of control, mental health distress, sense of coherence, frequency of contact, social involvement, recent life events, immigrant, education, income adequacy, language, main activity, living arrangements, marital status, urbanization, working status, work-stress/status combination. |                      |

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

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

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

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

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

| Author, year published  | Study type (cohort)                                                          | Country | sample size, n | Female gender, %<br>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<br>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<br>Psychological<br>Interpersonal<br>Contextual |
| Marrie et al., 2009     | EMR cohort (Manitoba Health)                                                 | Canada  | 25132          | Both<br>≥20 yrs. <sup>b</sup>                            | Fibromyalgia (ICD-9 or ICD-10)                                       | 20.0                        | Multiple sclerosis+, age+.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Biological<br>Contextual                                   |
| Marshall et al., 2006   | Prospective study (Walkerton Health Study)                                   | USA     | 2069           | 55.5<br>46.6 <sup>b</sup>                                | 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<br>49.3 (15.5)                                      | IBS (Self-report & clinical record, Rome I criteria)                 | 8.0                         | Acute gastroenteritis+                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Biological                                                 |
| Masters et al., 2015    | EMR cohort (Humedica)                                                        | USA     | 587961         | 64.6<br>53 <sup>b</sup>                                  | Fibromyalgia (ICD-9:780.73, at least 2x)                             | 1.0                         | Comorbid conditions: any musculoskeletal pain condition+, lupus+, diffuse diseases of connective tissue+, arthritis/other arthropathies+, 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 limb+, other polyneuropathies+, back-neck pain with neuropathic involvement+, any sleep disorder+, insomnia/sleep disorder/ apnoea+, restless-leg syndrome+, | Biological<br>Psychological<br>Health behaviour            |

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

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

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

| Author, year published               | Study type (cohort)           | Country     | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition) | Length of follow-up (years) | Measured factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Investigated domains                                                         |
|--------------------------------------|-------------------------------|-------------|----------------|----------------------------------------------------------|----------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Monden et al., 2020</b>           | Prospective study (Lifelines) | Netherlands | 135862         | 55.0<br>48.8 (13.1)<br><sup>b</sup>                      | IBS & CFS & fibromyalgia (Self-report) | 1.4, 2.4                    | <b>Gender+</b> (female), age, race, living style, lower education level, lower income, <b>work status+</b> , duration of searching job, diabetes, cancer, hypertension, stroke, asthma/COPD, health-related disorder, <b>gastrointestinal disorders+</b> , neurological disorder, blood related disorder, skin related disorders, no listed disorder, <b>IBS+, FM+, kidney disease+, musculoskeletal disorders+, psychiatric disorders+, high cholesterol+, allergy+, BMI+/-, medications+</b> (ATC -codes: A02B, A03A, A03F, A06A, G03A-, G03H, H03A, M01A, R01A, R03A, S01X), <b>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; <b>bodily pain-, general health-, vitality-</b>), depression diagnosis, anxiety.</b> | Biological<br>Psychological<br>Interpersonal<br>Contextual, Health behaviour |
| <b>Mork et al., 2010<sup>R</sup></b> | Prospective study (HUNT1+2)   | Norway      | 15990          | 100.0<br><br>≥ 20 <sup>b</sup>                           | Fibromyalgia (Self-report)             | 11.0                        | <b>Exercise per week, exercise sessions per week, usual intensity of exercise, BMI+/-.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Biological<br>Health<br>behav.                                               |

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

| Author, year published               | Study type (cohort)                            | Country | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition)                               | Length of follow-up (years) | Measured factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Investigated domains                                             |
|--------------------------------------|------------------------------------------------|---------|----------------|----------------------------------------------------------|----------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <b>Mork et al., 2012<sup>a</sup></b> | Prospective study (HUNT1+2)                    | Norway  | 12350          | 100.0<br>≥ 20 <sup>b</sup>                               | Fibromyalgia (self-report)                                           | 11.0                        | <b>Sleep problems+.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Biological                                                       |
| <b>Mork et al., 2013</b>             | Prospective study (HUNT)                       | Norway  | 27715          | 57.5<br>≥ 20 <sup>b</sup>                                | Chronic arm pain (self-report, ≥ 3 months)                           | 11.0                        | <b>Exercise per week-, exercise sessions per week-, usual intensity of exercise-, BMI+/-.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Biological<br>Health<br>behav                                    |
| <b>Mork et al., 2014</b>             | Prospective study (HUNT1+2)                    | Norway  | 26896          | both<br>≥ 20 <sup>b</sup>                                | Chronic back pain (self-report, ≥ 3 months)                          | 11.0                        | <b>Sleep problems+.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Biological                                                       |
| <b>Mundal et al., 2014</b>           | Prospective study (HUNT2+3)                    | Norway  | 19192          | 53.8<br>44.5 <sup>b</sup>                                | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 11.0                        | <b>Anxiety+, depression+, alcohol use-, sleep problems+, BMI+/-, smoking status+.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Biological<br>Psychological<br>Health<br>behaviour               |
| <b>Muthuri et al., 2018</b>          | Birth cohort (British Birth cohort (MRC NSHD)) | UK      | 2453           | both<br>31-69                                            | Chronic back pain (self-report, recurring)                           | 68.0                        | Childhood: <b>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-.</b>                                                                                                                                                                                                                                                                                                                                            | Biological<br>Psychological<br>Contextual                        |
| <b>Myrtveit et al., 2013</b>         | Prospective study (HUNT 2+3)                   | Norway  | 20799          | 54.4<br>44.4 (11.9) <sup>b</sup>                         | Chronic whiplash (self-report)                                       | 11.0                        | Gender, <b>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 &amp; depression+.</b> | Biological<br>Psychological<br>Contextual<br>Health<br>behaviour |

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

| Author, year published       | Study type (cohort)                            | Country | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.) | Outcome (measurement type, definition)                               | Length of follow-up (years) | Measured factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Investigated domains                                          |
|------------------------------|------------------------------------------------|---------|----------------|----------------------------------------------------------|----------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| <b>Mundal et al., 2014</b>   | Prospective study (HUNT2+3)                    | Norway  | 19192          | 53.8<br>44.5 <sup>b</sup>                                | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 11.0                        | <b>Anxiety+, depression+, alcohol use-, sleep problems+, BMI+/-, smoking status+.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Biological<br>Psychological<br>Health behaviour               |
| <b>Muthuri et al., 2018</b>  | Birth cohort (British Birth cohort (MRC NSHD)) | UK      | 2453           | both<br>31-69                                            | Chronic back pain (self-report, recurring)                           | 68.0                        | Childhood: <b>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-.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Biological<br>Psychological<br>Contextual                     |
| <b>Myrtveit et al., 2013</b> | Prospective study (HUNT 2+3)                   | Norway  | 20799          | 54.4<br>44.4 (11.9) <sup>b</sup>                         | Chronic whiplash (self-report)                                       | 11.0                        | Gender, <b>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+.</b> | Biological<br>Psychological<br>Contextual<br>Health behaviour |

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

| Author, year published            | Study type (cohort)          | Country     | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.)                                      | Outcome (measurement type, definition)                                                                  | Length of follow-up (years) | Measured factors                                                                                                                                                                                            | Investigated domains                         |
|-----------------------------------|------------------------------|-------------|----------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Nakamura et al., 2014             | Prospective study            | Japan       | 4797           | 56.0<br>≥20 yrs. <sup>b</sup>                                                                 | Chronic pain (Self-report, >6 months)                                                                   | 1.0                         | Female gender+, age group, area, urbanization+, occupation+, marital status, living condition, BMI+, alcohol+, smoking+, education+, income.                                                                | Biological<br>Contextual<br>Health behaviour |
| Nicholl et al., 2010 <sup>†</sup> | NCC cohort (EPIFUND & EMAS)  | UK          | 994            | 66.0<br>non-cases: 48.5 – cases: 52.6 <sup>b</sup>                                            | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia)                                    | 25.0                        | Single nucleotide polymorphisms (SNP): COMT, rs4680.                                                                                                                                                        | Biological                                   |
| Nicholl et al., 2011 <sup>†</sup> | NCC cohort (EPIFUND & EMAS)  | UK & Europe |                | 36.6<br>48.5 - 59.5 (medians of 4 groups) <sup>b</sup>                                        | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia)                                    | 25.0                        | Single nucleotide polymorphisms (SNP): rs12584920+.                                                                                                                                                         | Biological                                   |
| Nilsen et al., 2011               | Prospective study (HUNT 1+2) | Norway      | 32417          | 51.5<br>43-45                                                                                 | Musculoskeletal pain in the low back or neck/shoulders (self-report, standardized Nordic Questionnaire) | 11.0                        | Weight+, activity level-.                                                                                                                                                                                   | Biological<br>Health<br>behaviour            |
| Nitter et al., 2012               | Prospective study            | Norway      | 577            | 100.0<br>20-49 <sup>†</sup>                                                                   | Chronic pain (Self-report + validation interview, ≥ 3 months)                                           | 17.0                        | Disrupted sleep+, fatigue+, non-restorative sleep+, anxious/frightened/nervous+, regular headache+, rumbling stomach+, stool, numbness/tingling, joints feel swollen, non-specific health complaints+, age. | Biological<br>Psychological<br>Contextual    |
| Odegard et al., 2011              | Prospective study (HUNT 2+3) | Norway      | 14042          | non-exposed: 48.4 - with exposed: 53.4<br>non-exposed: 48.1 - with exposed: 55.2 <sup>b</sup> | 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, %<br>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      | 763428<br>1    | Both<br>≥20 yrs <sup>b</sup>                             | IBS (ICD-9-CM: code 564.0)                                                                      |                             | Age+, female sex+.                                                                                                                                                                                                                                                                                                                                                                                                                 | Contextual                  |
| Pang et al., 2010 <sup>i</sup>    | Birth cohort (1958 British Birth Cohort)           | UK          | 8572           | both<br>45                                               | Chronic widespread pain (Self-report, ACR criteria for fibromyalgia)                            | 38.0                        | Parent and teacher reported: <b>maladaptive childhood behaviour age 7+, age 11+, 16+.</b>                                                                                                                                                                                                                                                                                                                                          | Inter-personal              |
| Persson et al., 2015 <sup>f</sup> | Retrospective study (Bergen)                       | Norway      | 1571           | 67.3<br>≥18                                              | IBS, functional dyspepsia, chronic fatigue, overactive bladder syndrome (Self-report, Rome III) | 6.0                         | <b>Giardia+.</b>                                                                                                                                                                                                                                                                                                                                                                                                                   | Biological                  |
| Picavet et al., 2002              | Prospective study (DMC3)                           | Netherlands | 1161           | 57.3<br>25-64                                            | Chronic LBP (validated questionnaire)                                                           | 0.5                         | <b>Pain catastrophizing+, kinesiophobia.</b>                                                                                                                                                                                                                                                                                                                                                                                       | Biological Psychological    |
| Pico-Espinosa et al., 2017        | Prospective study (Stockholm Public Health Cohort) | Sweden      | 10044          | 49.4<br>45-84                                            | Back, neck and shoulder pain (BNSP) (self-report)                                               | 4.0                         | <b>Diabetes+ (only male), hyperlipidaemia+.</b>                                                                                                                                                                                                                                                                                                                                                                                    | Biological                  |
| Puroila et al., 2015              | Birth cohort (1966 NFBC)                           | Finland     | 5466           | 52.2<br>31                                               | Musculoskeletal pain (self-report, at least 2 sites, quite often during 12 months)              | 17.0                        | <b>Physical activity+ (only female), sports club membership, body weight+, smoking+, alcohol consumption+.</b>                                                                                                                                                                                                                                                                                                                     | Biological Health behaviour |
| Raphael et al., 2002              | Retrospective study                                | USA         | 1312           | 100.0<br>38.6 (1.3)                                      | Chronic fatigue (Interview, ≥ 6 months)                                                         | 0.4                         | 9/11 terrorist attack.                                                                                                                                                                                                                                                                                                                                                                                                             | Inter-personal              |
| Raslau et al., 2016               | NCC (Olmsted County)                               | USA         | 178            | 61.0<br>median 48 (range: 25–70)                         | IBS (Self-report, Rome III)                                                                     | 48.0                        | <b>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.</b> | Biological                  |

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

| Author, year published     | Study type (cohort)                             | Country | sample size, n | Female gender, %<br>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<br>36.9 (8.6)                                                     | Vulvodynia (Self-report, $\geq 3$ months)              | 36.9                        | Oral contraceptives.                                                                                                                                                                                                                                                    | Biological                                                    |
| Reed et al., 2014          | Prospective study                               | USA     | 1786           | 100.0<br>cases: 45.6 (14.4)<br>– non-cases: 51.0 (16.7)<br><sup>b</sup> | Vulvodynia (Self-report, $\geq 3$ months)              | 6.0                         | Age-, ethnicity, marital status+, sleep dysfunction+, any chronic pain+/-, pain with intercourse+, vulvar symptoms (in past)+, sleep dysfunction+, psychological distress+ (PTSD, depression), other chronic comorbid pain conditions+ (FM, interstitial cystitis, IBS) | Biological<br>Psychological<br>Contextual                     |
| Rodriguez & Ruigomez, 1999 | EMR cohort (General Practice Research Database) | UK      | 584626         | 47.9<br>25-74 <sup>b</sup>                                              | IBS (Doctor diagnosed, random sample for confirmation) | 1.0                         | Gastroenteritis+.                                                                                                                                                                                                                                                       | Biological                                                    |
| Ruigomez et al., 2003      | EMR cohort (General Practice Research Database) | UK      | 90119          | 100<br>50-69 <sup>b</sup>                                               | IBS (Doctor diagnosed, random sample for confirmation) | 6.0                         | Hormonal replacement therapy+, age, consultation frequency+, mental- and CNS-disorders+, pain related disorders+, gastroenteritis+, hysterectomy.                                                                                                                       | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| Ruigomez et al., 2007      | EMR cohort (General Practice Research Database) | UK      | 6105           | Both<br>$\geq 20$ yrs. <sup>b</sup>                                     | IBS (Doctor diagnosed, random sample for confirmation) | 10.0                        | Gastroenteritis (bacterial)+, gastroesophageal reflux+, dyspepsia+, peptic ulcer, appendicitis, diarrhea+, depression+, anxiety+, stress+, sleep disorders+, asthma, COPD, ischemic heart disease, diabetes+, smoking, BMI+, alcohol consumption+.                      | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| Ruigomez et al., 2009      | EMR cohort (General Practice Research Database) | UK      | 6421           | Both<br>$\geq 20$ yrs. <sup>b</sup>                                     | 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, %<br>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<br>54 (18.1) <sup>b</sup>                           | 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<br>Psychological<br>Contextual |
| Shih et al., 2017      | EMR cohort (NHIRD)               | Taiwan  | 741720         | 45.7<br>≥ 18 <sup>b</sup>                                | 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, NSAIDs, geographic location+ (northern is reference), urbanization level+, insured premium+/-. | Biological<br>Contextual                  |
| Shih et al., 2018      | EMR cohort (NHIRD)               | Taiwan  | 123120         | 48.2<br>56.4 (17.5) <sup>b</sup>                         | BPPV (ICD-9-CM: 386.11)                                                                             | 14.0                        | Non-apnoea sleep disorders+, gender, age group, hypertension+, diabetes, congestive heart failure+, stroke, COPD, liver cirrhosis+, chronic kidney disease+, migraine, osteoporosis, hyperlipidaemia, charlson comorbidity index+.                                                                                                                            | Biological<br>Contextual.                 |
| Sivertsen et al., 2014 | Prospective study (HUNT 2+3)     | Norway  | 24715          | 56.9<br>45.3 (19-67)                                     | Fibromyalgia (Self-report)                                                                          | 11.0                        | Insomnia+.                                                                                                                                                                                                                                                                                                                                                    | Psychological                             |
| Skarpsno et al., 2019a | Prospective study (Tromsø study) | Norway  | 6356           | 50.6<br>53.5 (11.2) - 59.7 (10.3) <sup>b</sup>           | Chronic musculoskeletal pain & Chronic widespread pain (Self-report, ACR criteria for fibromyalgia) | 8.0                         | Sleeplessness+, high sensitivity C-reactive protein (only joint effect with sleeplessness).                                                                                                                                                                                                                                                                   | Biological<br>Psychological               |

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

| Author, year published         | Study type (cohort)          | Country     | sample size, n | Female gender, %<br>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<br><br>exposed: 43.5 (12) – non-exposed: 47 (11.8) <sup>b</sup> | Fibromyalgia (self-report)                  | 11.0                        | Insomnia+.                                                                                                                                                                                                                                                                                                     | Psychological                                                                  |
| Skarpsno et al., 2020          | Prospective study (HUNT 3+4) | Norway      | 10847          | 53.8<br><br>50.3 (13.7) – 46.0 (14.3)                                 | Chronic widespread pain (Self-report)       | 11.0                        | Insomnia+.                                                                                                                                                                                                                                                                                                     | Psychological                                                                  |
| Smith et al., 2004             | Prospective study            | Scotland    | 1431           | both<br><br>≥25                                                       | Chronic back pain (self-report, ≥ 3 months) | 4.0                         | Female gender+, age+, employment, <b>unable to work due to illness+</b> , living situation, education, housing tenure, marital status, <b>any chronic pain at baseline+</b> , SF-36+ (general health, physical functioning, social functioning, role physical, role emotional, energy & vitality, bodily pain) | Biological<br>Psychological<br>Interpersonal<br>Contextual<br>Health behaviour |
| Talley et al., 2001            | Birth cohort (Dunedin)       | New Zealand | 890            | 49.2<br><br>26                                                        | IBS (Questionnaire DSM-III criteria)        | 8.0                         | Mental health, anxiety, depression, substance dependence.                                                                                                                                                                                                                                                      | Psychological<br>Health<br>behav                                               |
| Tsai et al., 2014              | EMR cohort (NHIRD/LHID2005)  | Taiwan      | 46025          | 53.3<br><br>56 <sup>b</sup>                                           | CFS (ICD-9: 780.71)                         | 4.0                         | Herpes zoster infection+.                                                                                                                                                                                                                                                                                      | Biological                                                                     |
| Tsai et al., 2018 <sup>s</sup> | EMR cohort (NHIRD/LHID2000)  | Taiwan      | 86016          | 52.2<br><br>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<br>Psychological<br>Contextual                                      |
| Tsai et al., 2019 <sup>s</sup> | EMR cohort (NHIRD/LHID2000)  | Taiwan      | 13080          | 48.0<br><br>≥ 20 <sup>b</sup>                                         | CFS (ICD-9: 780.71)                         | 8.0                         | Psoriasis+ (only mild psoriasis), gender, age+, diabetes, depression+, anxiety+, sleep disorder+, renal disease+.                                                                                                                                                                                              | Biological<br>Psychological<br>Contextual                                      |

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

| Author, year published     | Study type (cohort)                 | Country | sample size, n | Female gender, %<br>Age at outcome, range or mean (s.d.)                      | Outcome (measurement type, definition)                                                               | Length of follow-up (years) | Measured factors                                                                                                                                                                                                                                                                                                                                                                      | Investigated domains                                          |
|----------------------------|-------------------------------------|---------|----------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Uhlrig et al., 2018        | Prospective study (HUNT)            | Norway  | 13429          | 59.3<br><br>Non-exposed: 43.4 (12.2),<br>exposed: 44.5 (12.2)<br><sup>b</sup> | 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<br><br>45                                                                | Chronic widespread pain (Self-report)                                                                | 12.0                        | Fruit/vegetable consumption+, fatty food+, chips+, alcohol+, physical activity+, employment+, physical exertion at work+, smoking+, BMI+, marital status+, social class+.                                                                                                                                                                                                             | Biological<br>Contextual<br>Health behaviour                  |
| Varinen et al., 2019       | Retrospective study (HeSSup)        | Finland | 11409          | 65.7<br><br>20-54 <sup>b</sup>                                                | Fibromyalgia (self-report)                                                                           | 10.0                        | Bullying+ (only severe bullying), age+, gender+ (female), education-, marital status-, depression+.                                                                                                                                                                                                                                                                                   | Psychological<br>Inter-personal                               |
| Viner et al., 2004         | Birth cohort (BGS70)                | UK      | 11266          | 62.8<br><br>30                                                                | CFS/ME (self-report)                                                                                 | 20.0<br>36.0                | Gender+ (female), Childhood: father professional occupation+, mother education, ethnicity, birth weight, birth order, longstanding medical condition+, atopy, obesity, leisure time sports-, school sports, school missed due to health, high abilities, illness in parent, behavioural problems, malaise, self-esteem, GHQ, Adulthood: malaise+, professional/managerial occupation. | Biological<br>Psychological<br>Contextual<br>Health behaviour |
| Waehrens et al., 2018      | EMR cohort                          | Sweden  | 196368<br>5    | 48.6<br><br>18-38                                                             | IBS (ICD-8 564.19, ICD-9 564B, ICD-10 K57)                                                           | 20.0                        | Gender+ (female), birth year-, fetal growth-, gestational age-, birthweight-, birth length-, multiple birth, birth order+, mat. age at delivery+/-, maternal marital status-, maternal/paternal educat-, caesarean+, parental history: IBS+, anxiety+, depression+.                                                                                                                   | Biological<br>Interpersonal<br>Contextual                     |

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

| Author, year published            | Study type (cohort)          | Country | sample size, n        | Female gender, %<br>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<br>52.3 (15.8) - 52.5 (15.6) (non-GERD - GERD) <sup>b</sup> | 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<br>Psychological<br>Contextual |
| Wensaas et al., 2011 <sup>f</sup> | Retrospective study (Bergen) | Norway  | 1875 (IBS), 1912 (CF) | 65.7<br>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<br>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<br>25-54 <sup>b</sup>                                      | IBS (ICD-9 564.1, at least 2x)                                          | 5.0                         | Endometriosis+.                                                                                                                                                                                                            | Biological                                |
| Wu CC et al., 2018                | EMR cohort (NHIRD/LHID2000)  | Taiwan  | 26764                 | 100<br>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<br>47                                                       | CFS (ICD-9: 780.71)                                                     | 5.3                         | Atopy+.                                                                                                                                                                                                                    | Biological                                |
| Yang CY et al., 2020              | EMR cohort (NHIRD/LHID)      | Taiwan  | 18472                 | 48.3<br>>20 yrs. <sup>b</sup>                                    | 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<br>Contextual                  |
| Yang TY et al., 2022              | EMR cohort (NHIRD/LHID2000)  | Taiwan  | 38329                 | 32.1<br>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<br>Contextual.                 |

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

