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Promoting early recognition of persistent somatic symptoms in primary care

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Chapter 5

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

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Submitted

Abstract

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

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

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

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

Introduction

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

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

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

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

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

Methods

Study design and participants

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

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

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

Measures

Predictors

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

Outcomes

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

Statistical analyses

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

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

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

Results

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

Table 1. Baseline Characteristics

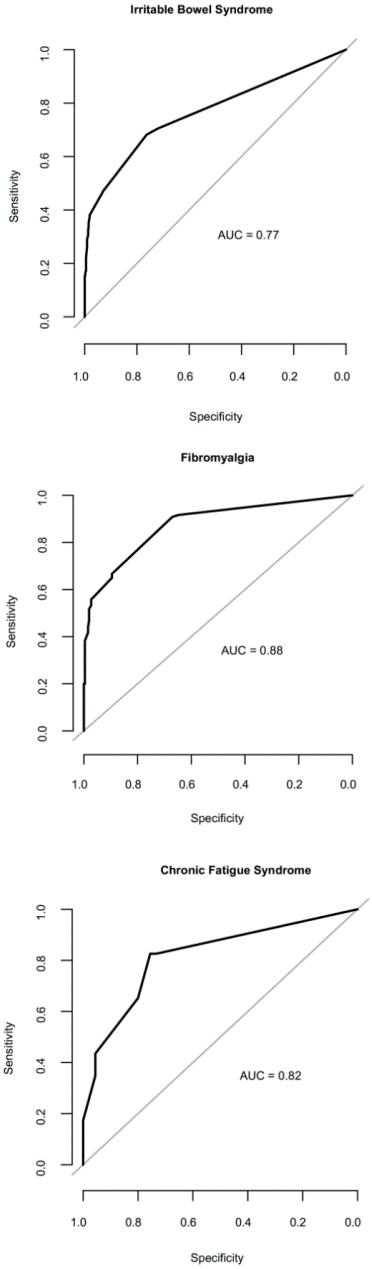
	IBS study		**CFS study**		**FM study**	
	Train	**Test**	**Train**	**Test**	**Train**	**Test**
n	**7341**	**1836**	**274**	**68**	**1512**	**378**
PSS frequency *n* (%)	2447 (33.3)	613 (33.4)	91 (33.2)	23 (33.8)	510 (33.7)	120 (31.7)
Mean age in years (*SD*)	46.1 (15.2)	45.4 (15.4)	44.7 (13.2)	46.8 (12.5)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

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

Model performance

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

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



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

Predictive Models for PSS

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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Appendixes

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

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

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

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

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

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

Appendix B. Psychopharmaceuticals and respective codes included in the variable

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

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

Appendix C. Frequencies of predictors per sample

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

Appendix C. Frequencies of predictors per sample (continued)

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

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

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

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