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Promoting early recognition of persistent somatic symptoms in primary care

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Chapter 1

General introduction

Persistent somatic symptoms in the general population

Experiencing somatic symptoms is common for most people in daily life. General population studies show that 80 to 95% of adults experience at least one somatic symptom at any given point in time.^{1–3} Symptoms may vary widely, but are most commonly forms of pain, fatigue, gastrointestinal complaints, and dizziness. While most of these symptoms are self-limiting, approximately 20% of adults experience persistent or recurring disabling somatic symptoms.^{1,4} It is commonly accepted that somatic symptoms are related to established physical disease, but it is also common knowledge that symptoms may also be present in individuals without such disease. Furthermore, research shows that most somatic symptoms are not fully explained by established biomedical pathophysiology and cannot be fully attributed to objectively determined disease severity.^{5–7} Hence, both individuals with biomedical disorders, such as cardiovascular disease⁸ and cancer,⁹ as well as individuals without such a disorder may experience somatic symptoms that persist without clear biomedical pathophysiological explanation.^{10–13} In all, up to 10% of the general population experience persistent somatic symptoms (PSS) that persist beyond biomedical expectation.^{7,14–16}

Distinguishing PSS from well-understood biomedical disorders

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

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

The societal burden of PSS

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

Etiology, terminology, and definitions of PSS

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

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

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

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

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

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

In countries such as the Netherlands, where GPs are the gatekeeper to specialist care, GPs are most likely to be the first to be consulted in case of somatic symptoms. Even so, in addition to identification problems described above, registrations of PSS in primary care are hampered, for example due to a lack of codes or consultation constraints such as overloaded surgery hours.^{27,61} In electronic medical records (EMRs) of Dutch GPs, the international classification of primary care (ICPC) is used. The ICPC does not include a code for PSS, which may complicate registration of PSS. Although the ICPC does include options to register complaints beyond the biomedical domain, availability of such codes is limited compared to biomedical codes. In recent years, research has increasingly utilized routine primary care data for mental health⁶² and PSS research.^{63–70} Predictive modeling of the broad spectrum of PSS based on routine care data showed moderate success^{63,64} and an EMR-based study on identification of patients with fibromyalgia showed promising results.⁶⁷ Even so, limitations of the re-use of EMR data should be heeded. For instance, the PSS index date (i.e., first date of PSS registration) may not represent the date of PSS-onset since diagnosis of PSS is often delayed.^{35,36,71} In addition, since EMR data are not collected for research purposes and data is only registered when the patient visit the GP and the GP chooses to register, EMR data is characterized by high levels of (non-random) missing data.⁷² Furthermore, as indicated above, registrations beyond the biomedical domain may be limited. Although disputed by some studies,^{73,74} machine learning techniques and data mining may circumvent problems with missing data and increase performance of predictive models.^{75,76} Furthermore, recent studies based on routine primary care data showed that theory driven and data driven machine learning approaches support early identification of patients at risk of non-biomedical problems.^{75,77,78} Therefore, this thesis explores the use of theory driven, data driven, and

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

Aim and outline of this thesis

The primary aim of this thesis is to promote early identification of PSS in primary care in order to reduce the burden of PSS on the patient, physician, and society. The theory and data driven approaches towards this aim are presented in this thesis as follows:

Firstly, **Chapter 2** presents an overview of predictors of PSS in the general population.

The predictors are construed from a large systematic review of the state of evidence regarding predictors of PSS and its subtypes, based on longitudinal cohort studies.

Predictors are categorized according to the dynamic biopsychosocial model and result in an overview of investigated domains and the importance of multidomain exploration in clinical practice.

In **Chapter 3**, results from a survey on GP's perspectives regarding the classification and registration of PSS in primary care is presented. Results provide insight in the methods of registration using ICPC coding and beyond, as well as GP's perspectives on their abilities and needs regarding PSS classification and registration. Subsequently, **Chapter 4** further explores how the broad spectrum of PSS can be identified in routine primary care data despite lacking unambiguous clinical coding. Subsequent exploration of the usability of routine primary care data and the differences and similarities of PSS-subtypes is presented in **Chapter 5**. Herein, the viability of psychological registration in primary care data and their predictive value were investigated in three most common PSS syndromes which have ICPC codes, namely irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS). The insights from all previously mentioned chapters come together in **Chapter 6**, in which theory and data driven approaches and a combination of both are utilized to identify patients at risk of the broad spectrum of PSS two years prior to their classification in primary care. Finally, **Chapter 7** presents a general discussion of all research presented in this thesis, including evaluations of the used methods and techniques, scientific and societal implications, and recommendations for future directions for research and clinical practice.

References

- 1 Hiller W, Rief W, Brähler E. Somatization in the population: from mild bodily misperceptions to disabling symptoms. *Soc Psychiatry Psychiatr Epidemiol* 2006; 41: 704–12.
- 2 Kjeldsberg M, Tschudi-Madsen H, Dalen I, Straand J, Bruusgaard D, Natvig B. Symptom reporting in a general population in Norway: Results from the Ullensaker study. *Scand J Prim Health Care* 2013; 31: 36.
- 3 Hinz A, Ernst J, Glaesmer H, et al. Frequency of somatic symptoms in the general population: Normative values for the Patient Health Questionnaire-15 (PHQ-15). *J Psychosom Res* 2017; 96: 27–31.
- 4 Rasmussen S, Jensen CT, Rosendal M, Vægter HB, Søndergaard J, Jarbøl DE. Multiple physical symptoms and individual characteristics – A cross-sectional study of the general population. *J Psychosom Res* 2020; 131: 109941.
- 5 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.
- 6 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.
- 7 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.
- 8 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.
- 9 Grassi L, Caruso R, Nanni MG. Somatization and somatic symptom presentation in cancer: A neglected area. *International Review of Psychiatry* 2013; 25: 41–51.
- 10 Verhaak PFM. Persistent presentation of medically unexplained symptoms in general practice. *Fam Pract* 2006; 23: 414–20.
- 11 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.
- 12 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.
- 13 Löwe B, Levenson J, Depping M, et al. Somatic symptom disorder: a scoping review on the empirical evidence of a new diagnosis. *Psychol Med* 2021; 52: 632–48.

- 14 Waal MWM de, Arnold IA, Eekhof JAH, Hemert AM van. Somatoform disorders in general practice: Prevalence, functional impairment and comorbidity with anxiety and depressive disorders. *The British Journal of Psychiatry* 2004; 184: 470–6.
- 15 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.
- 16 Lehmann M, Pohontsch NJ, Scherer M. Estimated frequency of somatic symptom disorder in general practice: cross-sectional survey with general practitioners. 2022; published online April 19.
- 17 Warren JW, Clauw DJ. Functional somatic syndromes: Sensitivities and specificities of self-reports of physician diagnosis. *Psychosom Med* 2012; 74: 891–5.
- 18 de Gucht V, Fischler B. Somatization: a critical review of conceptual and methodological issues. *Psychosomatics* 2002; 43: 1–9.
- 19 Spiegel BMR, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion?: A survey of primary care providers, gastroenterologists, and ibs experts. *American Journal of Gastroenterology* 2010; 105: 848–58.
- 20 Hartman TO, Blankenstein N, Molenaar B, et al. NHG-Standaard Somatisch Onvoldoende verklaarde Lichamelijke Klachten (SOLK). *Huisarts & Wetenschap* 2013; 56: 1–18.
- 21 Henningsen P, Zipfel S, Sattel H, Creed F. Management of Functional Somatic Syndromes and Bodily Distress. *Psychother Psychosom* 2018; 87: 12–31.
- 22 Claassen-van Dessel N, van der Wouden JC, Twisk JWR, Dekker J, van der Horst HE. Predicting the course of persistent physical symptoms: Development and internal validation of prediction models for symptom severity and functional status during 2 years of follow-up. *J Psychosom Res* 2018; 108: 1–13.
- 23 Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. *Soc Personal Psychol Compass* 2017; 11.
- 24 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.
- 25 Rask MT, Carlsen AH, Budtz-Lilly A, Rosendal M. Multiple somatic symptoms in primary care patients: A cross-sectional study of consultation content, clinical management strategy and burden of encounter. *BMC Fam Pract* 2016; 17.
- 26 Murray AM, Toussaint A, Althaus A, Löwe B. The challenge of diagnosing non-specific, functional, and somatoform disorders: A systematic review of barriers to diagnosis in primary care. *J Psychosom Res* 2016; 80: 1–10.
- 27 Lehmann M, Pohontsch NJ, Zimmermann T, Scherer M, Löwe B. Diagnostic and treatment barriers to persistent somatic symptoms in primary care - representative survey with physicians. *BMC Fam Pract* 2021; 22.
- 28 Johansen ML, Risor MB. What is the problem with medically unexplained symptoms for GPs? A meta-synthesis of qualitative studies. *Patient Educ Couns* 2017; 100: 647–54.

- 29 Löwe B, Gerloff C. Functional Somatic Symptoms Across Cultures: Perceptual and Health Care Issues. *Psychosom Med* 2018; 80: 412–5.
- 30 Rolfe A, Burton C. Reassurance After Diagnostic Testing With a Low Pretest Probability of Serious Disease: Systematic Review and Meta-analysis. *JAMA Intern Med* 2013; 173: 407–16.
- 31 Salmon P. Conflict, collusion or collaboration in consultations about medically unexplained symptoms: The need for a curriculum of medical explanation. *Patient Educ Couns* 2007; 67: 246–54.
- 32 Houwen J, Lucassen PLBJ, Stappers HW, Assendelft WJJ, Olde Hartman TC, van Dulmen S. Improving GP communication in consultations on medically unexplained symptoms: a qualitative interview study with patients in primary care. *Br J Gen Pract* 2017; 67: e716–23.
- 33 Weiland A, Blankenstein AH, van Saase JLCM, et al. Training Medical Specialists to Communicate Better with Patients with Medically Unexplained Physical Symptoms (MUPS). A Randomized, Controlled Trial. *PLoS One* 2015; 10.
- 34 Terluin B, Smits N, Brouwers EP, de Vet HC. The Four-Dimensional Symptom Questionnaire (4DSQ) in the general population: scale structure, reliability, measurement invariance and normative data: a cross-sectional survey. *Health Qual Life Outcomes* 2016; 14: 130.
- 35 Gendelman O, Amital H, Bar-On Y, et al. Time to diagnosis of fibromyalgia and factors associated with delayed diagnosis in primary care. *Best Pract Res Clin Rheumatol* 2018; 32: 489–99.
- 36 Comiskey C, Larkan F. A national cross-sectional survey of diagnosed sufferers of myalgic encephalomyelitis/chronic fatigue syndrome: pathways to diagnosis, changes in quality of life and service priorities. *Ir J Med Sci* 2010; 179: 501–5.
- 37 Kohlmann S, Löwe B, Shedden-Mora MC. Health Care for Persistent Somatic Symptoms Across Europe: A Qualitative Evaluation of the EURONET-SOMA Expert Discussion. *Front Psychiatry* 2018; 9: 646.
- 38 Joustra ML, Janssens KAM, Bültmann U, Rosmalen JGM. Functional limitations in functional somatic syndromes and well-defined medical diseases. Results from the general population cohort LifeLines. *J Psychosom Res* 2015; 79: 94–9.
- 39 Koch H, van Bokhoven MA, Riet G ter, van der Weijden T, Dinant GJ, Bindels PJE. Demographic characteristics and quality of life of patients with unexplained complaints: a descriptive study in general practice. *Qual Life Res* 2007; 16: 1483–9.
- 40 Zonneveld LN, Sprangers MA, Kooiman CG, Van't Spijker A, Busschbach JJ. Patients with unexplained physical symptoms have poorer quality of life and higher costs than other patient groups: A cross-sectional study on burden. *BMC Health Serv Res* 2013; 13.
- 41 Bermingham SL, Cohen A, Hague J, Parsonage M. The cost of somatisation among the working-age population in England for the year 2008–2009. *Ment Health Fam Med* 2010; 7: 71.
- 42 den Boeft M, Twisk JWR, Hoekstra T, et al. Medically unexplained physical symptoms and work functioning over 2 years: their association and the influence of depressive and anxiety disorders and job characteristics. *BMC Fam Pract* 2016; 17.

- 43 Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch Gen Psychiatry* 2005; 62: 903–10.
- 44 Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. *Br J Psychiatry* 2002; 180: 248–53.
- 45 Jackson J, Kincey J, Fiddler M, Creed F, Tomenson B. Differences between out-patients with physical disease and those with medically unexplained symptoms with respect to patient satisfaction, emotional distress and illness perception. *Br J Health Psychol* 2004; 9: 433–46.
- 46 Konnopka A, Schaefer R, Heinrich S, et al. Economics of medically unexplained symptoms: a systematic review of the literature. *Psychother Psychosom* 2012; 81: 265–75.
- 47 Berger A, Sadosky A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and patterns of healthcare utilization of patients with fibromyalgia in general practitioner settings in Germany. <https://doi.org/10.1185/03007990802316550> 2008; 24: 2489–99.
- 48 Maiden NL, Hurst NP, Lochhead A, Carson AJ, Sharpe M. Medically unexplained symptoms in patients referred to a specialist rheumatology service: prevalence and associations. *Rheumatology (Oxford)* 2003; 42: 108–12.
- 49 Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *J Psychosom Res* 2001; 51: 361–7.
- 50 Houwen J, Lucassen PLBJ, Stappers HW, et al. How to learn skilled communication in primary care MUS consultations: a focus group study. *Scand J Prim Health Care* 2021; 39: 101–10.
- 51 Johansen ML, Risor MB. What is the problem with medically unexplained symptoms for GPs? A meta-synthesis of qualitative studies. *Patient Educ Couns* 2017; 100: 647–54.
- 52 Peters S, Rogers A, Salmon P, et al. What do patients choose to tell their doctors? Qualitative analysis of potential barriers to reattributing medically unexplained symptoms. *J Gen Intern Med* 2009; 24: 443–9.
- 53 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.
- 54 Ford SH, Hodges E, Thoyre S, Baker M, Bartlett R. Model Integration: Can Understanding Biopsychosocial Gut-Brain Axis Mechanistic Pathways Improve our Clinical Reasoning in Primary Care? *J Nurse Pract* 2021; 17: 1208–13.
- 55 Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. *J Neurogastroenterol Motil* 2011; 17: 131–9.
- 56 Agirman G, Yu KB, Hsiao EY. Signaling inflammation across the gut-brain axis. *Science* 2021; 374: 1087–92.
- 57 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *The Lancet* 1999; 354: 936–9.
- 58 Witthöft 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.

- 59 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.
- 60 Rosmalen JGM, Tak LM, de Jonge P. Empirical foundations for the diagnosis of somatization: implications for DSM-5. *Psychol Med* 2011; 41: 1133–42.
- 61 Pohontsch NJ, Zimmermann T, Jonas C, Lehmann M, Löwe B, Scherer M. Coding of medically unexplained symptoms and somatoform disorders by general practitioners – an exploratory focus group study. *BMC Fam Pract* 2018; 19: 129.
- 62 Koning NR, Büchner FL, Vermeiren RRJM, Crone MR, Numans ME. Identification of children at risk for mental health problems in primary care-Development of a prediction model with routine health care data. *EClinicalMedicine* 2019; 15: 89–97.
- 63 Smith RC, Gardiner JC, Armatti S, et al. Screening for high utilizing somatizing patients using a prediction rule derived from the management information system of an HMO: A preliminary study. *Med Care* 2001; 39: 968–78.
- 64 Morriss R, Lindson N, Coupland C, Dex G, Avery A. Estimating the prevalence of medically unexplained symptoms from primary care records. 2012.
- 65 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.
- 66 Masters ET, Emir B, Mardekian J, Clair A, Kuhn M, Silverman SL. Identification of a potential fibromyalgia diagnosis using random forest modeling applied to electronic medical records. *J Pain Res* 2015; 8: 277.
- 67 Emir B, Masters ET, Mardekian J, Clair A, Kuhn M, Silverman SL. Identification of a potential fibromyalgia diagnosis using random forest modeling applied to electronic medical records. *J Pain Res* 2015; 8: 288.
- 68 Sitnikova K, Pret-Oskam R, Dijkstra-Kersten SMA, et al. Management of patients with persistent medically unexplained symptoms: A descriptive study. *BMC Fam Pract* 2018; 19.
- 69 van Westrienen PE, Pisters MF, Veenhof C, de Wit NJ. Identification of patients with moderate medically unexplained physical symptoms in primary care with a five years follow-up. *BMC Fam Pract* 2019; 20.
- 70 Hammerman O, Halperin D, Tsalihi D, Greenberg D, Kushnir T, Ezra Y. Characteristics and economic burden of frequent attenders with medically unexplained symptoms in primary care in Israel. *Eur J Gen Pract* 2021; 27: 294–302.
- 71 Varenna M, Crotti C, Ughi N, Zucchi F, Caporali R. Determinants of Diagnostic Delay in Complex Regional Pain Syndrome Type 1: An Observational Study of 180 Consecutive New Cases. *J Clin Rheumatol* 2021; 27: E491–5.
- 72 Mack C, Su Z, Westreich D. Types of Missing Data. 2018.

- 73 Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol* 2019; 110: 12–22.
- 74 Tate AE, McCabe RC, Larsson H, Lundström S, Lichtenstein P, Kuja-Halkola R. Predicting mental health problems in adolescence using machine learning techniques. *PLoS One* 2020; 15.
- 75 Półchłopek O, Koning NR, Büchner FL, Crone MR, Numans ME, Hoogendoorn M. Quantitative and temporal approach to utilising electronic medical records from general practices in mental health prediction. *Comput Biol Med* 2020; 125: 103973.
- 76 Kop R, Hoogendoorn M, Teije A ten, et al. Predictive modeling of colorectal cancer using a dedicated pre-processing pipeline on routine electronic medical records. *Comput Biol Med* 2016; 76: 30–8.
- 77 Amit G, Girshovitz I, Marcus K, et al. Estimation of postpartum depression risk from electronic health records using machine learning. *BMC Pregnancy Childbirth* 2021; 21.
- 78 Syed S, Gonzalez-Izquierdo A, Allister J, Feder G, Li L, Gilbert R. Identifying adverse childhood experiences with electronic health records of linked mothers and children in England: a multistage development and validation study. *Lancet Digit Health* 2022; published online May.