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 disease [8] and cancer,[9] as well as individuals without such a disorder may experience somatic symptoms that persist without clear biomedical pathophysiological explanation.[10–13] In all, up to 10% of the general population experience persistent somatic symptoms (PSS) that persist beyond biomedical expectation.[7,14–16]

Distinguishing PSS from well-understood biomedical disorders

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

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

The societal burden of PSS

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

Etiology, terminology, and definitions of PSS

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

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

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

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

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

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

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

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

Aim and outline of this thesis

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

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