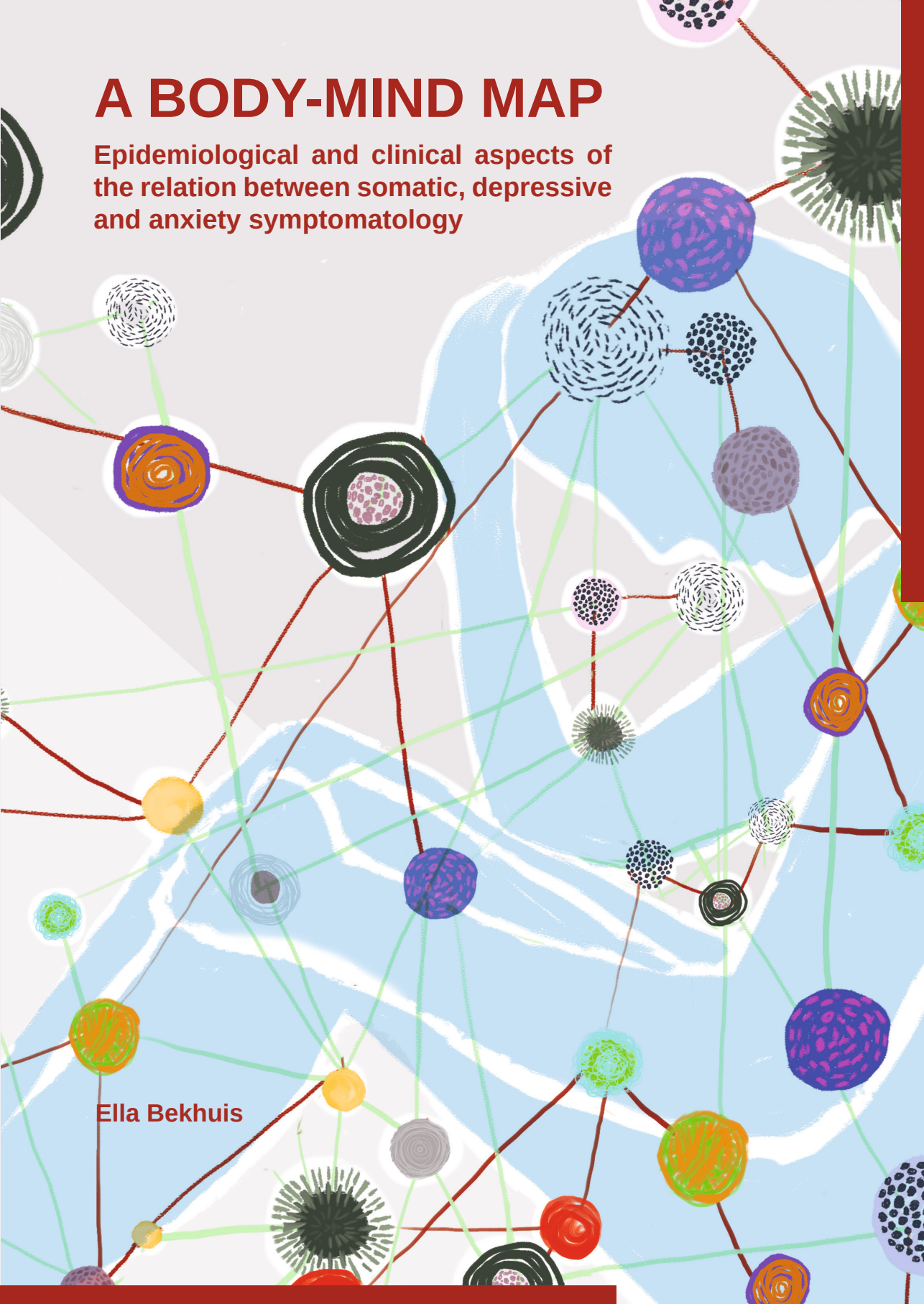
A BODY-MIND MAP

Epidemiological and clinical aspects of the relation between somatic, depressive and anxiety symptomatology



Ella Bekhuis

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Author: Ella Bekhuis
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Promotores

Prof. dr. J.G.M. Rosmalen

Prof. dr. R.A. Schoevers

Copromotor

Dr. L. Boschloo

Beoordelingscommissie

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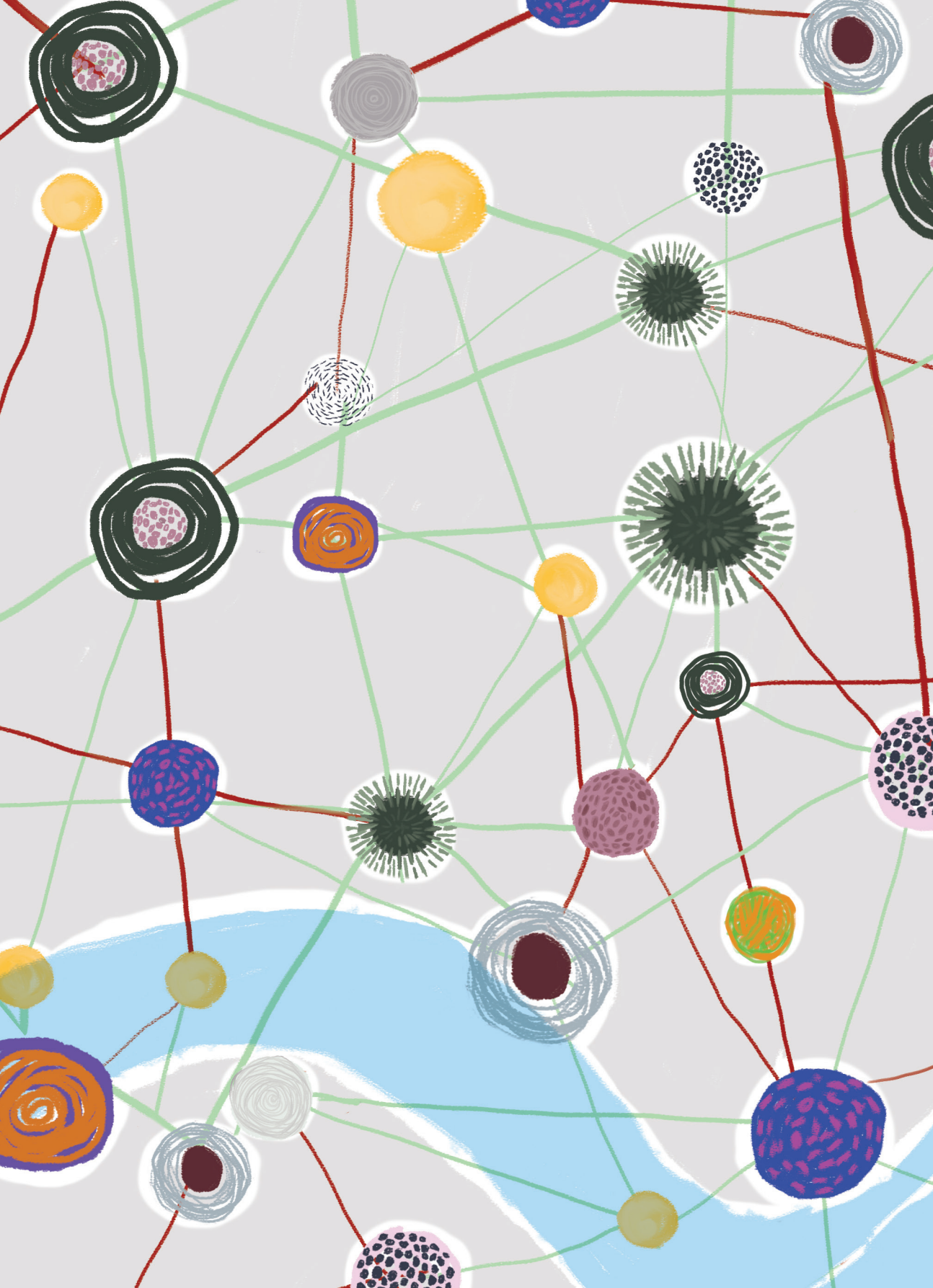
THESIS OUTLINE

Symptom networks



General introduction

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Narrative of patient

When I woke up one morning from a restless dream, I noticed that I had been transformed into a massive piece of putty. There was a nauseating weakness in my limbs, I couldn't hold my head up straight and while dressing I barely had the strength to zip my jeans. I assumed that I had drunk too much the previous night. I just wondered where the empty bottles were. […] Thankfully you do not realize this from the start, but a chronic disease appears to be a process of constant losses: loss of possibilities and skills, of control over your life, of practical and materialistic securities, of social contacts, of spontaneous or familiar activities, of freedom to move, of feelings of self-esteem. Even now that the months have become years, I still can't accept those losses. Someone else may compensate by thinking that life has become more focused, without unnecessary frills, or perhaps in some ways become more adventurous. I'm not that person: I find my life nowadays predominantly empty, dull, flat, unfulfilled and regularly pretty scary. No day passes in which I do not contemplate the things I miss, and often I play the sad game entitled "what do I miss most?". The answer is very simple: just the ability to enjoy.[1]

This story about how chronic fatigue syndrome is experienced by the famous Dutch writer Renate Dorrestein illustrates well how strongly depressive, anxiety and somatic symptoms are related in everyday life. Similar cases indicating the functional limitations associated with this relation have been described across varying cultures and historical periods [1,2] and many people will recognize the relation from their own experience. Despite its widely acknowledged importance, one crucial question remains unanswered: what is the nature of the relation between depressive, anxiety and somatic symptoms?

Historical perspective

The co-occurrence of depressive, anxiety and somatic symptoms has been described in the context of various labels, hypothesized underpinnings and treatments throughout history. In prehistoric times, it was commonly assumed that severe combined psychological and somatic symptoms were caused by supernatural powers such as demonic possession, for which exorcism was required [1]. Other explanations developed as early as the ancient Greek and Roman time when the label "hysteria" was introduced [3]. This label was derived from the Greek word for uterus and referred to symptoms such as nervousness, irritability, insomnia and faintness. Together with the general focus in medicine in this period, explanations for hysteria shifted to the body.

1 Translated from the autobiography "Heden ik" by Renate Dorrestein [466].

One of the earliest hypotheses was the humoral theory, stating that imbalance of four humors caused psychological as well as somatic symptoms [4]. An overload of black bile was for example believed to cause depression, whereas an excess of phlegm produced angina. Harmony could be restored with among others bloodletting and purging. Other theories in this period stated that hysteria could be attributed to specific organs such as the uterus, ovaries, stomach or nerves [1]. A typical affliction of women was described as “suffocation of the womb”, a retraction of the uterus towards the diaphragm and stomach causing women to suffocate and faint. This affliction was treated by subjecting the patient to specific odors.

The focus on individual organs was abandoned in the Industrial Age as the view arose that the body is a machine in which organs are connected via the nervous system [1]. Specific organs such as the uterus were assumed to have a central position in these reflex arcs and were the focus of treatment approaches, which included their surgical removal.

In the 19th century, the biomedical model originated, which described that disease can be ascribed to malfunctioning at the biological level [5]. The mind-body dualism inherent in this model can be traced back to the 17th century, when Descartes argued for the position that mind and body are different substances. The typical affliction of “neurasthenia” in this period was asserted to cerebral weakness [1]. Interventions targeted at the brain such as electrotherapy were developed.

In contrast to the biomedical theories, psychological theories also developed. Although the first psychological explanations already appeared in work of the ancient Greek-Roman physician Galen [4] and gained popularity in the Renaissance with the introduction of the concept of imagination [2], the psychological paradigm culminated in the 20th century. In this period, diagnostic labels indicating that patients present emotions somatically like “somatization” and “masked depression” became massively popular and with them various psychotherapies addressing these emotions [6,7].

Later in the 20th century, Engel developed the biopsychosocial model [8]. In this model, biological, psychological as well as social factors were interrelated and these relations could lead to feedback loops in the system. The model did not only broaden the view about which individual parts should be considered in medicine, but also stressed that the interplay between them is interesting [9]. Although critiques have indicated that Engel’s description of the model ignores important health aspects (e.g., at an existential level) and is not sufficient to understand the consequences of the dynamic nature of the system [10], the model has introduced the idea that treatments should be multi-dimensional and multidisciplinary.

Despite the increased attention for psychological and social aspects of illness and their dynamics in the biopsychosocial model, the current medical field still strongly relies on singling out specific parts of the human from a biomedical perspective [5]. For example, psychiatric disorders are frequently called brain diseases [11-14] and their symptoms are often depicted as a result of nothing more than the disorders themselves (notes from clinicians commonly say: “The patient attempted to commit suicide because of his depressive disorder.”) [15]. Furthermore, the education that medical students receive focuses in particular on biological mechanisms underlying diseases.

DEPRESSIVE AND ANXIETY SYMPTOMS

Although ‘depression’ and ‘anxiety’ can refer to specific symptoms (depressed mood versus an anxious feeling), the terms currently are more broadly defined. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [16], a depressive disorder includes symptoms with a cognitive nature (e.g., concentration problems), affective nature (e.g., hopelessness) and somatic nature (so-called neurovegetative symptoms; e.g., insomnia). Anxiety disorders also cover cognitive symptoms (e.g., worry), affective symptoms (e.g., panic) and neurovegetative symptoms (e.g., palpitations) alongside behavioral symptoms (e.g., avoidance) [16]. Besides the presence of these symptoms, a diagnosis for a depressive or anxiety disorder requires that the symptoms are persistent and associated with clinically significant distress or impairment in functioning [16].

Depressive and anxiety disorders are among the most common mental disorders, as lifetime prevalence rates of both disorders are approximately 20% [17,18]. The mental disorders often co-occur as around 60% of patients with a depressive disorder also have an anxiety disorder and similar prevalence rates have been reported for depressive disorders in patients with an anxiety disorder [19,20]. The disorders have a serious impact on patients’ lifes. Firstly, they negatively interfere with physical, social and occupational functioning [21-23]. In addition, the life expectancy of patients with depressive or anxiety disorder is eight years lower than that of persons without those disorders [24]. This is partly due to their increased risk of developing physical diseases and having a worse prognosis of these diseases [25,26], as well as their higher risk of suicide [27]. Together, these consequences constitute a large economic burden on society [21-23].

SOMATIC SYMPTOMS

Somatic symptoms cover a broad spectrum of symptoms that refer to the body, such as fatigue, back pain, dizziness and headache. The symptoms are part of everyday experience: nearly all persons in the general population report at least one somatic symptom during one month [28]. Most of these symptoms are self-limiting, but they become persistent and impairing in a small proportion of persons [29]. Such symptoms are associated with negative consequences for quality of life [30-32], increased use of health services and higher health costs [32,33].

Somatic symptoms are increasingly recognized as representing a complex interplay between peripheral and central processes [34-36]. Peripheral processes that generate bodily signals include normal bodily functions (e.g., digestion of food), physical diseases (e.g., a stomach ulcer), and emotions (e.g., anxiety accompanied by arousal) [34]. Central

processes are largely involuntary and refer to how a signal is processed in and predicted by the brain [34]. For example, the brain intensifies a signal when it interprets it as a danger to health while it damps the signal down when it interprets it as a normal process [37]. Together, these processes determine if a signal is experienced as a symptom by the patient or not.

Somatic symptoms are often classified based on whether they can be explained in the context of an underlying physical or psychiatric disease. Symptoms that cannot adequately be explained in terms of such diseases are highly common [38,39]. They are described with varying labels in the literature including generic descriptions (e.g., functional somatic symptoms/syndromes, medically unexplained symptoms, psychosomatic symptoms), syndrome descriptions (e.g., chronic fatigue syndrome, fibromyalgia syndrome, irritable bowel syndrome) and disorder descriptions (e.g., somatization disorder in the DSM-IV [40]). In this thesis, we will mainly use the labels "functional somatic symptoms" and "functional somatic syndromes" as they have been shown to be more acceptable to patients than other labels, capture symptoms from all bodily systems and avoid simple denial of disease [41,42].

The distinction between somatic symptoms that are suffiently and insufficiently explained by diseases is increasingly abandoned in new classification systems [16,43]. A reason for this abondonment includes that it is practically difficult to establish the distinction, while advancing insights indicate that these symptoms' underlying mechanisms and clinical needs show more similarities than differences [35]. The DSM-5 has adopted the novel diagnosis somatic symptom disorder, which is based on the presence of one or more distressing and persisting symptoms as well as excessive thoughts, feelings or behaviors related to these symptoms [16]. For primary care, a classification has recently been proposed based on the prognosis of symptoms: self-limiting physical symptoms are infrequent and unobtrusive, persistent physical symptoms are longer lasting and recurrent and associated with reduced quality of life, and a symptom disorder (which should not be confused with the more specifically defined somatic symptom disorder in the DSM-5) refers to the co-occurrence of multiple symptoms associated with substantial disability and healthcare use [43].

COMBINATION OF DEPRESSIVE, ANXIETY AND SOMATIC SYMPTOMS

Depressive and anxiety disorders commonly occur in combination with somatic symptoms [44,45]. Persons with a depressive or anxiety disorder have approximately twice as many somatic symptoms as persons without these disorders, and this number

further increases in patients who have both a depressive and an anxiety disorder [45]. In addition, the presence of somatic symptoms is associated with a 1.5-2.5 times higher risk of having a depressive or anxiety disorder [46]. This combination, which we will call “comorbidity” when refererring to disorders and “co-occurrence” when referring to symptoms, leads to more physical and social limitations and a worse perceived health than the pathologies apart [47]. Furthermore, it is associated with higher medical care utilization and higher in- and outpatient costs [48].

There are three main theories about the mechanisms underlying the relation between depressive, anxiety, and somatic symptoms. The first perspective states that the symptom types are presentations of the same underlying construct. It has for instance been indicated that depressive and anxiety symptoms are accompanied by body signals, which are interpreted and presented by some patients as somatic symptoms [49,50]. The other two theories assume that depressive, anxiety and somatic symptoms represent different constructs, which can be related to each other in two ways. One of these perspective indicates that depressive, anxiety and somatic symptoms directly influence each other [44,51,52]. Somatic symptoms could for instance provoke depression via negative consequences for functioning, or anxiety via uncertainty about known or unknown pathology [52]. Depression and anxiety, on the other hand, could lead to somatic symptoms by increasing the patient’s attention to and awareness of symptoms [37]. The third perspective assumes that depressive, anxiety and somatic symptoms have common underlying risk factors. These may include biological (e.g., female sex), psychological (e.g., trauma) and social factors (e.g., lack of a social network) [44,53].

SEE THE TREES FOR THE FOREST

As becomes apparent from the description of depressive, anxiety and somatic symptoms, their current conceptualization strongly relies on the way these symptoms are classified in diagnostic manuals such as the DSM-5 [54,55]. These classifications have enhanced standardization in research, offered a shared language for clinicians and bridged the gap between the scientific and clinical world [56]. Their criteria are based on a long history of clinical insights of experts from various disciplines and have repeatedly been described to be useful to make sense of clinical pictures [56]. Although classification systems are an essential basis for science and clinical care, expanding critiques focus on the questionable validity, reliability and utility of their diagnoses [57-60]. For example, neither neuroscience studies nor genetic studies have convincingly demonstrated biological underpinnings that are specific for individual psychiatric diagnoses [61-63]. Furthermore, there is striking heterogeneity in course trajectories and symptom profiles

within the diagnostic categories [64,65]. Other concerns regard the high comorbidity across categories [58] and their overlapping and inconsistent criteria within and across classification systems. Depressive, anxiety and somatic symptom disorders, for example, share physical criteria such as fatigue and weight loss [16]. Another problem is that questionnaires used to assess psychiatric disorders include different items [66]. For instance, the Hamilton Depression Rating Scale [67] includes somatic and anxiety items that are not found in the Quick Inventory for Depression [68].

A novel movement in research has shifted the focus from pre-defined disorders to smaller elements of psychopathology [14,69-73]. With this deconstruction of disorders, the movement aims to yield specific (types of) symptoms that play a crucial role in the development, course and treatment response of disorders [71]. This could inform on the diagnostic value of symptom criteria and their role in explaining comorbidity between disorders [74]. In addition, it could help to identify (types of) symptoms that require specific interventions. Finally, since symptom profiles differ across patients [65], this perspective may advocate “precision medicine” by enhancing the translation of research findings to the situation of individual patients [69,71,75].

One approach deconstructs disorders by focusing on symptom dimensions, which include groups of symptoms that commonly co-occur. Previous studies have for example shown that depressive and anxiety symptoms consist of a cognitive/affective and a neurovegetative symptom dimension [76,77], and somatic symptoms of a cardiopulmonary, musculoskeletal, gastrointestinal and general dimension [78,79]. These dimensions, which are also called clusters or categories, have varying characteristics in terms of their naturalistic course and response to interventions [80-82]. Symptom dimensions can be identified with data-driven algorithms in latent variable models [70,83], and can be seen as a parsimonious summary of common variation in the data. Although latent variable models have been suggested to assume a common causal basis of symptoms [84-86], many experts have argued that a descriptive and non-causal interpretation is more in line with the characteristics of the models [87,88].

Another approach focuses on the smallest unit of pathology: individual symptoms. This approach has mainly been applied to depressive symptoms, which has revealed their differential risk factors, consequences for functioning, and treatment responses [89-93].

A perspective that builds on the heterogeneity of individual symptoms is the network approach [15,94]. This approach conceptualizes an illness as the emerging structure of its symptoms and their correlations. Furthermore, comorbidity is viewed as the result of the pattern in which the individual symptoms of two different disorders co-occur [74]. The theory behind this model states that disorders arise as the result of causal relations among symptoms in a complex system [15,55]. Worry can provoke headache and insomnia, leading to fatigue and concentration problems, which, due to reduced

efficiency at work, could induce feelings of guilt, exacerbating insomnia. If a person has a single symptom, he or she can develop a full disorder via the interplay among symptoms. In a similar way, an improvement in one symptom during treatment can lead to a cascade of improvements in other symptoms and could potentially result in a healthy state.

COLORING THE BODY-MIND MAP: AIMS AND OUTLINE OF THIS THESIS

Despite the relevance of having a proper understanding of the co-occurrence of depressive, anxiety and somatic symptoms, many issues regarding its basic pattern, underlying mechanisms and specificity remain unresolved. The aim of this thesis is to examine these important epidemiological and clinical aspects of the association, both from the level of symptom dimensions and symptom networks.

Epidemiological aspects

The first section of this thesis examines how depressive and anxiety symptoms map onto somatic symptoms from an epidemiological perspective.

Symptom dimensions

The thesis starts by examining the co-development of depressive and anxiety versus functional somatic somatic symptoms from childhood to adulthood. Chapter 2 examines the development of these symptoms from age 10 to 26 years using data from a large general population cohort that is part of the Tracking Adolescents' Individual Lives Survey (TRAILS). We take into account heterogeneity across symptoms and persons and examine if different developmental patterns are associated with sociodemographic charactersitics, negative life events and perceived parenting style.

Then, the thesis moves on to the co-occurrence of depressive, anxiety and somatic symptoms in adults. Since earlier epidemiological research has investigated this association while focusing on broad scale scores, its specificity on the level of symptom dimensions remains elusive. In Chapter 3, we investigate cross-sectionally how specific depressive and anxiety disorders are associated with specific dimensions of somatic symptoms. In addition, we study if these associations can be explained by sociodemographic characteristics, lifestyle factors, and somatic diseases.

In Chapter 4, the associations of somatic symptom dimensions with the two-year persistence of major depressive disorder are investigated. We examine if these associations are independent of psychiatric characteristics, somatic diseases, lifestyle factors and disability. The studies in Chapter 3 and 4 are conducted with data from

the Netherlands study of Depression and Anxiety (NESDA), a cohort of patients with depressive and anxiety disorders as well as healthy controls.

Symptom networks

The next epidemiological studies focus on the dissection of the association of depressive, anxiety and somatic symptoms on the symptom-level. We explore connections of individual depressive and anxiety symptoms with somatic symptoms in a network model in Chapter 5. Using data from NESDA, we examine if associations to the somatic domain differ between cognitive/affective and neurovegetative depressive and anxiety symptoms, and whether there is further heterogeneity on the level of individual symptoms.

In Chapter 6, we examine associations among symptom criteria for the functional somatic syndromes chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome. While these syndromes are classified as different syndromes, it has been argued that they are different names for the same problem. We examine clustering of the symptom criteria in a network model in the large general population study of LifeLines to gain a better understanding of their interrelations.

Clinical aspects

The second section of this thesis examines the characteristics of depressive, anxiety and somatic symptoms in a clinical setting.

Symptom dimensions

The thesis first focuses on the clinical characteristics of these symptoms within primary care consultations. As many general practitioners find it challenging to recognize patients with functional somatic symptoms, we examine in Chapter 7 if consultation characteristics can help to predict if a patient is at risk for these symptoms. We hypothesize that higher diversity in prior reasons for encounter is associated with an increased risk of functional somatic symptoms. Consultation data are derived from the primary care electronic registration system of the Family Medicine Network (FaMe-Net).

In Chapter 8, we focus on patients' descriptions of the relation between negative emotions and somatic symptoms in consultations. Although primary care guidelines emphasize that GPs should create a common understanding with patients of this relation, little is known about the starting points of patients in such discussions. In this study, we conduct a qualitative analysis of the relations between negative emotions and somatic symptoms that patients present in consultations for persistent physical symptoms that are part of the Symptoms Clinic Intervention (SCI).

Consultations from the SCI are also used to study the proposal and creation of symptom management strategies for patients with persistent physical symptoms in Chapter 9.

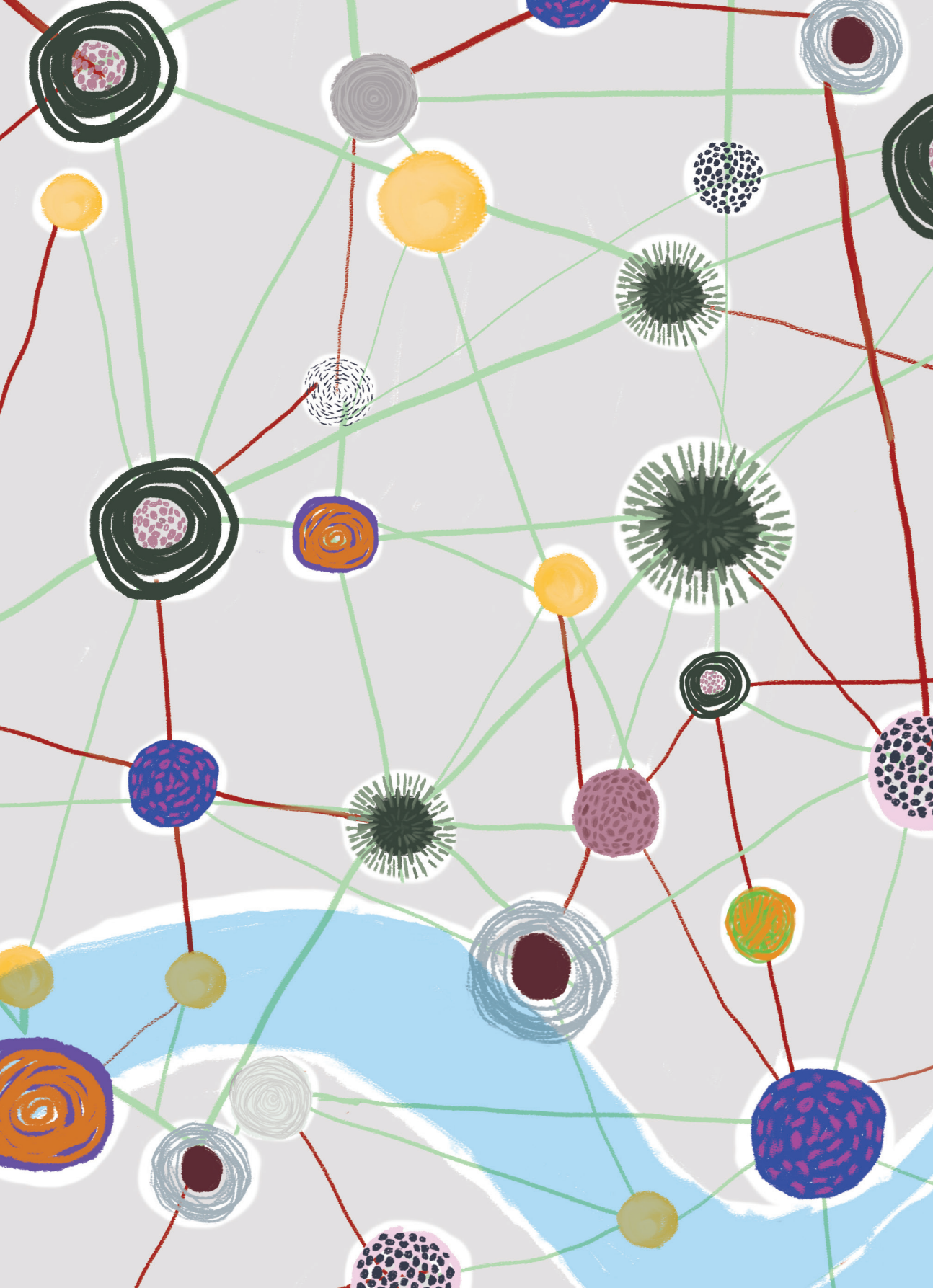
These strategies, which include actions that patients can conduct themselves to reduce the intensity or impact of their symptoms, constitute a key component of the management for persistent physical symptoms. We explore how these strategies emerge through the course of consultations, and how the pattern of their discussion is related to the adoption of these strategies by patients.

Symptom networks

The final section of this thesis focuses on the effects of different interventions on individual depressive symptoms. Since the efficacy of psychological and pharmacological treatment for depressive symptoms has mainly been established on the level of diagnoses, their symptom-specific effects remain elusive. In Chapter 10, we present a study of the symptom-specific effects of psychotherapy relative to this therapy combined with antidepressants in the treatment of patients with a mild to moderate depressive disorder. We make use of network models to differentiate between symptoms that respond directly to the interventions and those that may respond indirectly (i.e., via changes in other symptoms). Data are derived from a randomized controlled trial conducted by the Mentrum Research group in Amsterdam, the Netherlands.

Chapter 11 expands this work by examining symptom-specific effects of cognitive behavioral therapy versus antidepressants using a similar network approach. We examine how individual symptoms respond directly and indirectly to these interventions relative to each other. We additionally explore if symptom profiles of patients at baseline can predict an advantage of one intervention compared to another. The study is based on a large individual patient data meta-analysis including data of 17 randomized clinical trials.

Finally, the interpretation of our results is discussed in Chapter 12. We end with the implications of our results for clinical care and research.



EPIDEMIOLOGICAL ASPECTS

1. Symptom dimensions

Trajectories of functional somatic, depressive and anxiety symptoms during adolescence and young adulthood

Bekhuis E, Monden R, Kiers HAL, Boschloo L, Hartman CA, Schoevers RA, Rosmalen JGM.

Submitted.

ABSTRACT

Introduction: Functional somatic symptoms (FSS) frequently co-occur with depressive and anxiety symptoms in children, but it remains unclear how these symptoms simultaneously develop during adolescence. We studied how FSS co-develop with depressive and anxiety symptoms from late childhood to early adulthood in an explorative data-driven manner. We examined associations of this co-development with external factors.

Methods: We included 1,439 participants (56.4% female) of the Dutch TRacking Adolescents' Individual Lives Survey (TRAILS). FSS and depressive and anxiety symptoms were assessed with the Youth Self Report (11, 14 and 16 years) and the Adult Self Report (19, 22 and 26 years). Tucker 2 analysis was applied to capture heterogeneity across symptoms and persons to describe the co-development of symptoms. Correlations of different developmental patterns with sociodemographic characteristics, negative life events, and parenting style were computed.

Results: Symptom heterogeneity was decomposed into "functional somatic" and "depressive/anxiety" components. These symptom components followed similar as well as divergent developmental patterns from late childhood to early adulthood in specific individuals. Still, no person experienced increasing levels of the functional somatic and decreasing levels of the depressive/anxiety symptom component. Associations of developmental patterns with sociodemographic characteristics, negative life events, and parenting style were weak.

Conclusions: A parsimonious set of empirically derived components and their interactions explained a considerable part (explained variance=44%) of the variation of the co-development in FSS and depressive and anxiety symptoms. None of the external variables was associated with co-developmental patterns, indicating the complexity of the symptoms' development.

INTRODUCTION

Functional somatic symptoms (FSS) are somatic symptoms not conclusively explained by organic pathology [95]. The symptoms are reported by 25% of adolescents and can be greatly debilitating [96,97]. Furthermore, FSS have negative consequences for long-term mental health of youth [98]. FSS frequently co-occur with depressive and anxiety symptoms [51,99,100]. A review article concluded that a wide variety of FSS, including abdominal pain, headache, chest pain, musculoskeletal pain, and fatigue, were associated with an increased risk of depressive and anxiety symptoms in adolescents [51].

Three mechanisms have been suggested to explain the co-occurrence of FSS with depressive and anxiety symptoms in children and adolescents. The first mechanism is based on that many clinicians assume that children have difficulties recognizing and verbalizing emotions associated with depression and anxiety [49,50,101,102]. Still, children are aware of the physical sensations accompanying these emotions, which they are believed to present as FSS [95,101]. This concept is related to the condition of 'alexithymia' in adults (i.e., a reduced ability to experience, verbalize and differentiate between emotional feelings), but is believed to be a natural stage in the emotional development of children [103]. With naturally expanding emotional skills and maturation of brain areas during adolescence, reporting depressive and anxiety symptoms is believed to become easier for children [49,95,101,104]. This could be in line with the finding that at a population level the severity of FSS decreases during adolescence [96].

The second mechanism that could explain the association between FSS and depressive and anxiety symptoms includes that the symptom types directly cause and/or perpetuate each other [51]. One study investigated this mechanism in the large population sample of TRAILS and reported that depressive and anxiety symptoms predicted FSS after two years in adolescents, suggesting that they directly perpetuated the symptoms [105]. Although the reverse relation was less prominent [105], the predictive effect of FSS for depressive and anxiety symptoms has been indicated by other research [98].

The third mechanism suggested to underlie the co-occurrence is that FSS share risk factors with depressive and anxiety symptoms [51]. These could include genetic, hormonal as well as psychosocial factors [51]. Indeed, it has been shown that children with FSS and children with depressive and anxiety symptoms have other sociodemographic characteristics and have experienced a higher number of negative life events and a more negative parenting style compared to children without these symptoms [106-112]. Interestingly, these external factors have also been suggested to comprise the development of expression of affective states [49,113], suggesting that the relation of FSS with not fully developed affect expression could also be explained by common causes.

Although previous studies have given some clues about mechanisms that might underlie the co-occurrence of FSS with depressive and anxiety symptoms, much remains unclear about their specific role in the development of these symptoms. A first step to explore this is to examine the way FSS and depressive and anxiety symptoms co-develop from late childhood to young adulthood. For instance, the theory of changing affect expression would suggest that depressive and anxiety symptoms increase while FSS decrease during adolescence. If depressive and anxiety symptoms on themselves become more or less severe if a child matures, however, the explanation could lead to other developmental patterns (e.g., if depressive and anxiety symptoms decrease, one would expect to find a more extreme decrease in reported FSS levels). If FSS and depressive and anxiety symptoms directly reinforce each other, on the other hand, this would suggest that the symptom types follow similar developmental patterns such as parallel increasing or decreasing symptom levels. Finally, if the symptom types have common causes, parallel patterns would be expected with associations to sociodemographic characteristics, negative life events and/or perceived parenting style.

Although insight into the developments of FSS versus depressive and anxiety symptoms during adolescence is highly valuable to generate hypotheses about mechanisms underlying their co-occurrence, they have never been studied conjointly. This is important as developmental patterns of FSS and depressive and anxiety symptoms are heterogeneous. That is, it has been demonstrated that most FSS decrease during adolescence and young adulthood, but some types of FSS and particular individuals follow other developmental patterns (e.g., rising symptom levels for fatigue in girls [96,114]). Similarly, specific types of depressive and anxiety symptoms and persons show developmental patterns that differ from others (e.g., depressed mood increases while anhedonia decreases, with more prominent changes in girls than in boys [115]). To gain an understanding of the co-development of FSS and depressive and anxiety symptoms, it is therefore important to account for heterogeneity across symptoms and persons.

An analysis technique that distinguishes developmental patterns while capturing heterogeneity on different levels is Tucker 2 analysis [116,117]. This multi-way version of regular Principal Component Analysis (PCA) identifies a parsimonious number of components for symptoms and persons as well as their interactions in an integrated model [118,119]. As such, Tucker 2 can describe how persons differ in their developmental patterns on specific symptom domains [120,121]. An advantage of this technique compared to growth mixture models or latent class growth analysis is that is assigns flexible component scores rather than forcing symptoms or persons into specific trajectories. As the approach therefore allows each individual symptom and person to have a unique developmental pattern, the approach does more justice to the complexity of the development of FSS and depressive and anxiety symptoms in reality [121].

The current study explores the simultaneous development of FSS and depressive and anxiety symptoms during adolescence and young adulthood. Our main aim is to examine the association between changes in FSS and changes in depressive and anxiety symptoms while considering heterogeneity across symptoms and persons with Tucker 2 analysis. Secondly, we study the characteristics of developmental patterns by exploring their association with external factors.

METHODS

Participants

Data were derived from the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study of Dutch adolescents and young adults aiming to contribute to the understanding of the determinants of mental health and social development. The TRAILS study was approved by the Dutch Central Committee of Research Involving Human Subjects. Both parents and participants gave written informed consent. Detailed information about the study procedure is reported elsewhere [122].

Briefly, five municipalities in the North of the Netherlands were asked to give information from the community register of all citizens born between 1 October 1989 and 30 September 1990 (first two municipalities) or 1 October 1990 and 30 September 1991 (last three municipalities), yielding 3,483 names. All 135 schools within the municipalities were approached, and 123 (90.4%) agreed to participate. As school participation was a requirement for study participation, 3,145 adolescents were eligible for inclusion. A total of 210 of these adolescents were excluded due to mental retardation, a serious physical illness or handicap, or because they did not have a Dutch-speaking parent or guardian (except for Moroccan and Turkish parents, who were interviewed in their own language). Of all 2,935 adolescents who were approached for participation, 76.0% (N=2,230, mean age 11.1 years [SD=0.6], 51% female) participated in the first wave, which ran from March 2001 to July 2002. Follow-up waves were conducted every two to three years, with response rates of 96.4% at T2 (N=2,149, mean age 13.6 years [SD=0.5], 51% female), 81.4% at T3 (N=1,816, mean age 16.3 years [SD=0.7], 53% female), 84.3% at T4 (N=1,881, mean age 19.1 years [SD=0.6], 52% female), 79.7% at T5 (N=1,778, mean age 22.3 years [SD=0.7], 53% female), and 72.5% at T6 (N=1,617, mean age 25.7 years [SD=0.6], 55% female).

Participants with missing scores on all FSS and depressive and anxiety symptoms on more than one wave (N=791, 35.3%) were excluded from the study to avoid introducing bias by the multiple imputation procedure (see 'Missing data'). The main sample for this study therefore consisted of 1,439 participants. Excluded participants were less often

female (40.5% versus 56.4%, p<.001), older at study entry (11.2 versus 11.1 years, p<.001), and had lower baseline sum scores on the somatic (3.15 versus 3.25, p<.001), affective (3.26 versus 3.34, p<.001) and anxiety (1.89 versus 2.07, p<.001) problems scales than included participants.

Measures

FSS and depressive and anxiety symptoms

FSS and depressive and anxiety symptoms were assessed with self-report questionnaires from the Achenbach System of Empirically Based Assessment (ASEBA), using a version for adolescents (the Youth Self Report (YSR) [123]) at T1, T2 and T3 and a version for adults (the Adult Self Report (ASR) [124]) at T4, T5 and T6. The YSR and ASR have been shown to have high test-retest reliability and validity [123,124]. We included all items of the somatic problems scale (measuring somatic symptoms without a medical cause), the affective problems scale (measuring symptoms of DSM depressive disorders) and anxiety problems scale (measuring symptoms of DSM anxiety disorders) [125]. A total of 25 items were identical across the YSR and ASR and were included in the current study (see **Table 1**). Eight items (i.e. insomnia, fear of school, indecisiveness, feeling of failing, worry about the future, worry about family, palpitations and numbness or tingling in limbs) were not similar across scales and were therefore excluded. All symptoms during the past six months were scored on a 3-point scale (0='not at all', 1='a bit or sometimes', 2='a lot or often').

Due to a technical problem, the online version of the ASR at T4 (filled in by 82.3% of participants) assessed the somatic problems scale in a different way. In contrast to the other assessments, it included the screening question: "Did you experience any somatic symptoms without a medical cause?". If participants answered that they had never experienced such symptoms, the separate items on the somatic problems scale (i.e., dizziness, aches, headaches, stomachaches, nausea, eye problems, skin problems and vomits) were not shown to the participant and automatically scored as 'not at all'. As this resulted in lower scores on these symptoms at T4, we performed a sensitivity analysis (see 'Main analyses').

External factors

External factors included sociodemographic characteristics, negative life events, and perceived parenting style.

Table 1. Loadings of symptom components on specific symptoms.

	Functional somatic component	Depressive/anxiety component
Symptom	**Loading**	**Loading**
Headaches	**0.49**	0.00
Skin problems	**0.45**	-0.04
Stomachaches	**0.40**	-0.05
Vomits	**0.28**	-0.10
Aches	**0.28**	0.00
Dizziness	**0.21**	0.09
Nausea	**0.20**	-0.06
Overtired	-0.13	**0.42**
Worries	-0.03	**0.42**
Underactive	-0.07	**0.36**
Doesn't eat well	0.03	**0.28**
Nervous	0.14	**0.27**
Sad	-0.02	**0.27**
Sleep problems	0.10	**0.22**
Worthless	-0.03	**0.21**
Sleeps more	-0.05	**0.20**
Fears	0.14	**0.19**
Dependent	0.07	**0.17**
Cries	0.13	**0.16**
Fearful	0.07	**0.15**
Eye problems	0.14	0.06
Feels too guilty	0.13	0.10
Enjoys little	0.10	0.10
Talks suicide	0.05	0.03
Harms self	0.02	0.02

Loadings ≥0.15 are printed in bold font.

Sociodemographic characteristics

Sociodemographics of participants included sex and self-reported highest level of education at T6 (elementary education, lower tracks of secondary education, higher tracks of secondary education, senior secondary vocational training or higher vocational education/university). Socio-economic status of the parents was assessed by parent-report at T1 and T4 with the International Standard of Classification of Occupations, from which a self-computed standardized score by TRAILS was derived based on household income, education, and occupational level of both parents (higher scores indicate a higher parental socio-economic status) [126].

Negative life events

Whether participants had experienced parental divorce and/or the death of a parent or sibling was reported by parents at T1 and by participants at T2-T6 [127]. The experience

of sexual abuse, physical abuse or other trauma (e.g., having been involved in a life-threatening accident) ever during life was assessed at T4 with a questionnaire specifically designed for TRAILS [128] that was inspired by the Childhood Trauma Questionnaire [129].

Perceived parenting style

How participants perceived the style of parenting was measured with the overprotection, rejection and emotional warmth subscales of the Egna Minnen Beträffande Uppfonstran for Children (EMBU-C) [130] at T1. At T4, shortened versions of the rejection and emotional warmth subscales were assessed [131]. Average scores for perceived parenting style of the mother and the father were computed (ranging from 0 [lowest level of perceived overprotection, rejection and emotional warmth] to 4 [highest level of perceived overprotection, rejection and emotional warmth]).

Data analysis strategy

Missing data

Missing items were imputed in R version 3.4.3 with package Amelia II [132]. A total of 4.5% of data on FSS and depressive and anxiety symptoms were missing, which were imputed 20 times (for the analysis code, see https://www.researchgate.net/publication/336983768_Analysis_code_of_Chapter_2_Trajectories_of_functional_somatic_depressive_and_anxiety_symptoms_during_adolescence_and_young_adulthood). All analyses were conducted on each imputed dataset separately and summarized by averaging results and calculating their standard deviations across the imputed datasets to explore stability of the estimates.

Main analyses

To study the simultaneous development of FSS and depressive and anxiety symptoms, we applied Tucker 2 analysis [117]. This method summarizes heterogeneity in developmental patterns by identifying a limited set of components for symptoms and persons as well as their interactions in an integrated model. Interactions at each time point are summarized in a core array, from which basic patterns of the components can be obtained. The basic patterns function as standard developments by which numerous other developmental patterns occurring in the dataset can be described in a systematic way. Tucker 2 selects the basic patterns that can explain most variance in the dataset as opposed to developmental patterns that are most common or most extreme. Therefore, they can be interpreted as the processes that best summarize the heterogeneous developmental patterns of the symptoms in the dataset. Each symptom and person is assigned a component loading (measured on a continuous scale) indicating how much a symptom

or person follows the basic patterns characteristic for a specific component. This loading can be used to calculate developmental patterns for each symptom and person separately (positive loadings indicate developmental patterns in the same direction and negative loadings in the opposite direction as the basic developmental patterns in the component). As component loadings are non-standardized, no cut-offs for the interpretation of their absolute values are available. Rather, component loadings should be interpreted relative to each other. As Tucker 2 captures variation in item scores across participants and over time without assumptions about normality of the data, its results cannot be affected by skewed or low item scores in the dataset.

We conducted Tucker 2 analysis in R version 3.4.3 and Matlab version 2017b. Detailed information about the analytical procedure of Tucker 2 can be found elsewhere [117], and the analysis code used in this study is provided online **(**https://www.researchgate.net/publication/336983768_Analysis_code_of_Chapter_2_Trajectories_of_functional_somatic_depressive_and_anxiety_symptoms_during_adolescence_and_young_adulthood). First, we selected the number of components for symptoms and persons by balancing complexity with explained variance (% of explained sum of squares) using the generalized scree test in each imputed dataset [133]. The maximum number of components was set to six for symptoms and six for persons. Second, we applied the orthogonal Joint Orthomax rotation [134] to obtain interpretable component structures in each imputed dataset. Weights were set to 12.5 for symptom components (25 symptoms/2 symptom components, defined as “standard weight” [134]) and 0 for person components to maximize simplicity in the loadings on symptom components. Results were summarized over the imputed datasets using generalized Procrustes rotation [117,135,136]. Next, we explored the characteristics of the identified components. We inspected loadings of symptom components on individual symptoms and explored basic patterns of symptom and person components. Furthermore, we examined heterogeneity across persons in detail by inspecting their loadings on person components and calculating the developmental patterns of symptom components corresponding to these loadings. Associations of person components loadings with external factors were calculated using Pearson or Spearman correlations (absolute correlation coefficients of 0.1-0.3=weak, 0.3-0.5=moderate, >0.5-1=strong [137]). Finally, to test the effect of the screening question in the somatic problems scale at T4, we repeated the Tucker 2 procedure on data of all time points except T4 as a sensitivity analysis.

RESULTS

Sample characteristics

In our sample, 812 of the 1,439 (56.4%) adolescents were female and mean age at baseline was 11.1 (range=10.0-12.6) years (**Supplementary Table 1**). Mean symptom scores ranged from 0.0 for harms self at T5 to 0.7 for worries at T6 (scores ranging from 0-2).

Model selection

First, we selected the number of components. The generalized scree test indicated that the best balance of complexity and fit was found for the solution with two symptom and two person components (2,2-structure, mean fit=44.1% [ranging from 44.0% to 44.1% across the 20 imputed datasets]) and that with two symptom and three person components (2,3-structure, mean fit=45.7% [ranging from 45.7% to 45.8% in the different imputed datasets]). As the 2,3-structure had only 1.6% higher fit and the 2,2-structure was easier to interpret, the 2,2-structure was chosen.

Component characteristics

Subsequently, we applied the rotation to obtain better interpretable components and averaged results over the imputed datasets. Results were highly stable across imputed datasets, as reflected in small standard deviations (all <0.02) of the estimated component loadings.

Symptom components

The first symptom component was labeled the ‘functional somatic component’ as it had high loadings on somatic items without a medical cause such as headache and skin problems (**Table 1**). The second component was called the ‘depressive/anxiety component’ since it had high loadings on depressive and anxiety symptoms like sad and worries.

Person components

To interpret the developmental patterns that were identified, we first describe the person components that were found by the Tucker 2 analysis. Their basic patterns do not have any special value on their own but are standard developments from which the specific developmental patterns of individual participants can be constructed. We subsequently inspected loadings of all persons on the person components and explored their corresponding person-specific developmental patterns. Finally, associations of person components with external variables were examined.

Basic patterns

The first person component identified by Tucker 2 was called the 'parallel-course component'. Its basic pattern was characterized by moderate scores of the functional somatic component and the depressive/anxiety component at baseline, which both decreased over time (**Figure 1**). The second person component was called the 'divergent-course component'. The basic pattern of this component showed high baseline scores of the functional somatic component as well as the depressive/anxiety component. While scores of the functional somatic component decreased, those of the depressive/anxiety component increased.

Loadings and corresponding developmental patterns

Next, we inspected loadings of participants on the two person components. Loadings on person components differed considerably across participants (ranging from -0.12 to 0.11 on the parallel-course component and from 0.00 to 0.09 on the diverging-course component; **Figure 2**). Nearly all possible combinations of positive and negative loadings on the two person components were also found across persons, indicating that a high variety of developmental patterns was present in the dataset. Some examples of these developmental patterns include stable low scores of both symptom components (bottom panel in Figure 2), parallel increasing scores (left panel in Figure 2) and parallel decreasing scores of both symptom components (right panel in Figure 2), and decreasing scores of the functional somatic and increasing scores of the depressive/anxiety component (top panel in Figure 2). Despite the high number of combinations of loadings, negative loadings on the diverging-course trajectory did not occur. This indicates that variations of a trajectory with increasing scores of the functional somatic and decreasing scores of the depressive/anxiety component were absent.

Associations with external factors

In general, associations between loadings on the specific person components and external variables were weak (**Table 2**). Only the associations between diverging-course person component loadings and being female (r=0.34) and perceiving a rejective parenting style at T4 (r=0.31) were in the low range of moderate correlations. To explore whether these external factors were associated with specific combinations of loadings on the two person components, we inspected their distribution in a scatter plot (**Supplementary Figure 1**). No association with the combination of loadings on the two person components was observed.

Figure 1. Basic patterns in the parallel-course and diverging-course person component.

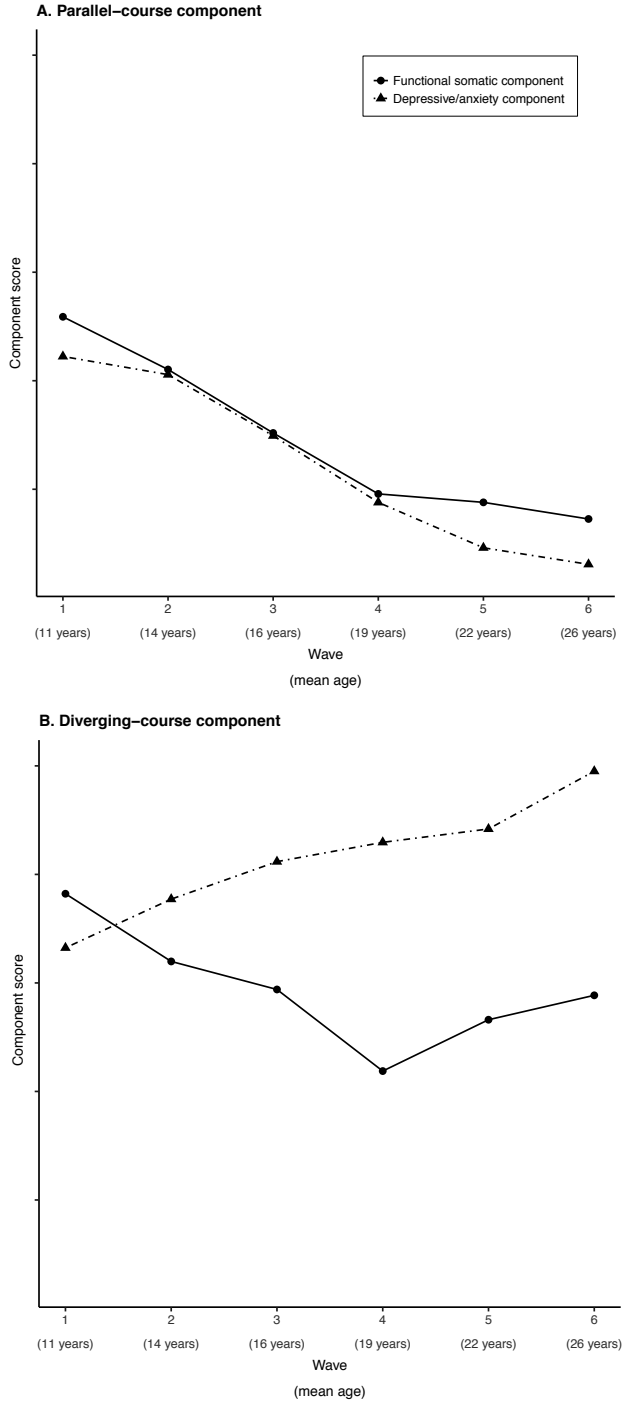
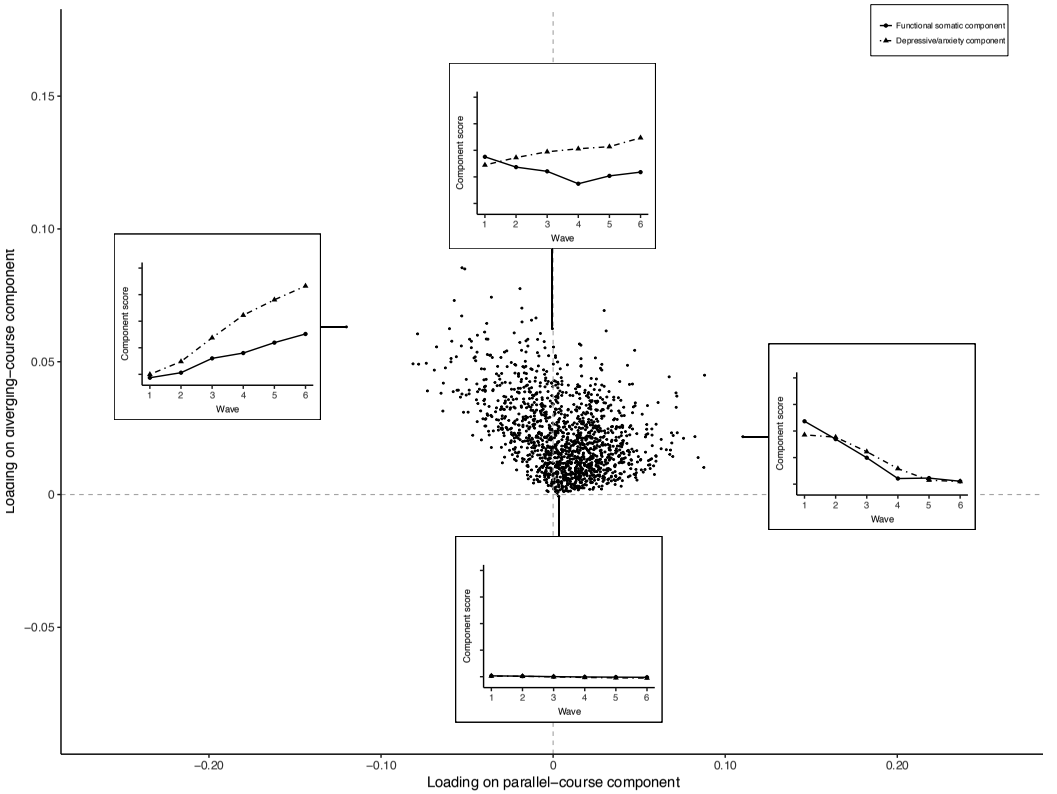


Figure 2. Loadings of specific participants on person components and their corresponding sets of developmental patterns.



The loadings of individual participants on the two person components are presented with dots. Four examples of trajectories corresponding to specific combinations of person component loadings are shown in the figure. Note that a high loading on the parallel-course component and a loading of 0 on the diverging-course component refers to the trajectory in **Figure 1A**, and a loading of 0 on the parallel-course component and a high loading on the diverging-course component to the trajectory in **Figure 1B**.

Table 2. Correlations of person component loadings with external factors.

	Parallel-course component loadings						Diverging-course component loadings					
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
Descriptive characteristics												
Sex (female)	-0.09						0.34					
Socio-economic status of parents	-0.01			0.01			-0.06			0.01		
Highest education						0.00						-0.08
Negative life events												
Parental divorce	-0.05	-0.06	-0.06	-0.05	-0.05	-0.05	0.09	0.09	0.09	0.09	0.09	0.10
Death of family member	-0.02	-0.03	-0.04	-0.05	-0.03	-0.02	0.04	0.05	0.06	0.07	0.08	0.06
Sexual abuse				-0.06						0.19		
Physical abuse				-0.09						0.21		
Other traumatic events				-0.01						0.13		
Perceived parenting style												
Overprotection	0.10						0.18					
Rejection	0.15			-0.09			0.16			0.31		
Emotional warmth	-0.07			0.03			-0.06			-0.17		

Correlations are presented for the wave at which an external variable was assessed (T1 to T6).

Sensitivity analysis

To examine the influence of the somatic problems scale screening question, we repeated the Tucker 2 analysis without T4 (**Supplement 1**). The results did not substantially differ. Still, given that the dip in scores of the functional somatic component at T4 in both person components disappeared, change became slightly more gradual over time.

DISCUSSION

This study identified different developmental patterns of FSS and depressive and anxiety symptoms from late childhood to early adulthood across persons. We found that nearly all possible patterns of parallel and divergent symptom co-development occurred in the dataset. However, a trajectory with increasing FSS and decreasing depressive and anxiety symptoms

was clearly absent. The developmental patterns did not show relevant associations with sociodemographic characteristics, negative life events, and perceived parenting style. Given the considerable proportion of explained variance by the model (explained variance 44%), the identified components and their interactions are highly valuable to summarize the complex co-development of FSS with depressive and anxiety symptoms.

An important strength of the current study is the prospective design in which assessments were conducted bi- to triennially for 15 years. Moreover, the population-based sample of 1,439 adolescents increased the generalizability of our results. Another strength is the use of Tucker 2 analysis, which allowed us to take into account heterogeneity of both symptoms and persons using a data-driven approach. The use of a data-driven algorithm to study symptom components is a considerable advantage given the conceptual overlap between FSS and depressive and anxiety symptoms that refer to the body (e.g., overtired) that complicates the categorization of these symptom before analysis. A limitation of the study is that the somatic problems scale of the ASR at T4 included a screening question, leading to lower symptom ratings at this wave. This may have led to a small drop in functional somatic component scores at T4 (age 19 years), but we showed that it did not affect the overall developmental patterns. Secondly, eight assessed FSS and depressive/anxiety symptoms could not be included in the analyses since they were not consistently measured across the YRS and ASR. Furthermore, all symptoms were assessed by self-report using the same instrument, which could have led to same-rater and same-instrument bias. We are also not certain that the self-reported FSS are indeed unexplained by somatic diseases. Still, the questionnaire clearly stated that the symptoms should occur without a medical cause or an obvious reason [123,124]. Moreover, scores on this scale were considerably higher than can be expected for explained symptoms given the low number of somatic diseases in the adolescent and young adult population [138].

This study is the first to examine the simultaneous development of FSS and depressive and anxiety symptoms from late childhood to early adolescence. The patterns of symptom development found in this study are comparable to previously found trajectories for FSS and depressive and anxiety symptoms separately. For example, that the functional somatic component followed stable, decreasing and increasing developmental patterns is in line with a previous TRAILS study using growth mixture models [114]. Similar developmental patterns of depressive and anxiety symptoms were also identified in other studies using growth mixture models [139,140]. As our study period was longer than in these studies (11-26 years as opposed to e.g. 11-17 years [114]), our findings provide insight into the continuation of these developmental patterns into young adulthood, which was characterized by similar changes in symptom levels as during adolescence. The use of Tucker 2 allowed us to capture more heterogeneity across persons than previous studies.

That developmental patterns differed considerably across persons indicates the strength of Tucker 2 to describe how these symptoms develop in varying patterns in real life [121]. We did not find relevant associations of symptom developmental patterns with external factors. Previous studies [110-112], some of which were based on the same sample [106,107,114,127,141], have found associations of these factors with trajectories of FSS and depressive and anxiety symptoms separately. Although these studies found statistically significant associations, the strength of associations in most studies was weak [110-112]. It is therefore not surprising that correlations of developmental patterns with external variables in the current study were also low. For some external variables, however, stronger associations with symptom trajectories have been identified in previous work [112,114]. For example, female sex has been associated with a five times increased risk of an unfavorable trajectory of FSS [114] and a two times higher risk of a unfavorable trajectory of depressive symptoms [142]. This inconsistency with our results could be explained by that previous studies focused on categories of extreme trajectories [112,114], while we identified components of developmental patterns along which persons and symptoms could vary. That we did not find relevant associations with external factors indicates that the symptoms' co-development is more complex than can be explained with such external factors alone. This contrasts with the development of cognitive depressive symptoms alone, which has been shown to be captured for a large part by scores on neuroticism [143]. This illustrates the value of the identified components and their interactions by Tucker 2 to summarize the way FSS and depressive and anxiety symptoms co-develop during adolescence.

The found developmental patterns of FSS and depressive and anxiety symptoms in this study could point to several potential mechanisms underlying their co-occurrence. First, they might be in line with the theory of developing affect expression during adolescence [49,95,101]. This theory could explain that some adolescents reported decreasing FSS and increasing depressive and anxiety symptoms while they matured. Depressive and anxiety symptoms can also become more or less severe over time on themselves [112] and, therefore, some adolescents could have experienced parallel increasing or decreasing FSS and depressive and anxiety symptoms even though their emotion expression skills developed. Supporting this suggestion is that within parallel developmental patterns, scores on the functional somatic component showed a less extreme increase or more prominent decrease than those of the depressive/anxiety component (as indicated by that negative and positive loadings on the parallel-course component occurred in combination with relatively high positive loadings on the diverging-course component). On the other hand, if no depressive or anxiety symptoms were present throughout the life of an adolescent, stable low symptom levels would have occurred.

Although other suggested mechanisms cannot explain all developmental patterns, it is possible that specific mechanisms underlie the co-development of the symptom

types in particular individuals. The diverging trajectory could for instance result from the presence of factors that negatively influence depressive and anxiety symptoms but not FSS. The parallel-course developmental patterns, in contrast, could be explained by two mechanisms. One possible mechanism is that FSS directly cause or perpetuate depressive or anxiety symptoms or vice versa [51]. Another mechanism that may underlie the parallel developmental patterns is that FSS and depressive and anxiety symptoms have common causes [51,110]. Although our findings indicated that sociodemographic characteristics, negative life events and perceived parenting style probably do not have a central role in this mechanism, it is possible that FSS and depressive and anxiety share genetic, hormonal or other psychosocial risk factors [51]. That the parallel developmental patterns were characterized by gradual changes over time rather than sudden changes suggests that age-independent factors such as insecure attachment constitute a more likely involved factor in this context than age-dependent risk factors such as pubertal hormonal changes [111].

As much remains unknown about the mechanisms underlying the co-occurrence of FSS and depressive and anxiety symptoms in adolescents, more research is warranted. Although previous studies have linked affect expression dysfunction to FSS [50,103,144] and depressive and anxiety symptoms [145-147], we are not aware of any studies that examined the relation between emotional development and patterns of FSS and depressive and anxiety symptoms in adolescents. This would be especially important as the previous literature is not conclusive about whether inadequate affect regulation and expression is a cause of, mediator of, or result of shared risk factors with the co-occurrence of FSS with depressive and anxiety symptoms [103]. As no assessments of language or cognitive development were conducted in TRAILS, we were not able to study it directly. One important direction for future studies is therefore to measure emotion regulation and expression skills as well as FSS and depressive and anxiety symptoms from early childhood onwards, as the development of important aspects of emotion understanding and expression occurs between early childhood and late childhood [148].

CONCLUSIONS

In summary, the current exploratory study demonstrated that FSS and depressive and anxiety symptoms show varying patterns of co-development from late childhood to young adulthood. More research is needed to investigate the mechanisms we hypothesized to underlie this co-developmental relation. One interesting direction for future studies is to directly measure development in emotion regulation and expression skills and examine if it is related with the onset and course of FSS and depressive and anxiety symptoms.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Sample characteristics (N=1,439).

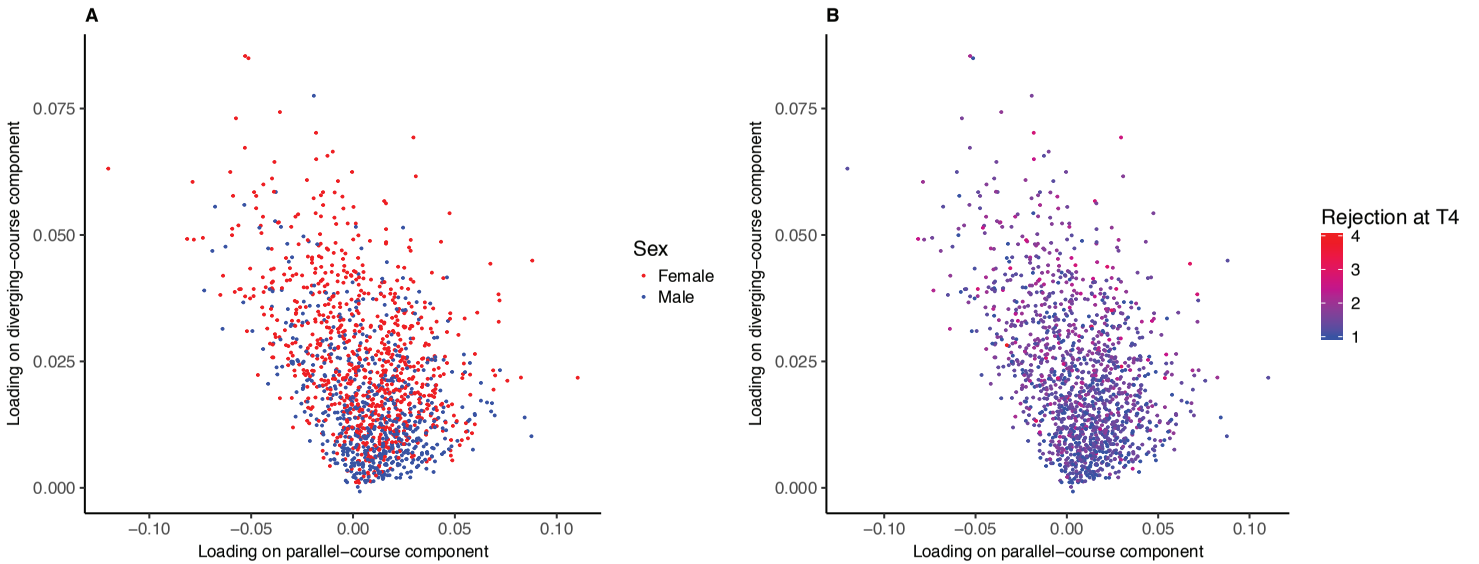
	T1	T2	T3	T4	T5	T6
	N (%)/Mean (range*)					
Symptoms (scores ranging from 0-2)						
Dizziness	0.36	0.39	0.35	0.26	0.22	0.26
Aches	0.44	0.28	0.25	0.13	0.19	0.23
Headache	0.75	0.61	0.53	0.17	0.44	0.47
Stomach ache	0.52	040	0.32	0.12	0.20	0.21
Nausea	0.27	0.05	0.06	0.03	0.05	0.08
Eye problems	0.28	0.23	0.23	0.09	0.21	0.30
Skin problems	0.64	0.47	0.35	0.14	0.27	0.30
Vomits	0.33	0.14	0.08	0.04	0.06	0.06
Enjoys little	0.30	0.23	0.22	0.17	0.17	0.24
Cries	0.42	0.31	0.29	0.31	0.34	0.32
Harms self	0.04	0.06	0.05	0.03	0.02	0.03
Doesn’t eat well	0.41	0.44	0.46	0.48	0.46	0.58
Worthless	0.21	0.20	0.20	0.22	0.24	0.32
Feels too guilty	0.33	0.27	0.22	0.19	0.20	0.25
Overtired	0.23	0.43	0.53	0.49	0.58	0.61
Sleeps more	0.24	0.15	0.20	0.29	0.29	0.34
Talks suicide	0.09	0.09	0.07	0.05	0.05	0.07
Sleep problems	0.44	0.34	0.38	0.37	0.45	0.45
Underactive	0.35	0.36	0.43	0.44	0.49	0.57
Sad	0.29	0.29	0.29	0.34	0.32	0.43
Dependent	0.34	0.37	0.33	0.31	0.30	0.38
Fears	0.50	0.61	0.34	0.49	0.41	0.39
Nervous	0.56	0.59	0.52	0.50	0.43	0.60

Supplementary Table 1. Continued.

	T1	T2	T3	T4	T5	T6
	N (%)/Mean (range*)					
Fearful	0.29	0.23	0.19	0.20	0.20	0.30
Worries	0.37	0.58	0.67	0.54	0.57	0.68
Sociodemographic characteristics						
Sex (female)	812 (56.4%)					
Age (in years)	11.08 (10.0-12.6)	13.52 (12.2-15.0)	16.23 (14-7-18.4)	19.01 (18.0-20.9)	22.25 (21.0-24.1)	25.63 (24.4-27.3)
Socio-economic status of parents	0.12 (-1.8-1.7)			-0.02 (-2.2-1.4)		
Highest education						
Elementary education						11 (0.8%)
Lower tracks secondary education						57 (4.0%)
Higher tracks secondary education						41 (2.8%)
Senior secondary vocational						443 (30.8%)
Higher vocational/university						887 (61.6%)
Negative life events						
Parental divorce	247 (17.2%)	301 (20.9%)	348 (24.2%)	388 (27.0%)	424 (29.5%)	445 (30.9%)
Death of family member	42 (3.1%)	56 (3.9%)	66 (4.6%)	81 (5.6%)	105 (7.3%)	128 (8.9%)
Sexual abuse				131 (9.1%)		
Physical abuse				387 (26.9%)		
Other traumatic events				350 (24.3%)		
Perceived parenting style						
Overprotection	1.83 (1.0-3.5)					
Rejection	1.48 (1.0-3.5)			1.46 (1.0-4.0)		
Emotional warmth	3.24 (1.1-4.0)			3.16 (1.0-4.0)		

*Range of all symptoms was 0-2.

Supplementary Figure 1. Distribution of A) sex and B) perceived parental rejection at T4 across different combinations of loadings on the two person components.



Supplement 1. Sensitivity analysis

To examine whether the screening question in the somatic problem scale at T4 had altered our conclusions, we repeated the Tucker 2 procedure excluding this wave. In line with the main analyses, a 2,2-structure was chosen.

Components

Symptom components
Similar to the main analyses, a functional somatic component and a depressive/anxiety component were found (**Supplementary Table 2**). Loadings were highly comparable to those found in the main analyses.

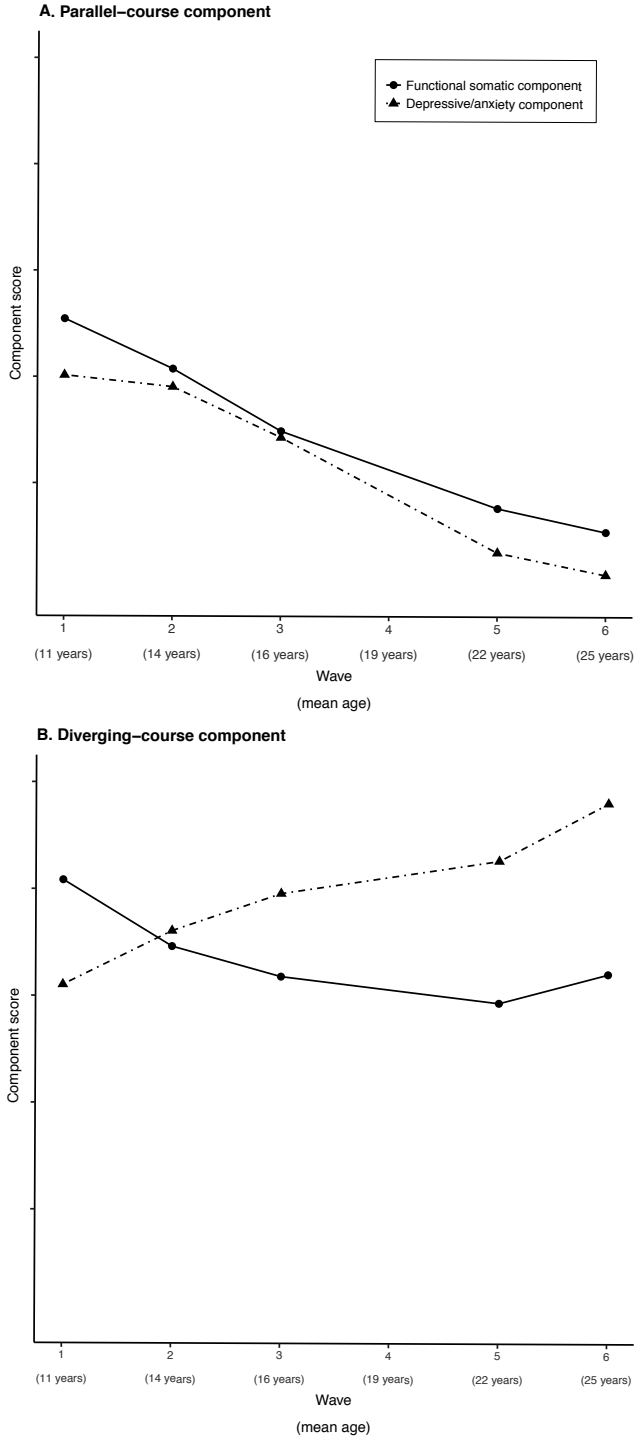
Person components
Person components included a parallel-course component and an diverging-course component, with similar basic patterns as in the main analyses (**Supplementary Figure 2**). As the dip in the functional somatic component at T4 disappeared in both person components, the decrease in this symptom component over time was more gradual than in the main analyses.

Supplementary table 2. Loadings of symptom components on specific symptoms in the analyses excluding T4.

	Functional somatic component	Depressive/anxiety component
Symptom	**Loading**	**Loading**
Headache	**0.44**	0.01
Skin problems	**0.43**	-0.06
Stomach ache	**0.39**	-0.07
Vomits	**0.28**	-0.14
Aches	**0.28**	-0.03
Dizziness	**0.23**	0.06
Fears	**0.23**	0.11
Nausea	**0.20**	-0.08
Cries	**0.17**	0.12
Overtired	-0.12	**0.45**
Worries	-0.02	**0.45**
Underactive	-0.05	**0.37**
Doesn't eat well	0.07	**0.26**
Nervous	**0.18**	**0.24**
Sad	0.00	**0.26**
Sleep problems	0.13	**0.20**
Worthless	-0.02	**0.22**
Sleeps more	-0.03	**0.19**
Dependent	0.09	**0.16**
Feels too guilty	0.14	0.09
Eye problems	0.11	0.08
Enjoys little	0.10	0.09
Fearful	0.08	0.14
Talks suicide	0.05	0.03
Harms self	0.03	0.02

Loadings ≥0.15 are printed in bold font.

Supplementary figure 2. Basic patterns in specific person components in the analyses excluding T4.



Differential associations of specific depressive and anxiety disorders with somatic symptoms

Bekhuis E, Boschloo L, Rosmalen JGM, Schoevers, RA.

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ABSTRACT

Introduction: Previous studies have shown that depressive and anxiety disorders are strongly related to somatic symptoms, but much is unclear about the specificity of this association. This study examines the associations of specific depressive and anxiety disorders with somatic symptoms, and whether these associations are independent of comorbid depressive and anxiety disorders.

Methods: Cross-sectional data were derived from the Netherlands Study of Depression and Anxiety (NESDA). A total of 2,008 persons (mean age: 41.6 years, 64.9% women) were included, consisting of 1,367 patients with a past-month DSM-diagnosis (established with the Composite International Diagnostic Interview [CIDI]) of depressive disorder (major depressive disorder, dysthymic disorder) and/or anxiety disorder (generalized anxiety disorder, social phobia, panic disorder, agoraphobia), and 641 controls. Somatic symptoms were assessed with the somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ), and included cardiopulmonary, musculoskeletal, gastrointestinal, and general symptoms. Analyses were adjusted for covariates such as chronic somatic diseases, sociodemographics, and lifestyle factors.

Results: All clusters of somatic symptoms were more prevalent in patients with depressive and/or anxiety disorders than in controls (all $p<.001$). Multivariable logistic regression analyses showed that all types of depressive and anxiety disorders were independently related to somatic symptoms, except for dysthymic disorder. Major depressive disorder showed the strongest associations. Associations remained similar after adjustment for covariates.

Conclusion: This study demonstrated that depressive and anxiety disorders show strong and partly differential associations with somatic symptoms. Future research should investigate whether an adequate consideration and treatment of somatic symptoms in depressed and/or anxious patients improves treatment outcomes.

INTRODUCTION

Depressive and anxiety disorders are among the most common mental disorders in the general population [18,149], with 12-month prevalence rates ranging from 1.8% for panic disorder to 6.9% for major depressive disorder [150]. The burden of disease is high, as the disorders affect social, personal, and occupational functioning [21-23], and constitute a considerable economic burden on society [23,151].

Extensive evidence suggests that depressive and anxiety disorders are strongly related to somatic symptoms [45,99,100,152,153]. Two pediatric studies, for example, showed that nearly all somatic symptoms were more prevalent in patients with a depressive and/or anxiety disorder than in controls [99,100]. In addition, somatic symptoms have been shown to be associated with at least a twofold increased risk of having a depressive and/or anxiety disorder [38,152,153]. The co-occurrence of depressive and anxiety disorders with somatic symptoms is associated with more functional disability, higher medical care utilization, and higher costs than the pathologies apart [47,48]. Both for clinical and scientific reasons, it is important to improve our understanding of this association.

Three mechanisms have been hypothesized to explain the association of depressive and anxiety disorders with somatic symptoms. First, in the antecedent hypothesis, depressive and anxiety disorders cause the onset of somatic symptoms [52,154-156] via, for example, an increased awareness and an altered perception of physical sensations [37,157]. Second, according to the consequence hypothesis, somatic symptoms predict the onset of depressive and anxiety disorders [52,158-161], as, for example, the bodily inconvenience and physical limitations of somatic symptoms might cause symptoms of depression and anxiety [44,162]. Third, in the common etiology hypothesis, shared etiological factors (e.g., environmental, psychological, and biological factors) independently cause the onset of depressive and anxiety disorders as well as somatic symptoms [44,52,53].

Although the co-occurrence of depressive and anxiety disorders with somatic symptoms has often been reported, little is known about the specificity of this association. For example, it is unclear whether the association is conditional on the type of depressive or anxiety disorder. In addition, previous studies have speculated that depressive disorders may be more strongly associated with pain symptoms such as musculoskeletal symptoms [78,163], whereas anxiety disorders might show stronger associations with cardiopulmonary symptoms [153,164]. Developing a better understanding of the specificity of the association may provide important insights into its etiology, and could be of help in developing therapies for patients with depressive and/or anxiety disorders as well as somatic symptoms.

Previous studies examining the specificity of associations have an important limitation as they have often not considered the comorbidity of different depressive and anxiety disorders [38,165]. This is problematic, since depressive and anxiety disorders often co-occur [19,166], and, as a consequence of the confounding effects of comorbid disorders, previous studies could incorrectly have reported similar associations across specific depressive and anxiety disorders. In addition, it would be important to take into account the effects of covariates [38,163,167]. As depressive and anxiety disorders are associated with somatic diseases [168], and somatic symptoms are often consequences of somatic diseases [38], it is essential to get insight into the effects of these diseases by adjusting for their presence. Similarly, it would be important to take into account the effects of sociodemographics and lifestyle factors as these factors have shown associations with the presence of depressive and anxiety disorders [169] and somatic symptoms [38,170,171].

The present study focuses on the associations of specific depressive and anxiety disorders with somatic symptoms by using a large dataset of patients with DSM-IV depressive and/or anxiety disorders (N=1,367) as well as healthy controls (N=641). The aims of this study are:

a. To examine the associations of specific depressive disorders (i.e., major depressive disorder, and dysthymic disorder) and anxiety disorders (i.e., generalized anxiety disorder, social phobia, panic disorder, and agoraphobia) with different clusters of somatic symptoms;
b. To determine whether these associations are independent of comorbid depressive and anxiety disorders;
c. To determine whether these associations can be explained by the potentially confounding effects of chronic somatic diseases, sociodemographics and lifestyle factors.

METHODS

Study sample

Data were derived from the baseline measurements of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study aimed at examining the development and long-term prognosis of depressive and anxiety disorders among adults (18-65 years). For the baseline assessment, 2,981 persons were included, consisting of healthy controls (N=625, 22%), persons with a current (past-month) depressive and/or anxiety disorder (N=1,411, 47%), and persons with a prior history of a depressive and/or anxiety disorder (N=918, 31%). To represent various settings and developmental

stages of psychopathology, recruitment took place in the community (19%), primary care (54%), and specialized mental health care (27%). Exclusion criteria were a primary clinical diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder or severe substance use disorder, and insufficient command of the Dutch language. The baseline assessment consisted of an extended face-to-face interview, including a standardized diagnostic psychiatric interview, as well as paper-and-pencil questionnaires. The research protocol was approved by the Ethical Committee of the three participating universities, and all participants gave written informed consent. A detailed description of the NESDA study design can be found elsewhere [172].

For the present study, we selected both healthy controls without a lifetime depressive or anxiety disorder (N=652), and patients with a current (past-month) depressive and/or anxiety disorder (N=1,411). Participants with missing data on somatic symptoms (N=55, 2.7%) were excluded, resulting in a total sample of 2008 persons. Persons with valid data on somatic symptoms were less likely to have an anxiety disorder (p=.04) compared to non-responders, whereas age (p=.75), gender (p=.67), education (p=.60), and depressive disorder (p=.17) were not associated with non-response.

Depressive and anxiety disorders

Lifetime and current diagnoses of depressive and anxiety disorders were established with the Composite International Diagnostic Interview (CIDI) [173], version 2.1. The CIDI is a reliable instrument, which classifies diagnoses according to the DSM-IV criteria [40], and was administered by specially trained research staff. The following types of disorders were distinguished: major depressive disorder, dysthymic disorder, generalized anxiety disorder, social phobia, panic disorder, and agoraphobia.

Somatic symptoms

The presence of somatic symptoms was measured with the somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ) [174]. This scale assesses the frequency of experiencing 16 somatic symptoms in the past week (scores ranging from 1=Never to 5=Very often or constantly). Based on previous studies [78,79], four clusters of somatic symptoms were distinguished: cardiopulmonary symptoms (i.e., excessive perspiration, pain in chest, palpitations, pressure or tight feeling in chest, shortness of breath), musculoskeletal symptoms (i.e., back pain, neck pain, muscle pain, tingling in fingers), gastrointestinal symptoms (i.e., bloated feeling in abdomen, nausea or upset stomach, pain in abdomen or stomach area), and general symptoms (i.e., dizziness or feeling lightheaded, fainting, headache). The symptom ‘blurred vision or spots in front of your eyes’ was excluded, since it did not fit the clusters of somatic symptoms [79]. A specific cluster of somatic symptoms was considered present when at least one of its symptoms was experienced regularly or more often (score 3 or higher).

Covariates

Analyses were adjusted for the potential effects of chronic somatic diseases, sociodemographics and lifestyle factors. First of all, the number of self-reported chronic diseases for which persons received treatment was considered. For the assessment, participants were asked whether they had specific diseases (i.e., lung disease, heart disease, diabetes mellitus, CVA, arthritis, osteoarthritis, rheumatic complaints, tumor, hypertension, gastrointestinal ulcer or disorder, liver disease, epilepsy, chronic fatigue syndrome, allergy, thyroid gland disease, injury) or potential additional chronic somatic diseases that were not explicitly asked, and whether they received treatment for the reported diseases. Sociodemographics included age (in years), gender, education (in years), partner status (partner versus no partner), and working status (employed versus unemployed). Lifestyle factors included smoking status (never, former, current; assessed by self-report), alcohol use (defined as the total score on the Alcohol Use Disorders Identification Test [175]), and physical activity (measured with the International Physical Activity Questionnaire in MET-minutes [ratio of energy expenditure during activity compared with rest times the number of minutes performing the activity] a week [176]).

Statistical analyses

Analyses were conducted using SPSS version 20.0 (SPSS Inc, Chicago, Illinois). Characteristics of the study sample were summarized using descriptive statistics. Subsequently, χ^2 analyses were used to compare the prevalence of all clusters of somatic symptoms in patients with any depressive or anxiety disorder with healthy controls. To explore whether associations with somatic symptoms were conditional on the type of depressive or anxiety disorder, χ^2 analyses were performed for all specific depressive and anxiety disorders separately versus healthy controls (i.e., separate models for major depressive disorder, dysthymic disorder, generalized anxiety disorder, social phobia, panic disorder, and agoraphobia versus healthy controls). Crosstabs were used to describe comorbidity patterns between specific depressive and anxiety disorders. To determine whether specific depressive and anxiety disorders showed *independent* associations with somatic symptoms, multivariable logistic regression analyses were performed including all types of depressive and anxiety disorders as independent variables in a single model. Differences in odds ratios were considered significant when the odds ratio of one association showed no overlap with the 95% confidence interval of the other association, and vice versa. To get insight in the potential effects of multicollinearity, variance inflation factors (VIF) were calculated for all depressive and anxiety disorders. Finally, analyses were adjusted for chronic somatic diseases, sociodemographics, and lifestyle factors.

RESULTS

Sample

The characteristics of our sample (N=2,008) are presented in **Table 1**. Of the whole sample, 641 (32%) persons were healthy controls, and 1,367 (68%) persons had a current depressive and/or anxiety disorder. Mean age was 41.6 years (SD=13.1), and 64.9% were women. The prevalence of somatic symptoms ranged from 35.1% for gastrointestinal symptoms to 55.2% for musculoskeletal symptoms.

Table 1. Sample characteristics (N=2,008).

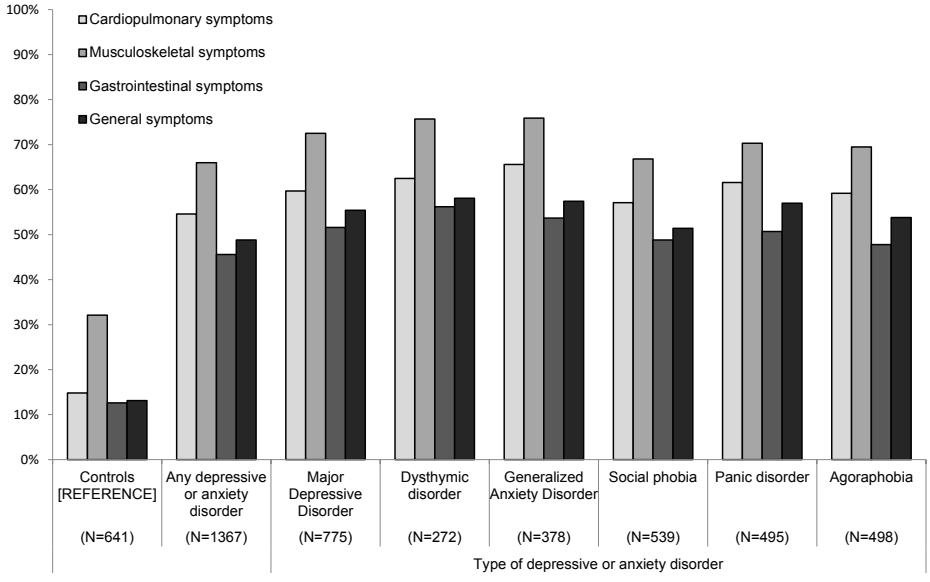
	N (%) / mean (SD)[a]
Sociodemographics	
Age in years	41.6 (13.1)
Female gender	1303 (64.9%)
Education in years	12.0 (3.3)
Having a partner	1368 (68.1%)
Being employed	1146 (57.1%)
Lifestyle factors	
Smoking status	
Never	586 (29.2%)
Former	647 (32.2%)
Current	775 (38.6%)
Alcohol usage (score AUDIT questionnaire)	4.8 (4.8)
Physical activity (in 1,000 MET-minutes/week)	3.6 (3.1)
Chronic somatic diseases	
Number of chronic somatic diseases	0.6 (0.9)
Depressive and/or anxiety disorder	
Any depressive and/or anxiety disorder (general)	
Absent	641 (31.9%)
Present	1367 (68.1%)
Type of depressive or anxiety disorder	
Major depressive disorder	775 (38.6%)
Dysthymic disorder	272 (13.5%)
Generalized anxiety disorder	378 (18.8%)
Social phobia	539 (26.8%)
Panic disorder	495 (24.7%)
Agoraphobia	498 (24.8%)
Cluster of somatic symptoms	
Cardiopulmonary symptoms	842 (41.9%)
Musculoskeletal symptoms	1108 (55.2%)
Gastrointestinal symptoms	705 (35.1%)
General symptoms	751 (37.4%)

[a] Based on descriptive statistics.

Associations of depressive and anxiety disorders with somatic symptoms

Figure 1 summarizes the prevalence of all clusters of somatic symptoms in healthy controls, and patients with depressive and anxiety disorders. The prevalence of all clusters of somatic symptoms was significantly (all p<.001) higher in patients with any depressive and anxiety disorder than in healthy controls (e.g., gastrointestinal symptoms: 45.6% versus 12.6%; musculoskeletal symptoms: 66.0% versus 32.1%). The same pattern of results was found for all types of depressive and anxiety disorders, suggesting that associations were similar across specific disorders.

Figure 1. Prevalence of clusters of somatic symptoms across controls and patients with a depressive and/or anxiety disorder.



Independent associations of depressive and anxiety disorders with somatic symptoms

Table 2 shows the comorbidity rates between specific depressive and anxiety disorders. Comorbidity rates ranged from 18.7% for comorbid dysthymic disorder in agoraphobic patients to 82.0% for comorbid major depressive disorder in dysthymic patients. As comorbidity rates were high, we examined whether specific depressive and anxiety disorders showed *independent* associations with somatic symptoms by performing multivariable logistic regression analyses including all types of depressive and anxiety disorders as independent variables in a single model (see **Table 3**). Variance inflation factor (VIF) values for all depressive and anxiety disorders were between 1.10 and

1.62, indicating that the model was unlikely to be affected by high multicollinearity. Major depressive disorder consistently showed strong and significant associations with all clusters of somatic symptoms. In addition, generalized anxiety disorder, social phobia, and panic disorder were also significantly associated with all clusters of somatic symptoms (all p<.01), while agoraphobia was significantly related to cardiopulmonary, musculoskeletal, and general symptoms but not gastrointestinal symptoms. Dysthymic disorder was not related to any cluster of somatic symptoms. The associations of major depressive disorder were stronger than associations of all other specific depressive and anxiety disorders. In general, associations were similar for all clusters of somatic symptoms. However, generalized anxiety disorder was more strongly related to cardiopulmonary symptoms (OR=2.12, 95% CI=1.64-2.74) than to gastrointestinal symptoms (OR=1.61, 95% CI=1.25-2.07).

Table 2. Comorbidity across specific depressive and anxiety disorders.

	Comorbid disorder					
	Major depressive disorder	Dysthymic disorder	Generalized anxiety disorder	Social phobia	Panic disorder	Agoraphobia
Major depressive disorder (N=775)	-	28.8%	31.2%	32.4%	30.5%	27.2%
Dysthymic disorder (N=272)	82.0%	-	44.5%	43.8%	36.4%	34.2%
Generalized anxiety disorder (N=378)	64.0%	32.0%	-	41.8%	36.5%	36.5%
Social phobia (N=539)	46.6%	22.1%	29.3%	-	41.0%	40.1%
Panic disorder (N=495)	47.7%	20.0%	27.9%	44.6%	-	70.5%
Agoraphobia (N=498)	43.0%	18.7%	27.7%	43.4%	70.1%	-

Impact of covariates

Subsequently, we examined whether associations of specific depressive and anxiety disorders with somatic symptoms could be explained by the effects of covariates (see **Table 3**). Adjustment for chronic somatic diseases did not substantially change results. In addition, associations generally remained similar after additional adjustment for sociodemographics and lifestyle factors. However, odds ratios slightly decreased, and, consequently, the association between agoraphobia and musculoskeletal symptoms lost significance (OR=1.42, p=.02 decreased to OR=1.29, p=.09), whereas dysthymic disorder became significantly associated with gastrointestinal symptoms (OR=1.32, p=.07 increased to OR=1.39, p=.04).

Table 3. Independent associations of specific depressive and anxiety disorders with clusters of somatic symptoms.

	Cardiopulmonary symptoms			Musculoskeletal symptoms			Gastrointestinal symptoms			General symptoms		
Depressive or anxiety disorder	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Adjusted for all types of depressive and anxiety disorders[a]												
Major depressive disorder	2.74	2.22-3.38	<.001	2.69	2.18-3.32	<.001	2.63	2.13-3.24	<.001	2.93	2.37-3.62	<.001
Dysthymic disorder	1.14	0.84-1.55	.39	1.33	0.96-1.85	.09	1.33	0.99-1.79	.06	1.20	0.89-1.62	.23
Generalized anxiety disorder	2.12	1.64-2.74	<.001	1.99	1.51-2.61	<.001	1.61	1.25-2.07	<.001	1.68	1.31-2.17	<.001
Social phobia	1.67	1.33-2.08	<.001	1.42	1.13-1.77	.003	1.65	1.32-2.06	<.001	1.58	1.26-1.97	<.001
Panic disorder	1.80	1.37-2.38	<.001	1.45	1.09-1.93	.01	1.64	1.24-2.16	<.001	1.91	1.45-2.52	<.001
Agoraphobia	1.56	1.18-2.06	.002	1.57	1.19-2.08	.002	1.28	0.97-1.68	.09	1.47	1.12-1.94	.006
Additionally adjusted for chronic somatic diseases[b]												
Major depressive disorder	2.65	2.15-3.28	<.001	2.60	2.09-3.22	<.001	2.54	2.06-3.14	<.001	2.86	2.32-3.54	<.001
Dysthymic disorder	1.12	0.83-1.53	.46	1.32	0.95-1.84	.10	1.32	0.98-1.77	.07	1.19	0.88-1.60	.26
Generalized anxiety disorder	2.08	1.60-2.70	<.001	1.93	1.46-2.55	<.001	1.58	1.22-2.03	<.001	1.66	1.29-2.14	<.001
Social phobia	1.70	1.36-2.13	<.001	1.44	1.14-1.81	.002	1.68	1.34-2.10	<.001	1.59	1.27-1.99	<.001
Panic disorder	1.88	1.42-2.49	<.001	1.53	1.15-2.05	.004	1.69	1.28-2.24	<.001	1.95	1.48-2.58	<.001
Agoraphobia	1.44	1.09-1.91	.01	1.42	1.06-1.89	.02	1.19	0.90-1.57	.24	1.41	1.07-1.87	.02
Additionally adjusted for sociodemographics and lifestyle factors[c]												
Major depressive disorder	2.53	2.04-3.14	<.001	2.42	1.94-3.02	<.001	2.34	1.88-2.91	<.001	2.66	2.14-3.30	<.001
Dysthymic disorder	1.09	0.80-1.49	.60	1.30	0.93-1.83	.13	1.39	1.02-1.88	.04	1.25	0.92-1.70	.16
Generalized anxiety disorder	2.05	1.58-2.67	<.001	1.90	1.43-2.52	<.001	1.58	1.22-2.04	.001	1.65	1.28-2.14	<.001
Social phobia	1.66	1.32-2.08	<.001	1.41	1.12-1.78	.004	1.62	1.29-2.04	<.001	1.56	1.24-1.96	<.001
Panic disorder	1.83	1.38-2.42	<.001	1.44	1.07-1.93	.02	1.56	1.17-2.08	.002	1.82	1.37-2.41	<.001
Agoraphobia	1.38	1.04-1.83	.03	1.29	0.96-1.73	.09	1.13	0.85-1.51	.39	1.34	1.01-1.79	.04

[a] Based on multivariable logistic regression analyses including all types of depressive and anxiety disorders.
[b] Based on multivariable logistic regression analyses including all types of depressive and anxiety disorders and chronic somatic diseases.
[c] Based on multivariable logistic regression analyses including all types of depressive and anxiety disorders, chronic somatic diseases, age, gender, education, partner status, working status, smoking status, alcohol usage and physical activity.

DISCUSSION

The present study showed that all depressive and anxiety disorders, except for dysthymic disorder, were independently associated with all clusters of somatic symptoms. In general, associations were similar across specific depressive and anxiety disorders, although major depressive disorder showed the strongest associations with all somatic symptom clusters. Adjustment for chronic somatic diseases, sociodemographics, and lifestyle factors did not substantially change results.

This study has both strengths and limitations. To our knowledge, this is the first study to examine independent associations of depressive and anxiety disorders with different clusters of somatic symptoms. The importance of taking into account comorbid depressive and anxiety disorders has been demonstrated clearly in this study, as the comorbidity across disorders was high (i.e.,18.7%-82.0%), and the associations differed significantly between disorders. Another strength is the large sample of 2,008 persons, consisting of patients with specific types of depressive and anxiety disorders (N=1,367), and controls (N=641). In addition, psychiatric diagnoses were established with a well validated psychiatric interview among all participants. When interpreting our results, it is also important to keep some limitations in mind. First, as the recruitment of patients with depressive and anxiety disorders largely took place in primary care and specialized mental health care, patients from our sample may have had more severe psychiatric problems, and, consequently, more co-occurring somatic symptoms than patients from the community. Therefore, our results cannot be generalized to the general population. Another limitation is that we dichotomized data on somatic symptoms and we only considered self-rated somatic symptoms in the past week. Furthermore, participants were not asked to grade the severity of their somatic symptoms, so even mild symptoms with limited clinical significance may have been reported. However, excluding such mild symptoms from analyses would probably not have changed our conclusion about the strong association of depressive and anxiety disorders with somatic symptoms, since persons with depressive and anxiety disorders have a tendency to report more severe somatic symptoms than persons without these disorders [152]. In addition, the assessment of covariates was based on self-report only, which could have affected data on somatic diseases and lifestyle factors, as these factors may be influenced by recall bias and reporting bias, respectively. Furthermore, as the assessment of somatic diseases included only somatic diseases with a chronic course, the effects of acute somatic diseases (e.g., acute respiratory tract or gastrointestinal infections) were not taken into account. Still, it is highly unlikely that the found associations between depressive and anxiety disorders and somatic symptoms were based on the presence of somatic diseases, as the self-report of somatic diseases has shown to be accurate

[177], and the number of somatic symptoms reported in this study was substantially higher than could be explained by somatic diseases alone.

The association between depressive and anxiety disorders with somatic symptoms has been reported by a number of previous studies [38,47,48,154-156,163,178,179]. However, these studies have shown mixed results regarding the specificity of associations. For example, Means-Christensen et al. [163] demonstrated that major depressive disorder was associated with more types of pain symptoms than generalized anxiety disorder, panic disorder and social phobia, whereas other studies mainly reported similar symptom counts across all specific depressive and anxiety disorders [38,165]. As these studies often did not take into account the effects of comorbid depressive and anxiety disorders, one possible explanation for these inconsistencies might be different comorbidity rates across studies. The independent associations of specific depressive and anxiety disorders with specific types of somatic symptoms have, to the best of our knowledge, so far not been described in the literature. The only exception to this is the study by Beesdo et al. [167], who have examined independent associations of specific depressive and anxiety disorders with pain and showed, consistent with our study, that nearly all specific depressive and anxiety disorders were independently associated with functional pain symptoms. However, contrary to our results, a significant association of dysthymic disorder with functional pain, and a non-significant relation of social phobia and agoraphobia with functional pain were found. These inconsistencies may be explained by different definitions of depressive and anxiety disorders as well as somatic symptoms. As Beesdo et al. [167] assessed depressive and anxiety disorders during the past 12 months, in contrast to the one-month diagnoses in the current study, this could for example have resulted in differences in the severity of psychopathology across our studies. Furthermore, Beesdo et al. [167] considered lifetime pain symptoms, which are associated with recall bias and, consequently, are less reliable and consistent than symptoms in the past week, as suggested by previous research [180,181].

Several explanations for our results should be discussed. First, the association between depressive and anxiety disorders and somatic symptoms could have resulted from symptom overlap; that is, diagnostic criteria for depressive and anxiety disorders include somatic symptoms (e.g., cardiopulmonary symptoms are criteria for panic disorder) [40]. However, as non-overlapping somatic symptoms also showed strong associations with depressive and anxiety disorders, the association between depressive and anxiety disorders and somatic symptoms is unlikely to be explained solely by overlapping symptoms.

In addition, this study found that depressive and anxiety disorders generally showed similar associations with somatic symptoms, although some differences were observed. Major depressive disorder showed the strongest associations, while all anxiety disorders

showed moderate associations, and dysthymic disorder was not related to somatic symptoms. These differences in associations might be explained by variance in the severity of psychopathology [100]. For example, in the antecedent hypothesis, more severe depressive and anxiety disorders may cause more somatic symptoms, whereas in the consequence hypothesis, more somatic symptoms might cause more severe depression and/or anxiety. In the current study, the severity of psychopathology may have differed across specific depressive and anxiety disorders as for example a diagnosis of major depressive disorder requires more and more frequent symptoms than a diagnosis of dysthymic disorder [40]. Although the severity of psychopathology of specific depressive and anxiety disorders is difficult to compare, a previous study showed that current major depressive disorder was associated with higher functional impairment than current generalized anxiety disorder, social phobia, panic disorder, and agoraphobia [182], indicating that psychopathology of major depressive disorder might be more severe than psychopathology of all anxiety disorders. However, as the mentioned study did not examine dysthymic disorder, we are not able to draw conclusions about this explanation.

A second hypothesis concerning the specificity of associations, is whether depressive disorders show differential associations with specific clusters of somatic symptoms than anxiety disorders. Our results showed that associations with depressive and anxiety disorders were similar across specific clusters of somatic symptoms, suggesting that depressive and anxiety disorders are not differentially associated with specific types of somatic symptoms. However, it is important to note that we were not able to take into account the co-occurrence of somatic symptom clusters. In our sample, the percentage of persons reporting only one cluster of somatic symptoms ranged from 7.6% for those reporting general symptoms to 19.5% for those reporting musculoskeletal symptoms. Future studies should include more persons with only one somatic symptom cluster, which would enable them to explicitly consider associations independent of co-occurring somatic symptoms.

Another issue that should be discussed is the origin of somatic symptoms in this study. Somatic symptoms can be consequences of organic pathology, but previous studies have shown that up to two thirds of somatic symptoms could not be fully explained by a medical condition [38,39]. These functional somatic symptoms are strongly associated with both depressive and anxiety disorders [44,153]. As the somatization scale of the 4DSQ is a proper indicator of the general practitioner's suspicion of somatization [174], and the prevalence of somatic symptoms in our study was substantially higher than can be explained by medical conditions, we suggest that a major proportion of the somatic symptoms reported in the current study are indeed functional somatic symptoms.

Consequently, we suggest that functional somatic symptoms had an important role in the associations of depressive and anxiety disorders with somatic symptoms.
Previous studies have shown that somatic symptoms are associated with an unfavorable course of depressive and anxiety disorders [183-186]. An adequate consideration and treatment of somatic symptoms in patients with depressive and anxiety disorders might therefore improve the outcome of these patients. Validated screening instruments are available for a systematic assessment of somatic symptoms [187]. In addition, several treatment options such as cognitive behavioral therapy [188,189] and mindfulness [190-192] have shown to be effective for depressive and anxiety disorders as well as somatic symptoms. Future studies should examine whether systematic screening for somatic symptoms and treatment of these symptoms in patients with depressive and anxiety disorders results in better treatment outcomes and reduced health care utilization and costs.

CONCLUSIONS

Depressive and anxiety disorders are strongly related to somatic symptoms and these associations show some differences across specific depressive and anxiety disorders. Further research is needed to examine potential explanations for the variation in independent associations across specific depressive and anxiety disorders as well as to study whether an adequate consideration of somatic symptoms in patients with depressive and anxiety disorders improves treatment outcomes.

The impact of somatic symptoms on the course of major depressive disorder

Bekhuis E, Boschloo L, Rosmalen JGM, de Boer MK, Schoevers RA.

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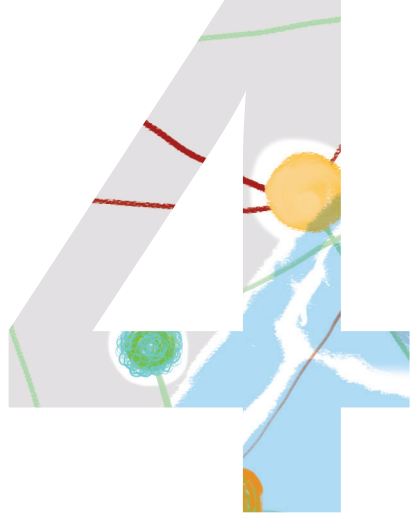


ABSTRACT

Introduction: Somatic symptoms have been suggested to negatively affect the course of major depressive disorder (MDD). Mechanisms behind this association, however, remain elusive. This study examines the impact of somatic symptoms on MDD prognosis and aims to determine whether this effect can be explained by psychiatric characteristics, somatic diseases, lifestyle factors, and disability.

Methods: In 463 MDD patients (mean age=44.9 years, 69.8% female) from the Netherlands Study of Depression and Anxiety (NESDA), we examined whether the type and number of somatic symptom clusters predicted the two-year persistence of MDD. Diagnoses of MDD were established with the Composite International Diagnostic Interview (CIDI) and somatic symptom clusters were assessed with the Four-Dimensional Symptom Questionnaire (4DSQ) somatization scale. Psychiatric characteristics, somatic diseases, lifestyle factors, and disability were taken into account as factors potentially underlying the association.

Results: The cardiopulmonary, gastrointestinal, and general cluster significantly predicted the two-year persistence of MDD, but only when two or more of these clusters were present (OR=2.32, 95% CI=1.51– 3.57, p<.001). Although the association was partly explained by MDD severity, the presence of multiple somatic symptom clusters remained a significant predictor after considering all potentially underlying factors (OR=1.69, 95%CI=1.07–2.68, p=0.03).

Conclusions: Somatic symptoms are predictors of a worse prognosis of MDD independent of psychiatric characteristics, somatic diseases, lifestyle factors, and disability. These results stress the importance of considering somatic symptoms in the diagnostic and treatment trajectory of patients with MDD. Future research should focus on identifying treatment modalities targeting depressive as well as somatic symptoms.

INTRODUCTION

Major depressive disorder (MDD) is highly prevalent in the general population [166,193] and has a substantial impact on physical, occupational, and social functioning [21,150]. The course of MDD varies widely across individual patients. Although the majority of patients achieve remission within the six months following disorder onset, 20% of patients develop a chronic disorder that lasts for two years or longer [194,195]. It is important to identify the factors that predict such an unfavourable course as more insight into their effects is essential for optimizing treatment strategies.

Somatic symptoms are often reported by patients with MDD [196,197]. Kroenke et al., for example, showed that patients with the mental disorder experienced an average of six somatic symptoms during the past month [152]. Several studies have shown that somatic symptoms are associated with a poor prognosis of MDD [198-200]. A study among patients with incident MDD, for example, demonstrated that remission rates were twice as low in patients with severe somatic symptoms as in patients without those symptoms [200]. In addition, a primary care study showed that somatic symptoms were related to chronicity of MDD [199]. Despite extensive research on the association between somatic symptoms and outcome of MDD, however, little is known about the specificity of this association. Somatic symptoms are a heterogeneous group of symptoms and specific symptoms may therefore show differential associations with the course of MDD [38]. Similarly, as somatic symptoms often co-occur [201], their association with the course of MDD could be conditional on the number of these symptoms. More insight into the specific characteristics of somatic symptoms that affect the course of MDD may contribute to better recognition of MDD patients at risk for a worse prognosis.

In addition, although the physical inconvenience of somatic symptoms may directly maintain feelings of depression, other mechanisms have also been hypothesized to underlie the association of these symptoms with the course of MDD. For example, somatic symptoms are associated with specific *psychiatric characteristics* such as more severe depressive symptoms and comorbid mental disorders [45,198], which are also well-known predictors of a poor course of MDD [64]. Similarly, depressed patients with somatic symptoms receive less optimal psychiatric treatment than patients without those symptoms [183] and this could also worsen the course of MDD [202]. Somatic diseases have also been shown to be associated with MDD prognosis [203] and have therefore been suggested to underlie somatic symptoms that affect the course of MDD. Furthermore, an unhealthy lifestyle (e.g., heavy alcohol use and lack of physical activity) could cause and/or result from somatic symptoms [204], and these factors are also predictors of an unfavorable course of MDD [205]. Finally, researchers have hypothesized that *disability* resulting from somatic symptoms may affect the course of

MDD [198]. To our knowledge, no previous study has simultaneously considered such a wide range of factors (i.e., psychiatric characteristics, somatic diseases, lifestyle factors, and disability) and has examined whether they explain the effect of somatic symptoms on MDD prognosis.

In this study, we aim to examine the impact of specific types and numbers of somatic symptoms on the 2-year course of MDD in a large sample of MDD patients (N=463). Second, we investigate potential mechanisms underlying this association by focusing on psychiatric characteristics, somatic diseases, lifestyle factors, and disability.

METHODS

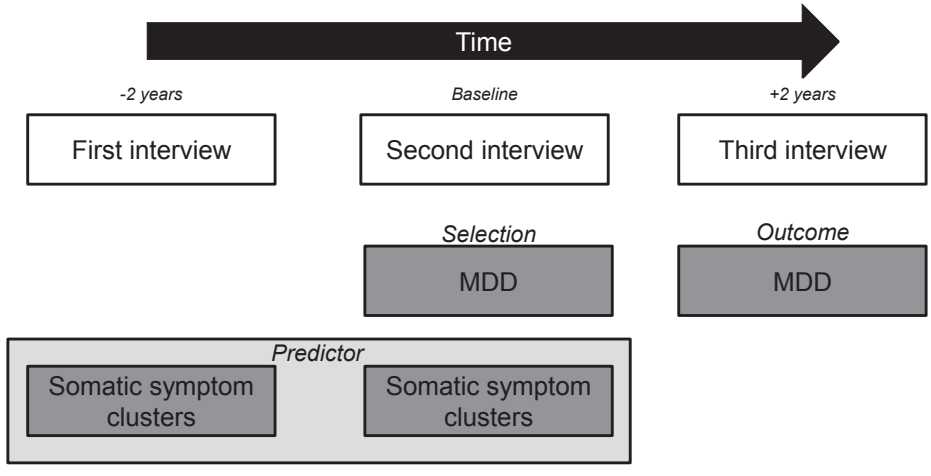
Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA), a large-scale longitudinal cohort study aimed at studying the long-term course of depressive and anxiety disorders. A total of 2,981 adults (18-65 years) were initially included, consisting of a healthy control group, people with a history of depressive or anxiety disorder and people with current depressive and/or anxiety disorder. Participants were recruited from community (19%), primary care (54%) and outpatient mental health care services (27%) to represent various settings and stages of psychopathology. Community-based participants had previously been identified in a population-based study, and primary care participants were selected from a random sample of consulting patients of 65 general practitioners through a three-stage screening procedure (involving the Kessler 10 scale [206] as screening questionnaire and the short-form Composite International Diagnostic Interview [CIDI] as phone-screen interview). Mental health care participants were recruited when newly enrolled at one of the seventeen participating mental health organization locations. Patients were excluded when they had insufficient command of the Dutch language or a primary clinical diagnosis of bipolar disorder, obsessive compulsive disorder, severe substance use disorder, psychotic disorder, or organic psychiatric disorder. The research protocol was approved by the Ethical Committee of the three participating universities and all participants gave written informed consent. A detailed account of the rationale, objectives, and methods of NESDA can be found elsewhere [172]. Interviews took place in 2004-2007 (first interview), two years later (second interview; response N=2,596 [87.1%] [207]), and four years later (third interview; response N=2,402 [80.6%]), and included a face-to-face assessment as well as paper-and-pencil questionnaires.

For the current study, we selected all participants with a diagnosis of MDD in the six months prior to the second interview with valid data on somatic symptoms (N=526; see

Figure 1 for a schematic representation of the study design). Compared to non-selected participants, the selected participants received education for a shorter time period (12.6 versus 11.9 years, p<.001), but no differences were found with respect to sex (65.4% versus 68.8% female, p=.15) or age (43.8 versus 44.9 years, p=.09). Of all selected persons, those with incomplete data on MDD at the follow-up assessment were excluded from the analyses (N=63 [12.0%]). Excluded persons received less education (10.5 versus 12.1 years, p=<.001) than persons with complete data; however, age (44.4 versus 44.9 years, p=.74), sex (61.9% versus 69.8% female, p=.25), and the number of somatic symptom clusters (1.8 versus 1.5, p=.06) were not associated with non-response.

Figure 1. Study design.



The two-year persistence of MDD

Diagnoses of MDD were established with the CIDI (version 2.1 [173]) according to the DSM-IV criteria [40], administered by especially trained research staff. The CIDI has shown high interrater and test-retest reliability and high validity [173]. MDD was considered persistent when a person also met the DSM-IV criteria for MDD in the six months before the third interview (i.e., after two years).

Somatic symptom clusters

The self-report somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ [174]) was used to score the frequency of 16 somatic symptoms (scoring 1='never' to 5='often') in the past week. In line with a previous study by our group [197], four clusters of somatic symptoms were distinguished: cardiopulmonary symptoms (i.e., excessive perspiration, pain in chest, palpitations, pressure or tight feeling in chest,

and shortness of breath), musculoskeletal symptoms (i.e., back pain, neck pain, muscle pain, and tingling in fingers), gastrointestinal symptoms (i.e., bloated feeling in abdomen, nausea or upset stomach, and pain in abdomen or stomach area), and general symptoms (i.e., dizziness or feeling lightheaded, fainting, and headache). A cluster was considered present when at least one of the symptoms included in that cluster was scored with 3 ('regularly') to 5 ('often') (see also [197]). A weakness of the 4DSQ is that it focuses on a one-week time frame, regardless of the duration of that symptom. This might be problematic as ample evidence shows that chronic and not temporary somatic symptoms are associated with the long-term course of MDD [198,208-213]. We therefore only considered somatic symptom clusters to be present when they were reported at the first as well as the second interview. To test whether the persistence of MDD was only increased in patients reporting somatic symptom clusters at both interviews and not in those reporting clusters at only one of the interviews, we performed a set of sensitivity analyses (see 'Statistical analyses').

Baseline factors

Since sociodemographic and socioeconomic factors have been shown to be associated with somatic symptoms as well as the course of MDD [38,64], basic covariates included age (in years), sex, years of education (in years, starting from primary school), marital status (married versus not married), and employment status (employed versus unemployed). We considered psychiatric characteristics, somatic diseases, lifestyle factors, and disability as potential mechanisms underlying the association of somatic symptoms with the course of MDD.

Psychiatric characteristics

Psychiatric characteristics were divided into MDD characteristics, comorbidity, and treatment.

MDD characteristics

The current severity of MDD and its history (age of onset and chronicity) were considered as MDD characteristics. The current severity of depressive symptoms was assessed with the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR; [68], a reliable and valid instrument which focuses on the symptoms included in the DSM-IV diagnostic criteria for MDD [40] during the past week. The age of onset was derived from the CIDI and the prior chronicity of MDD was defined as having a diagnosis of MDD, as established with the CIDI, in the six months prior to the first interview (i.e., the interview two years before baseline).

Comorbidity

The severity of anxiety during the past week was assessed with the subjective subscale of the Beck Anxiety Inventory (BAI [214,215]). The presence of (hypo)mania during the past six months was established with the CIDI.

Treatment

Treatment included frequent use of antidepressants and benzodiazepines as well as psychological treatment. Frequent use (at least 50% of the days) of psychoactive medication was assessed by drug container inspection of medication used in the past month, classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification [216]. We considered the use of SSRIs (selective serotonin reuptake inhibitors [ATC-code N06AB]), other antidepressants (ATC-codes N06AA, N06AF, N06AG, N06AX), and benzodiazepines (ATC-codes N03AE, N05BA, N05CD, and N05CF). Self-reported psychological treatment in the past six months included formal psychotherapy, counseling, and skills training.

Somatic diseases

Somatic diseases included the number of self-reported chronic diseases currently under treatment. For the assessment, participants were asked whether they had specific diseases (i.e., lung disease, heart disease, diabetes mellitus, CVA, arthritis, osteoarthritis, rheumatic complaints, tumor, hypertension, gastrointestinal ulcer or disorder, liver disease, epilepsy, chronic fatigue syndrome, allergy, thyroid gland disease, injury) or potential additional chronic somatic diseases that were not explicitly asked, and whether they received treatment for the reported diseases.

Lifestyle factors

Lifestyle factors included self-reported smoking status (never, former, current), alcohol use during the past year (total score on the Alcohol Use Disorders Identification Test [AUDIT]; [175]), and physical activity (measured in MET-minutes [ratio of energy expenditure during activity compared with rest times the number of minutes performing the activity] during the past week assessed with the International Physical Activity Questionnaire [IPAQ] [176]).

Disability

Disability was defined as the standardized score (score 0-100) on the self-report World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS II), assessing difficulties in six domains of life (i.e., cognition, mobility, self-care, interpersonal interactions, life activities, and participation in society) during the last 30 days [217].

Statistical analyses

All analyses were conducted with SPSS version 22.0 (SPSS Inc, Chicago, Illinois).

Main analyses: First, logistic regression analyses were used to explore the association of specific types of somatic symptoms with the persistence of MDD. As somatic symptom clusters often co-occur, we next examined whether the association between somatic symptom clusters and the course of MDD was conditional on the number of clusters. Subsequently, independent sample T-tests (for continuous variables) and chi-square tests (for categorical variables) were used to test whether patients with and without baseline somatic symptom clusters as well as patients with and without persistent MDD during follow-up differed in their psychiatric characteristics, somatic diseases, lifestyle factors, and disability. Baseline factors that were significantly related to both somatic symptom clusters and the persistence of MDD were considered as potential underlying mechanisms. Multivariable logistic regression analyses were performed to examine whether these factors could explain the association of the somatic symptom clusters with the persistence of MDD.

To determine which baseline factors were included in the multivariable model, a significance level of .10 was applied. For all other analyses, the significance level was set to .05.

Incomplete scores were found for several baseline factors, ranging from 0.002% for mania to 9.3% for physical activity. For variables based on scale scores, values were considered missing if the participant had not completed the minimum number of items required to reliably calculate the scale score according to the scale manual. Incomplete values on baseline factors were imputed with the mean (for continuous variables) or the most common score (for categorical variables) on this variable in our sample.

Sensitivity analyses: As a set of sensitivity analyses, we tested whether somatic symptom clusters reported at either the first or the second, or at both interviews were predictors of the persistence of MDD using logistic regression analyses. We expected that only chronic somatic symptom clusters (i.e., present at both interviews) were associated with an increased risk of having a persistent MDD at follow-up.

RESULTS

Sample characteristics

Mean age of the sample was 44.9 (SD=12.3) years and 69.8% of patients were female. The overall persistence rate of MDD at two-year follow-up was 42.8% (see **Table 1**).

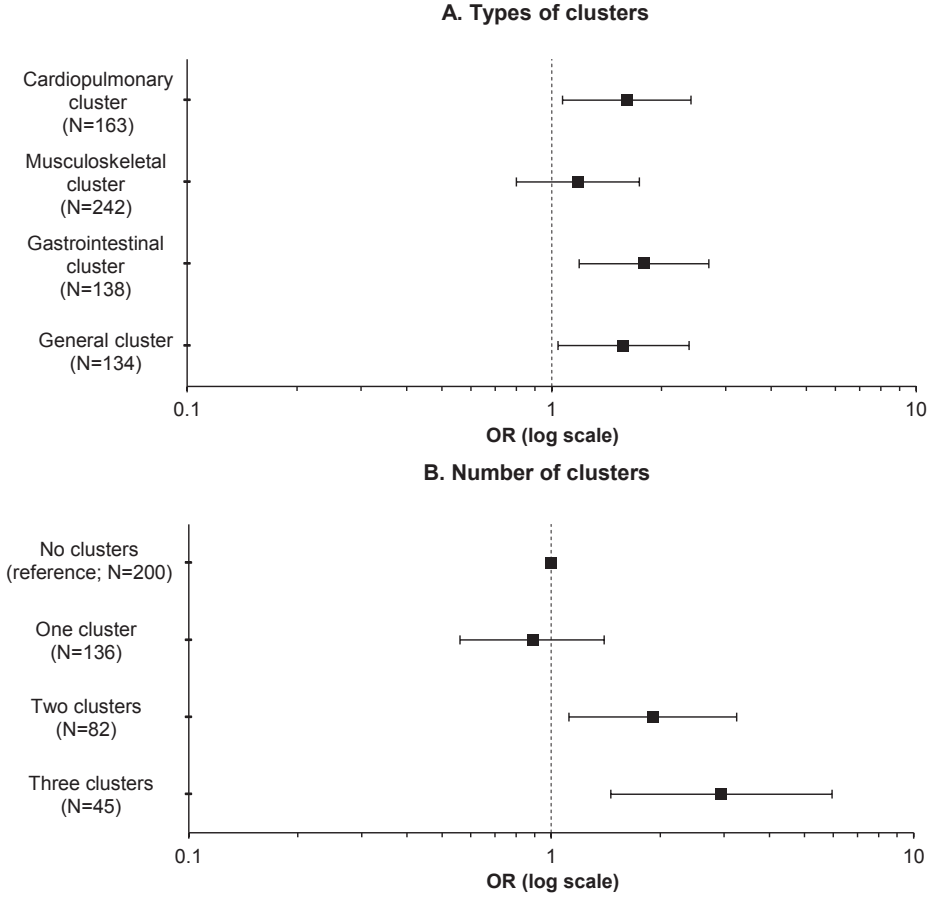
Table 1. Sample characteristics.

	mean (sd) / N (%)
Baseline characteristics	
Sociodemographics	
Age (in years)	44.9 (12.3)
Female	323 (69.8%)
Education (in years)	12.1 (3.3)
Married	169 (36.5%)
Employed	239 (51.6%)
Somatic symptom clusters	
Cardiopulmonary cluster	163 (35.2%)
Musculoskeletal cluster	242 (52.3%)
Gastrointestinal cluster	138 (29.8%)
General cluster	134 (28.9%)
Follow-up characteristics	
Persistent MDD at 2 year follow-up	198 (42.8%)

Somatic symptom clusters predicting the two-year persistence of MDD

Figure 2A shows associations between different types of somatic symptom clusters and the persistence of MDD. The cardiopulmonary, gastrointestinal, and general somatic symptom clusters were significant predictors of persistent MDD, whereas the musculoskeletal symptom cluster was not. To examine whether these associations were conditional on the number of reported clusters, we summed the three clusters of somatic symptoms that showed significant associations with the persistence of MDD (see **Figure 2B**). Persons with two or three somatic symptom clusters, but not those with one cluster, were at an increased risk of having MDD persistence at follow-up. Since groups of patients with specific numbers of clusters were small (N=136 for one cluster, N=82 with two clusters, and N=45 with three clusters), we focused on persons with no/single (no or one; N=336) and multiple (two or three; N=127) clusters of somatic symptoms in the subsequent analyses.

Figure 2. Types and numbers of somatic symptom clusters predicting the persistence of MDD.



Based on logistics regression analyses adjusted for basic covariates (i.e., age, sex, education, marital status and employment status).

Effects of baseline factors

We tested whether patients with multiple somatic symptom clusters at baseline differed from patients with no/single somatic symptom clusters in their psychiatric characteristics, somatic diseases, lifestyle factors, and disability (see **Table 2**). In addition, we examined whether these baseline factors differed across patients with and without persistent MDD at follow-up (see **Table 2**). Of all baseline factors, the severity of MDD, the severity of anxiety, use of benzodiazepines, and disability showed associations to the presence of multiple somatic symptom clusters as well as the persistence of MDD with $p<.10$. In **Table 3**, we explored whether these factors explained the association of somatic symptom clusters and MDD persistence. In the basic model, having multiple somatic

symptom clusters was a strong predictor of the persistence of MDD (OR=2.32, 95%CI=1.51-3.57, p=<.001). Adjustment for the severity of MDD resulted in a considerable reduction in the odds ratio (OR=1.69, 95%CI=1.07-2.67, p=.02), whereas further adjustment for the severity of anxiety (OR=1.78, 95%CI=1.12-2.82, p=.02), use of benzodiazepines (OR=1.79, 95%CI=1.12-2.85, p=.02), and disability (OR=1.78, 95%CI=1.11-2.85, p=.02) did not substantially change results.

Table 2. Baseline factors in patients with and without multiple somatic symptom clusters at baseline and persistent MDD at follow-up.

	Multiple somatic symptom clusters at baseline			**Persistent MDD at follow-up**		
	No N=336	Yes N=127		No N=265	Yes N=198	
Baseline factor	**mean (sd) / N (%)**	**mean (sd) / N (%)**	**p**	**mean (sd) / N (%)**	**mean (sd) / N (%)**	**p**
Psychiatric characteristics						
MDD characteristics						
Severity						
Symptom severity	9.7 (4.7)	13.2 (4.6)	<.001	9.5 (4.3)	12.3 (5.2)	.001
History						
Age of onset	27.5 (13.4)	27.8 (13.6)	.81	29.2 (14.0)	25.3 (12.3)	.002
Chronicity prior to baseline	208 (61.9%)	88 (69.3%)	.16	148 (55.8%)	148 (74.7%)	<.001
Comorbidity						
Severity of anxiety	5.3 (3.9)	8.0 (4.2)	<.001	5.6 (4.2)	6.7 (4.1)	.009
Mania	38 (11.3%)	16 (12.6%)	.75	30 (11.3%)	24 (12.1%)	.88
Treatment						
Use of SSRIs	69 (20.5%)	32 (25.2%)	.31	60 (22.6%)	41 (20.7%)	.65
Use of other antidepressants	57 (17.0%)	22 (17.3%)	>.99	34 (12.8%)	45 (22.7%)	.006
Use of benzodiazepines	26 (7.7%)	19 (15.0%)	.02	19 (7.2%)	26 (13.1%)	.04
Psychological treatment	220 (65.5%)	65 (51.2%)	.005	167 (63.0%)	118 (59.6%)	.50
Somatic diseases						
Number of chronic somatic diseases	0.6 (0.9)	1.1 (1.0)	<.001	0.7 (0.9)	0.7 (1.0)	.87
Lifestyle factors						
Smoking status			.45			.74
Never	99 (29.5%)	38 (29.9%)		77 (29.1%)	60 (30.3%)	
Former	117 (34.8%)	37 (29.1%)		92 (34.7%)	62 (31.3%)	
Current	120 (35.7%)	52 (40.9%)		96 (36.2%)	76 (38.4%)	
Alcohol use	5.0 (5.6)	4.6 (6.4)	.43	5.1 (5.7)	4.6 (6.0)	.33
Physical activity (in 1,000 MET-minutes)	4.0 (3.3)	4.0 (3.3)	.98	4.1 (3.4)	3.8 (3.2)	.33
Disability						
Level of disability	37.1 (20.2)	53.6 (20.6)	<.001	38.0 (21.5)	46.5 (20.8)	<.001

P-values based on independent sample T-tests for continuous variables and chi-square statistics for categorical variables.

Table 3. The effect of multiple somatic symptom clusters on the two-year persistence of MDD, adjusted for baseline factors.

	Two-year persistence of MDD		
Predictor	**OR**	**95% CI**	**p**
Basic model[a]			
Multiple somatic symptom clusters	2.32	1.51-3.57	<.001
Additionally adjusted for the severity of MDD[b]			
Multiple somatic symptom clusters	1.69	1.07-2.67	.02
Additionally adjusted for the severity of anxiety[c]			
Multiple somatic symptom clusters	1.78	1.12-2.82	.02
Additionally adjusted for benzodiazepine use[d]			
Multiple somatic symptom clusters	1.79	1.12-2.85	.02
Additionally adjusted for disability[e]			
Multiple somatic symptom clusters	1.78	1.11-2.85	.02

Based on stepwise logistic regression analyses with having no/single clusters as reference category. Baseline factors that were significantly (p<.10) associated with having multiple clusters as well as MDD persistence (see Table 1) were consecutively included in the model. [a] Adjusted for basic covariates (i.e., age, sex, education, marital status, and employment status). [b] Adjusted for basic covariates and the severity of MDD. [c] Adjusted basic covariates, the severity of MDD, and anxiety. [d] Adjusted basic covariates, the severity of MDD, the severity of anxiety, and benzodiazepine use. [e] Adjusted basic covariates, the severity of MDD, the severity of anxiety, benzodiazepine use, and disability.

Sensitivity analyses

Finally, we performed a set of sensitivity analyses to examine whether somatic symptom clusters reported at the first as well as the second interview (i.e., chronic clusters) were stronger predictors of the persistence of MDD than clusters reported at only one of these interviews (i.e., temporary symptoms). **Supplementary Figure 1** shows that most chronic clusters were predictors of having persistent MDD, whereas none of the temporary somatic symptom clusters were. Of the musculoskeletal cluster, neither temporary nor chronic symptoms were significantly associated with the persistence of MDD.

DISCUSSION

This study found that the somatic clusters of cardiopulmonary, gastrointestinal, and general symptoms predicted an unfavorable course of MDD, but only when two or more of these clusters were reported. Although the association was partly explained by the severity of MDD, somatic symptoms significantly predicted an unfavorable course of MDD independent of psychiatric characteristics, somatic diseases, lifestyle factors, and disability.

Strengths of this study are that we prospectively examined whether varying types and numbers of somatic symptom clusters predicted the course of MDD in a large sample

(N=463) of patients with a DSM-IV diagnosis of MDD. In addition, we are the first who considered such a wide range of psychiatric characteristics, somatic diseases, lifestyle factors, and disability as potential explanations for the association. A limitation of this study is that the assessment of somatic symptoms did not include their duration, while this is strongly associated with the course of MDD [208,213]. We aimed to overcome this limitation by only considering somatic symptoms clusters that were reported at baseline and two years earlier and sensitivity analyses indeed showed that only these chronic symptoms, and not those reported at either baseline or two years earlier, predicted the course of MDD. A second limitation is that the assessment of most baseline factors (e.g., somatic diseases, lifestyle factors) was based on self-report questionnaires, which might have resulted in recall and social desirability bias. Somatic diseases, however, have been shown to be reported accurately by patients [177].

In line with previous research [200,218], this study showed that somatic symptoms predicted a worse course of MDD. Our results increase insights into the specificity of this association as we showed that different types of somatic symptom clusters (i.e., cardiopulmonary, gastrointestinal, and general symptoms) as well as the number of clusters were important predictors of MDD persistence [185,198,200]. Our finding that the musculoskeletal cluster did not interfere with the course of MDD, however, is in contrast with previous research. Two studies focusing on individual musculoskeletal symptoms (e.g., back pain, muscle pain), for example, indicated that these symptoms significantly predicted worse treatment outcomes of MDD [219,220]. One explanation for the differential associations across the type of cluster in this study is that the number rather than the type of cluster may predict the course of MDD. Indeed, the musculoskeletal cluster less often co-occurred with other somatic symptom clusters (mean number of co-occurring clusters=1.4) than the other clusters (mean number of co-occurring clusters=1.7-1.8), which may explain that this cluster was the only that did not predict MDD prognosis.

As we demonstrated that somatic symptoms predicted a worse prognosis of MDD independent of psychiatric characteristics, somatic diseases, lifestyle factors, and disability, our findings suggest that the bodily inconvenience of somatic symptoms may directly elicit and maintain feelings of depression [45,52]. Depression, subsequently, can cause an increased somatic focus and negative interpretations of bodily sensations, which may result in a downward spiral in which somatic symptoms and depression reinforce each other [37,157]. Another possible mechanism behind the association between somatic symptoms and the course of MDD could be that underlying neurobiological pathways (e.g., inflammation, HPA-axis disturbance, monoamine abnormalities) may play a role in the etiology of somatic as well as depressive symptoms [221,222]. This theory may be in line with our finding that severity of depression partly explained the

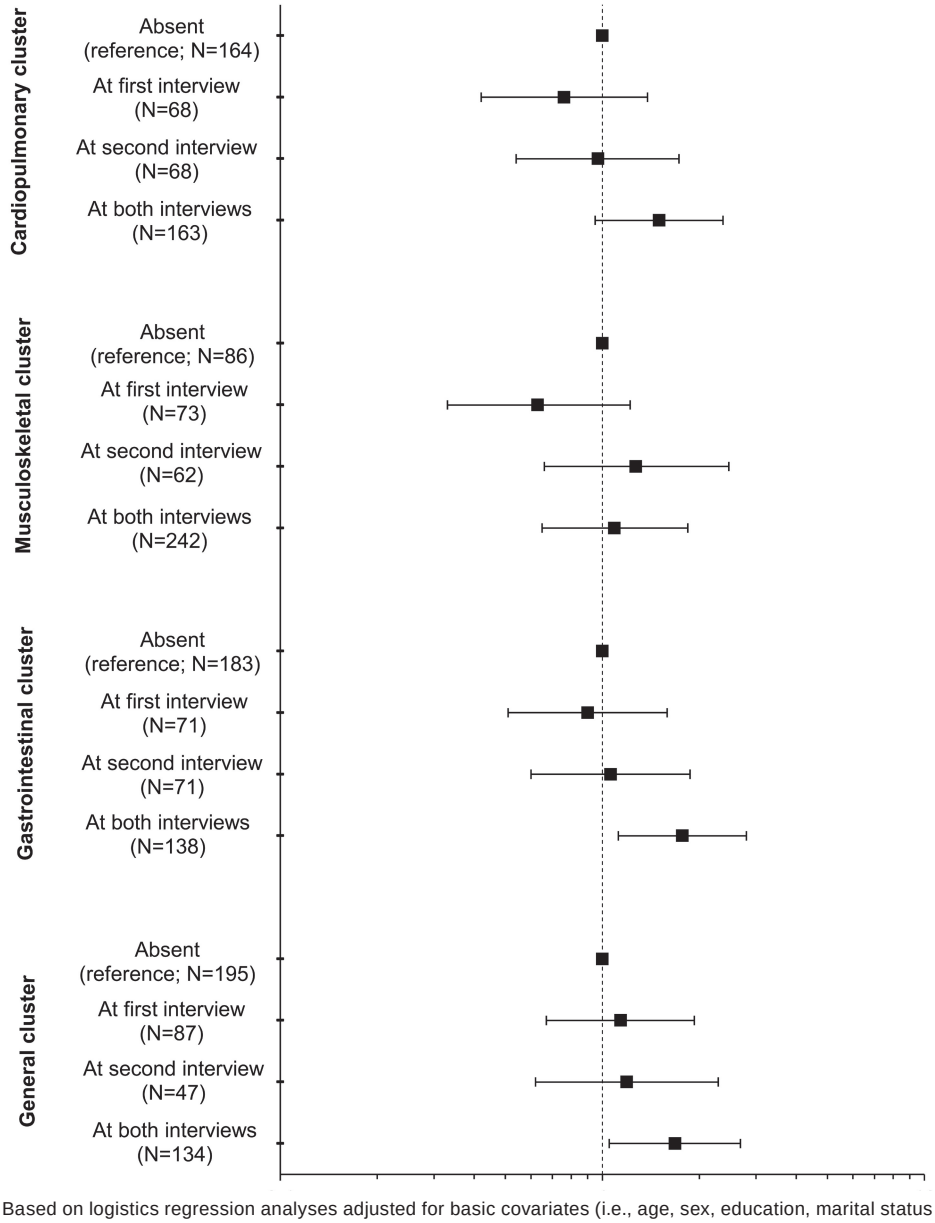
association between somatic symptoms and the course of MDD as patients with severe MDD show the largest neurobiological dysregulations [221].

Our finding that somatic symptoms independently predicted a worse course of MDD stresses the relevance to consider these symptoms in patients with MDD. This is even more important as we found that somatic symptoms are associated with more severe depression and higher levels of disability, and the symptoms have also been linked to an increased risk of suicide [179,220,223]. Applying therapies effective for somatic symptoms as well as MDD could therefore aid to optimize outcomes of patients with both types of symptoms. Antidepressants have been shown to effectively alleviate depressive as well as somatic symptoms such as pain [102,224] and may therefore constitute a valuable treatment option. Psychological treatment (e.g., cognitive behavioral therapy) may be a reasonable addition as it also targets both depressive and somatic symptoms [221,225]. Despite the potential benefits of these treatments, however, we found that patients with multiple somatic symptom clusters showed similar rates of antidepressant use (SSRIs: 25.2% versus 20.5%; other antidepressants 17.3% versus 17.0%) and lower rates of psychological treatment (51.2% versus 65.5%) compared to patients without multiple clusters. Explanations for this phenomenon may include that patients with somatic symptoms frequently do not tolerate optimal drug treatment due to a sensitivity to side effects [226,227], have a limited ability to attend psychological treatment as a result of physical disabilities, or prefer somatic treatment (e.g., analgesics) rather than psychiatric treatments [228]. As suboptimal psychiatric treatment may further worsen outcomes of patients with depression as well as somatic symptoms, our results therefore highlight the need to critically evaluate treatment in these patients.

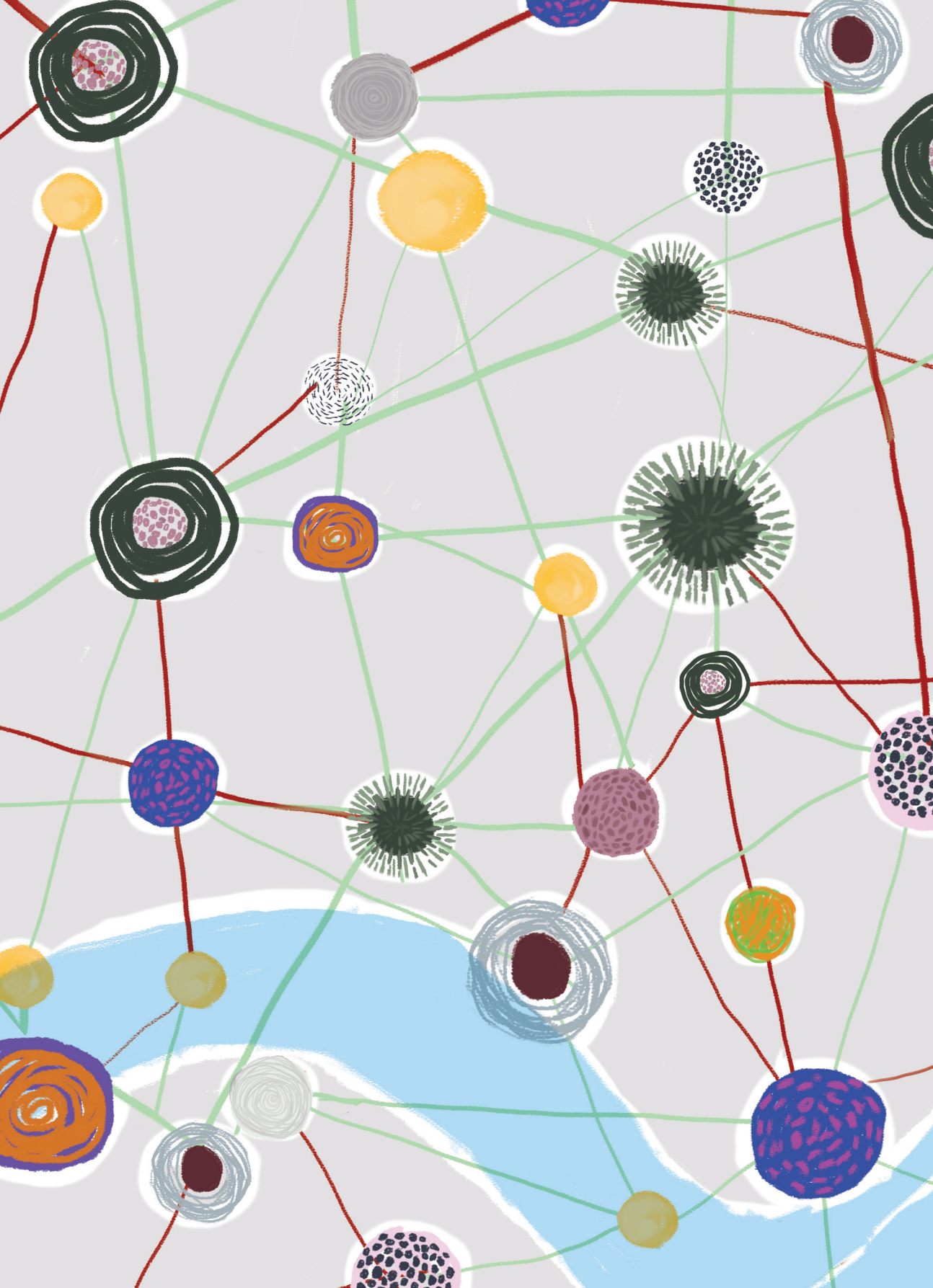
In conclusion, this study demonstrated that MDD patients with somatic symptoms have a worse prognosis independent of psychiatric characteristics, somatic diseases, lifestyle factors, and disability. Our findings highlight the importance of taking into account somatic symptoms while diagnosing and treating MDD. Future research should focus on integrating the treatment of depression and somatic symptoms in patients with these co-occurring symptoms.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Temporary and chronic somatic symptom clusters predicting the two-year persistence of MDD.



Based on logistics regression analyses adjusted for basic covariates (i.e., age, sex, education, marital status and employment status).



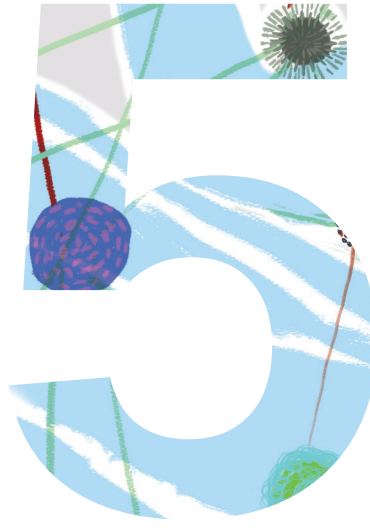
EPIDEMIOLOGICAL ASPECTS

2. Symptom networks

The network structure of major depressive disorder, generalized anxiety disorder and somatic symptomatology

Bekhuis E, Schoevers RS, van Borkulo CD, Rosmalen JGM, Boschloo L.

Psychological Medicine;46:2989-2998.



ABSTRACT

Introduction: Major depressive disorder (MDD) and generalized anxiety disorder (GAD) often co-occur with somatic symptomatology. Little is known about the contributions of individual symptoms to this association. More insight into their relations could help to identify symptoms that are central in the processes behind the co-occurrence. This study explores associations between individual MDD/GAD symptoms and somatic symptoms by using the network approach.

Methods: MDD/GAD symptoms were assessed in 2,704 participants (mean age 41.7 years, 66.1% female) from the Netherlands Study of Depression and Anxiety (NESDA) using the Inventory of Depressive Symptomatology (IDS). Somatic symptoms were assessed with the somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ). The technique eLasso was used to estimate the network of MDD/GAD and somatic symptoms.

Results: The network structure showed numerous associations between MDD/GAD and somatic symptoms. In general, neurovegetative and cognitive/affective MDD/GAD symptoms showed a similar strength of connections to the somatic domain. However, associations varied substantially across individual symptoms. MDD/GAD symptoms with many and strong associations to the somatic domain included anxiety and fatigue, whereas hypersomnia and insomnia showed no connections to somatic symptoms. Among somatic symptoms, excessive perspiration and pressure/tight feeling in chest were associated with the MDD/GAD domain, while muscle pain and tingling in fingers showed only a few weak associations.

Conclusions: Individual symptoms show differential associations in the co-occurrence of MDD/GAD with somatic symptomatology. Strongly interconnected symptoms are important in furthering our understanding of the interaction between the symptom domains, and may be valuable targets for future research and treatment.

INTRODUCTION

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are prevalent and debilitating [150,166]. The conditions are strongly connected as their symptoms frequently co-occur and show strong overlap [40,74]. Consequently, comorbidity rates between the disorders have been reported to be as high as 40-60% [229].

Previous studies have shown that MDD and GAD are associated with higher levels of somatic symptomatology [44,45,79,197]. A study of our own group, for example, demonstrated that patients with MDD or GAD have a 1.5-3 times higher risk of suffering from certain clusters of somatic symptoms than persons without those disorders [197]. However, as these studies have mainly used instruments based on diagnoses or scale scores, it is unclear whether individual MDD/GAD and somatic symptoms contribute equally to this association. It could be that only specific symptoms of MDD/GAD are related to somatic symptoms and vice versa. Such symptoms are called bridging symptoms [84] and they may be a valuable focus for future research in order to disentangle the general co-occurrence of MDD/GAD with somatic symptomatology. In addition, targeting treatment to bridging symptoms may help to improve the outcomes of MDD/GAD patients with somatic symptoms.

MDD/GAD symptoms are often classified into symptoms that are physical in nature (i.e., *neurovegetative symptoms* such as fatigue and insomnia) and symptoms that refer to cognition or mood (i.e., *cognitive/affective symptoms* such as depressed mood or anxiety). Neurovegetative symptoms are well-known to be associated with somatic symptomatology as these types of symptoms can be the result of the same somatic diseases or physical dysregulations (e.g., heart failure can cause fatigue as well as shortness of breath). In addition, neurovegetative symptoms show strong reciprocal relations with somatic symptoms (e.g., insomnia can cause the somatic symptom headache and vice versa) [230]. Cognitive/affective symptoms, however, are more strongly related to mental processes [93] and, consequently, could show only weak connections to somatic symptomatology [231]. Despite these general patterns, individual symptoms of MDD/GAD as well as individual somatic symptoms may also be differentially related with one another. Of neurovegetative MDD/GAD symptoms, for example, psychomotor agitation may be associated with somatic symptoms such as palpitations and excessive perspiration, whereas hypersomnia may not be connected to any somatic symptom.

The network approach is a conceptualization of psychopathology and related conditions that concentrates on individual symptoms and their associations [84]. In this approach, symptoms are represented as nodes and the associations between them as edges. Symptoms of multiple diagnoses or domains can be combined into one network

structure, which, consequently, offers the opportunity to study the patterns in which these symptoms co-occur [74]. In a recent study, for example, Boschloo et al. [232] presented the network structure of emotional and behavioral symptoms in preadolescents and revealed that depressive, anxiety, and somatic symptoms were related via a complex constellation of connections. While specific depressive and anxiety symptoms were strongly associated with somatic symptoms, others showed no connections at all, and individual somatic symptoms showed similarly differential associations. Although Boschloo et al. [232] did not include DSM symptoms of MDD/GAD and the number of somatic symptoms was limited, their findings indicate that combining MDD/GAD and somatic symptoms in a network structure could help to identify the bridging symptoms in their co-occurrence.

This study aims to examine the relations between individual MDD/GAD symptoms and somatic symptoms in a large sample (N=2,704) using the network approach. First, we explore the general structure of the network. Then, we specifically focus on associations between individual MDD/GAD symptoms and somatic symptoms. It is hypothesized that neurovegetative symptoms are more strongly interconnected with somatic symptoms than cognitive/affective symptoms. However, associations between the MDD/GAD and somatic symptom domain may differ across individual symptoms.

METHODS

Sample

Data were derived from the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study aimed at examining the long-term course and consequences of depressive and anxiety disorders in adults (18-65 years). A total of 2,981 participants were included for the baseline assessment in 2004-2007, consisting of 652 (22%) healthy controls with no lifetime depressive and/or anxiety disorder, 1,411 (47%) participants with a past-month diagnosis of a depressive and/or anxiety disorder and 918 (31%) participants with a prior history of a depressive and/or anxiety disorder (diagnoses were established with the Composite International Diagnostic Interview [CIDI] version 2.1 [173]). Recruitment took place in the community (19%), primary care (54%) and specialized mental health care (27%). Community-based participants had previously been identified in a population-based study, and primary care participants were identified through a three-stage screening procedure (involving the Kessler 10 scale [206] and the short-form CIDI by phone) conducted among a random sample of consulting patients of 65 general practitioners. Mental health care participants were recruited consecutively when newly enrolled at 1 of the 17 participating mental health

organization locations. Persons with insufficient command of the Dutch language or a primary clinical diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder or severe substance use disorder were excluded. The research protocol was approved by the Ethical Committee of the three participating universities and all participants gave written informed consent. A detailed description of the NESDA study design can be found elsewhere [172].

For the present study, participants with any missing data on MDD/GAD or somatic symptoms (N=277, 9.3%) were excluded, resulting in a total sample of 2,704 persons. Participants with complete data were younger (41.7 [SD=13.1] versus 43.5 [SD=12.6] years, p=.03), received education for a longer period (12.2 [SD=3.2] versus 11.5 [SD=3.5] years of education, p=.001), and were less likely to have past-month MDD (25.8% versus 37.9%, p<.001) or GAD (12.7% versus 19.1%, p=.004), but did not differ with respect to gender (66.1% versus 69.3% female, p=.29) from participants with missing data.

DSM-IV symptoms of MDD/GAD

The frequency/severity of fourteen DSM-IV MDD and/or GAD symptoms [40] during the past week was assessed with the Inventory of Depressive Symptomatology self-report version (IDS-SR_{30} [233,234]). As in prior studies [235-237], the criteria weight/appetite change, sleep change, and psychomotor change were disaggregated in an increase (i.e., weight/appetite increase, hypersomnia, and psychomotor agitation) or decrease (i.e., weight/appetite decrease, insomnia, psychomotor retardation). In addition, the symptoms loss of interest/pleasure, weight/appetite increase, weight/appetite decrease, and insomnia were composed from multiple items [236,237]. Based on dimensions identified in previous studies [76,77], all symptoms were classified as either neurovegetative (i.e., physical in nature) or cognitive/affective (i.e., mental in nature). An overview of all neurovegetative and cognitive/affective symptoms and their corresponding IDS items is included in **Supplementary Table 1**.

Symptoms were scored from 0 (absent) to 3 (frequent and/or severe) based on clearly stated anchors. However, the assumption of normality, which network estimation techniques for polytomous items (e.g., those based on partial correlations) rely on, was not satisfied in our data. Therefore, we dichotomized item-scores into either absent (score 0) or present (scores 1-3) and used a network estimation technique for binary data. The symptoms composed from multiple items were considered present when at least one of these symptoms was scored with ≥1.

Somatic symptoms

The frequency of 16 somatic symptoms (e.g., cardiopulmonary, musculoskeletal, and gastrointestinal symptoms) during the past week was scored from 1 (never) to 5 (often)

with the somatization scale of the Four-Dimensional Symptom Questionnaire (4DSQ [174]). Similar to the MDD/GAD items, the somatic items were recoded as absent (score of 1) or present (scores 2-5) as they were not normally distributed.

Statistical analysis

Main analyses

To estimate the network structure of the binary MDD/GAD and somatic symptoms, eLasso (available as the package 'IsingFit' in R [238]) was used. eLasso uses *l*1-regularized logistic regression to identify associations between symptoms, adjusted for all other symptoms in the network. In this procedure, logistic regression analyses are performed to determine associations between items and, then, an *l*1-penalty is imposed on the regression coefficients to identify models with an optimal balance between parsimony and goodness of fit [239]. To find the best fitting model, the extended Bayesian information criterion is used to assess goodness of fit [240]. As a result, eLasso identifies an accurate estimate of the network structure while it avoids multiple testing problems that would arise with significance testing in networks with many nodes [238]. Based on the estimated symptom associations, a weighted, undirected graph was visualized using package 'qgraph' [241] in R. In a network structure, nodes (circles) represent symptoms and edges (lines) represent associations between symptoms. Green edges indicate positive associations and red edges represent negative associations. The thickness of edges indicates the connection weight estimated by eLasso. The layout of the graph was based on the Fruchterman-Reingold algorithm, which iteratively computed the optimal layout; symptoms with stronger and/or more connections were placed closer to each other [242].

First, we explored the general structure of the network. To examine the general connectivity of the network, the density of the network was calculated by determining the proportion of actual connections over the number of potential connections between all symptoms [243]. Subsequently, we focused on associations connecting the MDD/GAD symptom domain with the somatic symptom domain. To examine the strength of all connections from an individual symptom to all symptoms of the opposite symptom domain (i.e., for an MDD/GAD symptom, all connections to the somatic symptom domain and vice versa), the weights of these connections were summed for all symptoms [244]. In addition, we examined whether neurovegetative and cognitive/affective MDD/GAD symptoms differed with respect to their connectivity to the somatic domain by calculating their mean summed weight of associations to the somatic domain. To test whether these means differed significantly, we used a permutation test described in [236] that compares the observed difference to a distribution of possible differences between the groups of

symptoms. To create this distribution, MDD/GAD symptoms were assigned randomly to two groups 100,000 times, and each time the groups were compared by calculating the difference in their mean strength of associations to the somatic domain. If the observed difference between neurovegetative and cognitive/affective symptoms was within the 2.5% on either side of this distribution (i.e., p≤.05), it was considered significant.

Sensitivity analyses

For our main analyses, we had dichotomized all items as the assumption of normality was not satisfied in our data. This, however, naturally results in a loss of information on the frequency and/or severity of symptoms. We examined whether dichotomization had influenced our conclusions by estimating the network structure of the non-dichotomized MDD/GAD and somatic symptoms with partial correlations using qgraph [241]. Similar to eLasso (for the dichotomized symptoms), an *l*1-penalty [239] and the extended Bayesian Information Criterion [240] were used.

RESULTS

Sample characteristics

Mean age of the sample was 41.7 (SD=13.1) years, 66.1% of participants were women, and participants received education for an average period of 12.2 (SD=3.2) years (see **Table 1**). **Supplementary Table 2** shows that prevalence rates of MDD/GAD symptoms varied from 26.7% (psychomotor retardation) to 79.5% (insomnia), while rates for somatic symptoms ranged between 3.3% (fainting) and 64.8% (muscle pain).

Table 1. Sample characteristics (N=2,704).

	N (%) / mean (SD)[a]
Sociodemographics	
Age in years	41.7 (13.1)
Female	1787 (66.1%)
Education in years	12.2 (3.2)
Psychiatric disorders	
MDD in past month	697 (25.8%)
GAD in past month	344 (12.7%)
Other depressive and/or anxiety disorder in past month	929 (34.4%)

[a] Based on descriptive statistics.

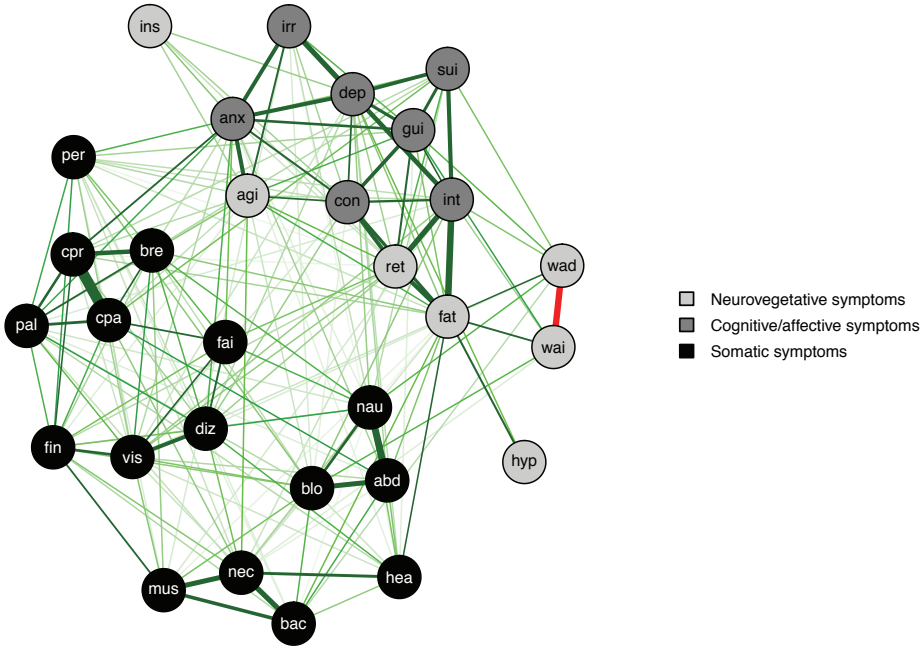
The general network structure of MDD/GAD and somatic symptoms

The estimated network structure of MDD/GAD and somatic symptoms is presented in **Figure 1** (for connection weights see **Supplementary Table 3**). All symptoms were directly or indirectly associated and the network had a high density (i.e., 44.1% of potential connections were observed in the network), indicating that the symptoms were highly connected. All connections were positive, except for the association between weight/appetite increase [wai] and weight/appetite decrease [wad]. Symptoms tended to form two clusters of highly connected MDD/GAD symptoms (the grey symptoms in Figure 1) and somatic symptoms (the black symptoms, Figure 1). In the MDD/GAD domain, neurovegetative and cognitive/affective symptoms were strongly interconnected, although the neurovegetative symptoms referring to weight/appetite change and sleep change had more peripheral positions. Between the MDD/GAD domain and somatic domain, numerous associations were observed.

Connections between MDD/GAD symptoms and somatic symptoms

To unravel the co-occurrence of MDD/GAD with somatic symptoms, we focused on associations between the MDD/GAD domain and the somatic domain. Neurovegetative symptoms were as strongly connected to somatic symptoms as cognitive/affective symptoms (mean b=0.75 versus mean b=0.65, p=0.77). Individual MDD/GAD symptoms, however, varied widely in their strength of associations to the somatic domain (see **Figure 2A**); that is, some symptoms showed strong and multiple connections, while others were not connected to any somatic symptom. The MDD/GAD symptom with the highest summed weight of connections to somatic symptoms (b=2.35) was the cognitive/affective symptom anxiety [anx]. It showed 10 connections, of which the associations with pressure/tight feeling in chest [cpr] (b=0.50) and palpitations [pal] (b=0.38) were the strongest. Next, the neurovegetative symptom fatigue [fat] had the highest summed weight of connections to somatic symptoms (b=1.65). Of its 10 connections, the associations with headache [hea] (b=0.43) and back pain [bac] (b=0.28) were the strongest. In contrast, the neurovegetative symptoms hypersomnia [hyp] and insomnia [ins] were not connected to any somatic symptom.

Figure 1. The network structure of neurovegetative and cognitive/affective symptoms of MDD/GAD and somatic symptoms.



Symptoms are represented by nodes (color refers to type of symptom), and their associations by edges (green = positive association, red = negative association). Thicker edges represent stronger associations.

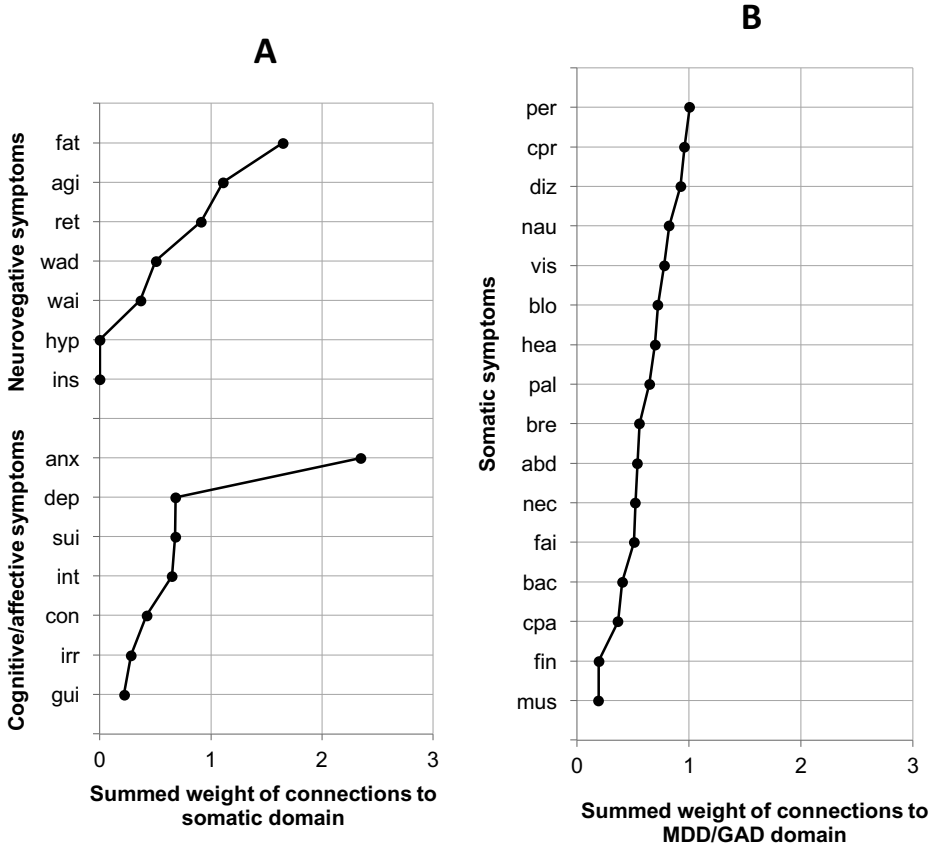
Neurovegetative symptoms	
agi	Psychomotor agitation
fat	Fatigue
hyp	Hypersomnia
ins	Insomnia
ret	Psychomotor retardation
wai	Weight/appetite increase
wad	Weight/appetite decrease
Cognitive/affective symptoms	
anx	Anxiety
con	Concentration problems
dep	Depressed mood
gui	Guilt/worthlessness
irr	Irritable
int	Loss of interest/pleasure
sui	Suicidality

Somatic symptoms	
abd	Abdominal pain
bac	Back pain
blo	Bloated feeling in abdomen/stomach area
bre	Shortness of breath
cpa	Chest pain
cpr	Pressure/tight feeling in chest
diz	Dizziness/feeling lightheaded
fai	Fainting
fin	Tingling in fingers
hea	Headache
mus	Muscle pain
nau	Nausea
nec	Neck pain
pal	Palpitations
per	Excessive perspiration
vis	Blurred vision/spots in front of eyes

Similarly, individual somatic symptoms differed substantially in their associations with MDD/GAD symptoms (see **Figure 2B**). The somatic symptom with the highest summed weight of connections to MDD/GAD symptoms (b=1.00) was excessive perspiration [per].

This symptom showed 7 associations, of which the strongest were with anxiety [anx] (b=0.34), guilt/worthlessness [gui] (b=0.16), and psychomotor agitation [agi] (b=0.14). Pressure/tight feeling in chest [cpr] was also strongly related to MDD/GAD symptoms as it showed 5 connections with a summed weight of b=0.96. Its strongest connection was to anxiety [anx] (b=0.50). Interestingly, all somatic symptoms were related to the MDD/GAD symptom domain, but some somatic symptoms showed only weak associations. Muscle pain, for example, showed 3 weak connections with a summed weight of b=0.19 to loss of interest/pleasure [int] (b=0.08), irritable [irr] (b=0.07), and fatigue [fat] (b=0.04). Tingling in fingers [fin] was also weakly associated with MDD/GAD symptoms (summed weight of connections b=0.19) as it was only connected to psychomotor retardation [ret] (b=0.14) and psychomotor agitation [agi] (b=0.06).

Figure 2. The summed weight of all connections from specific symptoms to the opposite symptom domain.



A: Summed weight of connections from MDD/GAD symptoms to the somatic symptom domain; B: Summed weight of connections from somatic symptoms to the MDD/GAD symptom domain. Symptoms are ordered based on the strength of their connections.

Sensitivity analyses

Finally, we performed a set of sensitivity analyses to examine if the dichotomization of our data had affected the network structure. **Supplementary Figure 1** shows the network structure of the polytomous MDD, GAD, and somatic symptoms. The network had a somewhat higher density than the network based on the dichotomized items (53.8% versus 44.1%), but the general structure was similar. In addition, although some variation was observed in the strength of individual symptoms to the opposite symptom domain compared to the network of dichotomized items (e.g., polytomous insomnia was moderately associated with somatic symptoms whereas dichotomized insomnia was not), the patterns of associations to the other symptom domain were comparable. That is, anxiety [anx] and fatigue [fat] showed the strongest associations to the somatic domain, and excessive perspiration [per] and pressure/tight feeling in chest [cpr] were among the somatic symptoms with the strongest associations to the MDD/GAD domain.

DISCUSSION

This study presented the complex network structure of individual MDD/GAD symptoms and individual somatic symptoms. In contrast to our hypothesis, neurovegetative symptoms of MDD/GAD did not differ with respect to their strength of associations to somatic symptoms from cognitive/affective symptoms of MDD/GAD. In addition, specific MDD/GAD symptoms such as anxiety and fatigue showed strong associations whereas hypersomnia and insomnia were not connected to the somatic domain at all. Somatic symptoms with many and/or strong connections to MDD/GAD symptoms included excessive perspiration and pressure/tight feeling in chest, while muscle pain and tingling in fingers showed limited and weak associations.

This exploratory study is the first in applying a network estimation technique to data on MDD/GAD and somatic symptomatology, which enabled us to provide insight into the unique contributions of individual symptoms in this co-occurrence. Another strength of this study is the use of the recently developed method eLasso to infer the network structure from the observed data, since this technique is not based on often untenable assumptions about psychopathology such as linearity and normality [238]. In addition, the technique does not rely on arbitrary cut-offs to determine the presence of connections in the network, as opposed to other network estimation techniques based on correlation or partial correlation [238]. Third, this study included a large sample (N=2,704) of persons with and without depressive and/or anxiety disorders, which ensured variability in symptom ratings and, consequently, prevented the network estimation to suffer from floor and ceiling effects.

Several limitations should also be discussed. First, MDD/GAD symptoms were assessed with the IDS, whereas somatic symptoms were assessed with the 4DSQ. Since these questionnaires had varying response categories, this might have impacted the empirical network structure of symptoms; that is, clustering of symptoms may have occurred based on these questionnaires. However, we recoded all items into either absent (the first response category in all instruments) or present (combining all other response categories) to create comparable response categories across instruments. In addition, although most DSM-IV criteria of MDD/GAD were included in the IDS, two criteria of GAD (i.e., criterion B: difficulty controlling worry and C5: muscle tension) were not assessed. Third, the network estimation technique eLasso has high specificity but moderate sensitivity [238]. This implies that the reported connections are most probably correct, but some weak connections in reality might have been missed. Fourth, the NESDA study mainly recruited participants with a lifetime DSM diagnosis of a depressive and/or anxiety disorder (2,081 of the 2,704 participants in our sample), who were selected for participation if they reported multiple DSM symptoms. Participants in our sample therefore probably had a higher number of DSM symptoms than persons from the general population, which could have led to stronger associations among these symptoms in our network structure. Generalization of our results may also be impaired as 9.3% of participants of the original NESDA study were excluded due to missing data, leading to a younger, higher educated sample with better mental health.

The classes of neurovegetative symptoms and cognitive/affective symptoms showed similar strengths of associations to somatic symptoms. This is in line with a study by Fried et al. [236] reporting that the most central symptoms in a network structure of depressive, anxiety, and some somatic symptoms included both neurovegetative and cognitive/affective symptoms. This indicates that these symptoms are equally important in their co-occurrence with somatic symptomatology and, therefore, highlights the importance of considering neurovegetative as well as cognitive/affective symptoms in persons with somatic symptoms. Additionally, these findings suggest that the strict mind-body dichotomy proposed in previous research might not apply for MDD/GAD symptoms [245,246], which was supported by the strong clustering of these symptoms in the network structure. Rather, the symptoms may be conceptualized as a dynamic system of related symptoms. A recent study [247], for example, demonstrated that neurovegetative and cognitive/affective depressive symptoms were intimately connected through patterns of temporal influence.

In addition, individual symptoms of MDD/GAD as well as somatic symptoms differed considerably in the number and the strength of their associations in the network and, as a result, the MDD/GAD domain and somatic domain were connected via specific symptom pairs. This corroborates findings of an earlier study reporting that individual symptoms

of depression and anxiety were associated with unique sets of somatic symptoms and vice versa [232]. Similar to our results, anxiety symptoms were more strongly related to somatic symptoms than symptoms such as guilt and suicidal ideation, and dizziness showed more connections to depressive and anxiety symptoms than symptoms like nausea and headache [232]. These findings imply that studying the co-occurrence of these symptom domains by using sum scores obfuscates important differences in the patterns of associations shown by specific symptoms [69]. Consequently, they stress the relevance of an approach focusing on individual symptoms and their connections.

Concentrating on individual symptoms is especially important as the connectivity of symptoms in a network may have important implications for prognosis. A recent study, for example, showed that MDD symptoms with a higher connectivity in a similar cross-sectional network more strongly predicted the onset of a full-blown MDD during six years of follow-up than MDD symptoms with a lower connectivity [237]. This indicates that bridging MDD/GAD and somatic symptoms, which show strong connections to the other symptom domain, may be more central in the mechanisms leading to and/or maintaining the co-occurrence of MDD/GAD and somatic symptomatology than non-bridging symptoms [84]. Consequently, a decrease of a bridging symptom is likely to result in a deactivation of symptoms of the other symptom domain in the network, whereas change in a non-bridging symptom may have little effect on these symptoms. Hence, it could be valuable to target prevention and intervention strategies specifically to the bridging symptoms in our network.

As the network approach focuses on specific associations between individual symptoms, it could also help to formulate hypotheses regarding the mechanisms behind the association of MDD/GAD with somatic symptomatology. For instance, some associations in the network structure might be causal (e.g., weight/appetite increase → bloated feeling abdomen; dizziness → concentration problems), whereas common causes may underlie others (e.g., HPA-axis disturbances could explain the strong associations of anxiety and psychomotor agitation with cardiopulmonary symptoms [248,249]). Although these suggestions are speculative, they indicate that different mechanisms may underlie associations between specific symptom pairs in the network. Longitudinal data from ecological momentary assessments that record individual symptoms repeatedly over time might aid in unraveling the dynamic relations between MDD/GAD and somatic symptoms.

The general structure of the network is also of relevance for the ongoing discussion on the validity of the current classification of MDD/GAD and somatic symptomatology in the DSM. First, in line with other studies [74,250], we found that symptoms of MDD and symptoms of GAD formed one cluster in the network. This raises the question whether symptoms of MDD and GAD should be conceptualized as expressions of separate disorders, which was addressed in the DSM-5 by adding an anxiety distress specifier

to the diagnosis of MDD [16]. In addition, it has repeatedly been argued that somatic symptomatology should be included in the diagnostic criteria of MDD/GAD as they are important features of depressed and anxious states [102,224,251]. Our network, however, showed separate domains of MDD/GAD symptoms and somatic symptoms. This is also in accordance with a factor analysis in patients with a depressive disorder showing that MDD items loaded on other factors than pain symptoms [252] and may imply that somatic symptomatology should not be part of the DSM criteria of MDD/GAD. This study demonstrated the differential associations of individual symptoms in the co-occurrence of MDD/GAD diagnoses and somatic symptomatology. We would like to encourage other researchers to consider the contributions of individual symptoms to this co-occurrence in longitudinal studies and to focus on the bridging symptoms found in this study. In addition, targeting interventions to bridging symptoms may help to improve outcomes of patients with MDD/GAD and/or somatic symptomatology.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Classification of MDD/GAD symptoms.

Symptom	Abbreviation	MDD criterion	GAD criterion	IDS item(s)
Neurovegetative symptoms				
Weight/appetite increase	wai	A3	-	12,14
Weight/appetite decrease	wad	A3	-	11,13
Hypersomnia	hyp	A4	-	4
Insomnia	ins	A4	C6	1,2,3
Psychomotor agitation	agi	A5	C1	24
Psychomotor retardation	ret	A5	-	23
Fatigue	fat	A6	C2	20
Cognitive/affective symptoms				
Depressed mood	dep	A1	-	5
Loss of interest/pleasure	int	A2	-	19,20
Anxiety	anx	-	A	7
Guilt/worthlessness	gui	A7	-	16
Concentration problems	con	A8	C3	15
Suicidality	sui	A9	-	18
Irritable	irr	-	C4	6

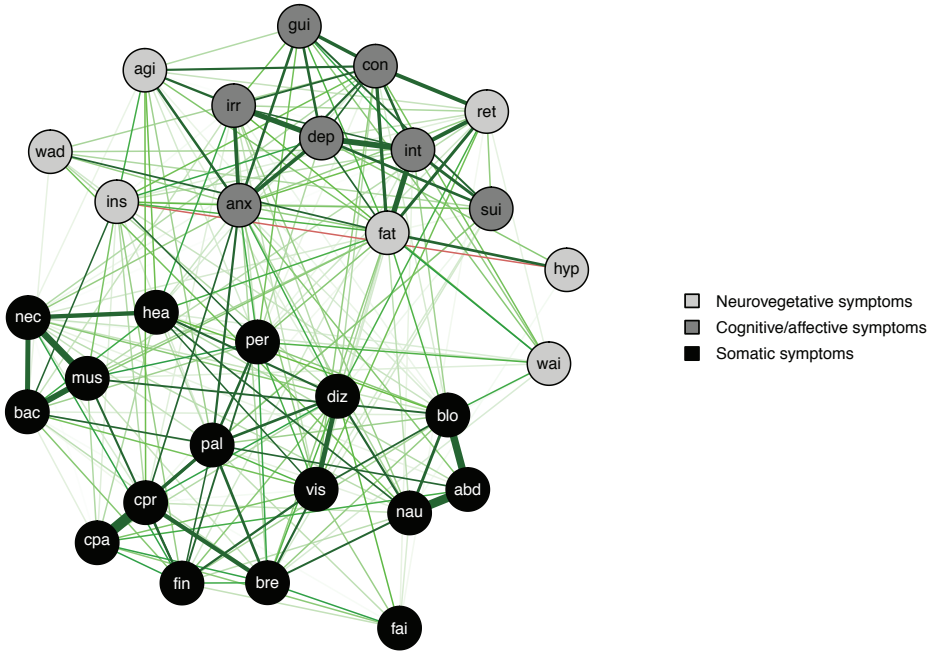
Supplementary Table 2. Symptom prevalence.

Symptom	Prevalence N (%)
MDD/GAD symptoms	
Neurovegetative symptoms	
Fatigue	1537 (56.8%)
Hypersomnia	991 (36.6%)
Insomnia	2151 (79.5%)
Psychomotor agitation	1201 (44.4%)
Psychomotor retardation	723 (26.7%)
Weight/appetite increase	950 (35.1%)
Weight/appetite decrease	860 (31.8%)
Cognitive/affective symptoms	
Anxiety	1699 (62.8%)
Concentration problems	1589 (58.8%)
Depressed mood	1558 (57.6%)
Guilt/worthlessness	1252 (46.3%)
Irritable	1713 (63.4%)
Loss of interest/pleasure	1307 (48.3%)
Suicidality	736 (27.2%)
Somatic symptoms	
Abdominal pain	1074 (39.7%)
Back pain	1685 (62.3%)
Bloated feeling in abdomen/stomach area	1404 (51.9%)
Blurred vision/spots in front of eyes	1128 (41.7%)
Chest pain	593 (21.9%)
Dizziness/feeling lightheaded	1424 (52.7%)
Excessive perspiration	1342 (49.6%)
Fainting	89 (3.3%)
Headache	1697 (62.8%)
Muscle pain	1753 (64.8%)
Neck pain	1498 (55.4%)
Nausea	1154 (42.7%)
Palpitations	1138 (42.1%)
Pressure/tight feeling in chest	942 (34.8%)
Shortness of breath	903 (33.4%)
Tingling in fingers	875 (32.4%)

Supplementary Table 3. Estimated connection weights (b) between neurovegetative and cognitive/affective MDD/GAD symptoms and somatic symptoms. Connection weights >0 are printed in bold.

		Neurovegetative symptoms							Cognitive/affective symptoms							Somatic symptoms															
		agi	fat	hyp	ins	ret	wad	wai	anx	con	dep	gui	int	irr	sui	abd	bac	blo	bre	cpa	cpr	diz	fai	fin	hea	mus	nau	nec	pal	per	vis
Neurovegetative symptoms	agi	-	**0.34**	0.00	**0.16**	**0.29**	0.00	0.00	**0.95**	**0.46**	0.00	**0.34**	**0.12**	**0.51**	0.00	0.00	0.00	**0.09**	**0.09**	**0.11**	**0.13**	0.00	0.00	**0.06**	0.00	0.00	0.00	**0.28**	**0.20**	**0.14**	0.00
	fat	**0.34**	-	**0.53**	**0.11**	**0.97**	**0.42**	**0.49**	0.00	**0.79**	**0.21**	**0.23**	**1.44**	0.00	0.00	**0.23**	**0.28**	0.00	**0.21**	0.00	**0.15**	0.00	0.00	0.00	**0.43**	**0.04**	**0.03**	**0.08**	0.00	**0.10**	**0.09**
	hyp	0.00	**0.53**	-	0.00	0.00	0.00	0.00	0.00	0.00	**0.27**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ins	**0.16**	**0.11**	0.00	-	0.00	0.00	0.00	**0.22**	**0.17**	**0.18**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ret	**0.29**	**0.97**	0.00	0.00	-	0.00	0.00	**0.09**	**0.95**	**0.17**	**0.53**	**1.20**	0.00	**0.33**	0.00	0.00	0.00	0.00	0.00	**0.04**	**0.18**	**0.24**	**0.14**	0.00	0.00	0.00	**0.10**	0.00	**0.03**	**0.19**
	wad	0.00	**0.42**	0.00	0.00	0.00	-	**-1.42**	0.00	0.00	0.00	**0.30**	**0.22**	0.00	**0.24**	0.00	**0.13**	0.00	0.00	0.00	0.00	**0.07**	0.00	0.00	0.00	0.00	**0.31**	0.00	0.00	0.00	0.00
	wai	0.00	**0.49**	0.00	0.00	0.00	**1.42**	-	0.00	0.00	0.00	**0.40**	**0.17**	0.00	0.00	0.00	0.00	**0.30**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.06**	0.00	0.00	0.00
Cognitive/affective symptoms	anx	**0.95**	0.00	0.00	**0.22**	**0.09**	0.00	0.00	-	**0.53**	**0.93**	**0.65**	0.00	**0.92**	**0.21**	**0.16**	0.00	0.00	**0.12**	0.00	**0.50**	**0.34**	**0.27**	0.00	**0.05**	0.00	**0.05**	0.00	**0.38**	**0.34**	**0.14**
	con	**0.46**	**0.79**	0.00	**0.17**	**0.95**	0.00	0.00	**0.53**	-	**0.47**	**0.86**	**0.58**	**0.16**	0.00	0.00	0.00	**0.05**	0.00	0.00	0.00	**0.18**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.11**	**0.07**
	dep	0.00	**0.21**	**0.27**	**0.18**	**0.17**	0.00	0.00	**0.93**	**0.47**	-	**0.76**	**1.06**	**1.18**	**0.87**	**0.15**	0.00	0.00	0.00	0.00	0.00	**0.14**	0.00	0.00	**0.12**	0.00	**0.19**	0.00	0.00	0.00	**0.09**
	gui	**0.34**	**0.23**	0.00	0.00	**0.53**	**0.30**	**0.40**	**0.65**	**0.86**	**0.76**	-	**0.45**	**0.31**	**0.73**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.06**	0.00	0.00	0.00	0.00	**0.16**	0.00
	int	**0.12**	**1.44**	0.00	0.00	**1.20**	**0.22**	**0.17**	0.00	**0.58**	**1.06**	**0.45**	-	**0.33**	**0.96**	0.00	0.00	**0.20**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.08**	0.00	0.00	**0.07**	**0.12**	**0.19**
	irr	**0.51**	0.00	0.00	0.00	0.00	0.00	0.00	**0.92**	**0.16**	**1.18**	**0.31**	**0.33**	-	0.00	0.00	0.00	**0.07**	0.00	0.00	0.00	0.00	0.00	0.00	**0.03**	**0.07**	**0.11**	0.00	0.00	0.00	0.00
	sui	0.00	0.00	0.00	0.00	**0.33**	**0.24**	0.00	**0.21**	0.00	**0.87**	**0.73**	**0.96**	0.00	-	0.00	0.00	0.00	**0.14**	**0.26**	**0.13**	**0.02**	0.00	0.00	0.00	0.00	**0.13**	0.00	0.00	0.00	0.00
Somatic symptoms	abd	0.00	**0.23**	0.00	0.00	0.00	0.00	0.00	**0.16**	0.00	**0.15**	0.00	0.00	0.00	0.00	-	**0.35**	**1.13**	0.00	**0.42**	0.00	0.00	0.00	0.00	**0.23**	0.00	**1.54**	**0.05**	**0.06**	0.00	**0.14**
	bac	0.00	**0.28**	0.00	0.00	0.00	**0.13**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.35**	-	**0.32**	0.00	0.00	0.00	**0.06**	0.00	**0.15**	**0.20**	**0.84**	**0.03**	**1.18**	0.00	**0.06**	**0.10**
	blo	**0.09**	0.00	0.00	0.00	0.00	0.00	**0.30**	0.00	**0.05**	0.00	0.00	**0.20**	**0.07**	0.00	**1.13**	**0.32**	-	**0.12**	0.00	0.00	0.00	0.00	**0.21**	**0.10**	**0.25**	**0.66**	**0.09**	**0.14**	**0.21**	**0.23**
	bre	**0.09**	**0.21**	0.00	0.00	0.00	0.00	0.00	**0.12**	0.00	0.00	0.00	0.00	0.00	**0.14**	0.00	0.00	**0.12**	-	**0.46**	**1.02**	**0.32**	**0.30**	**0.15**	0.00	**0.19**	**0.32**	0.00	**0.47**	**0.23**	**0.40**
	cpa	**0.11**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.26**	**0.42**	0.00	0.00	**0.46**	-	**2.28**	0.00	**0.48**	**0.35**	0.00	0.00	0.00	**0.20**	**0.68**	0.00	**0.12**
	cpr	**0.13**	**0.15**	0.00	0.00	**0.04**	0.00	0.00	**0.50**	0.00	0.00	0.00	0.00	0.00	**0.13**	0.00	0.00	0.00	**1.02**	**2.28**	-	**0.17**	0.00	**0.43**	0.00	0.00	0.00	0.00	**0.64**	0.00	**0.09**
	diz	0.00	0.00	0.00	0.00	**0.18**	**0.07**	0.00	**0.34**	**0.18**	**0.14**	0.00	0.00	0.00	**0.02**	0.00	**0.06**	0.00	**0.32**	0.00	**0.17**	-	**0.51**	**0.25**	**0.33**	0.00	**0.40**	**0.26**	**0.40**	**0.09**	**0.91**
	fai	0.00	0.00	0.00	0.00	**0.24**	0.00	0.00	**0.27**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.30**	**0.48**	0.00	**0.51**	-	**0.25**	0.00	0.00	**0.33**	0.00	0.00	0.00	**0.46**
	fin	**0.06**	0.00	0.00	0.00	**0.14**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.15**	**0.21**	**0.15**	**0.35**	**0.43**	**0.25**	**0.25**	-	0.00	**0.49**	**0.12**	**0.22**	**0.33**	**0.40**	**0.66**
	hea	0.00	**0.43**	0.00	0.00	0.00	0.00	0.00	**0.05**	0.00	**0.12**	**0.06**	0.00	**0.03**	0.00	**0.23**	**0.20**	**0.10**	0.00	0.00	0.00	**0.33**	0.00	0.00	-	0.00	**0.24**	**0.71**	**0.14**	0.00	**0.09**
	mus	0.00	**0.04**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.08**	**0.07**	0.00	0.00	**0.84**	**0.25**	**0.19**	0.00	0.00	0.00	0.00	**0.49**	0.00	-	0.00	**1.13**	0.00	**0.06**	**0.22**
	nau	0.00	**0.03**	0.00	0.00	0.00	**0.31**	0.00	**0.05**	0.00	**0.19**	0.00	0.00	**0.11**	**0.13**	**1.54**	**0.03**	**0.66**	**0.32**	0.00	0.00	**0.40**	**0.33**	**0.12**	**0.24**	0.00	-	**0.15**	**0.09**	0.00	0.00
	nec	**0.28**	**0.08**	0.00	0.00	**0.10**	0.00	**0.06**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.05**	**1.18**	**0.09**	0.00	**0.20**	0.00	**0.26**	0.00	**0.22**	**0.71**	**1.13**	**0.15**	-	**0.11**	**0.10**	0.00
	pal	**0.20**	0.00	0.00	0.00	0.00	0.00	0.00	**0.38**	0.00	0.00	0.00	**0.07**	0.00	0.00	**0.06**	0.00	**0.14**	**0.47**	**0.68**	**0.64**	**0.40**	0.00	**0.33**	**0.14**	0.00	**0.09**	**0.11**	-	**0.38**	**0.29**
	per	**0.14**	**0.10**	0.00	0.00	**0.03**	0.00	0.00	**0.34**	**0.11**	0.00	**0.16**	**0.12**	0.00	0.00	0.00	**0.06**	**0.21**	**0.23**	0.00	0.00	**0.09**	0.00	**0.40**	0.00	**0.06**	0.00	**0.10**	**0.38**	-	**0.17**
	vis	0.00	**0.09**	0.00	0.00	**0.19**	0.00	0.00	**0.14**	**0.07**	**0.09**	0.00	**0.19**	0.00	0.00	**0.14**	**0.10**	**0.23**	**0.40**	**0.12**	**0.09**	**0.91**	**0.46**	**0.66**	**0.09**	**0.22**	0.00	0.00	**0.29**	**0.17**	-

Supplementary Figure 1. The network structure of neurovegetative and cognitive/affective symptoms of MDD/GAD and somatic symptoms based on polytomous items.



Symptoms are represented by nodes (color refers to type of symptom), and their associations by edges (green = positive association, red = negative association). Thicker edges represent stronger associations.

The network structure of diagnostic symptom criteria for functional somatic syndromes

Joustra ML, Bekhuis E, Rosmalen JGM.

Submitted.

ABSTRACT

Background: There is a longstanding discussion on whether functional somatic syndromes (FSS) are different names for the same problem, since they are known for substantial clinical and diagnostic overlap.

Objectives: The aim of this study was to investigate the co-occurrence of the most well-known FSS (i.e., chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS)) on a symptom-level using network analyses, in the general population and in a subgroup consisting of patients fulfilling the diagnostic criteria for FSS.

Method: This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the LifeLines cohort study. The diagnostic symptoms of the three FSS were assessed by questionnaire based on the CDC (CFS), ACR (FMS) and ROME IV (IBS) criteria. A partial correlation network of the diagnostic criteria was estimated to study how diagnostic symptoms were interrelated within and between diagnoses. Clustering of symptoms was examined using the walktrap algorithm.

Results: Network analyses showed that all diagnostic symptoms were highly connected, with similar levels of clustering in the general population and patients with FSS. The network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Clustering of diagnostic symptoms revealed a general, musculoskeletal and abdominal symptom cluster in the general population, and an abdominal and combined general and musculoskeletal cluster in patients with FSS.

Conclusions: FSS may reflect the same underlying syndrome with different subtypes based on symptoms' bodily systems rather than their current classification into criteria for CFS, FMS or IBS. The diagnostic criteria for FSS should be further examined and reconsidered.

INTRODUCTION

Functional somatic syndromes (FSS) comprise clusters of persistent somatic symptoms for which no conclusive underlying organic pathology can be found [253]. The main three syndromes are chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). FSS are often co-morbid: patients with CFS, FMS or IBS are more likely to meet lifetime symptom and diagnostic criteria for other FSS than control subjects [254]. For example, lifetime rates of IBS were significantly higher in patients with CFS (92%) or patient with FMS (64%) compared with controls (18%) [254]. Since the three main FSS are known for substantial clinical and diagnostic overlap, there is a longstanding discussion in the literature on whether these syndromes are different names for the same problem, also known as the lumper-splitter discussion [255]. Lumpers state that the different FSS identify one group of patients, while splitters state that the different FSS should be considered as distinct entities. One argument in favour of the lumpers is that the case definitions of FSS overlap. For example, both CFS and FMS diagnostic criteria describe both musculoskeletal symptoms, fatigue, cognitive symptoms, and sleep disturbance or waking unrefreshed. On the other hand, the finding of syndrome-specific risk factors supports the splitters perspective [256]. More recently, it has been suggested that both lumpers and splitters are right and that there is commonality as well as heterogeneity between and within FSS in both onset-related factors and psychosocial or physiological patient characteristics [257].

In the current literature, attempts have been made to investigate whether FSS are different names for the same problem by examining the interrelatedness or clustering of symptoms that characterize FSS. Different statistical techniques have been used, including latent class analyses [79,258,259], principle component analysis [39,78,260], and cluster analysis [261,262]. Most studies have found multiple underlying classes or clusters and concluded that there are both similarities and dissimilarities between FSS. However, there were also some inconsistencies between these studies: some findings indicated that patients with FSS could be distinguished by the number of symptoms [78,79], while other findings suggested that both the number of symptoms and the type of symptoms were relevant [259,262,263]. The number of classes or clusters also varied widely, ranging from two to eleven [78,262]. A possible explanation for these inconsistencies is that different symptom clusters might be the result of the experience of milder or lower numbers of symptoms, while in the more severe cases the overlap of clusters becomes larger [259,262-264]. There are also several limitations of the current literature in the context of the lumper-splitter discussion: the somatic symptoms included more than those in the diagnostic algorithms of the different FSS, the time frame of symptom assessment was relatively long in most studies, and lastly, symptoms were frequently dichotomized (i.e. present or not), not taking into account the severity of symptoms.

Currently there is a new approach to analyze symptom patterns, known as the network approach [84]. This approach focuses on individual symptoms and the unique patterns in which they co-occur with other symptoms [74]. The advantage of the network approach compared to latent class analyses, principle component analysis, and standard cluster analysis, is that it naturally accommodates the unique role of each of the individual symptoms. As such, it can provide insight into how varying symptoms of a specific syndrome relate differentially to symptoms from the same or other syndromes. Recent studies have used the network approach to study comorbidity and have shown promising results [263,265-267]. One study investigated for example the network structure of psychiatric symptoms and showed that although clustering of the symptoms generally corresponded with the classification of symptoms in the DSM, symptoms within the same diagnosis could show unique patterns in which they co-occurred with each other [265]. Another study showed that individual depressive/anxiety symptoms had different levels of importance in explaining their general co-occurrence with somatic symptoms [267]. More recently, network analysis was performed in patients with CFS, FMS, or IBS and revealed that 61 symptoms could be classified into eleven categories, which showed more overlap as FSS severity increased [263]. As the study did not focus on diagnostic criteria of the FSS and their individual roles in the network, however, important information about the role of individual diagnostic symptoms within the specific FSS syndromes as well as in their co-morbidity is missing in the context of the lumper-splitter discussion.

The aim of this study is to investigate networks of the diagnostic symptoms composing the criteria for the three most well-known FSS. To the best of our knowledge, no studies have investigated the relatedness of symptoms that compose the diagnostic algorithms of the different FSS using network analyses. This study will be performed in a large population-based cohort study. First, we will examine the general network structure of the diagnostic criteria for FSS in both the entire cohort and in a subgroup consisting of patients with FSS experiencing more severe symptoms, to investigate the influence of experiencing more severe symptoms on network structure and clustering. Second, we will examine the role of the individual symptoms within and between the CFS, FMS and IBS diagnostic symptom criteria. Lastly, we will examine clustering of symptoms in the network models.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study [268]. LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort

study examining health and health-related behaviors of more than 167,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language were excluded. Parents and children were not excluded in case of the mentioned criteria when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website and then participate.

All participants received written information on the purpose and methods of the study and written informed consent was obtained after the procedure was fully explained. All data are kept confidential and are only used for medical research. Approval by the Medical Ethical Committee of the University Medical Center Groningen was obtained for the study.

Data collection

The first participants were included at the end of 2006, and the recruitment period was closed after reaching the target number of participants in 2013. Participants who were included in the LifeLines study will be followed for at least 30 years. At baseline, participants visited one of the LifeLines research sites for a physical examination. Prior to these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires were administered to all participants approximately every 18 months, and participants have been invited for a renewed physical examination at the LifeLines research site on average every five years. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and lastly, the CogState computerized cognitive battery and

the digital neuropsychiatric questionnaire were conducted respectively. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. Data of the second assessment was used in the current study, since the diagnostic algorithms for FSS were included in the second assessment.

FSS diagnostic criteria

The diagnostic criteria for the three FSS were included in the LifeLines questionnaire. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) [269], FMS using the 2010 American College of Rheumatology criteria (ACR) [270], and the diagnosis for IBS was assessed using the ROME III criteria [271]. However, the IBS criteria which were based on a minimal frequency of symptoms were adjusted in accordance with the ROME IV criteria [272]: instead of symptoms 3 days per month, participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (**Supplement 1: scoring algorithm**).

Descriptives

Educational level was assessed using the question: “What is your highest completed education?”, resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational level. Medical diseases were assessed by a questionnaire asking to indicate for each disease whether the participant had or had had them.

Statistical analyses

The characteristics of the participants were described using SPSS version 22. For all continuous variables, means ± standard deviations (SDs) were calculated. Network analyses were performed on a combination of binary main criteria (fatigue for at least 6 months, locomotor pain complaints for at least 3 months, abdominal pain for at least 6 months with a frequency of at least 1 day/week), and categorical and continuous data on additional symptoms. Two diagnostic criteria of CFS and FMS were very similar, namely cognitive symptoms (forgetfulness or memory problems/difficulty with thinking or concentrating in CFS; thinking requires effort/I have trouble concentrating in FMS) and unrefreshed sleep (unrefreshing sleep in CFS; waking up unrefreshed in FMS). Therefore, these items were combined by taking the mean of the CFS and the FMS symptom.

We performed the network analyses in both the general population cohort and in a subset with persons who fulfilled the diagnostic criteria for CFS, FMS and/or IBS. Weighted networks of symptoms for both the general population and FSS were estimated and visualized in R version 3.4.2 with package qgraph [241]. A correlation matrix for all

symptoms (with polyserial correlations for symptom pairs including categorical or binary symptoms and Pearson correlations for symptom pairs consisting only of continuous symptoms) was calculated. Partial correlations were calculated for all pairs of variables, which indicate correlations among symptoms while controlling for all other variables in the network. To prevent overfitting, an /1-penalty was used to estimate possible networks with different levels of sparsity [239]. The model with the best fit to the data was selected using the extended Bayesian information criterion (EBIC) [240] with hyperparameter y=0.5 [273]. This technique has been shown to yield adequate network structures [235,273,274]. The accuracy of estimated connections in the networks was also investigated by calculating 95% confidence intervals around connection weights with R-package bootnet [275]. Bootstrapped confidence intervals were calculated by drawing 1,000 bootstrap samples of the data and recalculating connection weights for each sample. The lay-outs of the networks were based on the Fruchterman-Reingold algorithm, which places symptoms with stronger and/or more connections closer to each other [242].

First, we explored the general structure of the network. To examine the general connectivity of the network, the density of the network was calculated by determining the proportion of actual connections over the number of potential connections between all symptoms [243]. In addition, the network clustering coefficient was calculated by determining the proportion of actual connections of adjacent nodes in the network over the number of potential connections between adjacent nodes. Subsequently, we focused on the strength of the individual FSS symptoms to symptoms of the same diagnosis, and the strength of all connections from an individual symptom to all symptoms of other FSS diagnoses by summing the weight of these connections [244]. Lastly, clustering of symptoms was examined using the walktrap algorithm from package “Igraph” [276]. This random walk method identifies groups of symptoms with high intragroup but low intergroup connectedness.

RESULTS

This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Of these participants, 11.5% (n=9,217) fulfilled criteria for one or more FSS: 3.1% of the participants fulfilled the CDC criteria for CFS, 6.4% fulfilled the ACR criteria for FMS, and 5.5% fulfilled the ROME IV criteria for IBS. Patients with FSS were more often female (75% female) and were slightly younger (52.3±12.4 years) than the general population (59.2%, 52.9±12.6; **Table 1**). In addition, patients with FSS were lower educated than the general population. The prevalence of somatic and psychiatric disorders is summarized in **Table 2**.

Table 1. General characteristics of the study groups

	General population	One or more FSS	CFS	FMS	IBS
n (%)	79,966 (100)	9,217 (11.5)	2,490 (3.1)	5,122 (6.4)	4,377 (5.5)
Female n (%)	47,341 (59.2)	6,917 (75.0)	1,848 (74.2)	3,922 (76.6)	3,307 (75.6)
Age in years (SD)	52.9 (12.6)	52.3 (12.4)	54.2 (11.8)	52.8 (11.7)	50.9 (12.9)
Education (% low-middle-high)	2.6 65.9 29.2	3.5 69.9 24.0	4.7 72.7 19.6	3.9 73.6 19.9	2.5 66.4 28.6

FSS = functional somatic syndrome; CFS = chronic fatigue syndrome; FMS = fibromyalgia syndrome; IBS = irritable bowel syndrome.

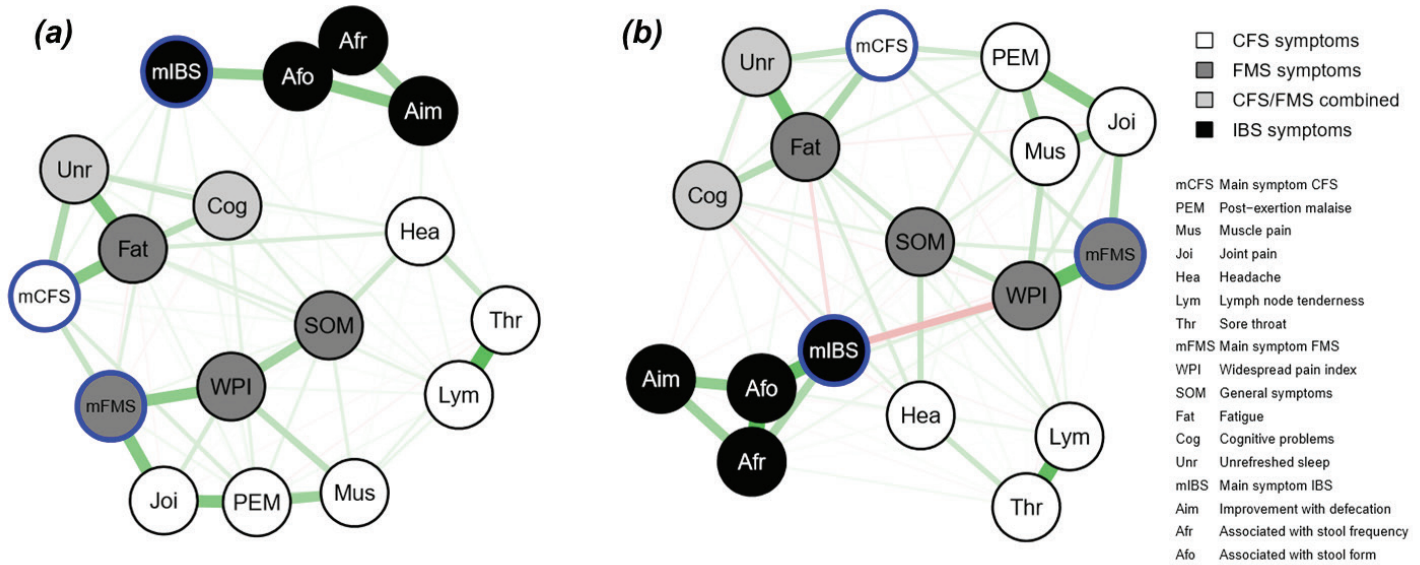
Table 2. Prevalence rates of somatic and psychiatric disorders in the general population (lifetime).

	n	%
Anxiety disorder	5,712	7.1
Cancer	1,625	2.0
Celiac disease	381	0.5
Dementia	74	0.1
Eating disorder	1,107	1.4
Heart failure	1,603	2.0
Hepatitis B	66	0.1
Inflammatory bowel disease	924	1.2
Mood disorder	2,368	3.0
Multiple sclerosis	185	0.2
Rheumatoid arthritis	2,858	3.6
Schizophrenia	65	0.1

General network structure

The network structure of FSS diagnostic symptoms in the general population is presented in **Figure 1A** and in patients with FSS in **Figure 1B**. **Supplementary Tables 1A** and **1B** show that accuracy of connection weights was excellent, reflected in very small confidence intervals of associations. The diagnostic symptoms were highly connected: 89.2% of potential connections in the general population network and 90% in the FSS group network were observed, with a mean strength of connections of r=0.055 in the general population and r=0.048 in patients with FSS. In addition, both networks had a high level of clustering (i.e., clustering coefficient = 0.79 in the general population and 0.80 in patients with FSS). Most connections were positive or slightly negative, except for the association of the main criterion of IBS of abdominal pain ≥ 6 months (mIBS) with the widespread pain index of FMS (WPI, r=-0.17) and fatigue of FMS (Fat, r=-0.07) in patients with FSS.

Figure 1. Estimated network structures of FSS diagnostic symptoms for (a) the general population and (b) patients with FSS.



Symptoms are represented by circles and associations between them by lines. The color of circles refers to the diagnosis symptoms belong to. Main criteria for CFS, FMS and IBS are delineated in blue. Green lines indicate positive associations and red lines negative associations. The thickness of lines is proportional to the strength of associations.

Associations of symptoms within diagnoses

In order to test how well the single diagnostic symptoms were representative of the corresponding syndrome, we looked at the interrelations of the different diagnostic symptoms within each FSS (**Supplementary Table 2**). The within-diagnosis density, reflecting how well the symptoms are associated to each other, for the CFS diagnostic symptom criteria was respectively 86.1% in the general population and 69.4% in the FSS group, with a mean strength of connections of r=0.52 in both groups. The CFS symptom post-exertional malaise (PEM) had the highest within-diagnosis strength (r=0.73 in the general population and r=0.87 in patients with FSS), while headaches (Hea) had the lowest within-diagnosis strength in both the general population (r=0.27) and patients with FSS (r=0.32). Although sore throat (Thr) and lymph node tenderness (Lym) had a high within-diagnosis strength (r=0.62 and 0.58 in the general population and r=0.55 and 0.54 in the FSS group), this was mainly the result of their strong associations with each other (r=0.43 in both groups). Thus, based on this analysis, PEM seems to be a core symptom of this symptom cluster, while headache, sore throat and lymph node tenderness are less relevant symptoms for the CFS diagnosis.

For the diagnostic symptom criteria of FMS, the within-diagnosis density was 80% in both the general population and patients with FSS, with a mean strength of connections of r=0.42 in the general population and r=0.51 in patients with FSS. The FMS symptom fatigue (Fat) had the highest within-diagnosis strength (r=0.57 in the general population and r=0.71 in patients with FSS), while the main criterion of FMS of locomotor pain complaints for ≥ 3 months (mFMS) had the lowest within-diagnosis strength in the general population (r=0.24), and cognitive symptoms (Cog) in patients with FSS (n=0.34). In summary, this analysis suggests that fatigue is a core symptom of FMS.

Lastly, the within-diagnosis density of the IBS symptom criteria was 83.3% in both groups, with a mean strength of connections of r=0.73 in the general populations and r=0.83 in patients with FSS. As such, this syndrome showed the strongest within-diagnosis connections of all syndromes. The IBS symptom abdominal pain associated with change in stool form (Afo) had the highest within-diagnosis strength (r=1.18 in both groups), while the symptoms with the lowest within-diagnosis strength were the main criterion of recurrent abdominal pain or discomfort in the general population (mIBS; r=0.15) and improvement of abdominal pain after defecation in patients with FSS (Aim; r=0.56). Thus, abdominal pain associated with change in stool form seems to be a core symptom of IBS based on these analyses

Associations of symptoms between diagnoses

In order to study the diagnostic boundaries between FSS, we modelled networks consisting of all diagnostic symptoms of the three FSS together. The associations of

symptoms between FSS diagnoses in the general population and patients with FSS can be found in **Supplementary Table 3**. The between-diagnosis density for CFS with FMS and IBS diagnostic symptom criteria was 66.2% with a mean strength of connections of r=0.04 in the general population and 74.6% with a mean strength of r=0.03 in patients with FSS. The main criterion of CFS of fatigue for ≥6 months had the highest between-diagnosis strength (mCFS; r=0.92 in the general population and r=0.52 in patients with FSS respectively), while the symptom sore throat (Thr) had the lowest between-diagnosis strength (r=0.10 in both groups). This indicates that the main criterion of CFS of chronic fatigue is an important symptom in explaining co-morbidity between the syndromes.
The between-diagnosis density for FMS with CFS and IBS diagnostic symptom criteria was 73.1% with a mean strength of connections of r=0.04 in the general population and 80.8% with a mean strength of r=0.03 in patients with FSS respectively. For FMS the symptom fatigue (Fat) had the highest between-diagnosis strength (r=1.07 in the general population and r=0.84 in patients with FSS), reflecting its importance in explaining co-morbidity with other syndromes. In contrast, cognitive symptoms in the general population (Cog; r=0.33) and the main criterion of locomotor pain for ≥3 months in FSS patients (mFMS; r=0.21) had the lowest between-diagnosis strength.
Lastly, the between-diagnosis density was 44.2% and 50% for IBS with CFS and FMS diagnostic symptom criteria in the general population and patients with FSS respectively, with corresponding mean strengths of connections of r=0.02 and r=0.00. This syndrome had therefore the weakest between-diagnosis connections of all three syndromes. The main symptom of IBS (mIBS) of abdominal pain for ≥6 months had the highest between-diagnosis strength in the general population (r=0.23), indicating that it connected the syndrome to other syndromes. Still, it had a negative between-diagnosis strength in patients with FSS (r=-0.57).

Cluster analyses

Cluster analysis of the network in the general population revealed four clusters. Firstly, an abdominal symptom cluster with inclusion of all IBS diagnostic symptoms was found. Second, a general symptom cluster was identified including the main criterion of CFS of fatigue for ≥6 months (mCFS), the combined CFS/FMS symptoms cognitive problems (Cog) and unrefreshed sleep (Unr), and the FMS symptoms fatigue (Fat) and general somatic symptoms (SOM). Third, a musculoskeletal cluster was identified with inclusion of the main FMS criterion of locomotor pain for ≥3 months (mFMS), the widespread pain index (WPI), and the CFS diagnostic symptoms joint pain (Joi), muscle pain (Mus), and post-exertional malaise (PEM). Lastly, analyses revealed an “other symptoms” cluster with inclusion of the CFS criteria headaches (Hea), sore throat (Thr), and tender lymph nodes (Lym).

When analyzing clustering in the network of the FSS group, two clusters were found: one abdominal symptom cluster with inclusion of all IBS diagnostic symptoms, and a combined general and musculoskeletal symptom cluster including all diagnostic symptoms of CFS and FMS.

DISCUSSION

This was the first study that investigated the diagnostic criteria of the different FSS using network analyses. First, we found that all diagnostic symptoms were connected, either directly or via other symptoms, with similar levels of clustering in the general population and patients with FSS. Second, the network density between diagnoses was in most cases slightly lower than within diagnosis, but differences were small. Main symptoms were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. Lastly, clustering of symptoms in the general population revealed a general, musculoskeletal, abdominal, and other symptom cluster; in patients with FSS only an abdominal and a combined general and musculoskeletal symptom cluster were found.

The main strength of the current study is that the symptoms that compose the diagnostic criteria for the three main FSS were assessed concurrently in one cohort. We were therefore able to examine the networks of the diagnostic symptoms criteria in a large population-based sample, as well as in a subgroup consisting of patients fulfilling the diagnostic criteria for one or more FSS. Since we assessed the diagnostic symptom criteria for all three FSS in a general population cohort, it was possible to examine the relatedness of symptoms that compose the diagnostic criteria of the different FSS irrespective of help-seeking behavior or diagnostic biases. Lastly, instead of dichotomized additional symptoms, we used the continuous symptom variables taking into account the severity or frequency of symptoms.

There are also limitations in the current study. First, the FSS symptoms and diagnoses were based on the responses to a questionnaire, without an assessment by a physician. Because LifeLines is a large population cohort study that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to determine whether participants met the diagnostic criteria for FSS based on clinical examinations. Second, co-morbid conditions that could explain the FSS symptoms were not excluded when determining the FSS diagnoses, mainly because only the CFS diagnostic criteria and not the FMS and IBS criteria specifically mention the exclusion of medical health conditions. Nevertheless, FSS diagnoses rely heavily on subjective symptoms and to a lesser extent on the absence of objective clinical or laboratory findings. Furthermore, although we combined items with the

same definitions (i.e., cognitive problems and unrefreshed sleep), the estimated network structures contained several symptoms with partially overlapping definitions. Examples include the main criterion of CFS of fatigue for ≥3 months and the additional symptom fatigue in FMS, and muscle pain or joint pain in CFS and the main symptom of locomotor pain for ≥3 months or the widespread pain index in FMS. The correlations between these variables will naturally be stronger, and therefore these (partially) overlapping symptoms might have changed clustering in the network structure. We decided not to combine these partially overlapping symptoms as they are included in this way in the diagnostic criteria and they differ in important aspects (e.g., their time frame).

Our networks had high density, and many connections among diagnostic symptoms within and between the different FSS were found. The between-diagnosis density was comparable to the within-diagnosis density for CFS and FMS, indicating that overlap among CFS and FMS diagnostic symptoms is very high. Despite strong within-diagnosis connectedness of IBS symptoms, this symptom cluster seemed to be more isolated from the rest due to its lower between-diagnosis density. Still, this syndrome was also strongly related to symptoms from the other FSS. Furthermore, symptoms in the networks clustered based on bodily systems rather than their current classification into CFS, FMS and IBS symptoms. This suggests that the three different FSS reflect one syndrome consisting of varying bodily system subtypes [259,262,263].

Within and between diagnoses of FSS, individual diagnostic criteria had differential roles. The highest within-diagnosis strengths were found for the additional criteria of post-exertional malaise in CFS, fatigue in FMS, and abdominal pain associated with change in stool frequency in IBS, while the syndromes' main criteria had low within-diagnosis strength. Main criteria, however, were important in connecting the different FSS diagnoses as they had high between-diagnoses strength. This is interesting as it would be expected that main criteria have a particularly central role in strengthening the internal connectedness of the diagnostic criteria of a syndrome. Indeed, previous studies have identified main criteria of mental disorders as the most central within-diagnosis symptoms [235,237].

Recently, the Institute of Medicine (IOM) published a new proposal for diagnostic criteria for CFS based on extensive literature review [277]. These criteria are based on three main symptoms: disabling fatigue, post-exertional malaise and unrefreshing sleep; with at least one of two specific additional symptoms (cognitive impairment or orthostatic intolerance). In line with the literature review of the IOM, our networks revealed that fatigue symptoms clustered with cognitive problems and unrefreshed sleep, and that sore throat, lymph node tenderness, and headaches formed a separate symptom cluster. One remarkable finding is that the CFS symptom post-exertional malaise was included in the musculoskeletal cluster in the general population. In contrast to the 1990 diagnostic

criteria [278], the revised 2010 FMS criteria also include non-pain symptoms that overlap with the CFS diagnostic symptom criteria such as fatigue, cognitive symptoms, unrefreshed sleep, and general symptoms [270]. As mentioned by the IOM, the revised ACR diagnostic criteria for FMS may therefore greatly increase the overlap between CFS and FMS [277]. We indeed found that CFS and FMS diagnostic symptoms formed one cluster in FSS patients.

We also examined whether the level of clustering depended on general symptom severity by comparing clusters in the general population and FSS patients. The clustering coefficient was similar in the general population and the FSS group, contrasting with the idea that with higher symptom severity more overlap between symptoms occurs. Supporting this idea, however, is that the between-diagnosis density was higher in the FSS group than in the general population. In addition, although there were four clusters in the general population, only two clusters were found in the FSS group. This could have been an artifact as negative associations appeared in the network of FSS patients because patients were selected based on the fulfilment of the criteria of either of the three FSS syndromes. However, that there is more overlap in patients with FSS than in the general population is in line with an earlier network study showing that symptoms showed more overlap in patient with higher symptom severity [263].

In summary, we revealed that all FSS diagnostic symptoms were connected, either directly or via other symptoms. Furthermore, we found that symptoms clustered based on bodily systems rather than their current classification into the different FSS. Our results are therefore in line with recent suggestions supporting both the lumpers' and splitters' views in that there is commonality as well as heterogeneity within and between FSS [257]. Future studies will be necessary to examine and reconsider the diagnostic criteria for FSS.

SUPPLEMENTARY MATERIAL

Supplement 1: scoring algorithm to determine the functional somatic syndrome diagnosis

Chronic fatigue syndrome

The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention (CDC) criteria [269]. To meet the CDC diagnostic criteria participants had to indicate [a] that they had experienced chronic fatigue for 6 or more months (box 1), and [b] that the fatigue significantly interfered with daily activities and work (box 2). In addition, [c] the participant had to report concurrently four or more of the eight mentioned additional symptoms (box 3).

BOX 1

Question chronic fatigue duration:
"I have had my tiredness complaints for about:"

Code	Label
1	not applicable because I do not have tiredness complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ….. years and ... months
6	I have been feeling tired my entire life

To meet the CDC diagnostic criteria, participants had to indicate that they experienced chronic fatigue for 6 or more months (code 4-6). In the network analysis, this binary variable was used as the main criterion for CFS.

BOX 2

Question interference:
"To what extent did your tiredness hamper your normal activities (both work outside the home and household chores) in the past 6 months?"

Code	Label
1	not applicable, because I did not have any tiredness in the past 6 months
2	not at all
3	a little bit
4	quite a bit
5	a lot
6	very much

To meet the CDC diagnostic criteria, participants had to indicate that the fatigue significantly interfered with daily activities and work quite a bit, a lot or very much the past 6 months (code 4-6). As the interference question did not constitute a symptom, it was not included in the network analyses.

BOX 3
Question additional symptoms (items from the CDC CFS Symptom Inventory):
"How often did you have the complaints listed below in the past 6 months?

- Sore throat;
- Tender lymph nodes;
- Muscle pain;
- Joint pain;
- Headaches;
- Unrefreshing sleep;
- Unusual fatigue after exertion;
- Forgetfulness or memory problems;
- Difficulty with thinking or concentrating."

Code	Label
1	not at all
2	several times a month
3	several times a week
4	every day

To meet the CDC diagnostic criteria, participants had to indicate that they had concurrently four or more of the mentioned complaints several times a week or every day in the past 6 months (code 3 or 4), where forgetfulness and/or difficulty concentrating were scored as one symptom. These symptoms were in our network analyses included as polytomous items. As the items "unrefreshed sleep" and "difficulty with thinking or concentrating"/"forgetfulness or memory problems" strongly resembled symptom criteria of FMS, we combined these items with those of FMS by taking their mean in the network (see statistical analyses).

Fibromyalgia syndrome

The diagnosis for FMS was assessed using the 2010 American College of Rheumatology (ACR) criteria [270]. To meet the ACR criteria participants had to indicate that they experienced pain symptoms for at least 3 months (box 4). Participants were asked to indicate in which of 19 mentioned body areas they had had pain during the last week using the widespread pain index (WPI, box 5). The Symptom Severity (SS) scale was calculated based on the severity of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms participants reported (box 6). The severity of fatigue and cognitive symptoms were determined using items of the Checklist Individual Strength (CIS) [279]. An additional item that determined to which extent participants are waking unrefreshed was added. To determine the level of somatic symptoms, the 12-item somatization scale of the Symptom Checklist-90 (SCL-90 SOM) was used [280]. To meet the ACR diagnostic criteria, participants were required to have a WPI score ≥7 and an SS-scale score ≥5 or a WPI score of 3-6 and an SS-scale score of ≥9.

BOX 4

Question musculoskeletal pain complaints duration:
"I have had my musculoskeletal pain complaints for about:"

Code	Label
1	not applicable because I do not have musculoskeletal pain complaints
2	shorter than 3 months
3	3 months to 6 months
4	6 months to 1 year
5	longer than 1 year: ... years and ... months

To meet the ACR diagnostic criteria, participants had to indicate that they experienced musculoskeletal pain complaints for 3 or more months (code 3-6). In our network analyses, this binary item was included as the main criterion for FMS.

BOX 5

Questions Widespread Pain Index:
"Please indicate whether the parts of the body listed below were painful and/or tender in the past 7 days:

- *Abdomen;*
- *Chest;*
- *Left hip;*
- *Left lower arm;*
- *Left lower leg;*
- *Left shoulder;*
- *Left side of jaw;*
- *Left upper arm;*
- *Left upper leg;*
- *Lower back;*
- *Neck;*
- *Right hip;*
- *Right lower arm;*
- *Right lower leg;*
- *Right shoulder;*
- *Right side of jaw;*
- *Right upper arm;*
- *Right upper leg;*
- *Upper back."*

Code	**Label**
1	yes
2	no

The WPI score was determined by counting the number of body areas in which the participant had pain during the last week, and was included as a continuous measure in our network analyses.

BOX 6

The symptom severity scale score was based on separate questions about fatigue, cognitive symptoms, waking unrefreshed and the SCL-90 somatization scale to assess somatic symptoms.
Separate symptoms:
"The last two weeks in general:
- *I feel tired;*
- *I have difficulty thinking;*
- *It takes an effort to concentrate;*
- *I do not wake up rested."*

Code	Label
1	yes, true
2	2
3	3
4	4
5	5
6	6
7	no, not true

This scale was converted for each symptom into a 0-3 scale (0) "No problem" (score 7), (1) "Slight or mild problems" (score 4-6); (2) "Moderate to considerable problems" (score 2, 3); and (3) "Severe, pervasive, continuous problems" (score 1).

Questions somatic symptoms (SCL-90 SOM items):
"In the previous week, how much were you bothered by:
- *Headaches;*
- *Faintness or dizziness;*
- *Pains in heart or chest;*
- *Pains in lower back;*
- *Nausea or upset stomach;*
- *Soreness of your muscles;*
- *Trouble getting your breath;*
- *Hot or cold spells;*
- *Numbness or tingling in parts of your body;*
- *A lump in your throat;*
- *Feeling weak in parts of your body;*
- *Heavy feeling in your arms or legs."*

Code	Label
1	not at all
2	a little bit
3	moderately
4	quite a bit
5	extremely

The scores of the 12 items of the SCL-90-SOM were summed, and converted into (0) "No problem" (0 symptoms), (1) "Slight or mild problems" (1-3 symptoms); (2) "Moderate to considerable problems" (4-5 symptoms); and (3) "Severe, pervasive, continuous problems" (>=6 symptoms). The SS scale score was created by summing the 0–3 scores of fatigue, cognitive symptoms, waking unrefreshed and somatic symptoms as measured with the SCL-90-SOM into a 0–12 scale.
The separate symptoms and SCL-90-SOM converted score were included as polytomous items in our network analyses. As the items "I do not wake up rested" and "I have difficulty thinking"/"it takes an effort to concentrate" were very similar to symptom criteria of chronic fatigue syndrome, these items were combined in the network analyses by taking the mean of the CFS and FMS symptom (see statistical analyses).

Irritable bowel syndrome

The diagnosis for IBS was assessed using the ROME III criteria [271]. However, the criteria including occurrence of symptoms was adjusted in accordance to the ROME IV criteria [272], namely participants should indicate that they have recurrent abdominal pain or discomfort at least 1 day per week (instead of 3 days per month), with a symptom onset at least 6 months in the past to meet the research diagnosis. And for women, this abdominal pain or discomfort should not only occur during menstrual bleeding (box 7). Participants were asked if [1] this recurrent abdominal pain or discomfort was associated with improvement after defecation, [2] the onset was associated with change in stool frequency or [3] the onset was associated with change in (appearance) of stool (box 8). To meet the ROME III diagnostic criteria participants should have indicated that the recurrent abdominal pain or discomfort was sometimes to always accompanied by at least 2 of the 3 additional symptoms.

BOX 7

Question 1. Occurrence of symptoms:
"How often did you have abdominal pain or an unpleasant feeling in your abdomen in the past 3 months?"

Code	Label
1	never
2	less than 1 day a month
3	1 day a month
4	two to three days a month
5	1 day a week
6	more than 1 day a week
7	every day

Question 2. Symptom onset:
"Have you had this unpleasant feeling in your abdomen or this abdominal pain for 6 months or longer?"

Code	Label
1	yes: ….. Years and ... Months
2	no

Question 3. Menstrual bleeding:
"For women: did you have this unpleasant feeling in your belly only during your menstruation and not at other times?"

Code	Label
1	yes
2	no
3	not applicable, because I do not menstruate (any more)

To meet the ROME IV diagnostic criteria participants indicated that they have recurrent abdominal pain or discomfort at least 1 day per week (code 5-7, question 1), with a symptom onset at least 6 months prior to meet the research diagnosis (code 1, question 2), and for women, this abdominal pain or discomfort should not only occur during menstrual bleeding (code 2 or 3, question 3). This binary item was included in our network analyses as the main criterion for IBS.

BOX 8

Questions additional symptoms:

1. *"How often did this unpleasant feeling in your abdomen or abdominal pain improve or disappear after bowel movement?;*
2. *Did you have more frequent bowel movements after this unpleasant feeling in your abdomen or abdominal pain started?;*
3. *Did you have less frequent bowel movements after this unpleasant feeling in your abdomen or abdominal pain started?;*
4. *Were the stools softer or thinner after this unpleasant feeling in your abdomen started?;*
5. *How often did you have harder stools after this unpleasant feeling in your abdomen or abdominal pain started?"*

Code	**Label**
1	rarely or never
2	sometimes
3	often
4	most of the time
5	always

Above questions were divided in three main additional symptoms: [1] this recurrent abdominal pain or discomfort was associated with improvement after defecation (question 1), [2] the onset is associated with change in stool frequency (question 2,3) or [3] the onset is associated with change in (appearance) of stool (question 4,5). An additional symptom was scored positive when participants indicated that they sometimes to always experienced any of the symptoms (code 2-5). In our network analyses, these three additional symptoms were all included.

Supplementary Table 1. Connection weights of the estimated network structures of FSS diagnostic symptoms for (A) the general population and (B) patients with FSS.

A. General population																
	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.08	-															
Mus	-0.01	0.26	-														
Joi	-0.01	0.32	0.15	-													
Hea	0.01	0	0.03	-0.03	-												
Lym	0.03	0.01	0.03	0.01	0.02	-											
Thr	-0.01	-0.03	0.08	-0.02	0.15	0.43	-										
mFMS	0.17	0.05	0	0.35	0.01	-0.01	-0.01	-									
WPI	0	0.04	0.16	0.12	0.05	0.05	-0.01	0.26	-								
SOM	0.04	0.06	0.07	0.03	0.13	0.03	0.02	0.05	0.17	-							
Fat	0.33	0.04	0	-0.02	0.10	0.04	0.02	-0.04	0.02	0.07	-						
mIBS	0.07	0	0.08	-0.05	-0.02	0.14	0.03	-0.06	0.01	0.03	0	-					
Aim	0.01	0	0.01	0	0.07	0	0.03	0	0.01	0	0.03	0	-				
Afr	0	0	0	0	0	0	0	0	0.01	0	0	0.03	0.26	-			
Afo	0	0	0	0	0.01	0	0	0	0.02	0.02	0	0.13	0.32	0.73	-		
Cog	0.08	0.07	0	0	0.02	0.04	-0.01	-0.03	0	0.05	0.19	-0.02	0	0.01	0	-	
Unr	0.23	0.01	0.01	0	0.07	0	0.02	0	0	0.03	0.34	0.03	0	0	0.01	0.14	-

Supplementary Table 1. Continued.

B. FSS patients																	
	mCFS	PEM	Mus	Joi	Hea	Lym	Thr	mFMS	WPI	SOM	Fat	mIBS	Aim	Afr	Afo	Cog	Unr
mCFS	-																
PEM	0.14	-															
Mus	0.02	0.25	-														
Joi	0.02	0.32	0.26	-													
Hea	0	0.03	0	-0.01	-												
Lym	-0.01	0	0.05	0	0.03	-											
Thr	0	0	0	-0.03	0.14	0.43	-										
mFMS	0.10	0	0	0.23	0	-0.01	0	-									
WPI	-0.03	0.02	0.17	0.10	0	0.08	0.02	0.42	-								
SOM	0.02	0.10	0.07	0.02	0.15	0.07	0.03	0.09	0.15	-							
Fat	0.22	0.02	-0.01	-0.04	0.10	0.05	0.02	0.01	0	0.14	-						
mIBS	-0.02	-0.01	-0.03	-0.02	-0.04	-0.03	-0.01	-0.04	-0.19	-0.02	-0.09	-					
Aim	-0.01	0	0	-0.01	-0.01	-0.02	-0.02	0	0	-0.03	-0.03	0	-				
Afr	0	0	0	0	0.02	0.01	0.03	-0.02	0.05	0.02	0	0.23	0.26	-			
Afo	0	0	0	-0.01	0.03	0.05	0.02	-0.04	0.08	0.05	0.04	0.42	0.30	0.46	-		
Cog	0.07	0.07	0	0	0.08	0.04	0	0	-0.04	0.07	0.20	-0.06	0	0	0.03	-	
Unr	0.17	0.07	0.01	0.02	0.03	0	0.01	0	-0.01	0.02	0.37	-0.01	-0.03	0	0	0.10	-

mCFS = main symptom chronic fatigue syndrome; PEM=post-exertion malaise; Mus = muscle pain; Joi = joint pain; Hea = headaches; Lym = lymph node tenderness; Thr = sore throat; ACR = main symptom fibromyalgia syndrome; WPI = widespread pain index; SOM = general symptoms; Fat = fatigue; ROME = main symptom irritable bowel syndrome; Aim = improvement with defecation; Afr = associated with stool frequency; Afo = associated with stool form; Cog = cognitive problems; Unr = unrefreshed sleep.

Supplementary Table 2. Associations of symptoms within FSS diagnoses in the general population and patients with FSS.

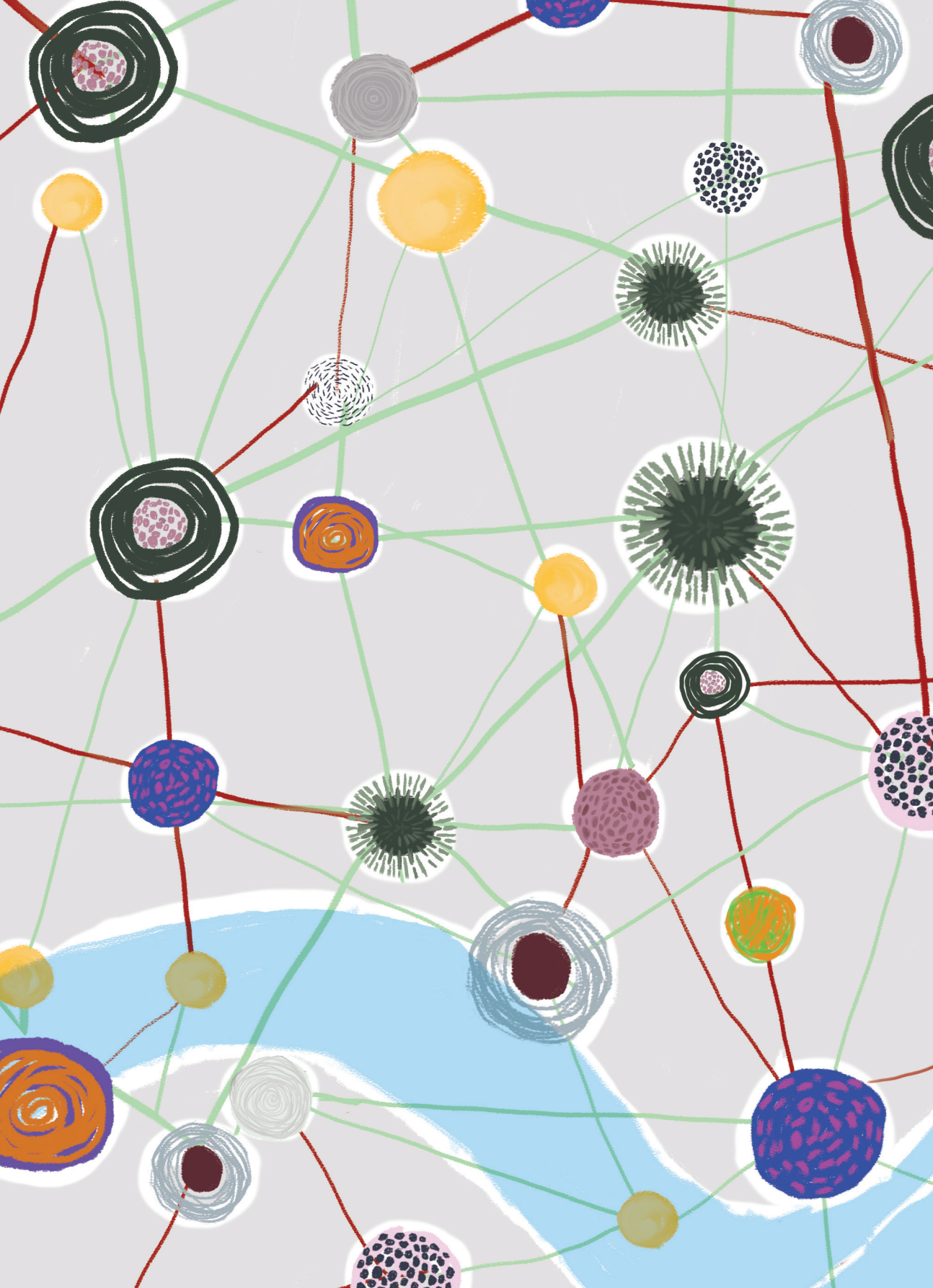
CFS				FMS				IBS			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
PEM	0.73	=	0.87	Fat	0.57	=	0.71	Afo	1.18	=	1.18
Thr	0.62	↑Mus	0.58	Unr	0.51	↑mFMS	0.52	Afr	0.95	=	0.95
Lym	0.58	↑Joi	0.57	WPI	0.45	=	0.52	Aim	0.65	↑mIBS	0.65
Mus	0.54	↓Thr	0.55	SOM	0.37	↓Unr	0.49	mIBS	0.56	↓Aim	0.56
Unr	0.49	↓Lym	0.54	Cog	0.36	↓SOM	0.46				
Joi	0.43	↓Unr	0.41	mFMS	0.24	↓Cog	0.34				
mCFS	0.4	=	0.4								
Cog	0.34	=	0.35								
Hea	0.27	=	0.32								

Symptoms are ordered based on the strength of their connections.
CFS = chronic fatigue syndrome; PEM = post-exertional malaise; Mus = musculoskeletal pain; Joi = joint pain; Thr = sore throat; Lym = tender lymph nodes; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Cog = cognitive symptoms; Hea = headaches; FMS = fibromyalgia syndrome; Fat = fatigue; mFMS = main criteria fibromyalgia syndrome; WPI = widespread pain index; SOM = symptoms in general; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; mIBS = main criteria irritable bowel syndrome; Aim: improvement of abdominal pain after defecation.

Supplementary Table 3. Associations of symptoms between FSS diagnoses in the general population and patients with FSS.

CFS				FMS				IBS			
Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients	Symptom	General population	Symptom	FSS patients
mCFS	0.92	=	0.52	Fat	1.07	=	0.84	mIBS	0.23	↑Afo	0.26
Unr	0.55	=	0.45	SOM	0.52	=	0.59	Aim	0.12	↑Afr	0.12
Hea	0.43	=	0.36	mFMS	0.47	↑Unr	0.38	Afo	0.02	↓Aim	-0.15
Joi	0.42	↑Cog	0.31	WPI	0.46	↑Cog	0.33	Afr	0	↓mIBS	-0.57
Cog	0.35	↓Joi	0.29	Unr	0.38	↓WPI	0.25				
Mus	0.33	↑PEM	0.26	Cog	0.33	↓mFMS	0.21				
Lym	0.31	=	0.25								
PEM	0.28	↓Mus	0.22								
Thr	0.1	=	0.1								

Symptoms are ordered based on the strength of their connections.
CFS = chronic fatigue syndrome; mCFS = main criteria chronic fatigue syndrome; Unr = unresreshed sleep; Hea = headaches; Cog = cognitive symptoms; Joi = joint pain; PEM = post-exertional malaise; Lym = tender lymph nodes; Mus = musculoskeletal pain; Thr = sore throat; FMS = fibromyalgia syndrome; Fat = fatigue; SOM = symptoms in general; WPI = widespread pain index; mFMS = main criteria fibromyalgia syndrome; IBS = irritable bowel syndrome; Afo = abdominal pain associated with change in form; Afr = abdominal pain associated with change of frequency; Aim: improvement of abdominal pain after defecation; mIBS = main criteria irritable bowel syndrome.



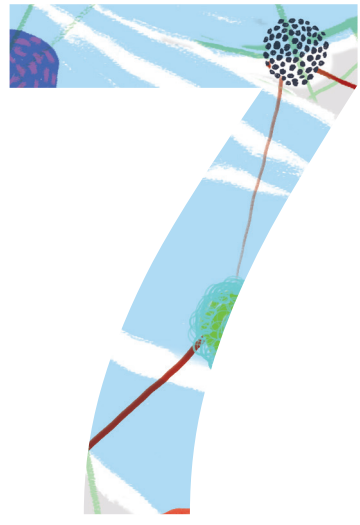
CLINICAL ASPECTS

1. Symptom dimensions

Diversity in reasons for encounter as a predictor of functional somatic symptoms: Results from an electronic primary care records study

Bekhuis E, Rosmalen JGM, van Boven K, Olde Hartman TC, Burton CD.

In preparation.



ABSTRACT

Introduction: Somatic symptoms that cannot be wholly explained by organic pathology, so-called functional somatic symptoms (FSS), are common in primary care. Although offering matched care at an early stage is important to improve the outcome of patients with FSS, the symptoms are inconsistently recognized by GPs. We hypothesized that greater diversity in reasons for encounter is a useful marker for patients at risk of FSS.
Methods: Four years of consultation data were derived from the electronic records of the Family Medicine Network (FaMe-Net). Since diversity metrics are most meaningful if patients consult frequently, our main analyses were conducted in the top 25% frequent attenders with ≥24 consultations (N=1,689, mean year of birth=1956, 71.3% female) and repeated in all attenders (N=6,440, mean year of birth=1962, 59.1% female). We examined if diversity in patients' reasons for encounter (based on their unique types, Shannon entropy, and Shannon adjusted for the number of types) predicted whether the subsequent new health problem was coded as a symptom or functional syndrome (as a proxy for FSS) by the GP. A sensitivity analysis was conducted to examine the influence of chronic somatic diseases.
Results: The number of unique types of reasons for encounter (OR=1.08, 95%CI=0.99-1.17), their Shannon entropy (OR=1.15, 95%CI=0.91-1.45) and Shannon adjusted for their number (OR=1.01, 95%CI=0.83-1.22) did not predict FSS. Although later year of birth, female sex and consultations for a psychosocial reason did not predict FSS in frequent attenders, these predictors were associated with a higher risk of FSS in all attenders (OR=1.01, 95%CI=1.01-1.01; OR=1.14, 95%CI=1.03-1.26; OR=1.17, 95%CI=1.06-1.30, respectively). Results were similar when patients with chronic somatic diseases were excluded.
Conclusion: Diversity in reasons for consulting does not predict if patients are at risk for FSS. To improve the detection of FSS, future research should search for other markers of FSS, for instance by looking at the patient's style of symptom presentation.

INTRODUCTION

Patients frequently consult in primary care with somatic symptoms [201]. Despite the strong focus in medicine on symptoms as signs of physical diseases, many symptoms develop because of processes which are not conclusively explained by detectable diseases [201,281,282]. A large proportion of these functional somatic symptoms (FSS) are self-limiting and cause little distress, but some patients experience multiple persistent or recurrent symptoms from different body systems [29,283]. FSS are captured in classifications for functional somatic syndromes which may be limited to one body system (such as irritable bowel syndrome) or may involve multiple systems (such as bodily distress syndrome) [284]. Functional symptom syndromes are associated with impaired quality of life and repeated consultations [31-33].

The management of FSS has a central position in primary care, but many general practitioners experience challenges to recognize the symptoms [43,285,286]. As a result, some patients with FSS may not be offerred appropriate explanation and effective interventions [287-289]. A descriptive study of the management strategies in primary care indeed indicated that GPs frequently prescribe medication and advise additional tests or referrals for FSS, while effective psychological interventions are seldomly offered [288]. As more diagnostics and ineffective treatments are associated with iatrogenic complications and increased costs [43], it is highly important to improve the recognition of FSS in primary care. This could help GPs in the diagnostic process and offer stepped care management effective for FSS at an early stage, such as self-help strategies [290,291].

Prior studies have shown that a potential way to improve the identification of the symptoms is by extracting information from electronic registration systems of consultations [292,293]. One study developed a model based on patient characteristics, specific diagnoses, diagnostic tests and interventions [292]. Of all specific diagnoses, psychosocial problems and diagnoses of functional somatic syndromes in particular increased the risk of FSS [292]. Another algorithm focused on the number of consultations, the absence of chronic conditions, and the presence of diagnoses suggestive of FSS [293,294]. A limitation of these algorithms was that they focused on the detection of all FSS irrespective of whether these symptoms were new [292,293]. Therefore, it is possible that they captured consultations for the same FSS as they predicted, rather than the patients' vulnerability for new FSS. Furthermore, the algorithms had high specificity, but their sensitivity was low [292,293].

A recent discussion paper proposed that the presentation of *multiple symptoms* in *multiple body systems* at *multiple times* is a useful rule of thumb for encouraging a clinician to think of FSS [43]. This is based on clinical observations and epidemiological studies indicating that patients with more symptoms from different body systems have

an increased risk of FSS [29,43,284]. Diversity can be quantified with complexity measures, which are derived from the complex systems theory [295-298]. Applied to consultations, these measures can provide insight into the number of unique types of reasons for encounter as well as the pattern in which they occur. In a recent study, it was demonstrated that these measures provide unique insight into diversity in reasons for encounter of high users of primary out of hours care [299]. While the number of unique types of reasons helped to differentiate between patients who consulted for a few or many different reasons, their Shannon entropy revealed if patients consulted primarily for one of these reasons or for a variety of them in equal quantities [299]. Examining such diversity measures in relation to FSS constitutes a promising way to examine if FSS are associated with higher diversity in presenting complaints registered in electronic records. In this study, we examine if diversity in reasons for encounter in electronic records predicts FSS among newly presented health complaints in primary care. We focus on symptoms without a formal diagnosis as a proxy for FSS, since they were either unexplained by diseases, self-limiting, or the GP was uncertain about the diagnosis. We hypothesize that higher diversity in reasons for encounter increases the risk that a patient has symptoms without a formal diagnosis.

METHODS

Data source

Data were derived from the Family Medicine Network (FaMe-Net) [300], a Dutch practice-based research network that is a fusion of the Transition Project [301] and the Continuous Morbidity Registration [302]. The primary care practices in the network have uniformly registered all contacts with patients according to the International Classification of Primary Care (ICPC) coding rules [303,304] since 1971. The practices are located in different geographic regions and their patient populations are representative of the general population of the Netherlands in terms of age and sex [305]. Participating GPs regularly had meetings to discuss their registration system and received monthly feedback on an assignment to enhance adherence to the coding rules.

In entering a consultation into the system, GPs register and code 1) the patient's reason for encounter (RFE), 2) the medical assessment for the health problem and 3) the processes of care structured in an episode of care model. The coded RFE reflects the patient's words for the consultation reason, without any judgement from the GP as to the correctness or accuracy of this reason for consulting. The RFE can be presented by the patient in the form of a disease, symptom, syndrome, and process of care (e.g., administrative or diagnostic request). The medical assessment comprises the code

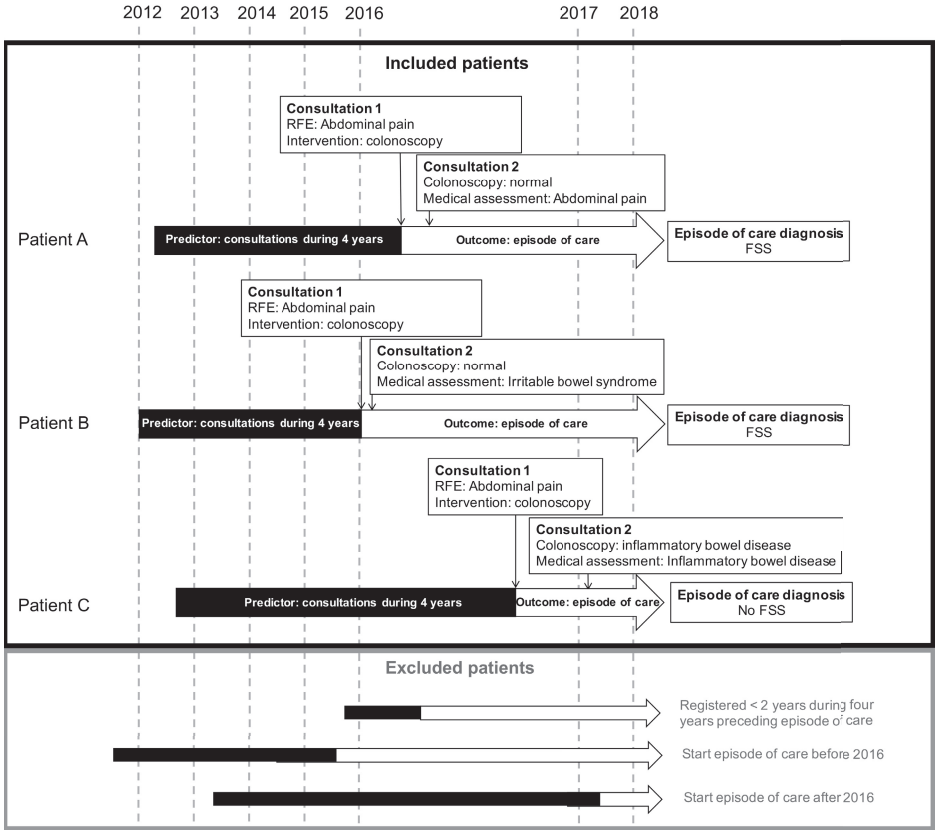
that best reflects the health problem according to the GP. This can be a disease, but also a symptom or a syndrome when the symptoms or complains cannot (yet) be linked to a disease. An episode of care is defined as a health problem in a patient starting at the first encounter and completed at the last encounter for that health problem [306]. The GP adjusts final diagnoses of the episode of care retrospectively. Changes and additives are recorded per date. As varying health problems can be presented during one consultation, multiple RFEs, medical assessments and episodes of care can be registered per consultation. Although each consultation was linked through a unique patient number, the data did not include patient-identifying information except for year of birth and sex.

Data selection

For the current study, we used data from each direct patient contact with a GP (face-to-face consultations at the practice, phone consults, electronic consults and home visits). We included patients of ≥18 years who consulted in 2016 for a new episode of care that had the potential of receiving a diagnosis of FSS in the end. We selected episodes of care which first consultation included at least one RFE matching any of the symptoms of bodily distress syndrome [284] (**Supplementary Table 1**). These symptoms were used as their symptoms are commonly presented in primary care and frequently cannot be ascribed to an organic cause [284].

For each patient, we extracted consultation data from the four years previous to the start of this new episode of care in 2016 to calculate predictor variables. As some patients were registered for a shorter period than four years with their GP practice, we explored the minimum inclusion time after which diversity metrics were reasonably stable (see 'Analyses'). Patients who were included in the system shorter than this minimum period were excluded from our study. The selection of patients and predictor and outcome data for this study is described in **Figure 1**.

Figure 1. Examples to illustrate patient selection and the construction of predictor and outcome variables.



Outcome variable

For each first new episode of care in 2016, we extracted the diagnosis code of its episode of care. This reflects the GP's final conclusion about the diagnosis for the health problem after one or more consultations, diagnostic tests and referrals have taken place. This extraction took place in June 2018, allowing the episode of care 18 months (if it started on 31-12-2016) to 30 months (if it started on 01-01-2016) to reach a final diagnosis. If no disease was identified during this period, the coding rules indicated that a symptom code (e.g., abdominal pain) or a functional syndrome code (e.g., irritable bowel syndrome) should be assigned to the episode of care. In contrast, if a disease was detected, a disease code (e.g., inflammatory bowel disease) should be coded for the episode of care. Episode of care diagnoses were labelled as possible FSS in our study if they included codes matching any of the symptoms of bodily distress syndrome or a functional syndrome (**Supplementary Table 1**).

Predictor variables

Predictor variables included patient characteristics and consultation characteristics.

Patient characteristics

Patient characteristics were year of birth and sex.

Consultation characteristics

Consultation characteristics were calculated using all consultations from the four years preceding the first new episode of care in 2016 for each patient. They included the number of consultations and whether the patient had consulted for at least one psychosocial RFE (see **Supplementary Table 2** for the definition of psychosocial RFE). In addition, diversity in RFE was calculated. If multiple RFE per consultation were registered, we took all of them into account in the calculation of diversity metrics. We categorized ICPC codes into systems based on their type (**Supplementary Table 2**). As a first diversity metric, we summed the number of unique categories of RFE to summarize diversity in their types. The second diversity metric comprised the pattern in which the types of RFE occurred quantified with Shannon entropy [307]. A low Shannon entropy indicates that one category of RFE dominates the consultation pattern of a patient, whereas a high entropy indicates that varying categories occur with similar frequency. It is calculated with the following formula (in which p is the proportion of a category of RFE i in the sequence of all RFE of a patient):

$$\text{Shannon} = -\sum p_i \log_2(p_i)$$

As the value of Shannon entropy depends on the number of unique categories of RFE, we additionally computed a metric based on Shannon entropy adjusted for this number. For each number of unique RFE categories, we indicated if Shannon entropy was lower versus equal to/higher than its median in this group.

Analyses

Analyses were conducted in R version 3.5.1. First, we explored the stability of diversity metrics based on how long patients were included in the electronic record of their GP practice. This was done by calculating these metrics after varying periods of inclusion in the system in a set of 20 random patients, and inspecting when the measures reached stability. Patients whose registration time was too short to reach stable values were excluded, and they were compared with included patients with respect to year of birth (independent sample t-test) and sex (chi square test). Diversity metrics are most meaningful and stable if patients consult frequently [299]. Therefore, we performed our main analysis in the top

25% frequent attenders in the four years preceding the first new episode of care in 2016. We explored if associations were similar in the complete sample as a sensitivity analysis. We checked if the registration time differed across patients with and without FSS for their first new episode of care in 2016 with an independent sample t-test.

Correlations among predictors were calculated with Spearman's Rho. Then, we examined if predictor variables were associated with an FSS diagnosis for the episode of care with univariable logistic regression models. Subsequently, multivariable logistic regression models were fitted to further examine the predictive value of diversity metrics. We first fitted models including individual diversity metrics, adjusted for year of birth, sex, the number of consultations and psychosocial RFE. Finally, we included all diversity metrics in the model to additionally adjust their effects for each other. To explore the potential influence of multicollinearity, we calculated variance inflation factors.

A sensitivity analysis was done to examine the effect of existing chronic somatic diseases that were potentially not registered in the episode of care analyzed. As our outcome variable was based on the diagnostic code provided by the GP, it cannot be ruled out that some FSS were actually presentations of a previously diagnosed somatic disease, but were not coded as such by the GP. To examine if our conclusions were influenced by such diseases, we repeated our analyses in a sample of patients without specific chronic somatic diseases registered in the four years analysed (**Supplementary Table 3**).

RESULTS

Sample characteristics

The database included 7,484 adult patients with a new episode of care in 2016 for an RFE suggestive of FSS. Diversity metrics were stable after four years and reasonably stable after two years of consultation data. Therefore, we excluded patients who were registered with their GP practice for less than two years in the four years preceding the episode of care (14.0%). Excluded patients were younger (mean year of birth 1973 versus 1962, $p<.001$) but did not differ with respect to sex (both groups 59.1%, $p>0.99$) from included patients. Included patients consulted for a median of 14 times (range 0-172) in the preceding four years. The top 25% frequent attenders (N=1,689) consulted for ≥24 times and constituted the main sample of this study. In this sample, mean year of birth was 1956 (range 1914-1993) and 71.3% was female (**Table 1**). Patients were registered within their GP practice for an average of 3 years and 11 months (range: 2-4 years) during the four years preceding this episode of care, which did not differ between patients with and without FSS (both groups 3 years and 11 months, $p=0.23$).

Table 1. Sample characteristics of patients included in main analyses (top 25% frequent attenders; N=1,689).

	N (%) / median (minimum-maximum, interquartile range (IQR))
Registered at primary care practice	
1	352 (20.8%)
2	148 (8.8%)
3	438 (25.9%)
4	370 (21.9%)
5	142 (8.4%)
6	50 (3.0%)
7	189 (11.2 %)
Predictors	
Patient characteristics	
Year of birth	1955 (1914-1993, IQR=30)
Female	1,205 (71.3%)
Consultation characteristics	
Number of consultations	34 (24-172, IQR=17)
At least one psychosocial RFE	1,136 (67.3%)
Number of unique RFE categories	7 (2-8, IQR=2)
Shannon of RFE categories	2.3 (0.2-2.9, IQR=0.5)
High Shannon adjusted for number of RFE categories	847 (50.1%)

RFE=Reason for encounter

Proportion of FSS

The first new episode of care in 2016 received a diagnosis of FSS in 56.4% of patients (**Table 2**). This percentage was highest for episodes with an initial psychosocial RFE (i.e., the only RFE in this category was 'Memory disturbance' [Supplementary Table 1]; 72.7% FSS), and lowest for episodes with an initial cardiopulmonary RFE (50.3% FSS).

Table 2. Outcome of FSS diagnosis of first new episodes of care in 2016.

First new episode of care in 2016	FSS diagnosis
	N (%)
All episodes of care (N=1,689)	952 (56.4%)
Episodes of care with initial RFE from specific category	
Episodes of care with a general RFE (N=359)	234 (65.2%)
Episodes of care with a digestive RFE (N=393)	209 (53.2%)
Episodes of care with a cardiorespiratory RFE (N=163)	82 (50.3%)
Episodes of care with a musculoskeletal RFE (N=811)	440 (54.3%)
Episodes of care with a psychosocial RFE (N=11)	8 (72.7%)

RFE=Reason for encounter

Predictors of FSS

We examined if patient characteristics and consultation characteristics were associated with a diagnosis of FSS for the new episode of care (**Table 3**; see **Supplementary Table 4** for correlations among these variables). None of the patient and consultation characteristics were significantly associated with a diagnosis of FSS. We further examined the predictive effects of diversity metrics by adjusting for year of birth, sex, the number of consultations and psychosocial RFE (**Table 4**). Diversity metrics were not associated with FSS after this adjustment. Finally, we included all predictors in one model to adjust for the effects of other diversity metrics (**Table 4**). As the number of unique categories of RFE showed a high level of collinearity with its Shannon entropy (variance inflation factors 4.7 and 5.3, respectively), we excluded Shannon entropy. In the resulting model, neither the number of unique categories of RFE nor high Shannon entropy adjusted for this measure significantly predicted FSS.

Table 3. The predictive effects of patient and consultation characteristics for an FSS diagnosis for the first new episode of care in 2016.

	FSS diagnosis	
	Odds ratio	95% confidence interval
Patient characteristics		
Year of birth	1.004	0.999-1.009
Female sex	1.010	0.816-1.248
Consultation characteristics		
Number of consultations	0.998	0.992-1.003
At least one psychosocial RFE	1.124	0.916-1.379
Number of unique RFE categories	1.075	0.988-1.170
Shannon of RFE categories	1.148	0.906-1.454
High Shannon adjusted for number of RFE categories	1.006	0.830-1.219

Based on univariable logistic regression models. RFE=Reason for encounter

Table 4. Adjusted predictive effects of consultation characteristics for an FSS diagnosis.

	FSS diagnosis	
	Odds ratio	95% confidence interval
Adjusted for year of birth, sex, the number of consultations and psychosocial RFE		
Number of unique RFE categories	1.085	0.984-1.197
Shannon of RFE categories	1.127	0.805-1.442
High Shannon adjusted for number of RFE categories	1.000	0.824-1.215
*Additionally adjusted for other diversity measures**		
Number of unique RFE categories	1.085	0.984-1.197
High Shannon adjusted for number of RFE categories	0.992	0.817-1.205

Based on multivariable logistic regression models. *Due to multicollinearity between the number of unique RFE categories and Shannon of RFE categories, the latter variable was excluded from the model. RFE=Reason for encounter

Sensitivity analyses

Finally, we performed two sensitivity analyses by repeating our analyses in different samples (see **Supplementary Table 5** for their characteristics). As a first sensitivity analysis, we repeated the analyses in the full sample (**Supplementary Table 6**). In general, the results were similar to those of the main analyses, although a later year of birth (OR=1.008, 95%CI=1.005-1.011), female sex (OR=1.142, 95%CI=1.034-1.262) and a psychosocial RFE (OR=1.174, 95%CI=1.063-1.298) became significant predictors of FSS. In a second sensitivity analysis, we excluded patients with specific chronic somatic diseases (**Supplementary Table 6**). These results were highly comparable to those of the main analyses.

DISCUSSION

Summary of main findings

This study showed that diversity in reasons for encounter does not predict if a new health problem concerns FSS. Although younger age, female sex and consultations for a psychosocial reason did not predict FSS in frequent attenders, these predictors were associated with a higher risk of FSS in all attenders. These findings indicate that the presence of *multiple symptoms in multiple systems at multiple times* in electronic primary care records is not a useful marker of new FSS.

Strengths and limitations

This study was the first to examine diversity in reasons for encounter as a predictor for FSS. A strength is that we used a recent and large dataset of consultations of a patient cohort representative of the general population of the Netherlands [305]. Predictor variables were based on four years of consultation data, which is longer than the algorithms in previous studies [292,293]. Another considerable strength is that GPs registered consultations according to well-defined diagnostic criteria and coding guidelines [303]. Moreover, our definition of FSS was based on the diagnosis assigned at the end of the episode of care by the GP, who had insight into the results of diagnostic tests and referrals and the character of the symptom [302]. A limitation of this method is that the symptom codes on which we focused did not all constitute FSS, but could also include self-limiting symptoms or symptoms of which the GP was not certain about the underlying diagnosis. We conducted a sensitivity analysis to explore the potential effects of underdiagnosis of somatic diseases by excluding patients with such diseases that could have explained the health problems. As the results were similar to the main analyses, the influence of unregistered diseases is probably limited. We

focused on episodes of care for which the patient consulted with a reason that matched the symptoms of bodily distress syndrome. Although this assured us that we captured symptoms that are frequently faced by GPs and often raise the question whether they constitute FSS, it is a limitation that we did not take into account all types of FSS. Finally, an issue that should be considered is that GPs in FaMe-Net could have checked prior consultation characteristics before assigning diagnostic codes and, therefore, it is possible that our predictors influenced the process of how GPs assigned diagnostic codes. However, as we studied complex metrics over a long period, it is unlikely that the assignment of diagnostic codes was strongly influenced by our predictor variables.

Comparison with other studies

Our study showed that patient and consultation characteristics do not predict FSS in frequent attenders. Still, younger age, female sex and psychosocial reasons for encounter significantly increased the risk of FSS in all attenders. The weak predictive effect of these variables has also been reported by other algorithms for the identification of FSS [292,308]. Such algorithms, however, found a stronger predictive effect of psychosocial problems [292,308]. As psychosocial reasons for encounter in our study included a wide variety of symptoms, behaviors and social situations in contrast to the psychiatric diagnoses in the previous studies, this could account for the weaker associations that we found. In contrast to previous algorithms, we did not identify a higher number of consultations as a predictor of FSS [292,293]. These studies differed in important aspects from our study. First, they focused on the detection of FSS irrespective of whether the symptom was new [292,293]. Therefore, it is possible that they captured previous consultations for the same FSS they predicted rather than that they identified markers of the patient's vulnerability for developing new FSS. A second difference is that one study predicted multiple and severe somatic symptoms without assessing whether they were explained by diseases [293]. As patients with more and severe somatic symptoms due to multimorbidity are known to consult their GP more often [309], this could have explained the found associations with the number of consultations in that study.

Our study showed that diversity in reasons for encounter was not significantly associated with new FSS. This is surprising as clinical observations and epidemiological studies have repeatedly linked a history of multiple and different symptoms to the presence of FSS [29,43,284]. One potential explanation for that we did not detect such associations is that clinicians notice features of diversity in the presentation of symptoms associated with FSS that are not registered in electronic records. For instance, clinicians may be triggered to think of FSS if patients emphasize diversity in symptoms during the consultation, or if they consult for insignificant symptoms from multiple systems. Another explanation for the lack of associations with diversity in our study is that previous

studies referred to symptoms patients experience, while patients are known to consult for a minority of them in primary care [310,311]. If patients with FSS indeed experience more and more diverse symptoms than patients with other types of symptoms, it is remarkable that their consultation patterns were similar. It might indicate that the help seeking behaviour of patients with FSS is more strongly determined by other factors (e.g., cultural norms) than the number of subjective complaints [312,313].

Implications for research and clinical practice

Our findings suggest that considering diversity in reasons for encounter registered in electronic records is not useful to predict patients' risk of new FSS. As FSS constitute a heterogeneous group of symptoms, however, more research is needed to examine if specific types of FSS can be predicted with consultation characteristics. Due to low numbers of functional somatic syndrome diagnoses in our study (N=22 in the full sample), for instance, we were not able to examine if consultation characteristics can be useful in the detection of patients with multiple persistent FSS that are part of such syndromes. This low number of syndrome diagnoses could have emerged because the ICPC does not capture all functional somatic syndromes. As codes of functional somatic syndromes were also rare in a previous study [293], however, it could also reflect the reluctance of GPs to use such labels. Furthermore, our study focused primarily on frequent attenders, who were naturally older than the average primary care population. Therefore, higher diversity in their reasons for encounter could have reflected multimorbidity, which is not likely to predict future FSS. Although our sensitivity analysis indicated that the influence of chronic somatic diseases on the predictive effect of diversity metrics is probably limited, further research is needed to test if higher diversity in reasons for encounter can signal FSS in young patients without multimorbidity.

Several consultations characteristics have been shown to slightly increase the likelihood that a patient has FSS [292,293]. Still, attempts to develop a screening algorithm from electronic records with adequate sensitivity and specificity have failed [292,293]. This suggests that consultation characteristics registered in electronic records may be of limited value to detect FSS. To provide GPs with clinically relevant tools to identify FSS, future research should therefore also focus on other sources of information. One interesting source is the way in which patients present symptoms during the consultation. Since the risk of FSS may be higher if patients experience more symptoms [29,43,284], a higher number of secondary symptoms (i.e., symptoms that are not the main reason for encounter, but are presented later during the consultation and were therefore not systematically registered in FaMe-Net) could for instance be a useful marker of FSS. In addition, important features of the style of verbal or non-verbal symptom presentation of the patient and the interaction with the GP may point to FSS. For instance, a linguistic

analysis of consultations for seizures has shown that the likelihood of a functional diagnosis was higher if the patient used a less detailed and less focused symptom presentation during the consultation [314,315].

CONCLUSION

Diversity in reasons for encounter does not predict new FSS. To identify clinically relevant markers of FSS, future research should search for other characteristics associated with these symptoms, like the style of symptom presentation during the consultation. Such markers could help GPs to identify patients with FSS and offer adequate stepped care management at an earlier stage.

SUPPLEMENTARY MATERIAL

Supplementary table 1. Mapping of ICPC codes to symptoms of bodily distress syndrome and functional somatic syndromes.

	ICPC code
Bodily distress syndrome symptoms	
Palpitations/heart pounding	K04 Palpitations/awareness of heart
	K05 Irregular heartbeat other
Precordial discomfort	K01 Heart pain
	K02 Pressure/tightness of heart
Breathlessness without exertion	R02 Shortness of breath/dyspnoea
Hyperventilation	R98 Hyperventilation syndrome
Hot or cold sweats	A09 Sweating problem
	A02 Chills
Dry mouth	-
Abdominal pains	D01 Abdominal pain/cramps general
	D02 Abdominal pain epigastric
	D04 Rectal/anal pain
	D06 Abdominal pain localized other
Frequent loose bowel movements	D18 Change faeces/bowel movements
Feeling bloated/full of gas/distended	D25 Abdominal distension
	D08 Flatulence/gas/belching
Regurgitations	D08 Flatulence/gas/belching
Diarrhoea	D11 Diarrhoea
Nausea	D09 Nausea
Burning sensation in chest or epigastrium	D03 Heartburn
Pains in arms or legs	L09 Arm symptom/complaint
	L12 Hand/finger symptom/complaint
	L14 Leg/thigh symptom/complaint
	L17 Foot/toe symptom/complaint
Muscular aches or pains	L18 Muscle pain
Pains in the joints	L08 Shoulder symptom/complaint
	L10 Elbow symptom/complaint
	L11 Wrist symptom/complaint
	L13 Hip symptom/complaint
	L15 Knee symptom/complaint
	L16 Ankle symptom/complaint
	L20 Joint symptom/complaint NOS
Feeling of paresis or localized weakness	N18 Paralysis/weakness
Back ache	L02 Back symptom/complaint
	L03 Low back symptom/complaint
Pain moving from one place to another	A01 Pain general/multiple sites
Unpleasant numbness or tingling sensation	N05 Tingling fingers/feet/toes
	N06 Sensation disturbance other
Concentration difficulties	-
Impairment of memory	P20 Memory disturbance
Excessive fatigue	A04 Weakness/tiredness general
Headache	N01 Headache
Dizziness	N17 Vertigo/dizziness
Functional somatic syndromes*	
Irritable bowel syndrome	D93 Irritable bowel syndrome
Somatization disorder	P75 Somatization disorder

*Other functional somatic syndromes (e.g., fibromyalgia) are not included within the ICPC.

Categorization of ICPC codes

To determine diversity in the type and complex pattern of RFE of a patient, we categorized all ICPC codes based on the type of body system they referred to. We used the standard classification of ICPC codes as a basis [316], which consists of seventeen categories. These categories were reduced down to eight main by merging categories that were closely linked by definition (e.g., female and male genital) or formed a cluster in previous studies (e.g., cardiovascular and respiratory) [78].

Supplementary table 2. Categorization of ICPC codes.

Category	ICPC category (ICPC codes)	Frequency among RFE in four years preceding first new episode of care in 2016 (% of total of 159,918 RFE)
General	General and unspecified (A01-A99) Blood, blood forming organs and immune mechanism (B01-B99) Neurological (N01-N99) Endocrine/Metabolic and nutritional (T01-T99)	26,657 (16.7%)
Digestive	Digestive (D01-D99)	12,505 (7.8%)
Eye/ear	Eye (F01-F99) Ear (H01-H99)	10,562 (6.6%)
Cardiorespiratory	Cardiovascular (K01-K99) Respiratory (R01-R99)	30,183 (18.9%)
Musculoskeletal	Musculoskeletal (L01-L99)	23,248 (14.5%)
Psychosocial	Psychological (P01-P99) Social (Z01-Z99)	16,248 (10.2%)
Skin	Skin (S01-S99)	18,371 (11.5%)
Genitourinary	Urological (U01-U99) Pregnancy, Childbearing, Family planning (W01-W99) Female genital (X01-X99) Male genital (Y01-Y99)	22,144 (13.8%)

Selection of chronic somatic diseases

Chronic somatic diseases were selected based on a high prevalence in the primary care population. We made sure that their ICPC codes clearly reflected a biomedical disease rather than a symptom or syndrome description. We focused in particular on diseases which presentation could match any of the RFE we selected (i.e., those in Supplementary Table 1A). In the sensitivity analysis, we excluded all patients with any of these diseases among their episode of care diagnoses in the full study period.

Supplementary Table 3. Selection of common chronic somatic diseases.

General	Digestive	Cardiorespiratory
A79 Malignancy NOS	D75 Malignant neoplasm colon/rectum	K74 Ischemic heart disease w. angina
B72 Hodgkin's disease/lymphoma	D76 Malignant neoplasm pancreas	K75 Acute myocardial infarction
B73 Leukemia	D77 Malig. neoplasm digest other/NOS	K76 Ischemic heart disease w/o angina
B74 Malignant neoplasm blood other	D85 Duodenal ulcer	K77 Heart failure
N74 Malignant neoplasm nervous system	D86 Peptic ulcer other	K78 Atrial fibrillation/flutter NOS
N86 Multiple sclerosis	D92 Diverticular disease	K82 Pulmonary heart disease
T71 Malignant neoplasm thyroid	D94 Chronic enteritis/ulcerative colitis	K83 Heart valve disease NOS
T85 Hyperthyroidism/thyrotoxicosis	**Genitourinary**	K89 Transient cerebral ischemia
T86 Hypothyroidism/myxoedema	U75 Malignant neoplasm of kidney	K90 Stroke/cerebrovascular accident
Musculoskeletal	U76 Malignant neoplasm of bladder	K91 Cerebrovascular disease
L71 Malignant neoplasm musculoskeletal	U77 Malignant neoplasm urinary other	R93 Pulmonary embolism
L88 Rheumatoid/seropositive arthritis	X75 Malignant neoplasm cervix	R95 Chronic obstructive pulmonary disease
L89 Osteoarthrosis of hip	X76 Malignant neoplasm breast female	R96 Asthma
L90 Osteoarthrosis of knee	X77 Malignant neoplasm genital other	
L91 Osteoarthrosis other	Y77 Malignant neoplasm prostate	
	Y78 Malign neoplasm male genital other	

Supplementary Table 4. Associations between predictor variables.

	Year of birth	Female sex	Number of consultations	At least one psychosocial RFE	Number of unique RFE categories	Shannon of RFE categories	High Shannon adjusted for number of RFE categories
Year of birth	-	0.17	-0.14	0.15	0.05	0.05	0.01
Female sex		-	0.04	0.08	0.13	0.13	0.02
Number of consultations			-	0.18	0.34	0.13	-0.12
At least one psychosocial RFE				-	0.46	0.29	-0.05
Number of unique RFE categories					-	0.73	0.00
Shannon of RFE categories						-	0.53

Correlations based on Spearman's rho. RFE=Reason for encounter

Supplementary Table 5. Sample characteristics for sensitivity analyses.

	Full sample (N=6,440)	Sample of 25% frequent attenders without specific chronic diseases (N=947)
	N (%) / median (minimum-maximum, interquartile range (IQR))	N (%) / median (minimum-maximum, interquartile range (IQR))
Registered at primary care practice		
1	1,603 (24.9%)	226 (23.9%)
2	584 (9.1%)	72 (7.6%)
3	1,567 (24.3%)	255 (26.9%)
4	1,226 (19.0%)	190 (20.1%)
5	571 (8.9%)	90 (9.5%)
6	266 (4.1%)	20 (2.1%)
7	623 (9.7%)	94 (9.9%)
Outcome: diagnosis of first new episode of care in 2016		
FSS	3,570 (55.4%)	553 (58.4%)
Predictors		
Patient characteristics		
Year of birth	1963 (1914-1993, IQR=25)	1964 (1916-1993, IQR=26)
Female	3,806 (59.1%)	726 (76.7%)
Basic consultation characteristics		
Number of consultations	14 (0-172, IQR=17)	32 (24-172, IQR=15)
At least one psychosocial RFE	2,695 (41.8%)	668 (70.5%)
Number of unique RFE categories	5 (0-8, IQR=2)	7 (2-8, IQR=2)
Shannon of RFE categories	2.0 (0.0-2.9, IQR=0.8)	2.3 (0.2-2.9, IQR=0.5)
High Shannon adjusted for number of RFE categories	3,353 (52.1%)	476 (50.3%)

RFE=Reason for encounter

Supplementary Table 6. The predictive effects of patient and consultation characteristics for an FSS diagnosis in the sensitivity analyses.

	FSS diagnosis			
	Full sample (N=6,440)		Sample of 25% frequent attenders without specific chronic diseases (N=947)	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Patient characteristics				
Year of birth	**1.008**	**1.005-1.011**	1.003	0.996-1.011
Female sex	**1.142**	**1.034-1.262**	1.001	0.736-1.358
Basic consultation characteristics				
Number of consultations	1.001	0.998-1.004	0.999	0.991-1.007
At least one psychosocial RFE	**1.174**	**1.063-1.298**	1.179	0.889-1.563
Number of unique RFE categories	1.025	0.999-1.051	1.056	0.943-1.183
Shannon of RFE categories	1.048	0.974-1.127	0.987	0.727-1.337
High Shannon adjusted for number of RFE categories	1.024	0.928-1.129	0.886	0.684-1.147

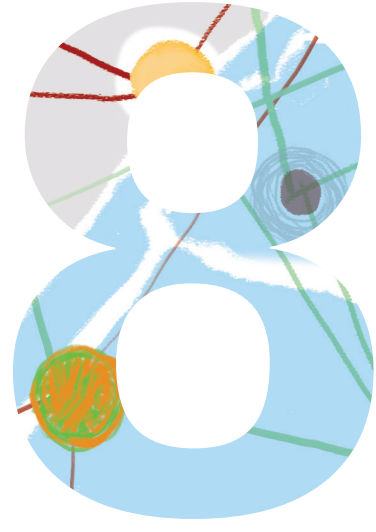
Based on univariable logistic regression models. Significant associations are printed in bold. RFE=Reason for encounter

Beyond dualism: A qualitative analysis of how patients describe the relation between persistent physical symptoms and negative emotions in extended primary care consultations

Bekhuis E, Gol JM, Burton CD, Rosmalen JGM.

Br J Gen Pract, in press.

With special thanks to Inge Stortenbeker for sharing her expertise and Rachel Grob for sending relevant literature about the analysis method.



ABSTRACT

Background: Guidelines for the management of persistent, often "medically unexplained", physical symptoms encourage GPs to discuss the relation of these symptoms with negative emotions with patients. However, many GPs experience difficulties in reaching a shared understanding with patients.

Aim: To explore how patients with persistent symptoms describe negative emotions in relation to physical symptoms in primary care consultations, in order to help GPs recognize the patient's starting points in such discussions.

Design and setting: A qualitative analysis of 47 audio-recorded extended primary care consultations with 15 patients with persistent physical symptoms.

Methods: The types of relationships patients described between physical symptoms and negative emotions were categorized using content analysis. In a secondary analysis, we explored whether patients showed transitions between the types of relations they described through the course of the consultations.

Results: All patients talked spontaneously about negative emotions. We identified three main categories of relations between these emotions and physical symptoms: separated (negation of a link between the two); connected (symptom and emotion are distinct entities that are connected); and inseparable (symptom and emotion are combined within a single entity). Some patients showed a transition between categories of relations during the intervention.

Conclusion: Patients describe different types of relations between physical symptoms and negative emotions in consultations. Awareness of the ways patients talk of these relations could help GPs to better understand the view of the patient and, in this way, collaboratively move towards constructive explanations and symptom management strategies.

INTRODUCTION

Persistent physical symptoms are prevalent in the general population and associated with reduced quality of life [31,47,317]. Although these symptoms are often referred to as medically unexplained, they are increasingly recognized as representing complex interactions between peripheral and central processes [34,36]. The management of the symptoms includes a combination of physical and psychological elements [318] and is often perceived as challenging by both patients and GPs [319,320]. Patients highly value care that addresses the breadth of biopsychosocial aspects provided by GPs [321,322]. One element of the management of persistent physical symptoms focuses on negative emotions [317,323]. These emotions have the potential to play a part in worsening or maintaining physical symptoms, in addition to being a response to the symptoms [34,37]. Furthermore, patients with physical symptoms as well as negative emotions report more functional and social limitations than patients without these emotions [47]. Therefore, primary care guidelines recommend GPs to address the relation of these negative emotions with symptoms [323-325]. Nevertheless, many GPs experience difficulties in arriving at a shared understanding with patients about this relation [326-328]. In particular, when GPs introduce inappropriate or premature psychosocial links, these are typically rejected by patients [326,327,329,330]. It has been suggested that this tension is related to the embedding of “medically unexplained symptoms” in psychiatric rather than somatic classification systems, which dualism leads patients to feel that the legitimacy of their symptoms is under threat [328].

Several authors have proposed that a shared understanding about the relation between symptoms and emotions should be formed while using the patients’ starting point as a basis [324,331-333]. In a process of constantly seeking agreement and adjusting explanations, the GP and patient can collaboratively broaden the conversation to other types of relations and, as such, formulate rich explanatory models [324,331,333]. However, despite the existence of theoretical models that refer to thought patterns of patients regarding the relation between physical symptoms and emotions [331], we were unable to find a classification of how patients describe it in consultations.

In this study, we aimed to systematically classify the types of relations between physical symptoms and emotions patients describe in primary care consultations. A secondary aim was to examine if patients moved between types of relations over time, to examine if the classification can be used to monitor a change in their presentation during interventions. We conducted a qualitative analysis of a series of extended consultations with specially trained general practitioners for patients with multiple persistent physical symptoms [325].

METHOD

Data source

We used data from the Multiple symptoms study 1 and 2 (for details see [325,334]), focusing on the effects of a consultation intervention in primary care for patients with multiple persistent physical symptoms. This intervention, consisting of three to four consultations of 20-40 minutes with trained GPs, is aimed at reducing the intensity and impact of symptoms [325,334]. GPs were instructed to explore emotions when openings were presented by the patient using a Socratic questioning technique. Furthermore, they were encouraged to consider emotions as parallel processes that can be connected to physical symptoms, rather than presenting them as the sole cause or label of symptoms. In both studies, patients were identified through a clinical database search in their usual GP practice and the completion of the Patient Health Questionnaire-15 (PHQ-15; or its shortened 14-item version) to assess the severity of physical symptoms [335]. Patients were eligible for inclusion if they had a diagnostic code in the clinical database for one or more functional somatic syndromes, had been referred to specialists at least two times in the preceding three years, and had a PHQ-15 score of ≥10. At study entry, patients filled in the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) to assess depressive and anxiety symptoms, respectively [335,336].

Ethical approval

Multiple symptoms study 1 and 2 were approved by the Lothian Research Ethics Committee (reference 09/S1102/34) and the North East Scotland Ethics Committee (reference 14/NS/1014) [325,334], which approvals also included a detailed analysis of the consultations as conducted in the current study. All participants signed informed consent.

Data analysis

Selection of consultations

All 112 consultations with 39 patients in which the intervention was delivered were audiotaped and transcribed verbatim. We purposively sampled patients based on key variables (i.e. age, sex, baseline scores on the PHQ-15, PHQ-9 and GAD-7 and the treating GP) to maximize variation. As one aspect of the study was the transition between different types of relations through the course of the consultations, we focused in particular on patients who completed at least three consultations. We started our analyses on a subset of 12 patients and aimed for saturation defined as that no new insights about types and characteristics of categories were gained in three sequentially analyzed patients. As the inclusion of three additional cases did not provide additional insights, our final sample constituted 15 patients (see **Table 1** for their characteristics).

Table 1. Sample characteristics.

Patient number	Age in category (years)	Sex	Main physical symptoms	PHQ-15 score	PHQ-9 score	GAD-7 score	Number of consultations	GP number
Multiple symptoms study 1								
1	35-49	F	Fatigue, musculoskeletal pain	13	6	2	4	1 (male, >15 years of experience)
2	50-64	M	Musculoskeletal pain, fatigue, headache	15	10	6	4	1
3	35-49	F	Fatigue	16	12	20	4	1
4	50-64	F	Musculoskeletal pain and weakness	13	21	18	1	1
Multiple symptoms study 2								
5	20-34	F	Gastrointestinal symptoms, fatigue, headache	12	11	14	4	2 (female, >15 years of experience)
6	35-49	F	Musculoskeletal pain, gastrointestinal symptoms	11	2	1	2	2
7	50-64	F	Gastro-intestinal symptoms, musculoskeletal pain, excessive perspiration	16	4	1	4	2
8	35-49	F	Gastrointestinal symptoms, musculoskeletal pain	13	4	3	3	3 (female, >15 years of experience)
9	35-49	F	Musculoskeletal pain, balance problems, headache	28	20	19	4	3
10	65+	F	Fatigue, headache	10	3	2	4	3
11	35-49	F	Palpitations, gastro-intestinal symptoms	19	3	8	1	4 (male, <5 years of experience)
12	20-34	F	Musculoskeletal pain and weakness	15	12	5	3	4
13	50-64	M	Musculoskeletal pain, “heart trouble” (breathlessness, lump in throat)	18	16	12	3	4
14	50-64	M	Musculoskeletal pain, gastrointestinal symptoms	12	13	9	3	5 (female, >15 years of experience)
15	35-49	F	Musculoskeletal pain, headache, tinnitus	15	5	0	3	5

Analysis method

First, patients' accounts of negative emotions were coded based on methods used in previous studies [337,338]. We defined these accounts as explicit and verbal expressions of a negative emotional state. Implicit accounts of emotions (e.g., a situational description of a distressing event such as a conflict without explicitly describing an emotion) were excluded to avoid imputation of the patient's narrative by the researchers. Descriptions were interpreted in the context of the conversation and while listening to the intonation of the patient. Specific attention was paid to words or phrases with multiple definitions; for example, "stress" can refer to external stressors as well as an internal state characterized by worry or agitation, and "I was like: oh my God!" may refer to a positive and negative emotion. Such quotations were included only when it could be inferred with confidence that the patient referred to a negative emotion. Accounts were categorized based on the type of emotion they concerned with open coding, and names of the categories were formulated while staying close to the words most often used by patients.

In a second step, all quotes in which patients described a relation between a negative emotion and physical symptom were selected. To stay closely to the message of the patient, we considered only relations that were semantically specified (e.g., "I feel down *because of* the pain"). In addition, it had to be clear that the relations included a negative emotion as well as a physical symptom; terms at the interface (e.g., "feeling tense") were excluded if their meaning could not be inferred from the conversation. The quotes were analyzed with conventional content analysis [339,340]. Using a one-sheet-of-paper (OSOP) method, quotes were written on one document and rearranged by looking at similarities and differences to form categories inductively [341]. To explore whether patients showed a transition in their presentation of categories through the course of the consultations, we performed a secondary analysis. For each patient, we analyzed his or her pattern of category use over time and searched for switches from one category to another while describing a specific situation.

Coding was done in Atlas-ti 8 and first performed independently and then compared by EB (last year medical and PhD student) and JG (psychiatrist and PhD student). The analysis was done by these researchers together and differences were discussed until agreement was reached. In order to ensure intersubjective reproducibility and comprehensibility, the analysis was regularly referred to senior researchers specialized in persistent physical symptoms CB (a GP) and JR (a medical biologist and psychologist).

RESULTS

All patients described some negative emotions, but the number of instances differed considerably across patients (ranging from 3-21). We identified five specific types of emotions: anxiety, frustration, low mood, embarrassment and guilt (**Table 2**). Patients who disclosed fewer emotions were generally less talkative and more focused on physical aspects of their symptoms. Typically, patients presented the first emotion within five minutes of the start of the first consultation, and the frequency of occurrence decreased as the intervention progressed. In most quotations, patients related the emotion to physical symptoms (1-16 accounts per patient). Patients initiated most descriptions of relations themselves, with the remainder in response to questioning by the GP. Spontaneous descriptions were more detailed than those occurring after a question from the GP. Some patients, particularly those going through major life events, tended to describe emotions without referring to their relation with physical symptoms. They elaborated on emotions in the context of external stressors or questioned if the emotion was part of an affective disorder. The pattern in which patients presented emotions or their relation with physical symptoms (i.e., number of times, types of categories, at which stage of the intervention) was not clearly related to the patients' sex or age nor the severity of somatic, depressive and anxiety symptoms.

Table 2. Categories of emotions.

Category	Examples of emotions within category	Number of occurrences
Anxiety	Anxiety Worry Panic Nervousness	69
Frustration	Frustration Annoyance Anger Irritation	49
Low mood	Depression Sadness Weariness Feeling down	47
Embarrassment	Embarrassment Shame Feeling humiliated Feeling mortified	19
Guilt	Guilt	1
Emotions that could not be fitted into specific category	Emotional crisis Feeling overwhelmed Feeling stressed out	64

Categories of relations between negative emotions and physical symptoms

We identified three main categories of relations between negative emotions and physical symptoms: separated, in which a link between the symptom and emotion was negated; connected, in which the symptom and emotion were presented as related but distinct entities; and inseparable, in which the symptom and emotion were combined within a single entity (**Table 3**).

Separated

In the separated category, patients explicitly negated a link between a symptom and an emotion. Characteristic for this category was that the negation concerned a relation in which the physical symptom was fully caused by or attributed to an emotion (see Quote 1 and Dialogue 1), and emotional labels like 'depression' or 'anxiety disorder' were used (see Quote 1). Patients used the category during various stages of the intervention and frequently indicated that they believed the relation to be true in general, but that they had not experienced it themselves (Dialogue 1). Some negated in a tense or angry way a relation suggested by a physician (Dialogue 1).

Quote 1:

Setting: At the start of the first consultation, patient 1 explains to GP 1 the potential causes that have been considered and ruled out for her fatigue.

Patient: "They looked at all the obvious signs because, I mean, they tested me physically, but they also looked at me emotionally as well, which is understandable. But I wasn't going through any great emotional crisis and I wasn't depressed and I wasn't stressed and I have… I don't know how most people work, but I'm a very strong faith so it keeps me sane, so I wasn't… I would've told them if I was depressed and I wasn't, so ***there wasn't an emotional trigger****".*

Dialogue 1:

Setting: At the end of the first consultations with patient 12, GP 4 introduces a relation between symptoms and negative emotions. The patient confirms it in general, but firmly rejects that the emotions are the cause of her symptoms.

GP: "They [pain and fatigue] are closely linked in with emotions and how all of that works, so being upset, being stressed, being angry."

Patient: "Yeah, correlation between sad feelings and pain. I get it."

GP: "So it starts to hold you back and you can get into a little bit of a cycle here."

Patient [starts crying and says angrily]: "A rut, yeah, I appreciate that. But then if you couldn't do half the things you wanted to do, you would feel overwhelmed and stressed out. ***But that's not why I'm sore.****"*

Table 3. Categories of relations between physical symptoms and emotions.

Category	Type of relation	Number of occurrences	Characteristics				
			Content	Form	Initiation	Category of emotions	Stage of intervention
Separated Physical symptoms and emotion are distinct entities that are unrelated.	**Negated relation**	12	Physical symptom is not caused by or attributable to emotion	Negation of (a previous) physician's suggestion, sometimes while expressing anger	Introduced by patient, either spontaneously or in response to GP's suggested relation	Anxiety Low mood	Any
Connected Physical symptom and emotion are distinct entities that are related.	**a) Isolated connection**	87	Regular experience of cause-effect relation	Short statements that are frequently repeated throughout the consultation	Spontaneously introduced by patient	Frustration Embarrassment Anxiety	Any
	b) Vicious circle	11	Complex vicious circle underlying symptom	Brief confirmation of GP's suggested relation	Introduced by GP, adopted by patient	Anxiety	Middle
Inseparable Physical symptom and emotion are combined within a single entity.	**a) Integrated whole**	11	Attribution of physical symptom to affective disorder	Exploratory narrative	Spontaneously introduced by patient	Anxiety Low mood	Start
	b) Fragments of a whole	8	Distressing state with physical and emotional aspects	Chaotic narrative	Spontaneously introduced by patient	Anxiety	Start

Connected

The connected category included descriptions of a symptom and an emotion as distinct, yet related entities. This category included confidently presented statements that could lead to the identification of targets for management strategies. It was found during all stages of the intervention with all patients. Connections were subdivided into two types: a) isolated connection and b) vicious circle.

In isolated connections, the symptom and the emotion either unidirectionally influenced each other or were linked in time. Typically, patients briefly described a regular experience in which the emotion was a consequence of the symptom, and in this way seemed to wish to underline the impact of the symptom on their daily life: *"I still have this massive sweating, it's a current one, it's just very, very annoying, embarrassing, frustrating, depressing"* (patient 7). A few patients described the emotion as a clear cause or a trigger of the symptom (Quote 2).

Quote 2:

Setting: During the third consultation, patient 4 describes the physical effects about worry about her ill sister in a conversation with GP 2. Following this quote, a management strategy is co-created by the two.

Patient: *"**Me stressing about her makes me not well**. So I kind of have to go - well, not I don't care - but if **it is making me ill to stress about her**, then I have to say: I'm just not going to."*

A vicious circle referred to a sequence of reciprocal cause and effect in which a symptom and an emotion intensified each other. Most patients adopted vicious circles after they had been introduced by the GP by briefly confirming the suggested relation (Dialogue 2). However, a few patients, particularly those who described complex biopsychosocial explanations for their symptoms, spontaneously introduced vicious circles (Quote 3).

Dialogue 2:

Setting: By the end of the first consultation, GP 4 suggests a vicious circle, which patient 13 briefly confirms. After this, they switch to the creation of management strategies.

GP: "The pain, the heart things that you're describing, and the shortness of breath, there's no doubt to my mind that those are complicated processes at play. And everything that's bad and making you feel depressed and making you feel down, that's going to be filtering down, and making things worse. So that's a vicious circle really, isn't it?"

*Patient: "**That's right, one that needs to be broken**. How I don't know, I really don't know."*

GP: "I think that naturally leads us on to thinking about how we can make things a little bit better."

Quote 3:
Setting: During the first consultation, patient 1 describes complex processes underlying her symptoms to GP 1, including a loop between symptoms and emotions.
*Patient: "**The headache adds to making me also tired because it wears you down**. It's not a - you know when you've got really bad headache that you go away and you get a paracetamol because it's an ache - it's not a throb. It's just a continuous there dullness that **wears you down**, and when I get really tired, it **starts to get quite bad**. That's more of a stabbing pain."*

Inseparable

Patients described a symptom and an emotion as combined within one entity in the inseparable category. This category was typically exploratory, included metaphors, and was introduced by patients at the beginning of the intervention. The symptom and emotion could be presented in two ways: a) an integrated whole or b) fragments of a whole.
In descriptions of an integrated whole, the symptom and emotion were presented as one entity (i.e., the symptom was part of the emotion or vice versa) (Quote 4). This category concerned an exploration of the source of the symptom, which was typically an affective disorder: *"I've been on a heart monitor and everything, but they haven't come up with anything, so whether it's a psychological thing or just some kind of panic attack?"* (patient 11). Most patients referred to their previous experiences with affective disorders: *"At one stage I just thought: is it depression again? Because I've been through it before."* (patient 3).

Quote 4:
Setting: Patient 11 introduces her headache to GP 3 during the first consultation, and presents it as an expression of worry (metaphor: "pain of the brain").
*Patient: "One night towards the end I woke up at 2.15 with this problem that's been harassing me for the last two years with my sister. And because of the meditation it was bringing it up. I had such a pain in my head with it, **the worry was very painful**. And so I sat on the end of the bed and started to do the 'scanning of the body'-meditation, and eventually overcame **the pain of the brain**."*

In fragments of a whole, patients described the symptom and the emotion as inseparable features of an experience. The quotations included a chaotic narrative of a distressing state and patients were searching for the right words to describe it (Quote 5). The quotations were part of an active process of trying to understand the nature of the experience (Quote 5).

Quote 5:
Setting: During a process of symptom exploration in the first consultation, patient 1 describes to GP 1 the moment-to-moment experience of a distressing state (metaphor: "the wall hit me").
Patient: "*The bit I can't work out is that I can just physically function all day and at some point it's like I just… It's like a wall hits me and it's… And you can physically, I've been told you can physically… And I know that it's hit me. I've been fine or I've been a bit tired all week, but Sunday night it was... I wasn't doing anything and the wall hit me and I just… it's like I just…* ***I can't cope with it. I can't cope with anything*** *and I have… it just… it's like a… it's like the…* ***just the fatigue engulfs me****."*

Transitions between categories
In a secondary analysis, we explored if patients could show a transition from one category to another through the course of the consultations. We found that three patients presented one category, eleven described two or three categories, and one patient described five categories of relations. However, most patients who described multiple categories referred to varying symptom-emotion combinations or contexts and therefore did not necessarily show a change in their presentation during the intervention. We identified four instances in which a patient showed a clear transition in the presentation of a specific situation. This number was not sufficient to describe transitional patterns in detail. However, in general these transitions occurred in a dialogue in which the patient and GP negotiated novel types of relations. Two patterns of category switches were encountered: 1) from separated to isolated connection, and 2) from isolated connection to vicious circle (Dialogue 3).

Dialogue 3:
Setting: GP 4 and patient 13 explore links between symptoms and emotions by the end of the first consultation. The patient first describes an isolated connection, and later expands this, encouraged by the GP, to a vicious circle.
GP: "And how are you feeling about all this [the pains], just as you are just now?"
Patient: "Well ***depressed****. What else can I say. I don't know, just depressed, just feel like I'm getting nowhere."*
[..]
GP: "And can you see that they [these feelings] might be ***feeding back*** *and, and making the symptoms worse as well?*
Patient: "Possible, yes, very possible. That's what I'm saying, my head's maybe playing with my mind. My mind's probably playing with me, making things worse. ***I work myself up, I get worse****."*

DISCUSSION AND CONCLUSION

Summary

This study showed that patients with persistent physical symptoms describe different types of relations between symptoms and emotions. Relationships constituted three main categories: separated (negation of a link), connected (physical symptom and emotion are two linked entities) and inseparable (physical symptom and emotion are combined within one entity). Some patients moved from one category to another through the course of the consultations.

Strengths and limitations

Strengths of this study are the dual independent coding and discussing of the analyses in a multidisciplinary team from general practice, psychiatry, and psychology [341]. Furthermore, we stayed closely to the message of the patient by focusing on explicit descriptions of emotions and their relation with physical symptoms. A limitation of this approach is that we may have missed accounts in which patients made implicit notice of emotions and/or relations, for example by using terms at the interface of the physical and emotional (e.g., “tense”) [338]. Furthermore, although we inferred if terms referred to physical or emotional aspects while staying as close to the description of the patient as possible, it should be noted that this distinction is a simplification of the complex biopsychosocial reality. Ambiguity with respect to the conceptual embedding of symptoms was extensively discussed in our team before quotes were subjected to further analysis. Thirdly, data were derived from extended primary care consultations with specially trained GPs and not typical short GP consultations. While these long consultations were more likely than short consultations to include discussions involving the relation of physical symptoms with negative emotions, the passages of discussions were brief and so compatible with “ordinary” consultations. Finally, as we identified only a few instances of clear transitions in patients’ use of categories over time, we were not able to study their pattern in detail. Still, that such transitions occurred confirms that our categories can be used in future studies, for example to identify interactional patterns related to transitions in patients’ presentations with conversation analysis [342].

Comparison with existing literature

Our finding that patients frequently present their emotions in primary care consultations is in line with previous studies [343-346]. Although this study was the first to systematically assess the types of relations patients present in primary care consultations, some other studies have indicated that many patients with persistent physical symptoms present their symptoms dualistically by negating a relation with emotions [329,330,347].

Interestingly, in these studies the GPs primarily used classic psychological reattribution techniques [329,347], which centralize the assignment of emotional causes or labels to symptoms [348]. We found that patients forcibly rejected this in the separated category [329,347], suggesting that patients may primarily use dualistic expressions in response to reattribution by the GP. It has been reported before that many patients find reattribution too simplistic and stigmatizing [321]. This could partly explain the limited efficacy of interventions based on reattribution for persistent physical symptoms [323,349,350]. Nevertheless, we found that other patients openly explored the possibility that their symptoms were part of an affective disorder in the inseparable category. This could indicate that patients can acknowledge emotional attribution or labels when they introduce them themselves, but tend to disagree when they are imposed upon them by the GP [331].

Implications for research and practice

The results of this study have several implications for care of patients with persistent physical symptoms. First, that patients spontaneously presented anxiety, frustration, low mood, embarrassment as well as guilt indicates the importance of considering a broad spectrum of emotions in consultations for persistent physical symptoms. However, clinical guidelines for the management of persistent physical symptoms encourage GPs mainly to concentrate on the narrow field of depressive and anxiety disorders [30,37,289], and a similar focus is adopted in screening instruments [174,335,336]. As all patients in this study, irrespective of the severity of depressive and anxiety symptoms, frequently presented emotions, our findings stress the importance of picking up on patients' emotional cues and encouraging patients to elaborate on them.

Interestingly, we found that patients tended to disclose fewer emotions as the intervention progressed. This might be related to the structure of the intervention, which gradually shifted the focus from symptom exploration to the creation of symptom management strategies. As the GP was increasingly in the lead in the follow-up consultations to create such strategies, the space for the patient was naturally reduced. This indicates that in ordinary consultations aimed at exploring the problem space, it is essential for GPs to create an open conversation in which they actively listen to and collaborate with the patient [351]. Allowing patients to arrive at explanations themselves rather than imposing it on them could also help to create richer explanatory models [331,352], as we found that relations that were spontaneously mentioned by patients were presented in more detail than those in response to directive questions of the GP.

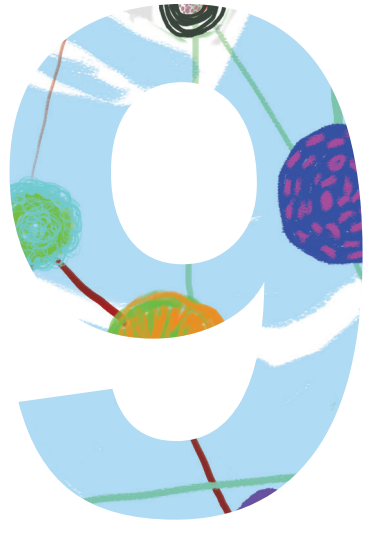
CONCLUSION

Patients with persistent physical symptoms present a wide variety of negative emotions in extended primary care consultations. In contrast to previous reports suggesting that patients have dualistic presentations, we found that patients do not only separate emotions from physical symptoms, but also describe them as entities that are connected to or inseparable from these symptoms.

Proposal and creation of symptom management strategies for persistent physical symptoms: qualitative study of enhanced primary care consultations

Gol JM, Bekhuis E, Burton C, Rosmalen JGM.

Submitted.



ABSTRACT

Aims: Symptom management strategies are currently recommended for patients with persistent physical symptoms (PPS). They comprise activities that patients can conduct themselves to reduce the severity or impact of their symptoms. Little is known about how symptom management strategies emerge during consultations. The aim of this study is to understand how strategies arise in primary care consultations and what contributes to their adoption.

Methods: Two raters analyzed audiotapes and transcripts of 12 sets of three to four extended consultations for PPS in primary care. We explored the sequential organization of the discussion of the symptom management strategies during the consultations, while examining the relation of these patterns with the adoption of strategies as indicated by patients during follow-up consultations. We formulated a conceptual model following a modified grounded theory approach.

Results: Symptom management strategies emerged especially from ongoing discussions between the GP and the patient. Most strategies were evaluated in follow-up consultations and approximately half were adopted by patients. We identified four themes related to adoption: proposal of the strategy by the patient, alignment of the strategy with the patient's narrative, co-creation of the strategy, and higher complexity of the creation process.

Conclusion: Patients' involvement in the creation of a symptom management strategy seems to be key to the adoption of symptom management strategies for PPS. If GPs deliberately use the input of patients in the creation of symptom management strategies, patients may benefit more from these strategies.

INTRODUCTION

Between 15 and 40 % of all consultations in general practice concern physical symptoms which are not wholly explained by organic pathology [282,286,317,353]. Most patients with these symptoms improve, but 10-30% of patients deteriorate and develop troublesome and persistent physical symptoms (PPS) [283]. Patients with PPS pose a challenge to the GP in terms of diagnosis [355], further testing [289] and management [289].

A key component of the management of PPS is symptom management, which includes actions by the patient to limit the intensity or the impact of their symptoms. Symptom management strategies are recommended by experts and guidelines [323,356] and have been shown to improve symptom levels and quality of life of patients with PPS [357]. Patients have also indicated that symptom management is important to them [322].

In a previous study, we examined symptom management strategies proposed in routine primary care consultations. We found that these strategies were proposed in nearly all consultations, and up to six strategies per consultation were found. We identified six different types of strategies: cognitions and emotions, interaction with health care professionals, body focus, symptom knowledge, activity level, and external conditions [291].

Primary care guidelines currently provide little guidance on how symptom management strategies should be advised [318,323,356]. In our previous study, strategies were mainly proposed by the GP, were discussed briefly and differed with respect to whether the given advice was specific and practical or generic and hypothetical [291]. While this study provided important insights, it left three areas of uncertainty. First, it did not focus specifically on the way the strategies emerged during the conversation, and therefore much remains unclear about how self-management recommendations were created. Second, since a single consultation per patient was available, it was unknown how symptom management strategies developed over time. Third, it was not known if patients adopted the strategies or not.

In this study, we aimed to explore the ways in which symptom management strategies are proposed, negotiated and adopted through a series of enhanced primary care consultations specifically for patients with PPS.

METHODS

We conducted a qualitative analysis based on grounded theory approach of audio recordings from a set of extended consultations with specially trained GPs for patients with persistent PPS.

Sample

We used data from two studies on the Symptom Clinic Intervention (SCI), a brief, semi–structured and supportive enhanced primary care intervention for patients with PPS. It focuses on explaining symptoms as well as on planning and implementing behaviors to reduce the severity and impact of symptoms [325,334]. As the SCI consists of a set of three or four consultations, it provides the opportunity to explore the way symptom management strategies are constructed and evaluated during follow-up appointments. The types of strategies in the intervention's manual included cognitions and emotions, interaction with health care professionals, body focus and activity level. Although GPs did not receive detailed instructions about how to create strategies, they were encouraged to reinforce what patients had learned and to build on new experiences in the follow-up consultations.

As recruitment and characteristics of the patient groups have been extensively described elsewhere [325,334], a brief summary is provided here. Data collection took place in two areas of Scotland (UK) in the period of 2009-2010 and of 2014-2015. Patients aged 18-64 were identified through a clinical database search in their usual GP practice. Patients who were diagnosed with one or more functional somatic syndrome(s) and were referred at least twice in the preceding three years to a medical specialist were sent a postal questionnaire (i.e., the PHQ-15, or its modified version, the PHQ-14 [180]). Patients were eligible for inclusion if their score on the PHQ-15 or PHQ-14 was ≥10. In the first study [325], the SCI was delivered to 16 patients by a male GP, the developer of the treatment with more than 15 year experience in general practice. In the second study [334], the intervention was delivered to 24 patients by four newly trained GPs, including three females with more than 15 year experience in general practice, and one male with less than five year experience in general practice. Approval of the studies and a detailed secondary analysis of their consultations were given by the Lothian Research Ethics Committee (reference 09/S1102/34) and the North East Scotland Ethics Committee (reference 14/NS/1014). All participants signed informed consent.

We used a selection of consultations, which were audio-recorded and transcribed verbatim. Consultations with 12 patients were purposefully sampled based on the variables age, sex, and anxiety and depression levels as measured with the GAD-7 and PHQ-9 [180,336], respectively, and the treating GP to ensure maximal variation. We included only patients with three or four completed consultations as an important aspect of this study was the analysis of follow-up consultations. In the resulting dataset, seven patients completed four consultations and five completed three consultations (**Table 1**). Nine patients were female. Patient's ages covered varying periods across the life span (20-34 years: 2 patients, 35-49 years: 5 patients, and 50+ years: 5 patients).

Table 1. Sample characteristics.

Patient number	Age in category (years)	Sex	Main physical symptoms	PHQ-15 score	PHQ-9 score	GAD-7 score	Number of consultations	GP number
Multiple symptoms study 1								
1	35-49	F	Fatigue, musculoskeletal pain	13	6	2	4	1 (male, >15 years of experience)
2	50-64	M	Musculoskeletal pain, fatigue, headache	15	10	6	4	1
3	35-49	F	Fatigue	16	12	20	4	1
Multiple symptoms study 2								
4	20-34	F	Gastrointestinal symptoms, fatigue, headache	12	11	14	4	2 (female, >15 years of experience)
5	50-64	F	Gastrointestinal symptoms, musculoskeletal pain, excessive perspiration	16	4	1	4	2
6	35-49	F	Gastrointestinal symptoms, musculoskeletal pain	13	4	3	3	3 (female, >15 years of experience)
7	35-49	F	Musculoskeletal pain, balance problems, headache	28	20	19	4	3
8	65+	F	Fatigue, headache	10	3	2	4	3
9	20-34	F	Musculoskeletal pain and weakness	15	12	5	3	4 (male, <5 years of experience)
10	50-64	M	Musculoskeletal pain, “heart trouble” (breathlessness, lump in throat)	18	16	12	3	4
11	50-64	M	Musculoskeletal pain, gastrointestinal symptoms	12	13	9	3	5 (female, >15 years of experience)
12	35-49	F	Musculoskeletal pain, headache, tinnitus	15	5	0	3	5

Analysis

We performed a qualitative analysis based on grounded theory in a modified form as the data were collected before analysis [358]. JG, a psychiatrist specialized in somatoform disorders, and EB, a general medical doctor, started by listening to the recordings and reading their transcripts with an open mind. A detailed line-by-line analysis was performed during which we identified the symptom management strategies that were proposed during the consultations. We defined these strategies as every effort proposed to be undertaken by the patient himself or herself in the nearby future to promote physical and/or emotional wellbeing. Discussions concerned both new strategies that were set up during the SCI and old strategies that were created and used before the SCI. In our analysis, we only included strategies that we were confident were new. We coded the strategies based on their type. We started with codes derived from our prior study: cognitions and emotions, interaction with health professionals, body focus, symptom knowledge, activity level, and external conditions [291]. We also looked for new types of symptom management strategies, which were marked with open coding. Coding was done independently by JG and EB. Coding inconsistencies were discussed until agreement was reached between these researchers; and if necessary, it was discussed with the senior researchers specialized in persistent physical symptoms CB, a general practitioner, and JR, a medical biologist and psychologist.

GPs and patients regularly returned to a specific management strategy at multiple points through the set of consultations. To understand the process of how such strategies were created and what contributed to their adoption, all text fragments referring to a specific symptom management strategy that came up during the set of consultations of a specific patient were linked (by JG and EB). We defined these text fragments as all utterances by the GP or patient that referred to that specific strategy, which began at the point the strategy was introduced, and ended when the conversation moved to another aspect of the consultation or the consultation ended. The text fragments were numbered based on the order in which they appeared in the consultations.

As our analysis focused on the adoption of the strategies, text fragments in which the strategy was evaluated by the GP and patient were marked. Based on these spontaneous evaluations, JG and EB independently coded strategies as adopted, not adopted or adoption-unknown. Definitions of these categories were formulated during the process of analysis and after extensive discussions in our team (JG, EB, CB, and JR). As we were interested in symptom management strategies that were possibly beneficial for the patient and therefore maintained, we defined the symptom management strategy as adopted if the patient described using it and appraised it positively or neutrally, and/or expressed a plan or likelihood to keep it up. Non-adopted strategies were defined as strategies that were rejected before using, or were used but negatively appraised and/

or dismissed as unworkable. Some strategies were not evaluated at all and were coded as adoption-unknown. Adoption-unknown strategies were included in the analysis, as they might give additional insight into the process of creating a symptom management strategy. However, strategies that were initiated in the final session and were not yet adopted were excluded because they could not be evaluated in follow-up appointments. To identify potential themes that were related to adoption of strategies, we compared adopted, not adopted and adoption-unknown strategies using a constant comparative method [358]. We focused on the characteristics of the strategy itself and how the strategy was negotiated during the consultation. To analyze the sequential organization of how strategies were negotiated, JG and EB described the way in which different text fragments of a specific strategy were related to each other. For each text fragment, we indicated whether if for instance concerned a repetition of previously discussed information, added information to the strategy, included information to make the strategy more practical, or included motivational elements for the patient. Furthermore, we explored via axial coding the interactional process between GP and patient in the creation of the strategy [358]. Based on these explorations, varying potential themes for analysis were derived. These themes were first discussed in our team to refine their definitions and core features, which were then used to recode the strategies by JG and EB. Through this recoding process, we identified the most significant and frequent themes (selective coding) [358]. We developed core themes and relationships into a conceptual model that explained the process of adoption. In the results section, we show quotes that illustrate the model. If applicable, we chose different text fragments (marked with suffices) referring to one specific symptom management strategy to clarify the process of creation through the set of consultations.

RESULTS

Types of symptom management strategies

A total of 76 symptom management strategies were identified, varying from four to ten per patient. Saturation of the types of management strategies was reached after the first two patients as no new types of strategies were found thereafter. All six types of symptom management strategies of our previous study (i.e., cognitions and emotions, interaction with health professionals, body focus, symptom knowledge, activity level, and external conditions) were identified. However, two differences with the previous study were found. First, while activity level focused on resting in the previous study, it comprised balancing activity and rest in most instances in our study. Second, an additional type of symptom management was observed in our study: social support.

Social support stood for involving family and friends for reasons such as practical help, encouragement or an emotional outlet (Quote 1).

Quote 1:
The GP suggests a strategy involving social support (talking to family about symptoms). Setting: end of first consultation, GP 4, patient 10, first text fragment out of four.
GP: "*What's probably going to help you, would be, would be getting your family onboard with this, and so talking to them about it."*

The most frequently proposed symptom management strategies in our study were cognitions and emotions, body focus, and activity level. Most symptom management strategies were introduced in the first consultation. Although some management strategies were discussed only once during the intervention, others were an ongoing part of follow-up consultations as patients and GPs advanced ideas and specified what the strategy should look like. In the set of consultations with a particular patient, one or two main strategies were elaborated on more extensively than others. In these instances, the discussion of one type of strategy sometimes led to another type of strategy. Such strategies could complement each other (Quote 2a).

Quote 2a:
The GP proposes a strategy targeting external conditions (reduce working hours). This is introduced as one way to give practical form to another type of strategy (activity level). The strategy refers to the information the patient gave earlier in the consultation that she had been more energetic when she worked part-time. Setting: end of first consultation, GP 4, patient 9, first text fragment out of 10.
GP: "And you're, you're not able to do as much. And what happens when you're down here is, you have kind of good days, you have bad days, and it can all, it can all scuffle about. But there isn't any real progress getting back up, getting back up to where you were, and this might be because you're, because you're trying to do too much just now. Um, and what that can do is, is that can kind of keep you, can keep you down a, a little bit. So sometimes what it's, what is good to do, is to step back. And I'm not at encouraging that we, that we think about doing less long term. But maybe you start to think about how you're going to get yourself doing more, but not have it knackering you out. Um, so work we can't do much about, unless you want to reduce your hours or anything like that."
Patient: "No, I had asked, but she [manager of patient] was a bit no, no, I need you. But she doesn't, because on a Thursday and a Friday, there's three receptionists, and we don't need three half the time. I'm either um, doing admin, which is, or like shredding, or crap like that. So I don't really need to be there half the time. And I did ask, so whether it's a case of asking her again."

GP: "I think so, yeah."
Patient: "You don't really need me on a Friday. Can I just drop? And seven hours wouldn't make that much, too big a dent in my pay."
GP: "So could, can we make that as a plan that you will?"

Evaluations of symptom management strategies

Evaluations were an important topic of conversation. They were often initiated by patients after a general question of the GP about the patient's well-being immediately at the start of a follow-up consultation (Quote 3). Some evaluations formed the basis for adjustments to make the strategy more suitable for the patient, which eventually enabled its adoption (Quote 3). Other strategies were not discussed at all in follow-up consultations and therefore not evaluated.

Quote 3 a, b and c:
The GP adjusts a strategy based on the evaluation of the patient, which enables its adoption. Setting: GP 1, patient 1.

Quote 3a:
The patient evaluates a strategy aimed at changing cognitions and emotions suggested by the GP in the previous consultation (imagining the door as the patient gets up as a way to distract her mind from the pain). Setting: Beginning of second consultation, third text fragment out of six.
GP: "Good. How've you been getting on?"
Patient: "All right. Still tired. Not sleeping very well."
GP: "No."
Patient: "I've been doing your cognitive, don't think about getting up, but walk to the door, and it's fine while you're standing, but the minute you start moving, it's not so good."
GP: "Okay, so we're getting part way."
Patient: "Well, we're..."
GP: "How do you mean?"
Patient: "Well, I can stand up, like, without thinking about it, and it's still painful, but then, the minute you start to walk, it's painful. So imagining the door doesn't really take away the pain. All if does is distract you for 30 seconds, 'til the pain kicks in. The trouble with being distracted, though, is because I'm not prepared for it, what I then get is, I get the pain, sometimes makes me stop, because it's quite bad. So before, where you were taking it easy, and easing yourself into it, I could most...sometimes I've had to just stand up and wait for a couple... In fact, one time, I nearly...my leg nearly went. It's been amusing, but I've tried it. I gave it a go."

Quote 3b:
The GP uses the evaluation to change the strategy. Setting: end of second consultation, fourth text fragment out of six.
GP: "Have a go at the sleepy stuff, and I want you to sort of have another go at the getting up stuff, and see if we can find a middle ground thing, that says, I'm not going to need help to get up, but I'm not going to try and jump to attention; you need a... You know, perhaps find a count-through. You know, are you going to do it in a count of four, or three? You're not going to do it in a one, but you're not going to do it in a one...in a ten, you know, six, seven, eight. What's the rhythm? And just see if you can find an approximate rhythm."

Quote 3c:
The patient evaluates the adjustment to the strategy. Setting: Start of third consultation, final text fragment out of six.
Patient: "It's been a good week... It's been, actually, a good week and a half. Last week was quite good, as well. So yes, I'm quite happy. I did your count as you get up, and that's okay. Just, it's more... It's like thinking about it, but in the sense of, more focusing what you're doing, like when you're getting out the chair, one, two, three."

Themes related to adoption
For the analyses of the adoption of strategies, we excluded seven strategies that were initiated in the final consultation and not yet adopted. Of the remaining strategies, 38 were adopted, while 11 were not adopted, and the adoption of 18 strategies was unknown. In the process of comparing and contrasting the three categories, we noticed several differences. These differences were summarized in four themes, based on how the strategies were proposed and created. Although we examined if the degree of adoption differed across the types of symptom management strategies, we found no clear differences for most types.

Adoption in relation to the proposal of the strategy
When exploring the proposal of strategies, we identified two important themes related to adoption: patient versus GP proposal and narrative-driven versus not narrative-driven proposal.

Patient versus GP proposal
The first theme concerned by whom the symptom management strategy was initiated. Although we found that patients took initiative in starting some new strategies (Quote 4), most initiatives were from the GP (Quote 2a). Strategies proposed by patients were in nearly all instances adopted, while approximately half of the GP initiated strategies were adopted.

Quote 4:
The patient initiates a strategy targeting the body after a question from the GP (having a bath). Setting: end of first consultation, GP 3, patient 7, first text fragment out of four.
GP: "What are you going to do this afternoon for you that's nice?"
Patient: "Well I'm going to go home and have a hot bath, I'm just going to snuggle with my husband on the sofa I think cause he's off today as well."

Narrative-driven versus not narrative-driven proposal
Another theme was how the symptom management strategy was initiated. Some initiatives naturally followed from information given by the patient about for instance as an already tried strategy, an expressed concern or a behavioral trait. They were proposed in line with specific details of the narrative of the patient, building on the content as well as the phrasing and emotions voiced by the patient (Quote 5a). Other initiatives were presented in generic terms independently of the narrative of the patient, for example after discussing a general explanatory model. The strategies could apply to all patients with similar symptoms (Quote 6). Less narrative-driven proposals were often followed by non-adoption or adoption-unknown, while more narrative-driven proposals were followed by adoption in most of the cases.

Quote 5a:
The GP initiates a strategy aimed at changing activity level (putting refuelling stops in the way). The strategy emerges within the context of the narrative in which the patient explains all her activities. Setting: the middle of the first consultation, GP 1, patient 3, first text fragment out of 15.
GP: "And I think, you know, the other thing that strikes me is that you just got so many things going on that, none on its own would stop you at all, but by the time you had the achy bones and all that sort of past baggage… Most of us just get achy knees and we think, oh, God I'm getting old, whereas you get achy knees and you go oh, God I'm getting old and, you know, I've had this for this length of time."
Patient: [Laughs] "Mmm."
GP: "And, the other thing, so you add all these things together and then because of your situation you just keep going or say I'll exercise more."
Patient: "Yes. Have to keep going."
GP: "Yes you do? Yes you do."
Patient: "Uh-huh."
GP: "But I wonder if there aren't ways to put some refueling stops in on the way, because sometimes symptoms build up and they get to a point where the sensible thing is to change the way you keep going so that sometimes you stop. And, you know, I can think

of some examples and *some ways that people do it but I'm going to ask you to think, you know, if you were to say… right, you've just sort of said yes. That's a fair point. Maybe I do sometime need to stop."*

Quote 6:
The GP initiates a strategy targeting activity level (graded activity) and a body focus (exercise), which emerges suddenly and without any natural connection to the narrative of the patient. The strategy is presented as a basic principle that can help all patients. Setting: end of first consultation, GP 4, patient 10, first text fragment out of ten.
GP: "Um, now you'll probably be wanting to hear how we can, how we can do that, and, and um, I think it's, it's going to be using, using some, some basic principles, and, and slowly working with them."
Patient: "Okay."
GP: "Okay, um, the first of those is, is something that we call graded activity, or graded exercise, and that's looking at, at making you more able to do things, and it's taking a very structured approach to it, and what it recognizes is that probably you're the, the amount that you can do varies a little bit, with how your back's feeling."

Adoption in relation to creation of the strategy
Two themes related to adoption were identified in the creation of the strategies: solo- versus co-creation and complex versus simple creation.

Solo-creation versus co-creation
One theme focused on who was involved in the creation process of the strategy. Most symptom management strategies were created by either the patient or GP alone. Some strategies, however, emerged from complementing ideas of both the GP and the patient. These instances, in which the GP initiated a strategy to which the patient added new ideas or vice versa, were defined as emerging through co-creation (Quote 5b and 5c). Co-creations arose from spontaneous additions of the interlocutor to the strategy, or from invitations of the initiator of the strategy to involve the interlocutor (Quote 5b). Strategies created by the patient alone and co-created strategies were in nearly all instances adopted. This contrasted with GP created strategies, which were adopted in a minority of instances.

Quote 5b and 5c:
Co-creation of a strategy targeting activity level (putting refueling stops in the way; see Quote 5a). Setting: GP 1, patient 3.

Quote 5b:
The patient is invited to co-create by the GP. Setting: End of first consultation, fifth text fragment out of 15.
DO: "Yes. What I would like you to do, I mean we've got another three scheduled appointments and the next one in two weeks. What I'd like you to do in the next two weeks is to think of some time, a couple of times in the week, where you can just have half an hour, or an hour to yourself. And where you might fit that in. I'm not asking you to do it yet because we've not worked what you're going to do in that block."

Quote 5c:
The patient explains her adjustments to the strategy (she put refueling stops in the way by starting to knit). Setting: start of the second consultation, sixth text fragment out of 15.
GP: "There we go. How are you doing?"
Patient: "Okay, trying to relax. I've taken up a new hobby."
GP: "Go on?"
Patient: "Knitting; my daughter was quite keen to know... to learn how to knit, so I thought we'd try it, you know, because my mom taught me when I was younger. And you had to knit, so I said to her, will you teach me how to know; so, I thought, a form of relaxation kind of. So we sit in the evenings, I give her half an hour in the evening, and show her how to knit."
GP: "How old is she?"
Patient: "She's eight."
GP: "I was just going to say, something like that, yes."
Patient: "Yes."
GP: "Okay."
Patient: "So I have been trying."
GP: "So you just deliberately sit yourself down."
Patient: "Yes, I just..."
GP: "Anything else?"
Patient: "Yes, just wait, for half an hour."
GP: "Has anything come to any harm because of it?"
Patient: "No."
GP: "No, the world hasn't stopped, the sky hasn't fallen in."
Patient: "No, exactly, so it's good actually, it's nice to sit down and not worry so much about getting other things done. So I've got to keep it up, try and keep it up."

Complex versus simple creation

The final theme related to adoption concerned the complexity of the strategy's creation. This complexity became apparent from several aspects of the creation process. First, complexly created strategies were discussed in more and longer text fragments than simple strategies. Furthermore, while simple strategies included repetitions, the creation of complex strategies included diverse motivational or practical elements, such as giving a rationale for the strategy, making the strategy more specific and practical, empowering the patient, and expanding on previously suggested concepts for the strategy (Quote 2b and c). In a variety of instances, complex strategies were also combined with other complementing strategies (Quote 2a). Complex strategies were more likely to be adopted than simple strategies. Within the creation process of strategies, we found that diversity in the used elements was a more important characteristic in relation to adoption than the extensiveness of the discussion. For instance, we observed one GP (GP 4, patient 10; strategy of Quote 6) who repeated several times what was already discussed about the content of the strategy, while in the end the strategy was not adopted.

Quote 2b, 2c:

Complex creation of a strategy (reduce working hours; see Quote 2a) by adding diverse elements. Setting: GP 4, patient 9.

Quote 2b:

The GP empowers the patient. Setting: end of the first consultation, sixth text fragment out of ten.

Patient: "But I'm worried."

GP: "It sounds to me like you're an awful good lady to have as an employee. I think they're probably pretty, pretty happy that they've, that they've got you. And if you sell it in such a way that this is you are trying to look after your, your health, so that you can work as hard as you can."

Quote 2c:

The GP makes the strategy specific by giving practical suggestions to the patient. Setting: end of the first consultation, seventh text fragment out of 10.

GP: "I think, I think you could say very honestly, that you've got weakness on your……"

Patient: "Well she [manager of patient] knows all that, I disclosed all that in my, um, interview, and she knows about it."

GP: "No, but if you, if you say that you've got that, and that's causing other problems, from you working hard, which is, which is what's happening, and that you're needing to, needing to take some time to, to redress that balance a little bit, to keep you, to keep

you fit for working. Because what will happen is, if you keep on struggling through, at some point in the future, you're going to reach a point where you, where you can't keep on struggling through, and that will, that will be bad for them, and it'll be bad for you, and we want to, we want to avoid that."
Patient: "Yeah, you burn out."
GP: "So you sell this as you looking after yourself."
Patient: "As a preventative, yeah, prevention, not a cure."

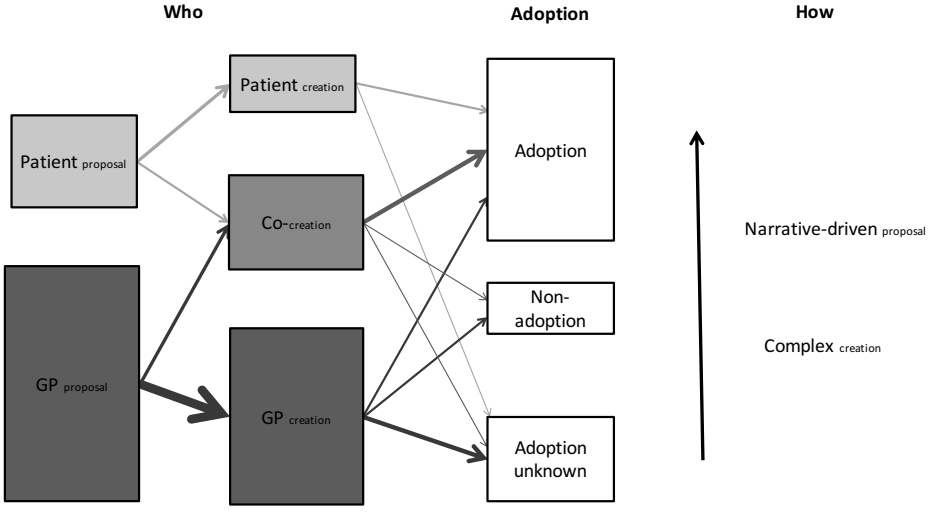
One exception to the pattern that complexly created strategies were more likely to be adopted than those with a simple creation style included strategies created by patients alone. These were often briefly discussed by the patient at one specific moment during the set of consultations, at the time the patient had already adopted the strategy (Quote 7). GPs typically did not further explore or encourage it. These strategies were highly specific and/or practical, suggesting that such characteristics strongly increased the likelihood of adoption.

Quote 7:
The patient introduces a new strategy aimed at changing cognitions and emotions (thinking 'let it take its course'). The strategy has already been adopted. Setting: middle of third consultation, GP 5, patient 11, only text fragment.
GP: "Did Dr. D check a sample of urine?"
Patient: "No."
GP: "That's maybe just the other thing that we should do there."
Patient: "Aye. No he didn't. Did the finger exam... up the rectum examination of prostate."
GP: "Yeah."
Patient: "So that was it, you know, I didn't... so generally that and, as I say, these just general aches and pains. I mean, just the general things that seem to be with me, like the stomach flares up every now and again. Some days you feel fine. The next day you're going 'oh god it's a wee bitty out of sync'. But again, it's not anything like it was before, you're more conscious now of well it's not... Well, when it happens out the blue you think what's causing this and what's the problem. That's been looked at so I'm more confident now to say 'well this isn't... let it take its course and settles down a bit' and if it flares up well fair enough, as long as it... again, if it was coming to be the stage it was getting really uncomfortable for a period, I'd just come back."
GP: "Yeah. What about the information that I gave you last time, did you have a chance to look at that at all?"

Model of adoption of symptom management strategies

Based on our analyses we propose the following conceptual model (**Figure 1**). There are several pathways to adoption of symptom management strategies, but some are more successful than others. A key element in the adoption of a strategy seems to be patient involvement, either in the proposal or in the creation of a strategy. Patients can join in spontaneously or can be encouraged by the GP to initiate or add suggestions to a strategy. GPs can create a successful strategy alone, but it may require specific effort. The likelihood that a strategy is adopted could increase if the GP aligns the strategy with the patient's narrative in a complex creation process.

Figure 1. Conceptual model of pathways to adoption.



To illustrate the success of different pathways to adoption, the dimensions of the figure reflect the number of strategies in our study that were created via specific pathways. The volume of the rectangles on the left side of the figure reflects the proportion of symptom management strategies that were proposed or created by the patient, the GP or them combined. The width of their arrows reflects the proportion of symptom management strategies created via a specific pathway. The right side of the figure shows characteristics of the proposal or creation of strategies that increase the likelihood of adoption.

DISCUSSION

Summary of main findings

Management strategies to reduce the intensity and impact of PPS in primary care emerged from an ongoing creation process by the GP and patient. We identified four themes related to the adoption of these strategies: proposal of the strategy by the patient, proposal driven by the narrative of the patient, co-creation of the strategy, and

higher complexity of the way in which the strategy was created. Our conceptual model highlighted that a key characteristic of successful pathways to adoption was involvement of the patient in the proposal or creation of a strategy.

Strengths and limitations

As far as we know, this is the first study in which the creation of symptom management strategies provided in a primary care setting is examined, specifically in relation to their adoption. The findings formed the initials steps to arrive at a working theory of action for how symptom management strategies are most likely to be adopted [358]. As to our knowledge no clear theories exist about how the adoption of symptom management strategies for PPS can be promoted [289], this conceptual model is valuable to improve the likelihood of acceptance of the strategies in daily practice. Methodological strengths of this study are the dual interdependent coding and the discussing of the analyses in a multidisciplinary team from psychiatry, psychology and general practice [358]. Although the sampling was constrained by the limited and pre-selected pool of trained GPs and patients open to a new treatment modality for PPS, we included consultations with varying characteristics, ensuring a rich data set. Another strength is that we analysed a set of three or four extended consultations, which allowed us to study the way the strategies developed over time and were evaluated in a naturalistic setting. An advantage of this method of evaluation is that it resembles evaluations as faced by GPs in daily practice. However, it has the limitation that evaluations confine themselves to what was topic of discussion during the consultations and, as a result, the adoption of some strategies was unknown and the evaluations of others could include socially desirable answers. Although we encountered several examples in which the patient seemed to try a strategy before rejecting it as a way of being polite to the GP, these strategies were coded as not adopted since patients did not indicate a promise to keep it up. We also discovered that the strategies of which the adoption remained unknown were often created by the GP, which is similar to the strategies that were not adopted. A lack of evaluation of a strategy in follow-up consultations might thus reflect a culturally determined way to politely reject the strategy. Another limitation of this study is that we cannot rule out that the GPs or patients modified an aspect of their behavior in response to their awareness of being audiotaped [322]. However, studies have shown that this effect is probably limited [359-361].

Comparison with existing literature

The types of symptom management strategies we encountered were generally in accordance with those identified in our previous study of regular primary care consultations [291]. This confirms the validity of these categories to summarize the

types of symptom management strategies for PPS. However, two differences were also apparent: we identified the novel category social support, and found that the category activity level focused on balancing activity and rest instead of resting alone. Although it was not the main aim of the previous study to explore how strategies emerged [291], the creation process of strategies differed in important aspects from our study. For example, while management strategies were mainly created by GPs with brief comments in regular consultations [291], we found that both GPs and patients extensively elaborated on some strategies in a constant process of adding elements in extended consultations. That involving patients in the therapeutic process is not a central element of the care of PPS in regular consultations was confirmed by a descriptive study [288]. Furthermore, patients with PSS have indicated that creating specific management plans is one of the aspects they miss most in regular consultation [362]. That we found that this aspect was extensively elaborated on in an enhanced primary care setting suggests that its set of extended consultations may be highly valuable to promote development of symptom management for PPS and participation of the patient herein [325].

That involvement of the patient in the creation of a strategy was the most important theme related to adoption is in line with reports that patients with PPS want to be taken seriously, to be seen as an individual and to be treated as an equal partner in the consultation [362]. This also corroborates our finding that adoption was more likely if a strategy was driven by the narrative of the patient. These findings are in accordance with the philosophical notion of the grounded theory that human beings are acting rather than responding beings and that their actions are purposeful and based on the meanings that the individual has for them [358]. Patient-centered care, which focuses on elements like patient tailoring and shared decision making [363], should therefore have a central role in guidelines for the delivery of symptom management for PPS.

Implications for research and practice

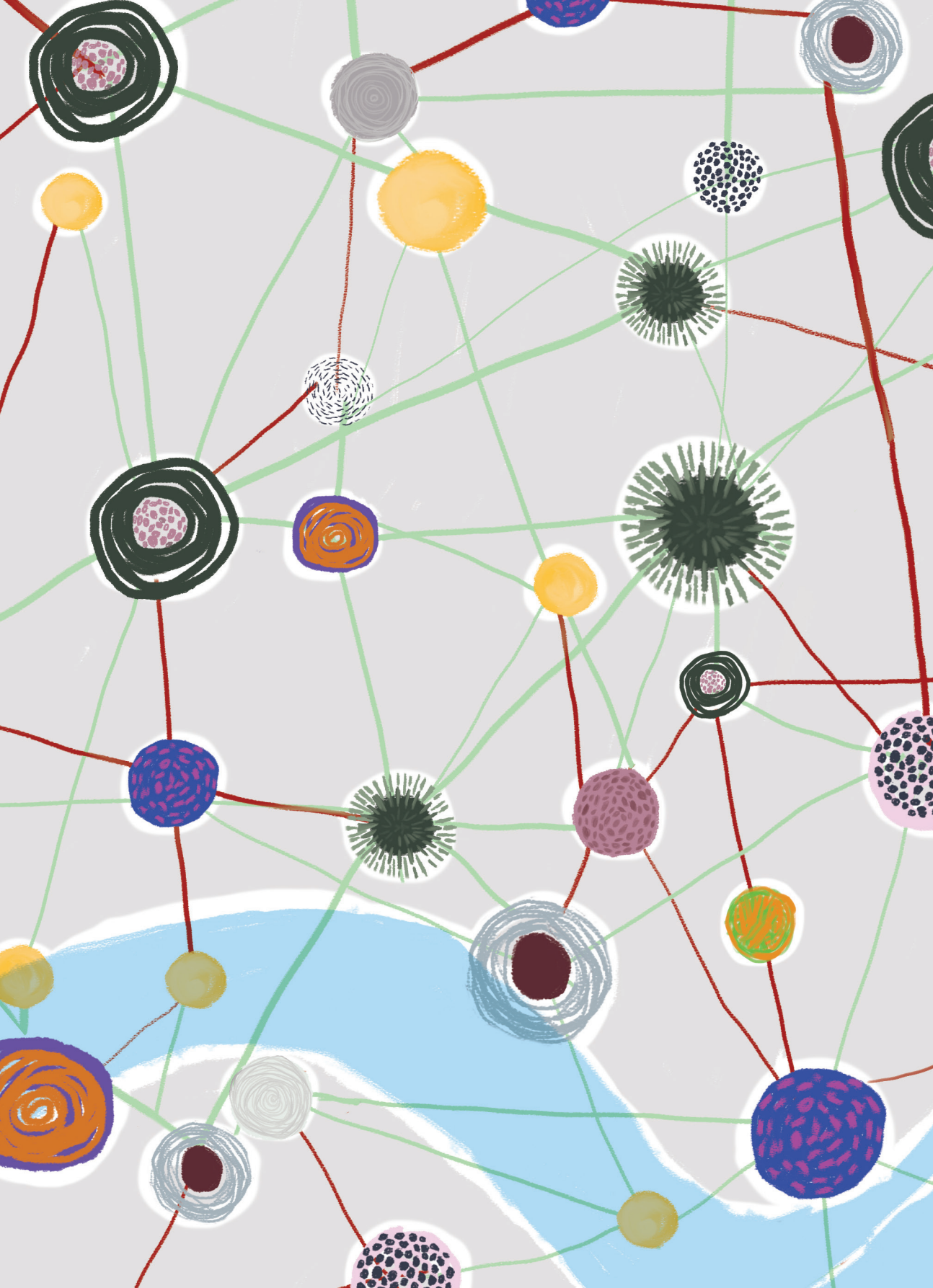
Over the last decades, a change in the traditional doctor-patient relationship has taken place, favoring a more leading role of the patient in their illness management and recovery. As a consequence, symptom management has received increasing scientific attention. Further studies are needed to increase insight into the way symptom management strategies for PPS emerge and are applied in daily practice. We realize that our conceptual model of pathways of adoption cannot be considered fully developed. Additional empirical studies and conceptual work are needed to confirm its broader applicability and usefulness. Hypothesis-testing studies could for example investigate if techniques for creating management strategies such as involving the patient are indeed associated with the adoption strategies. Furthermore, as our research focused on the adoption of strategies during a symptoms clinic, we do not know if patients put them into practice after the intervention or how effective these strategies were. Future studies

should therefore take into account how the strategies are implemented on long term and how their efficacy is rated by patients and GPs. Another potential subject for future study is to look for feedback from patients and GPs about our hypothesis that patient involvement is key to adoption. A mixed study in the form of consultation observation and a survey could refine insights about how patients and GPs can best collaborate in the creation of strategies [362].

Based on our conceptual model, GPs can focus on varying aspects in the promotion of symptom management. First of all, it is important that GPs invite patients to exchange ideas in order to involve them in the process of creation of strategies. We believe that co-creation is highly valuable as insights from patients about their preferences and symptoms can be complemented with the medical knowledge of the GP. Furthermore, it may be an efficient and effective way to promote adoption, as co-created strategies were adopted in nearly all instances while strategies created by the GP alone were adopted in less than half of the instances. If invitations for participation are turned down by patients, however, GPs can create strategies on their own. In these instances, it is essential that the GP aligns the strategy with the narrative of the patient and creates the strategy's in a complex and diverse way. Finally, natural time in between two follow-up consultations could help patients to try strategies and reflect on them and, as such, make adjustments that enable adoption. As earlier findings have suggested that follow-up consultations are only in a minority of cases planned on forehand in a regular primary care setting [288], it is important that guidelines encourage GPs to implement this as a standard element in the care for PPS.

CONCLUSION

This study showed that symptom management is extensively discussed in a consultation intervention for PPS. Involving patients in the creation of symptom management strategies by GPs has the potential to promote the adoption of these strategies, strengthened by narrative-driven proposal and more complexity in the creation. Future studies should investigate if such techniques can indeed increase the likelihood that strategies are adopted by patients, and whether they reduce symptoms and improve functioning.



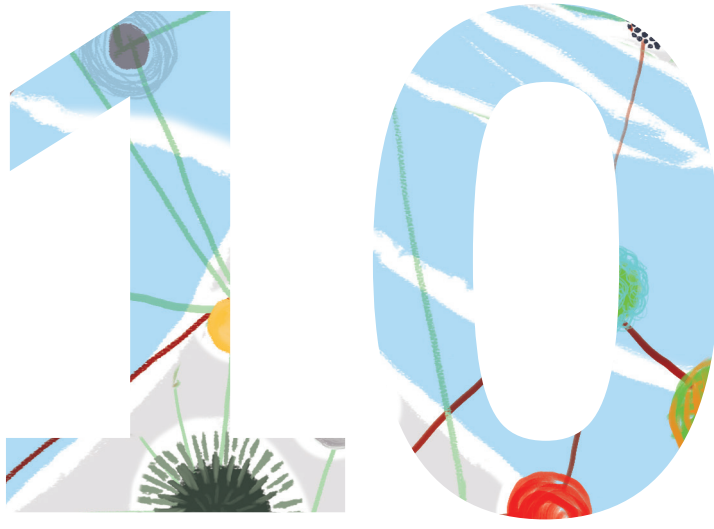
CLINICAL ASPECTS

2. Symptom networks

Symptom-specific effects of combined therapy versus psychotherapy in the treatment of mild to moderate depression: a network approach

Bekhuis E, Schoevers RA, de Boer MK, Peen J, Dekker JJM, Van HL, Boschloo L.

Psychotherapy and psychosomatics; 87:121-123.



A number of studies have reported that adding pharmacotherapy to psychotherapy has no or only small advantages in the treatment of mild to moderate depression [364-366]. These studies have used sum scores of depression rating scales as effect parameters [364-366]. However, as individual items on these scales have recently been shown to respond differentially to pharmacotherapy compared to placebo [91], effects of an addition of pharmacotherapy to psychotherapy may only be detectable by focusing on individual depressive symptoms.

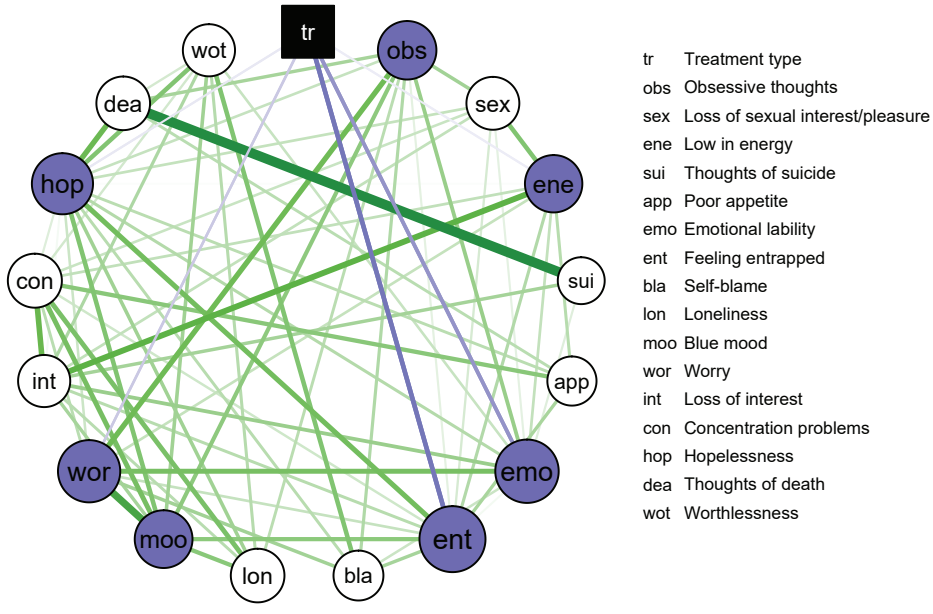
Previous studies investigating treatment responses of individual depressive symptoms did not take into account the potential interrelatedness of these symptoms. For example, patients who become less self-blaming in response to treatment may also be more likely to experience reductions in feelings of worthlessness or blue mood. Tools to consider symptom interrelatedness are offered by the network approach, which conceptualizes depression as a system of associated symptoms [94]. Earlier network studies have demonstrated that depressive symptoms are differentially related to one another [94,237,267]; however, it remains unknown if similar association patterns exist among changes in these symptoms during treatment. Taking into account these relations in a network structure provides the opportunity to determine effects of adjunctive pharmacotherapy on specific symptoms while adjusting for responses of other symptoms. This enables a differentiation between *direct* symptom-specific effects (i.e., those independent of changes in other symptoms) and *indirect* symptom-specific effects (i.e., those mediated by changes in other symptoms).

This is the first study to determine the relative efficacy of psychotherapy versus combined therapy on individual depressive symptoms. Data were derived from a randomized controlled trial comparing short-term psychodynamic supportive psychotherapy (SPSP) and this therapy combined with pharmacotherapy in patients with mild to moderate depression [364]. Participants consisted of newly registered patients at two outpatient facilities in Amsterdam (the Netherlands) of age 18-65 years with a DSM-IV defined major depressive disorder of mild to moderate severity. SPSP involves an open patient-therapist dialogue that uses supportive and insight-facilitating techniques to address the emotional background of depression and was delivered in 16 sessions of 45 minutes within a 24-week period. In the combined condition, antidepressants were provided for 24 weeks according to a protocol with several steps in case of intolerance or inefficacy: first venlafaxine, followed by fluoxetine and finally nortriptyline. Sixteen depressive symptoms were assessed at baseline and after 24 weeks with the depression subscale of the Symptom Checklist-90. Analyses were conducted in a sample consisting of all patients who started with the treatment they were allotted to (psychotherapy: N=103, combined therapy: N=83; see the online supplementary material for the sample characteristics) and the last outcome carried forward method was applied. First, we focus on the relative

efficacy of psychotherapy versus combined therapy by using individual symptoms as effect parameters and, then, differentiate between direct and indirect effects by taking into account symptom interrelatedness in a network model.

Symptom-specific efficacy of psychotherapy versus combined therapy was investigated using independent sample T-tests with change scores (post- minus pre-treatment) of depressive symptoms as dependent variables. Combined therapy was significantly more effective than psychotherapy in decreasing the symptoms feeling entrapped [ent] (Cohen's d=0.55, p<.001), emotional lability [emo] (Cohen's d=0.47, p=.002), worry [wor] (Cohen's d=0.44, p=.003), hopelessness [hop] (Cohen's d=0.41, p=.006), obsessive thoughts [obs] (Cohen's d=0.34, p=.02), blue mood [moo] (Cohen's d=0.32, p=.03) and low in energy [ene] (Cohen's d=0.31, p=.04). The remaining nine symptoms showed similar responses to psychotherapy and combined therapy (see **Figure 1**).

Figure 1. Symptom-specific effects of psychotherapy versus combined therapy.



The type of treatment is represented by the square and depressive symptoms by circles. Relative effect sizes of psychotherapy versus combined therapy on specific symptoms (all in favor of combined therapy) are indicated by the size of circles and their level of significance by circle color (violet=significant; white=non-significant). Connections in the network model are represented by lines, of which the thickness if proportional to the strength of associations. Direct associations between the type of treatment and change scores of symptoms (all in favor of combined therapy) are indicated by violet lines and associations between change scores of symptoms (all positive) by green lines.

Then, we took into account symptom interrelatedness to differentiate between direct and indirect effects of the addition of pharmacotherapy to psychotherapy. An L1-regularized partial correlation network of treatment type and change scores of all depressive symptoms was estimated (the network estimation procedure and tests for parameter estimate accuracy are described in the supplementary material). **Figure 1** shows that changes in depressive symptoms during treatment were strongly related. The strongest association was found between thoughts of death [dea] and thoughts of suicide [sui] (partial correlation=0.49), indicating that persons with an improvement in thoughts of death [dea] during treatment were more likely to experience an improvement in thoughts of suicide [sui] as well. Treatment type [tr] showed the strongest direct connections to feeling entrapped [ent] (partial correlation=0.16) and emotional lability [emo] (partial correlation=0.11), and was weakly connected to worry [wor] (partial correlation=0.04), low in energy [ene] (partial correlation=0.01) and hopelessness [hop] (partial correlation=0.01). All connections were in favor of combined therapy, suggesting that this therapy targeted these particular symptoms directly.

Despite their significant responses to the addition of pharmacotherapy to psychotherapy in our first analysis, obsessive thoughts [obs] and blue mood [moo] were not directly connected to treatment type in the network, and worry [wor], low in energy [ene] and hopelessness [hop] showed only weak direct associations to this variable. Interestingly, the network revealed that these symptoms were related to changes in feeling entrapped [ent] and emotional lability [emo], which in turn were more strongly connected to the type of treatment. This suggests that the effect of adjunctive pharmacotherapy on obsessive thoughts [obs], blue mood [moo], worry [wor], low in energy [ene] and hopelessness [hop] may largely have been indirect and could have been mediated by changes in feeling entrapped [ent] and emotional lability [emo].

A strength of this study is that the trial included a fairly random and representative sample of patients with a mild to moderate depressive disorder in secondary care. Furthermore, we estimated the network structure using l1-regularization to prevent overfitting, which has been shown to adequately control for false positive associations. However, in our relatively small sample of 186 persons, small true positive associations could have been overlooked [238]. As baseline scores in our sample differed across symptoms, it is also important to note that higher baseline severity of symptoms was associated with stronger responses to adjunctive pharmacotherapy, which is in line with previous reports [365].

In conclusion, this study showed that combined therapy outperformed psychotherapy in the treatment of some depressive symptoms and not others. Although our results are exploratory rather than conclusive, they suggest that adjunctive pharmacotherapy targeted specific symptoms (e.g., feeling entrapped, emotional lability) directly and other symptoms (e.g., obsessive thoughts, hopelessness) indirectly. As direct effects

are independent of changes in other symptoms, our findings imply that adjunctive pharmacotherapy can effectuate improvements in directly targeted symptoms in all patients irrespective of changes in other symptoms. Indirectly targeted symptoms, in contrast, may respond to an addition of pharmacotherapy to psychotherapy, but only in patients improving on symptoms mediating these responses during treatment and, therefore, reporting these symptoms before treatment. If replicated, these insights may help clinicians to predict which patients could benefit from an addition of pharmacotherapy to psychotherapy [367].

Given the differential treatment responses across symptoms, we would like to encourage other researchers to analyze individual depressive symptoms as well as their interrelatedness. Network models are highly promising in this approach as they can be expanded with other psychiatric or physical symptoms (e.g., anxiety, nausea) to provide insight into secondary or side effects of a treatment independent of its effects on depressive symptoms. Furthermore, dynamic networks of depressive symptoms during various treatment stages could reveal that changes in specific symptoms are preceded by changes in other symptoms, which may inform on pathways underlying indirect responses of symptoms to a treatment [368].

SUPPLEMENTARY MATERIAL

Sample characteristics

A total of 186 patients were included in this study, of whom 103 received psychotherapy and 83 received combined therapy. Mean age of the sample was 35.4 (SD=10.8) years and 67.7% were female. No differences in sociodemographic or depression characteristics were found between the treatment groups (see **Supplementary Table 1**).

Network estimation method

An L1-regularized weighted network of the type of treatment (psychotherapy versus combined therapy) and change scores of all depressive symptoms was estimated and visualized with R-package qgraph (see **Supplementary Table 2** for the input correlation matrix) [241]. The network estimation technique calculated partial correlations for all pairs of variables, which indicate associations among symptoms while controlling for all other variables in the network. To prevent overfitting, an /1-penalty [239] was used to estimate possible networks with different levels of sparsity. The model with the best fit to the data was selected using the extended Bayesian information criterion (EBIC) [240] with hyperparameter y=0.5 [273]. This technique has been shown to yield adequate network structures [238,273,274].

Accuracy of the estimates in the network

To investigate the accuracy of estimated connections in the network, R-package bootnet [275] was used to calculate 95% confidence intervals around connection weights. Bootstrapped confidence intervals were calculated by drawing 10,000 bootstrap samples of the data and recalculating connection weights for each sample. Although these confidence intervals can inform on the precision of parameter estimates, it is important to stress that they should not be interpreted as a test for significance of a connection being different from zero as the /1-penalty already ensured that connections included in the network model were of sufficient strength [275]. **Supplementary Table 3** shows that the confidence intervals of associations in the network were rather wide and showed overlap, implying that connection weights should be interpreted with caution. Still, several connections were significantly stronger than others. The association between thoughts of suicide [sui] and thoughts of death [dea] (partial correlation coefficient=0.49, 95%CI=0.37-0.62), for example, was significantly stronger than all other associations in the network, except for the association between depressed mood [moo] and worry [wor] (partial correlation coefficient=0.33, 95%CI=0.23-0.44). This indicates that the association between thoughts of suicide [sui] and thoughts of death [dea] is reliably one of the strongest in the network.

Supplementary Table 1. Sample characteristics at baseline

	Psychotherapy N=103	Combined therapy N=83	p
	N (%)/mean (SD)	N (%)/mean (SD)	
Sociodemographics			
Age	35.5 (11.0)	35.3 (10.6)	.94
Female	70 (68.0%)	56 (67.5%)	1.00
Education			.54
Low	13 (12.6%)	11 (13.3%)	
Middle	36 (35.0%)	35 (42.2%)	
High	54 (52.4%)	37 (44.6%)	
Depression characteristics			
Sum score of all symptoms	49.9 (8.9)	49.0 (9.5)	.49
Individual depressive symptoms			
Obsessive thoughts [obs]	3.6 (0.9)	3.5 (1.0)	.25
Loss of sexual interest/pleasure [sex]	2.6 (1.4)	2.7 (1.4)	.83
Low in energy [ene]	3.8 (1.1)	3.9 (1.0)	.44
Thoughts of suicide [sui]	1.7 (0.9)	1.6 (0.9)	.44
Poor appetite [app]	1.9 (1.2)	2.0 (1.2)	.68
Emotional lability [emo]	3.0 (1.3)	3.2 (1.4)	.47
Feeling entrapped [ent]	3.2 (1.2)	3.3 (1.2)	.49
Self-blame [bla]	3.2 (1.2)	2.9 (1.3)	.08
Loneliness [lon]	3.3 (1.2)	3.1 (1.2)	.20
Blue mood [moo]	3.8 (0.9)	3.8 (1.0)	.96
Worry [wor]	4.1 (0.8)	4.1 (0.9)	.58
Loss of interest [int]	3.3 (1.1)	3.1 (1.2)	.30
Concentration problems [con]	3.4 (1.1)	3.3 (1.1)	.44
Hopelessness [hop]	3.6 (1.1)	3.5 (1.1)	.62
Thoughts of death [dea]	2.1 (1.2)	2.1 (1.2)	.63
Worthlessness [wot]	3.3 (1.2)	3.2 (1.2)	.64

P-values are based on chi square analyses for categorical variables and independent t-tests for continuous variables.

Supplementary Table 2. Correlations between the type of treatment and change scores of depressive symptoms

	Treatment type [tr]	Obsessive thoughts [obs]	Loss of sexual interest/ pleasure [sex]	Low in energy [ene]	Thoughts of suicide [sui]	Poor appetite [app]	Emotional lability [emo]	Feeling entrapped [ent]
Treatment type [tr]	1.00	0.21	0.12	0.19	0.02	0.06	0.28	0.33
Obsessive thoughts [obs]	0.21	1.00	0.32	0.32	0.26	0.24	0.46	0.42
Loss of sexual interest/ pleasure [sex]	0.12	0.32	1.00	0.35	0.09	0.10	0.25	0.28
Low in energy [ene]	0.19	0.32	0.35	1.00	0.13	0.28	0.35	0.39
Thoughts of suicide [sui]	0.02	0.26	0.09	0.13	1.00	0.09	0.24	0.22
Poor appetite [app]	0.06	0.24	0.10	0.28	0.09	1.00	0.20	0.33
Emotional lability [emo]	0.28	0.46	0.25	0.35	0.24	0.20	1.00	0.38
Feeling entrapped [ent]	0.33	0.42	0.28	0.39	0.22	0.33	0.38	1.00
Self-blame [bla]	0.07	0.40	0.20	0.21	0.20	0.18	0.34	0.40
Loneliness [lon]	0.13	0.43	0.16	0.28	0.21	0.26	0.34	0.39
Blue mood [moo]	0.20	0.59	0.29	0.37	0.29	0.29	0.46	0.58
Worry [wor]	0.27	0.60	0.28	0.39	0.15	0.20	0.53	0.50
Loss of interest [int]	0.11	0.34	0.32	0.52	0.33	0.25	0.44	0.46
Concentration problems [con]	0.14	0.44	0.30	0.42	0.19	0.37	0.35	0.46
Hopelessness [hop]	0.25	0.50	0.30	0.37	0.33	0.34	0.45	0.57
Thoughts of death [dea]	0.13	0.38	0.10	0.19	0.62	0.27	0.25	0.22
Worthlessness [wot]	0.11	0.36	0.21	0.34	0.24	0.14	0.36	0.39

The correlation matrix consists of polyserial correlations between Treatment [tr] and change scores of depressive symptoms and Pearson correlations between change scores of depressive symptoms.

Self-blame [bla]	Loneliness [lon]	Blue mood [moo]	Worry [wor]	Loss of interest [int]	Concentration problems [con]	Hopelessness [hop]	Thoughts of death [dea]	Worthlessness [wot]
0.07	0.13	0.20	0.27	0.11	0.14	0.25	0.13	0.11
0.40	0.43	0.59	0.60	0.34	0.44	0.50	0.38	0.36
0.20	0.16	0.29	0.28	0.32	0.30	0.30	0.10	0.21
0.21	0.28	0.37	0.39	0.52	0.42	0.37	0.19	0.34
0.20	0.21	0.29	0.15	0.33	0.19	0.33	0.62	0.24
0.18	0.26	0.29	0.20	0.25	0.37	0.34	0.27	0.14
0.34	0.34	0.46	0.53	0.44	0.35	0.45	0.25	0.36
0.40	0.39	0.58	0.50	0.46	0.46	0.57	0.22	0.39
1.00	0.40	0.43	0.44	0.32	0.34	0.43	0.20	0.43
0.40	1.00	0.57	0.44	0.45	0.53	0.50	0.25	0.42
0.43	0.57	1.00	0.72	0.56	0.63	0.64	0.37	0.52
0.44	0.44	0.72	1.00	0.48	0.53	0.55	0.24	0.43
0.32	0.45	0.56	0.48	1.00	0.59	0.48	0.35	0.43
0.34	0.53	0.63	0.53	0.59	1.00	0.50	0.30	0.42
0.43	0.50	0.64	0.55	0.48	0.50	1.00	0.50	0.52
0.20	0.25	0.37	0.24	0.35	0.30	0.50	1.00	0.32
0.43	0.42	0.52	0.43	0.43	0.42	0.52	0.32	1.00

Supplementary Table 3. Partial correlations and their 95% confidence intervals between the type of treatment and change scores of depressive symptoms

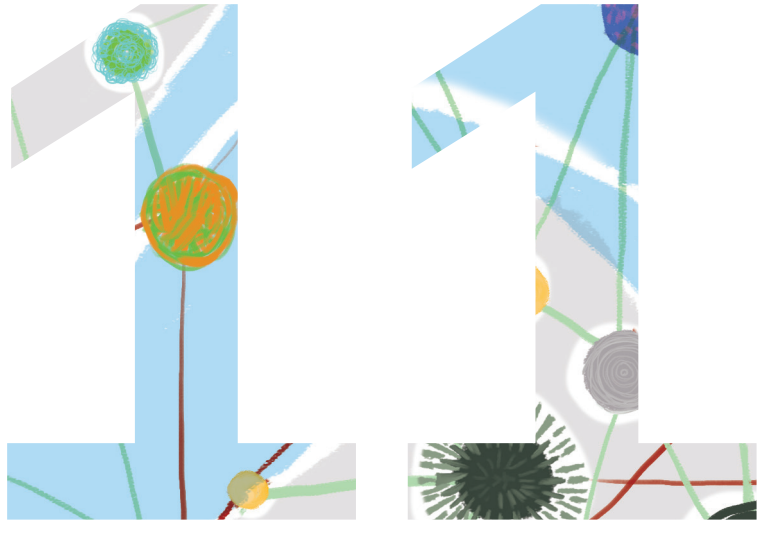
	Treatment type [tr]	Obsessive thoughts [obs]	Loss of sexual interest/ pleasure [sex]	Low in energy [ene]	Thoughts of suicide [sui]	Poor appetite [app]	Emotional lability [emo]	Feeling entrapped [ent]
Treatment type [tr]	-	0.00 (-0.08-0.08)	0.00 (-0.08-0.08)	0.00 (-0.09-0.10)	0.00 (0.08-0.08)	0.00 (0.07-0.07)	0.11 (-0.03-0.25)	0.16 (0.01-0.31)
Obsessive thoughts [obs]	0.00 (-0.08-0.08)	-	0.10 (0.00-0.21)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.00 (-0.07-0.07)	0.12 (-0.01-0.25)	0.01 (-0.07-0.10)
Loss of sexual interest/ pleasure [sex]	0.00 (-0.08-0.08)	0.10 (0.00-0.21)	-	0.16 (0.04-0.29)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.01 (-0.07-0.09)	0.02 (-0.06-0.11)
Low in energy [ene]	0.01 (-0.09-0.10)	0.00 (-0.07-0.07)	0.16 (0.04-0.29)	-	0.00 (-0.02-0.02)	0.07 (-0.06-0.20)	0.05 (-0.05-0.15)	0.07 (-0.02-0.17)
Thoughts of suicide [sui]	0.00 (-0.08-0.08)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.02-0.02)	-	0.00 (-0.04-0.04)	0.02 (-0.05-0.08)	0.00 (-0.03-0.03)
Poor appetite [app]	0.00 (0.07-0.07)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.07 (-0.06-0.20)	0.00 (-0.04-0.04)	-	0.00 (-0.05-0.05)	0.09 (-0.01-0.19)
Emotional lability [emo]	0.11 (-0.03-0.25)	0.12 (-0.01-0.25)	0.01 (-0.07-0.09)	0.05 (-0.05-0.15)	0.02 (-0.05-0.08)	0.00 (-0.05-0.05)	-	0.00 (-0.07-0.08)
Feeling entrapped [ent]	0.16 (0.01-0.31)	0.01 (-0.07-0.10)	0.02 (-0.06-0.11)	0.07 (-0.02-0.17)	0.00 (-0.03-0.03)	0.09 (-0.01-0.19)	0.00 (-0.07-0.08)	-
Self-blame [bla]	0.00 (-0.08-0.08)	0.08 (-0.03-0.18)	0.00 (-0.07-0.07)	0.00 (-0.03-0.03)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)	0.04 (-0.05-0.13)	0.09 (-0.02-0.21)
Loneliness [lon]	0.00 (-0.05-0.05)	0.06 (-0.04-0.16)	0.00 (-0.03-0.03)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)	0.00 (-0.08-0.08)	0.00 (-0.06-0.06)	0.00 (-0.06-0.06)
Blue mood [moo]	0.00 (-0.03-0.03)	0.14 (0.03-0.25)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.00 (-0.05-0.05)	0.14 (0.03-0.26)
Worry [wor]	0.04 (-0.06-0.14)	0.21 (0.08-0.35)	0.00 (-0.06-0.06)	0.05 (-0.02-0.12)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.19 (0.07-0.31)	0.05 (-0.04-0.13)
Loss of interest [int]	0.00 (-0.06-0.06)	0.00 (-0.02-0.02)	0.05 (-0.05-0.15)	0.25 (0.14-0.37)	0.10 (0.01-0.19)	0.00 (-0.04-0.04)	0.12 (-0.01-0.24)	0.07 (-0.05-0.19)
Concentration problems [con]	0.00 (-0.04-0.04)	0.01 (-0.07-0.08)	0.04 (-0.05-0.13)	0.05 (-0.06-0.17)	0.00 (-0.01-0.01)	0.15 (0.03-0.27)	0.00 (-0.03-0.03)	0.03 (-0.06-0.13)
Hopelessness [hop]	0.01 (-0.08-0.09)	0.04 (-0.04-0.13)	0.05 (-0.03-0.12)	0.00 (-0.07-0.07)	0.00 (-0.04-0.04)	0.06 (-0.03-0.16)	0.07 (-0.03-0.17)	0.20 (0.10-0.30)
Thoughts of death [dea]	0.00 (-0.06-0.06)	0.09 (0.00-0.18)	0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.49 (0.37-0.62)	0.06 (-0.03-0.16)	0.00 (-0.03-0.03)	0.00 (-0.03-0.03)
Worthlessness [wot]	0.00 (-0.05-0.05)	0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.05 (-0.04-0.14)	0.00 (-0.05-0.05)	0.00 (-0.06-0.06)	0.04 (-0.06-0.15)	0.00 (-0.06-0.06)

Self-blame [bla]	Loneliness [lon]	Blue mood [moo]	Worry [wor]	Loss of interest [int]	Concentration problems [con]	Hopelessness [hop]	Thoughts of death [dea]	Worthlessness [wot]
0.00 (-0.08-0.08)	0.00 (-0.05-0.05)	0.00 (-0.03-0.03)	0.04 (-0.06-0.14)	0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.01 (-0.08-0.09)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)
0.08 (-0.03-0.18)	0.06 (-0.04-0.16)	0.14 (0.03-0.25)	0.21 (0.08-0.35)	0.00 (-0.02-0.02)	0.01 (-0.07-0.08)	0.04 (-0.04-0.13)	0.09 (0.00-0.18)	0.00 (-0.06-0.06)
0.00 (-0.07-0.07)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)	0.00 (-0.06-0.06)	0.05 (-0.05-0.15)	0.04 (-0.05-0.13)	0.05 (-0.03-0.12)	0.00 (-0.03-0.03)	0.00 (-0.04-0.04)
0.00 (-0.03-0.03)	0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.05 (-0.02-0.12)	0.25 (0.14-0.37)	0.05 (-0.06-0.17)	0.00 (-0.07-0.07)	0.00 (-0.02-0.02)	0.05 (-0.04-0.14)
0.00 (-0.06-0.06)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.00 (-0.04-0.04)	0.10 (0.01-0.19)	0.00 (-0.01-0.01)	0.00 (-0.04-0.04)	0.49 (0.37-0.62)	0.00 (-0.05-0.05)
0.00 (-0.05-0.05)	0.00 (-0.08-0.08)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.15 (0.03-0.27)	0.06 (-0.03-0.16)	0.06 (-0.03-0.16)	0.00 (-0.06-0.06)
0.04 (-0.05-0.13)	0.00 (-0.06-0.06)	0.00 (-0.05-0.05)	0.19 (0.07-0.31)	0.12 (-0.01-0.24)	0.00 (-0.03-0.03)	0.07 (-0.03-0.17)	0.00 (-0.03-0.03)	0.04 (-0.06-0.15)
0.09 (-0.02-0.21)	0.00 (-0.06-0.06)	0.14 (0.03-0.26)	0.05 (-0.04-0.13)	0.07 (-0.05-0.19)	0.03 (-0.06-0.13)	0.20 (0.10-0.30)	0.00 (-0.03-0.03)	0.00 (-0.06-0.06)
-	0.10 (-0.01-0.21)	0.00 (-0.05-0.05)	0.10 (-0.01-0.21)	0.00 (-0.05-0.05)	0.00 (-0.05-0.05)	0.07 (-0.04-0.18)	0.00 (-0.03-0.03)	0.17 (0.05-0.28)
0.10 (-0.01-0.21)	-	0.15 (0.03-0.26)	0.00 (-0.04-0.04)	0.06 (-0.05-0.18)	0.18 (0.04-0.32)	0.10 (-0.02-0.23)	0.00 (-0.02-0.02)	0.07 (-0.05-0.19)
0.00 (-0.05-0.05)	0.15 (0.03-0.26)	-	0.33 (0.22-0.44)	0.09 (-0.01-0.20)	0.19 (0.06-0.32)	0.17 (0.06-0.27)	0.00 (-0.04-0.04)	0.10 (-0.01-0.22)
0.10 (-0.01-0.21)	0.00 (-0.04-0.04)	0.33 (0.22-0.44)	-	0.00 (-0.07-0.07)	0.06 (-0.03-0.15)	0.04 (-0.05-0.12)	0.00 (-0.02-0.02)	0.00 (-0.06-0.06)
0.00 (-0.05-0.05)	0.06 (-0.05-0.18)	0.09 (-0.01-0.20)	0.00 (-0.07-0.07)	-	0.23 (0.10-0.36)	0.00 (-0.05-0.06)	0.02 (-0.05-0.08)	0.08 (-0.03-0.19)
0.00 (-0.05-0.05)	0.18 (0.04-0.32)	0.19 (0.06-0.32)	0.06 (-0.03-0.15)	0.23 (0.10-0.36)	-	0.02 (-0.06-0.09)	0.00 (-0.04-0.04)	0.03 (-0.06-0.12)
0.07 (-0.04-0.18)	0.10 (-0.02-0.23)	0.17 (0.06-0.27)	0.04 (-0.05-0.12)	0.00 (-0.05-0.06)	0.02 (-0.06-0.09)	-	0.22 (0.12-0.31)	0.16 (0.05-0.27)
0.00 (-0.03-0.03)	0.00 (-0.02-0.02)	0.00 (-0.04-0.04)	0.00 (-0.02-0.02)	0.02 (-0.05-0.08)	0.00 (-0.04-0.04)	0.22 (0.12-0.31)	-	0.03 (-0.04-0.10)
0.17 (0.05-0.28)	0.07 (-0.05-0.19)	0.10 (-0.01-0.22)	0.00 (-0.06-0.06)	0.08 (-0.03-0.19)	0.03 (-0.06-0.12)	0.16 (0.05-0.27)	0.03 (-0.04-0.10)	-

The symptom-specific efficacy of cognitive behavioral therapy versus antidepressant medication in the treatment of depression: Results from an individual patient data meta-analysis

Boschloo L, Bekhuis E, Borsboom D, Weitz ES, Reijnders M, DeRubeis RJ, Dimidjian S, Dunner DL, Dunlop BW, Hegerl U, Hollon SD, Jarrett RB, Kennedy SH, Miranda J, Mohr DC, Simons AD, Parker G, Petrak F, Herpertz S, Quilty LC, John Rush A, Segal ZV, Vittengl JR, Schoevers RA, Cuijpers P.

World Psychiatry 2019;18:183-191.



ABSTRACT

A recent individual patient data meta-analysis showed that antidepressant medication is slightly more efficacious than cognitive behavioral therapy (CBT) in reducing overall depression severity in patients with a DSM-defined depressive disorder. We used an update of that dataset, based on seventeen randomized clinical trials, to examine the comparative efficacy of antidepressant medication vs. CBT in more detail by focusing on individual depressive symptoms as assessed with the 17-item Hamilton Rating Scale for Depression. Five symptoms (i.e., “depressed mood”, “feelings of guilt”, “suicidal thoughts”, “psychic anxiety” and “general somatic symptoms”) showed larger improvements in the medication compared to the CBT condition (effect sizes ranging from .13 to .16), whereas no differences were found for the twelve other symptoms. In addition, network estimation techniques revealed that all effects, except that on “depressed mood”, were direct and could not be explained by any of the other direct or indirect treatment effects. Exploratory analyses showed that information about the symptom-specific efficacy could help in identifying those patients who, based on their pre-treatment symptomatology, are likely to benefit more from antidepressant medication than from CBT (effect size of .30) versus those for whom both treatments are likely to be equally efficacious. Overall, our symptom-oriented approach results in a more thorough evaluation of the efficacy of antidepressant medication over CBT and shows potential in “precision psychiatry”.

INTRODUCTION

Previous studies have consistently shown that both antidepressant medication and cognitive behavioral therapy (CBT) are effective acute phase treatments for depression [369-371]. Conventional meta-analyses indicated that their efficacy is comparable [372], while a recent individual patient data meta-analysis (IPDMA) showed that antidepressant medication is slightly more efficacious than CBT [373].

IPDMA is a relatively new technique in the field of mental health, that has the advantage to use raw data rather than pooling outcomes as in conventional meta-analyses [374]. This results in higher statistical power and provides the opportunity to not only detect relatively small treatment effects but also to assess treatment efficacy in more detail.

Randomized clinical trials (RCTs) on the comparative efficacy of antidepressant medication vs. CBT have primarily focused on changes in overall depression severity, and related outcomes such as response and remission rates. Scales for assessing depression severity are often multifactorial [82,375,376], and some RCTs have shown that these subscales differ in their response to antidepressant medication vs. CBT [82,375,376].

Fried et al. [377] reported, however, that the multifactorial structure of several commonly used depression scales is not stable over time and, consequently, scale or subscale scores may be inappropriate as outcome measures. It would therefore be valuable to use data of an IPDMA, with its substantial statistical power, to assess the comparative efficacy of antidepressant medication vs. CBT in more detail; namely, by focusing on individual symptoms [91,266,378].

An additional advantage of a focus on individual symptoms is that it could help in generating hypotheses regarding the differential working mechanisms of treatment. Our group was the first to apply network estimation techniques in research on treatment efficacy, reporting that adjunctive antidepressant medication, relative to psychotherapy alone, was directly related to larger improvements in five specific symptoms (i.e., direct treatment effects), which were subsequently related to larger improvements in two other symptoms (i.e., indirect treatment effects) [266]. Adjunctive medication had no effects, neither directly nor indirectly, on nine other symptoms. As network estimation techniques can identify the complex patterns in which symptom improvements are related, they have great potential in shedding light on the processes taking place during treatment.

A detailed assessment of the symptom-specific comparative efficacy of antidepressant medication vs. CBT would be important, as it could inform clinicians more precisely about the preferred treatment option for patients with a depressive disorder in general. This is especially valuable as symptoms differ in their clinical relevance; for example, an effect on “suicidal thoughts” would be more relevant than an effect on “loss of weight”.

The findings might also help in identifying patients who, based on their pre-treatment symptomatology, would benefit the most from one treatment relative to the other. That is, patients primarily suffering from symptoms that are affected by one treatment would probably benefit more from that treatment than patients primarily suffering from other symptoms. A focus on individual symptoms may therefore also be an important step in "precision psychiatry".

To our knowledge, this is the first IPDMA that focused on individual symptoms in a more detailed assessment of the comparative efficacy of antidepressant medication vs. CBT in the treatment of depression. In a second step, we used network estimation techniques to test whether the identified effects were direct or indirect. Thirdly, we wanted to explore whether information about the symptom-specific effects of antidepressant medication vs. CBT could help in identifying patients who, based on their pre-treatment symptomatology, are likely to benefit more from one treatment relative to the other.

METHODS

Sample

Our starting point was a recent IPDMA including data of individual patients who participated in RCTs directly comparing antidepressant medication vs. CBT [373]. Only studies including outpatients with a primary diagnosis of a DSM-II, DSM-III or DSM-IV depressive disorder (major depressive disorder or dysthymia), as established by a standardized diagnostic interview, were included. In addition, CBT was required to be manualized and use cognitive restructuring as the main treatment component. Studies focusing on remitted patients or including patients younger than 18 years were excluded. Studies including patients with comorbid general medical disorders were not excluded, and no language restrictions were applied.

Twenty-four studies were identified for the IPDMA. Authors were invited via email to provide original data from their trial. If the authors did not respond to the request after one month, a reminder email was sent and efforts to contact co-authors were made. Authors of four studies were unreachable and authors of another four studies no longer had access to the data. Of the remaining sixteen studies, fourteen [379-392] used the Hamilton Depression Rating Scale (HAM-D) to assess depressive symptoms and were included in the current analyses (responsible for 1,472 patients). Three studies [393-395] were added (responsible for 384 patients) as an update of the dataset.

Of the 1,856 included patients, 843 (45.4%) were randomly assigned to CBT and 1,013 (54.6%) to antidepressant medication (i.e., several studies had double-sized medication conditions). In total, 1,513 (81.5%) had complete pre-treatment data on all individual

depressive symptoms, with no difference between antidepressant medication and CBT (82.0% versus 80.9%, p=0.53). Of the patients with complete pre-treatment data, 1,070 (70.7%) had complete post-treatment data on all individual items and comprised the sample for our analyses. Slightly more patients had incomplete post-treatment data in the medication relative to the CBT condition (31.4% versus 26.7%, p=0.04).

Assessment of depressive symptomatology

Individual depressive symptoms were assessed by separate items of the 17-item HAM-D [396], both before and after treatment (i.e., 8-20 weeks after the pre-treatment assessment). The HAM-D includes seventeen items, which are scored from 0 to 4 (items 1-3, 7-11,15-16) or 0 to 2 (items 4-6, 12-14, 17). We chose the HAM-D for the assessment of individual depressive symptoms, as this was the most often used instrument in studies on the comparative efficacy of antidepressants vs. CBT. Overall depression severity was calculated by the sum of all HAM-D items.

Statistical analyses

All non-network analyses were performed using SPSS (version 24). First, baseline characteristics were compared between patients in the medication vs. CBT condition using X^2 statistics for categorical variables (i.e., gender and recruitment setting) and independent samples t-tests for continuous variables (i.e., age, timing of post-treatment assessment, overall depression severity and individual depressive symptom scores). Then, paired t-tests were performed to compare post-treatment to pre-treatment symptom scores for medication and CBT separately. Independent samples t-tests were performed to determine whether change scores of individual symptoms differed between the two treatment conditions.

As a sensitivity analysis, we repeated the above tests in a dataset (N=1,513) in which change scores of patients with missing post-treatment symptom scores were imputed using multiple imputation with baseline symptom scores and socio-demographics as predictor variables.

In a next step, statistical software R (version 3.3.3) was used to estimate a network including treatment condition (medication vs. CBT) and changes in individual depressive symptoms. As this combines a dichotomous variable (treatment condition) with continuous variables (change scores), the network was estimated with package mgm [397] using a mixed graphical model. This package uses the glmnet package [398] to fit penalized generalized linear models to perform neighborhood selection [399]. Package qgraph [241] was used to visualize the network.

In this network, a direct connection between treatment condition and a change in a particular symptom indicates a direct symptom-specific effect, which is independent of

the symptom-specific effects on other symptoms. If treatment condition is connected to a particular symptom via one or more changes in other symptoms, it may be interpreted as an indirect symptom-specific effect.

As a sensitivity analysis, we estimated networks including changes in individual symptoms for antidepressant medication and CBT separately. The package network comparison test [400] was used to test whether the networks differed.

Lastly, we explored whether it was possible to identify those patients who are likely to benefit more from one treatment relative to the other. We expected that patients primarily suffering from symptoms that were affected by one treatment would benefit more from that treatment than patients primarily suffering from other symptoms. To test this, two specific severity measures were calculated, based on the simple sum of scores on those pre-treatment symptoms that: a) were significantly impacted by one treatment relative to the other; and b) were the least impacted by one treatment condition relative to the other. We expected that the effect of treatment condition on overall depression severity would be larger in patients with higher scores on the first specific severity measure, but not in patients with higher scores on the second specific severity measure.

RESULTS

Baseline characteristics

Of the 1,070 included patients, 500 received CBT and 570 received antidepressant medication. Patients in the two conditions did not differ in any of the socio-demographic and study characteristics, except for recruitment setting (see **Table 1**). In addition, no significant differences were found with respect to baseline overall depression severity or any of the individual depressive symptoms.

Table 1. Sample characteristics

	ADM condition (N=570)	CBT condition (N=500)	p
Gender (% female)	67.0	68.8	0.53
Age at baseline (years, mean±SD)	39.8±12.7	40.0±12.6	0.85
Recruitment (%)			<0.001
Community	29.1	18.6	
Clinical	51.2	59.2	
Both	19.6	22.2	
Timing of post-treatment assessment (weeks, mean±SD)	13.2±3.1	13.3±3.1	0.44
Overall depression severity (HAM-D total score, mean±SD)	18.6±4.8	18.3±4.5	0.30
HAM-D scores for individual symptoms (mean±SD)			
Depressed mood	2.2±0.8	2.2±0.8	0.64
Feelings of guilt	1.6±0.9	1.6±0.9	0.25
Suicidal thoughts	0.8±1.0	0.7±0.9	0.14
Early night insomnia	1.0±0.9	1.0±0.9	0.36
Middle night insomnia	1.1±0.8	1.1±0.8	0.57
Early morning insomnia	0.8±0.8	0.7±0.8	0.34
Work and activities	2.4±0.9	2.3±0.9	0.15
Retardation	0.5±0.7	0.6±0.7	0.38
Agitation	0.7±0.9	0.7±1.0	0.22
Psychic anxiety	1.7±0.9	1.7±0.9	0.65
Somatic anxiety	1.6±0.9	1.6±0.9	0.73
Gastrointestinal symptoms	0.6±0.7	0.5±0.7	0.18
General somatic symptoms	1.4±0.6	1.5±0.6	0.38
Genital symptoms	1.2±0.8	1.1±0.8	0.31
Hypochondriasis	0.6±0.8	0.7±0.8	0.16
Loss of weight	0.3±0.6	0.3±0.6	0.26
Insight	0.1±0.4	0.1±0.3	0.33

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

Symptom-specific comparative efficacy of antidepressant medication vs. CBT

Although overall depression severity improved significantly in both treatment conditions (both p<0.001), this improvement was slightly but significantly larger for antidepressant medication than for CBT (Cohen's d=.15) (see **Table 2**). All individual symptoms also showed significant improvements in both conditions (all p values ≤0.01 for CBT and ≤0.04 for antidepressant medication), but significant differences between the two conditions were found only for the symptoms "depressed mood", "feelings of guilt", "suicide", "psychic anxiety" and "general somatic symptoms". These symptoms showed larger improvements for medication than for CBT, although effect sizes were small (Cohen's

d ranging from .13 to .16). No significant effects of treatment condition were found for the other twelve symptoms.

The results of the sensitivity analysis based on the imputed dataset were similar; p values differed somewhat, but improvements between conditions remained comparable.

Table 2. Improvements in depressive symptomatology in the ADM versus CBT condition

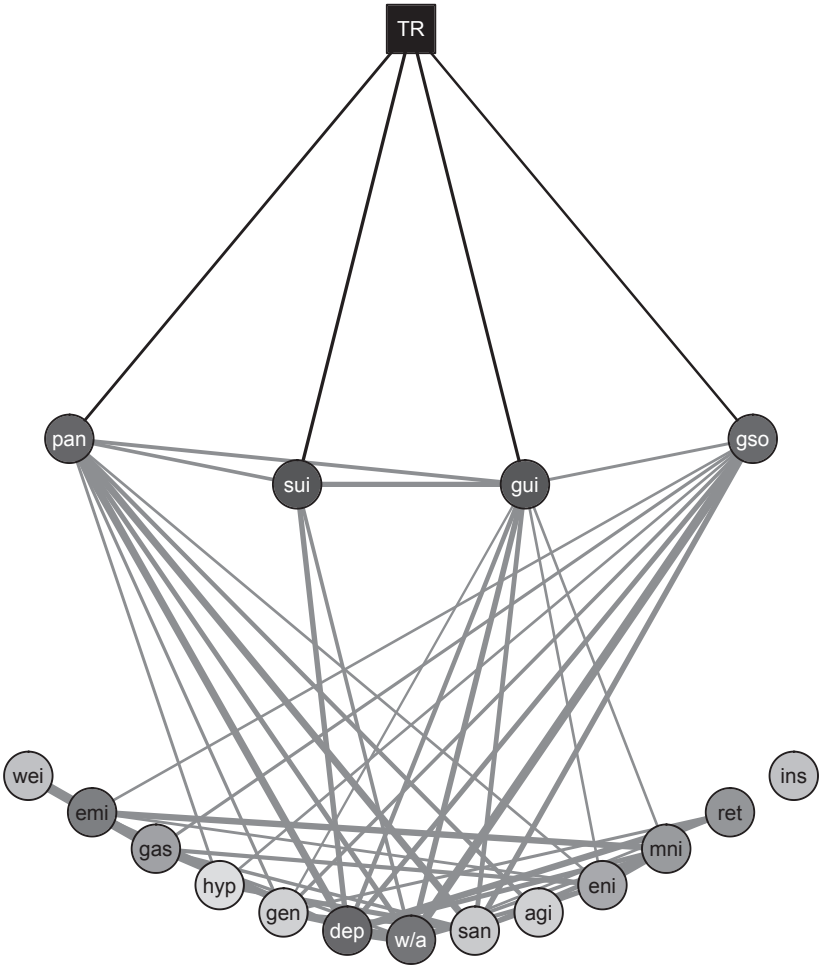
	ADM condition (N=570)	CBT condition (N=500)	p	Cohen's d
Overall depression severity (HAM-D total score, mean±SD)	10.49±6.84	9.43±6.87	0.01	.15
HAM-D scores for individual symptoms (mean±SD)				
Depressed mood [dep]	1.43±1.11	1.28±1.19	0.03	.13
Feelings of guilt [gui]	0.99±1.14	0.82±1.05	0.02	.16
Suicidal thoughts [sui]	0.60±1.04	0.44±0.97	0.007	.16
Early night insomnia [eni]	0.52±0.95	0.49±1.00	0.56	.03
Middle night insomnia [mni]	0.50±1.02	0.45±0.95	0.39	.05
Early morning insomnia [emi]	0.38±0.98	0.29±0.96	0.13	.09
Work and activities [w/a]	1.53±1.29	1.39±1.33	0.08	.11
Retardation [ret]	0.40±0.67	0.36±0.76	0.32	.06
Agitation [agi]	0.35±0.97	0.37±0.97	0.68	–.02
Psychic anxiety [pan]	1.00±1.09	0.85±1.17	0.03	.13
Somatic anxiety [san]	0.68±1.10	0.69±1.16	0.88	–.01
Gastrointestinal symptoms [gas]	0.32±0.78	0.29±0.71	0.47	.04
General somatic symptoms [gso]	0.75±0.92	0.64±0.83	0.05	.13
Genital symptoms [gen]	0.55±0.94	0.57±0.98	0.77	–.02
Hypochondriasis [hyp]	0.29±0.84	0.32±0.94	0.67	–.03
Loss of weight [wei]	0.15±0.69	0.15±0.66	0.91	–.00
Insight [ins]	0.04±0.40	0.04±0.40	0.78	–.00

ADM – antidepressant medication, CBT – cognitive behavioral therapy, HAM-D – Hamilton Depression Rating Scale

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

To provide more information about the direct and indirect symptom-specific effects of antidepressant medication vs. CBT, a network was estimated including treatment condition and changes in individual symptoms (**Figure 1**). The previously identified symptom-specific effects on "feelings of guilt", "suicide", "psychic anxiety" and "general somatic symptoms" were, at least partly, direct, indicating that the larger improvements for antidepressants relative to CBT could not be fully explained by any of the other direct or indirect symptom-specific effects.

Figure 1. Direct and indirect symptom-specific effects of antidepressant medication (ADM) vs. cognitive behavioral therapy (CBT).



Treatment type (ADM vs. CBT) is represented by the square, and individual symptoms as circles. Black lines indicate direct connections between treatment condition and improvements in individual symptoms (i.e., direct treatment effects), whereas grey lines indicate connections between improvements in individual symptoms (i.e., potential indirect treatment effects). Thicker lines represent stronger connections. Darker circles represent stronger effects of ADM over CBT. The network is presented at γ=0.25.

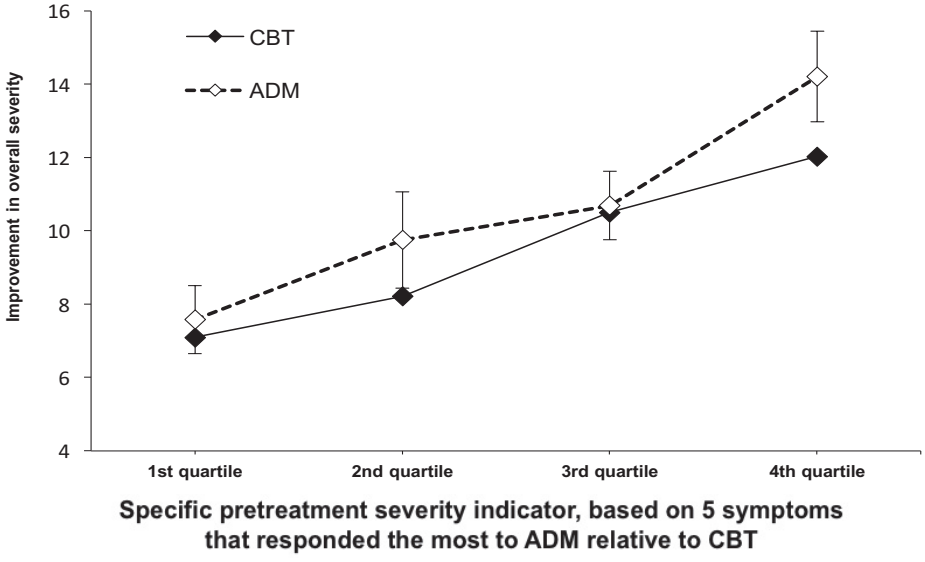
The previously identified symptom-specific effect on “depressed mood” was fully indirect, suggesting that improvements in the four symptoms that were directly affected by medication relative to CBT resulted, both directly and indirectly, in a larger improvement in “depressed mood”.

Sensitivity analyses showed that the two networks including changes in all seventeen individual symptoms did not differ for antidepressant medication vs. CBT (p=0.77 for global connectivity, and Holm-Bonferroni corrected p values all ≥0.95 for individual connections).

Identifying patients who benefit more from antidepressant medication relative to CBT

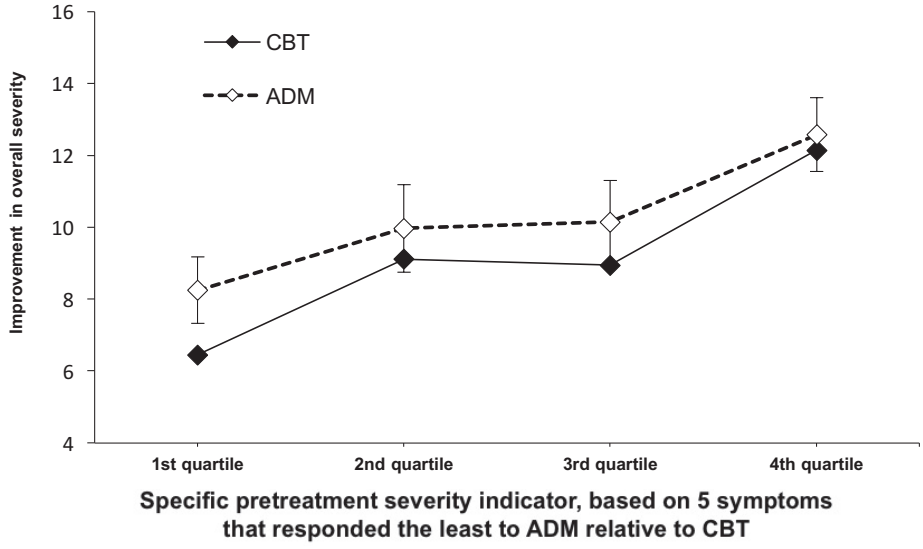
Lastly, we explored whether it was possible to identify patients, based on their pre-treatment symptomatology, who would benefit more from antidepressant medication than from CBT. A specific pre-treatment severity measure was calculated based on the five symptoms that were significantly affected by medication over CBT. As expected, only those patients with the highest scores on this measure improved significantly more from antidepressants than from CBT (Cohen's d=.30, see **Figure 2**).

Figure 2. Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the most to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT).



As a comparison, another specific severity measure was calculated based on the five symptoms that responded the least to antidepressant medication relative to CBT (i.e., "agitation", "somatic anxiety", "genital symptoms", "loss of weight", and "insight"; all non-significant effects), which was only weakly correlated with the first severity measure (r=.23, p<.001). As expected, patients with the highest scores on this measure did not show significantly larger improvements for antidepressant medication relative to CBT, but, interestingly, patients with the lowest scores did (Cohen's d=.33, see **Figure 3**).

Figure 3. Stratification based on increasing scores on a specific pre-treatment severity indicator calculated by summing the five symptoms that responded the least to antidepressant medication (ADM) relative to cognitive behavioral therapy (CBT).



DISCUSSION

Principal findings

To our knowledge, this study is the first IPDMA that considered individual depressive symptoms in the comparison of the efficacy of antidepressant medication vs. CBT. Five symptoms (i.e., “depressed mood”, “feelings of guilt”, “suicidal thoughts”, “psychic anxiety” and “general somatic symptoms”) showed larger improvements in the medication relative to CBT condition, whereas no differences were found for the twelve other symptoms. Network estimation techniques revealed that all effects were direct, except for the indirect effect on “depressed mood”. Our findings further suggest that information about the symptom-specific efficacy could help in identifying those patients, based on their pre-treatment symptomatology, who are likely to benefit more from antidepressant medication than from CBT.

Symptom-specific efficacy of antidepressant medication vs. CBT

Weitz et al. [373] recently demonstrated that antidepressant medication was slightly more efficacious in improving overall depression severity than CBT. This conclusion was not only confirmed by our updated IPDMA, but also extended by providing detailed information about the symptom-specific efficacy. As the effect on overall depression

severity was small (effect size of .15), it is not surprising that the five identified symptom-specific effects were also small (effect sizes ranging from .13 to .16).

Small effects are, however, not uncommon in studies on the comparative efficacy of treatments and, indeed, two studies comparing antidepressant medication with a placebo-control condition found larger effects on both overall depression severity (highest effect size was .40) and individual symptoms (highest effect size was .49) [91,401]. Interestingly, these studies showed that antidepressant medication was especially efficacious in improving several cognitive and affective symptoms, which is in line with our findings. Given the robustness of the findings as well as the clinical relevance of the identified symptom-specific effects (especially the effect on “suicidal thoughts”), we believe that it would be unwise to ignore the beneficial effects of antidepressant medication over CBT.

To our knowledge, no previous RCTs have examined a broad spectrum of individual depressive symptoms in comparing the efficacy of antidepressant medication vs. CBT, but some have considered subscales based on combinations of symptoms [82,375,376]. None of these studies have found differences in the efficacy on cognitive and affective symptoms [82,375,376], although two identified short-term effects that disappeared at a later stage [375,376].

An explanation for the identified symptom-specific effects in our study could lie in the use of IPDMA, which, with its substantial statistical power, makes it possible to detect relatively small effects. In addition, the strategy of combining symptoms into subscale scores may have obscured differential responses at the level of individual symptoms. Fournier et al. [82] found, for example, no differences between cognitive therapy and antidepressants on the “mood” subscale, which incorporates both symptoms that did (i.e., “depressed mood”) and did not (i.e., “work and activities” and “retardation”) differ between treatment conditions in our study. This combination of findings underlines the importance of sufficient statistical power as well as a focus on individual symptoms in research on treatment efficacy.

Although Fournier et al. did not find any differences in subscales of cognitive and affective symptoms, they did find that cognitive therapy was more efficacious than medication in improving atypical-vegetative symptoms [82]. Additional analyses showed that this effect was only present for hypersomnia, but not increased appetite. It is important to note that these two atypical-vegetative symptoms are not included in the 17-item HAM-D and, thus, are not considered as outcomes in our study.

We believe that it would be important for future studies to also consider atypical-vegetative symptoms as well as other clinically relevant symptomatology (e.g., anxiety symptoms or alcohol problems). In addition, it would be interesting to consider other outcomes that are clinically relevant, such as various aspects of quality of life or daily functioning, in order to provide a more thorough evaluation of treatment options.

Direct and indirect symptom-specific effects of antidepressant medication vs. CBT

Our study used network estimation techniques to shed light on the mechanisms of change during treatment. These analyses revealed that four of the five symptom-specific effects were direct (i.e., "feelings of guilt", "suicidal thoughts", "psychic anxiety" and "general somatic symptoms") and, thus, were independent of any of the other direct or indirect symptom-specific effects of antidepressant medication over CBT. The effect on "depressed mood" was indirect, indicating that the larger improvement was only present in patients who also experienced larger improvements in other symptoms in the medication relative to CBT condition.

It is however important to note that the network estimations employ regularization techniques that set very small connections to zero and, thus, conservatively identify the most relevant connections. This indicates that, in reality, treatment type may have a very weak direct effect on "depressed mood" and, thus, that the effect of antidepressant medication over CBT would not be fully indirect.

The network further revealed that improvements in symptoms were related in very complex patterns, with connections that were often intuitively plausible. It is, for example, easy to imagine that patients reporting less depressed mood after treatment often also reported fewer problems with work and activities, whereas patients reporting fewer gastrointestinal symptoms often reported less loss of weight. Interestingly, the networks were similar for the two treatment conditions, indicating that, regardless of the treatment, patients tend to report the same simultaneous symptom improvements. The only difference between the treatment conditions, thus, lies in the magnitude of improvement of the five symptoms that were specifically affected by antidepressant medication over CBT.

Although our findings demonstrate potential in generating hypotheses regarding the mechanisms of change during treatment, it is important to remark that changes in symptoms were assessed simultaneously and, consequently, the temporal relationships between them remain unknown. To examine the actual dynamics of symptoms over time, it would be more appropriate to use experience sampling method data, including multiple assessments with short time intervals [402]. For such research, it would be valuable to also consider other clinically relevant outcomes, as well as factors that are hypothesized to play a role in the working mechanisms of treatment, such as therapeutic alliance or social support.

Identifying patients who benefit more from antidepressant medication relative to CBT

Our findings showed that, in general, antidepressant medication was more efficacious than CBT in improving "depressed mood", "feelings of guilt", "suicidal thoughts", "psychic anxiety", and "general somatic symptoms" (effect sizes ranging from .13 to .16). This

suggests that patients primarily suffering from these five symptoms would benefit more from antidepressant medication than from CBT, which was supported by our exploratory analyses. Only patients with the highest scores on these five symptoms showed significantly and substantially larger improvements in overall depression severity after medication relative to CBT (effect size of .30). In contrast, antidepressants and CBT were equally efficacious for patients with lower scores on these symptoms. Our findings, thus, may be an important step in "precision psychiatry", as they can inform clinicians more precisely about the preferred treatment option based on the pre-treatment symptomatology of a patient.

Strengths and limitations

Strengths of the current study were that we used data from an updated IPDMA, which enabled us to assess treatment efficacy in more detail by focusing on individual symptoms. Although several studies have used network analysis techniques to examine the relations between depressive symptoms at a single time point [237,265,267,403], we were the first to use these techniques on changes in symptoms over time in order to distinguish direct and indirect treatment effects [266].

However, a focus on symptoms also brings challenges. For example, some studies have shown that the inter-rater reliability of several HAM-D items was poor [404], whereas others were more positive [405]. Therefore, more research is needed on the reliability and validity of assessing individual symptoms, especially as a measure of treatment efficacy. In addition, the number of response categories on the HAM-D differs across symptoms. Sensitivity to detect changes in symptom severity may be higher for symptoms with more response categories and this could explain the fact that, in general, the largest symptom-specific effects in our study, as well as in the study of Hieronymus et al. [91], were observed for symptoms with more response categories.

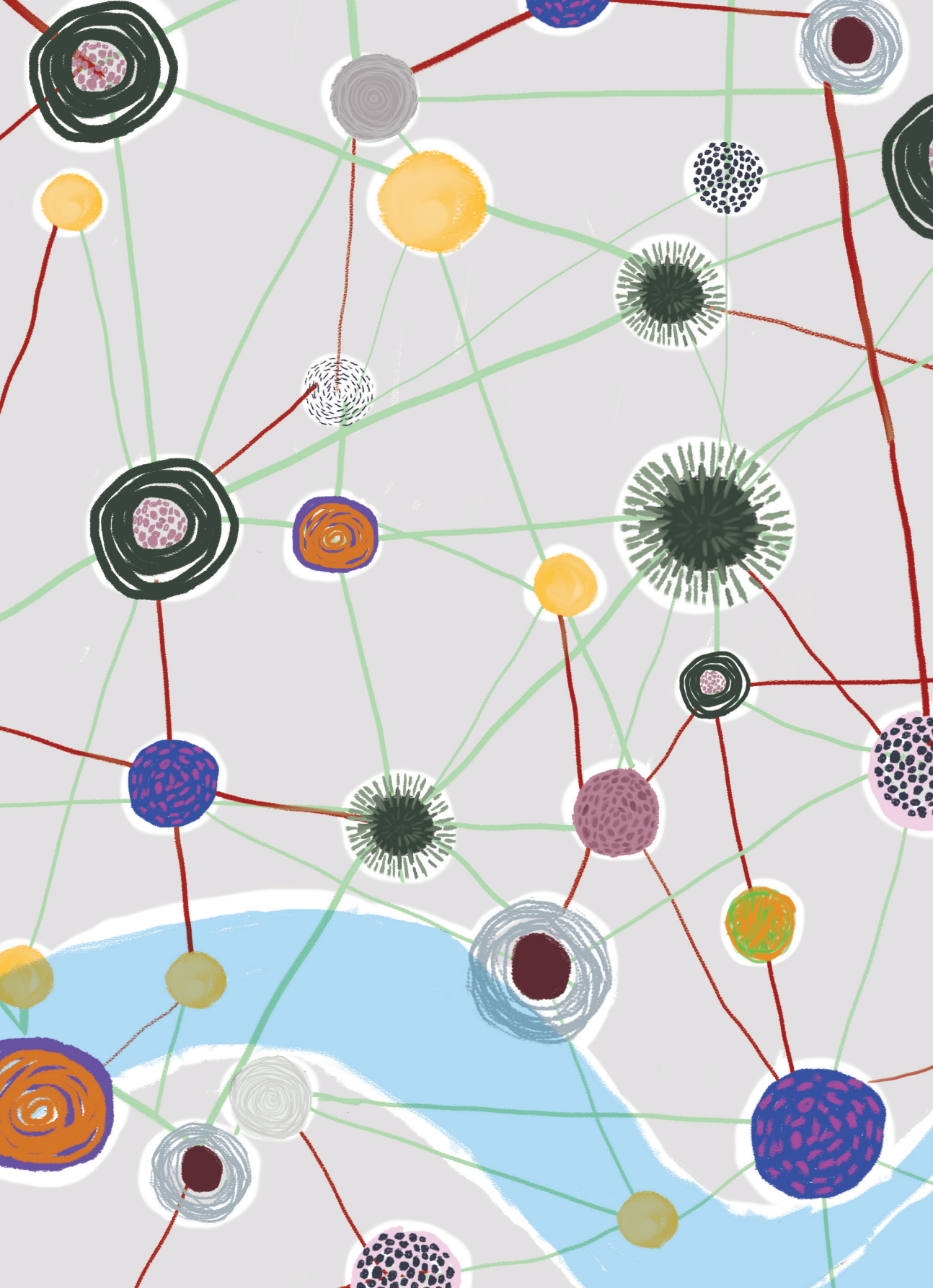
The HAM-D items comprise a relatively narrow scope of possible outcomes and, therefore, it would be valuable to also consider other outcomes that are clinically relevant. It would also be interesting to consider other treatment options and to differentiate between antidepressant medication types, which are known to have different side effects [401].

CONCLUSIONS

Our study showed that antidepressant medication was more efficacious than CBT in improving five, but not twelve other, depressive symptoms. Although the five symptom-specific effects were small (effect sizes of .13 to .16), the specific symptoms, such as "suicidal thoughts", were all clinically relevant and, therefore, it would be unwise to

ignore them. In addition, exploratory analyses suggested that this information could be helpful in “precision psychiatry”: based on the pre-treatment symptomatology of patients, it was possible to identify those who were likely to benefit more from antidepressant medication than from CBT (effect size of .30) and those for whom both treatments were equally efficacious.

We think that such a symptom-oriented approach will be a step forward in research on treatment efficacy and we strongly encourage other researchers to adopt this approach in studies on other treatment options and/or to consider other outcomes.



General discussion

Partly based on: Bekhuis E, Olde Hartman TC, Boschloo L, Lucassen PLBJ.
A novel approach to psychopathology: the example of depression.

Br J Gen Pract 2019;69:146-7.

The aim of this thesis was to get a deeper understanding of the co-occurrence of depressive, anxiety and somatic symptoms. The first part focused on epidemiological aspects of this co-occurrence, while the second part examined its clinical aspects in consultations and interventions. In this chapter, we draw up the balance. What do the results tell us about the map of body and mind? Which insights do we get into the association between depressive, anxiety and somatic symptoms, its underlying mechanisms and its specificity? Which implications do these findings have from a clinical and scientific perspective?

Findings in perspective

The association between depressive, anxiety and somatic symptoms

We showed that depressive and anxiety symptoms and somatic symptoms frequently co-occur. The prevalence of somatic symptom clusters was two to four times higher in patients with a depressive or anxiety disorder compared to persons without a depressive or anxiety disorder (Chapter 2). This association was apparent for both cognitive/affective and neurovegetative depressive and anxiety symptoms (Chapter 5). Furthermore, the co-occurrence has a negative effect on prognosis. We found that persons with multiple somatic symptom clusters had a two times higher risk of persistence of a major depressive disorder than patients without somatic symptoms (Chapter 4). It is therefore not surprising that the co-occurrence was an important subject of conversation between patients and physicians in primary care consultations (Chapter 8). The strength and consistency of the relation between depressive, anxiety and somatic symptoms underline that it is crucial for prevention and treatment programs to take into account all types of symptoms in order to improve patients' outcomes.

Our findings do not only indicate that the association between depressive, anxiety and somatic symptoms has negative consequences; they also showed that it could comprise an important treatment opportunity. That is, as depressive and anxiety symptoms improved during an intervention, somatic symptoms improved simultaneously (Chapter 10 and 11). We suggested that some of these improvements in somatic symptoms could be mediated by direct treatment effects on depressive or anxiety symptoms. For instance, the somatic symptom low in energy responded indirectly to the addition of pharmacotherapy to psychotherapy, and part of this effect may have been mediated by direct treatment effects on the depressive symptoms feeling entrapped or emotional lability (Chapter 10). On the other hand, we found that antidepressants indirectly effectuated a greater improvement in depressed mood than cognitive behavioral therapy, which may partly have been mediated by improvements in general somatic symptoms (Chapter 11). Targeting depressive and anxiety symptoms in patients with somatic

symptoms or vice versa could therefore be an effective strategy in the treatment of patients with both symptom dimensions. In primary care consultations, patients and GPs also took advantage of this simultaneous improvement by creating symptom management strategies aimed at negative emotions in order to improve somatic symptoms (Chapter 8 and 9).

Underlying mechanisms

To improve the outcome of patients with co-occurring depressive, anxiety and somatic symptoms, it is crucial to unravel the mechanisms leading to this association. Therefore, this thesis explored three mechanisms that have been suggested to explain their co-occurrence: 1) the symptom types are expressions of the same underlying construct, 2) they directly influence each other, and 3) they have shared risk factors. The first hypothesis that depressive, anxiety and somatic symptoms reflect one underlying construct was acknowledged by some patients in consultations for persistent physical symptoms, who described these symptoms as an integrated whole with depressive and anxiety symptoms (Chapter 8). Our empirical findings, however, provided conflicting evidence for this theory. The hypothesis was supported by that specific symptoms of the depressive, anxiety as well as somatic domain responded in a similar way to interventions (Chapter 10 and 11). In addition, we examined the co-development of depressive and anxiety versus functional somatic symptoms during adolescence, as it has been suggested that functional symptoms are expressions of depressive and anxiety symptoms in children [50]. Indeed, we found patterns of symptom development that could be in line with the theory that children learn to interpret and express the signals as affective rather than somatic symptoms while they mature (Chapter 2). As we were not able to study this underlying mechanism directly, however, our findings form a basis for further research.

In contrast to findings that might suggest a common underlying construct, we found that depressive and anxiety symptoms more strongly clustered with each other than with somatic symptoms (Chapter 2 and 5). Some patients with persistent physical symptoms also recognized this distinction between the symptoms as they firmly rejected that their somatic symptoms were part of an affective disorder in consultations (Chapter 8). Still, we found that the clusters of depressive/anxiety and somatic symptoms were strongly related (Chapter 2 and 5). This is in accordance with research in a large primary care sample [406], which demonstrated that the best fitting factor structure of these symptoms consisted of a general factor incorporating shared variance between the symptom domains, but also separate factors for depressive, anxiety as well as somatic symptoms incorporating their unique variance [406]. Our studies took a more detailed look, and demonstrated further heterogeneity within clusters of depressive/anxiety and

somatic symptoms as individual symptoms showed unique patterns of co-occurrence and responses to treatment (Chapter 5, 6, 10, 11). These findings indicate that although depressive, anxiety and somatic symptoms may have a common basis that accounts for some of their variance, they also have their own specific characteristics. These common as well as specific characteristics are captured in a hybrid model [407,408].

Our findings provided some evidence for the second mechanism: depressive, anxiety and somatic symptoms directly influence each other [51,178]. This theory was recognized by patients with persistent physical symptoms, who frequently described them in primary care consultations (Chapter 8). They described relations with unidirectional as well as bidirectional causal interferences and referred to vicious circles in which somatic symptoms and emotions kept worsening each other. We first examined this theory empirically by studying if somatic symptoms could influence depressive symptoms. We studied if specific clusters of somatic symptoms predicted the two-year prognosis of major depressive disorder (Chapter 4). We found significant predictive effects for cardiopulmonary, gastrointestinal and general symptoms. This association did not change substantially after adjusting for covariates (e.g., psychiatric characteristics, somatic diseases, lifestyle factors and disability; except for a small change after adjusting for the severity of baseline depressive symptoms), suggesting that the somatic symptom clusters had a direct negative impact on the depressive disorder. This association was specific for somatic symptom clusters that were chronic and occurred in combination with other clusters (Chapter 4). This might indicate a dose-response effect, which could be in line with the theory that symptoms directly influence each other.

Furthermore, we found that psychosocial reasons for encounter in primary care weakly predicted if a subsequent health problem constituted FSS (Chapter 7). This might indicate that the psychosocial problems caused functional somatic symptoms at a later moment in time. Interestingly, this association was not apparent in frequent attenders. This probably reflects the complex organization of consultation patterns, which is known to be influenced by a considerable number of interacting factors [311-313].

Other indirect support for the theory that symptoms directly impact on each other is provided by our finding that somatic symptoms may respond indirectly to an intervention, mediated by direct effects of this intervention on depressive and anxiety symptoms, and vice versa (Chapter 10 and 11). Interestingly, we found that the core depressive symptom depressed mood responded better to the addition of antidepressants to psychotherapy compared to psychotherapy alone (Chapter 10) and SSRIs compared cognitive behavioral therapy (Chapter 11). These responses seemed not to be direct, but indirect via improvements in other symptoms, which could include anxiety or somatic symptoms. This indicates that depressed mood may respond to these interventions because it is causally related with anxiety and somatic symptoms. These findings

highlight the importance of considering such causal trans-dimensional relations to understand the effects of interventions on core psychiatric symptoms. As we examined the responses of symptoms during the same time period, however, conclusions about the temporal ordering of indirect treatment effects are precluded. Still, a recent longitudinal study corroborated that somatic symptoms can mediate treatment effects of cognitive behavioral therapy for insomnia on depressive symptoms [409]. In order to gain more insight into the influence of causal relations among symptoms on their responses to an intervention, more longitudinal research with larger samples is warranted.

Finally, we investigated the third mechanism: depressive, anxiety and somatic symptoms share risk factors [51,222,410]. We investigated a number of suggested risk factors (including sociodemographic characteristics, psychiatric and somatic comorbidity, lifestyle, life events, parenting style) and found that none of them explained the co-occurrence (Chapters 2-4). Previous prospective studies have indicated that the magnitude of the effects of these factors on depressive, anxiety and somatic symptoms is very small, even though the effects were significant [51,106,107,114,178,228]. Therefore, these external factors on their own probably do not have an important role in explaining the co-occurrence.

Specificity of associations

It has repeatedly been argued that the complexity of the organization of symptoms does not match the rigid definitions of disorders in classification systems [411,412]. This realization has supported changes towards a more dimensional classification [411,412]. The DSM-5 has for instance abandoned the classification of somatic symptoms based on their organ system in somatic symptom disorder, included an anxiety specifier for depressive disorder, and introduced cross-cutting symptom dimensions regardless of the primary disorder [16,413]. Our findings support such a dimensional approach instead of a disorder-focused approach as we showed that all symptoms have common characteristics that lead to clustering on varying hierarchical levels between which boundaries are fuzzy [232,265,378,406]. For instance, we found that depressive/anxiety and somatic symptoms formed two dimensions (Chapter 2 and 5), which were strongly related. Similarly, although all somatic symptoms were connected within the somatic dimension, subdimensions formed based on body systems that did not match the categories of chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome (Chapter 5 and 6). The body system subdimensions had both differential and similar characteristics. All somatic subdimensions showed for example comparable cross-sectional associations to depressive and anxiety disorders (Chapter 3), while only three of the four predicted the course of major depressive disorder (Chapter 4).

Our results also underline that symptom domains are heterogeneous [69,80,93]. This heterogeneity was apparent for patterns of co-occurrence and response to treatment. For instance, although anxiety and guilt were both part of the cognitive/affective subdimension, anxiety showed a ten times stronger association with the somatic dimension than guilt (Chapter 5). Furthermore, antidepressants were more effective for the depressive symptoms depressed mood and guilt but not thoughts of suicide than cognitive behavioral therapy (Chapter 11). That individual symptoms within the same symptom domain show differential responses to treatment, even in opposite directions, has also been indicated by other work [91,409]. This is not surprising given that some somatic symptoms are well-known side effects of psychopharmaceutic agents [414]. Still, it underlines that clinically highly important characteristics of specific symptoms can be concealed when they are combined into a sum score [69,378].

A dimensional classification favors symptom or syndrome labels over diagnostic labels. Interestingly, we showed that most patients used this approach in consultations for persistent physical symptoms by referring to their complaints as “fatigue” or “worry” instead of “chronic fatigue syndrome” or “anxiety disorder” (Chapter 8). Labels for affective disorders that were introduced by physicians could be rejected firmly by patients. Nevertheless, other patients openly spoke about their experiences with affective disorders. This inconsistency probably reflects the different ways in which patients view such labels. Some patients have reported that they feel that labels for psychiatric disorders are helpful to remove blame from themselves and indicate that treatment options are available [415]. Other patients, however, feel that these labels are stigmatizing as they insinuate mind-body dualism and are too simplistic to fully explain their symptoms [321]. Furthermore, it has been highlighted that labels can lead to medicalization of everyday problems, alienate patients from their experience and decrease perceived self-control, and in this way worsen symptoms [61,416]. To avoid such unfavorable effects, it has been argued that physicians should introduce labels for psychiatric disorders with care [61]. Preferably, the patient and physician create a narrative together that captures the symptoms and their underlying mechanisms in the patient’s own words [417]. Still, clinical observations indicate that labels are increasingly incorporated in patients’ narratives. It should be noted, however, that it is unclear if this is a result of the integration of labels in everyday language, or if patients feel that this is the appropriate way to communicate with physicians.

Dueling with dualism in clinical care

Due to the ancient dualistic culture in Western medicine, the care for depressive, anxiety and somatic symptoms has become splintered. This is apparent from the split between psychiatry and somatic disciplines and the tendency of physicians to focus on either field

in the consultation [288,418]. This indicates that patients with co-occurring depressive, anxiety and somatic symptoms can easily be missed and/or undertreated. Our findings therefore stress that physicians from all disciplines should adequately consider this co-occurrence in their assessments and management. Nevertheless, some physicians have reported to find it challenging to bring up the combination of the symptom domains [326,327]. They sometimes unintendedly ignore or block emotional clues of patients with somatic symptoms [343], even though such patients typically seek social support [419]. To enhance integration of the care for these types of symptoms, important steps have been made in health care. Numerous multidisciplinary programs have been developed with encouraging effects on overall health [420-423]. A collaborative care treatment for depressive symptoms in patients with cancer, for example, lowered depressive symptoms, pain and fatigue severity and improved functioning [421]. Furthermore, more insight has been derived into the effects of interventions on symptoms from multiple dimensions (e.g., Chapter 10 and 11), which could help to identify treatment modalities that are most effective for patients with depressive, anxiety as well as somatic symptoms. Finally, training programs are currently being developed for general practitioners, who have a central role in the treatment of patients with depressive, anxiety as well as symptoms [325,362], which strongly focus on communication.

In consultations for patients with depressive, anxiety and somatic symptoms, clinical experts commonly advice patient-centered communication [318,356,362]. This concentrates on staying closely to the experience of the patient, showing empathy and shared decision making [424]. Central is that the patient feels understood and supported and is an equal partner in the consultation [424]. Patients have reported that they highly value such elements of patient-centered care as it gives them the feeling that they are taken seriously [322]. We found that involvement of the patient in the creation of management strategies was the most important characteristic associated with the adoption of symptom management strategies (Chapter 9). Furthermore, it has been shown that patients are much more likely to adopt explanations that are co-created than those that are created entirely by the physician [425]. This is in line with the development of patients' explanatory models we observed if the physician and the patient collaboratively moved towards novel types of explanations (Chapter 8).

Despite that physicians are frequently encouraged to adopt patient-centered communication, it has been demonstrated that some of the recommended pillars for this type of communication are inconsistently used in consultations for depressive, anxiety and somatic symptoms [343,426-431]. Adopting the network approach as an underlying framework may help physicians to adopt a patient-centered communication style. First, the approach encourages physicians to concentrate on symptoms that are relevant to the specific patient, as well as external triggers and causal relations that the patient has

experienced. In addition, symptoms in a network can be ordered according to view of the patient and, therefore, it may come naturally to avoid the use of diagnostic labels or dualism embedded in the medical realm. Third, since a network consists of small building blocks (symptoms) instead of large constructs (disorders), it may be easier to identify targets for treatment that seem manageable. Finally, the network approach advocates low-intensity treatment like symptom management strategies instead of long psychotherapies or medication, as small interventions can have dramatic effects via ongoing feedback loops among symptoms [15].

A potentially valuable tool to incorporate the network approach into clinical care is a data-driven network that can be constructed if a patient monitors symptoms during several weeks with ecological momentary assessment [15,84,432,433,433]. Such a personalized network provides a draft of the way symptoms and external triggers may interact in a specific individual, and can be used as a basis to create a person-specific network that is accordance with the experience of the patient. This person-specific network can be used in treatment to identify potential targets for interventions on three levels: 1) external triggers of symptoms, 2) central symptoms, or 3) connections among symptoms [15]. Trying to eliminate external triggers, for example by solving relational problems that triggered worry, is a good starting point. However, not all external triggers can be removed, and feedback loops among symptoms might continue even after triggers have been eliminated. The next step is to treat specific symptoms, especially if they are central in the network. For example, a short treatment of hot flushes in a depressed postmenopausal woman with hormone replacement therapy might improve insomnia and result in a cascade of improvements in other symptoms (less fatigue, more concentration, and less guilt, worry and sadness). In this context, interventions specifically targeted at individual symptoms such as web-based mini-interventions for worry and insomnia are highly promising [434]. A final treatment option is to target connections in the network, such as feeling guilty over concentration problems. In this instance, cognitive techniques to lessen the tendency of an individual to blame themselves could give symptoms the opportunity to recover and help to build resilience for when symptoms recur. Before data-driven networks can be implemented as a tool in clinical care, however, exploratory research on several fundamental terrains is warranted, including whether the graphs offer more insight into mechanisms underlying symptoms than a regular consultation, and whether they are feasible to use in time-restrained consultations.

By identifying specific targets for treatment, the application of the network approach could also help to identify interventions that are likely to be effective for an individual patient [433]. We found that this “precision medicine” has the potential to increase efficacy of interventions for depressive symptoms (Chapter 11). Furthermore, tailoring symptom management to the patient’s narrative seemed to be an important prerequisite

for the adoption of strategies (Chapter 9). An easily applicable way to personalize treatment in clinical care is to focus on symptom profiles of patients. Our findings indicated for example that SSRIs were more effective in the treatment of patients with specific depressive, anxiety and somatic symptoms (e.g., thoughts of suicide, panic, general somatic symptoms) than cognitive behavioral therapy (Chapter 11). Taking into account such responses of differential (types of) symptoms to interventions could help to balance whether the burden and side effects of an intervention outweigh its potential benefits for a particular person. In this respect, focusing on symptom dimensions such as cognitive/affective, neurovegetative and musculoskeletal symptoms has the advantage of offering parsimonious information that can easily be converted to clinical practice. However, individual symptoms capture a higher level of heterogeneity and, because they have varying levels of clinical urgency, could help to predict the benefits of an intervention for a person more specifically. For example, suicidality is of higher importance to target with an intervention than concentration problems, while the latter is more urgent when a patient's job requires a high concentration level than when the job does not.

Methodological considerations

For the interpretation of the results of this thesis, several methodological aspects should be taken into account. Although we have discussed various issues in detail in the corresponding chapters, we would like to highlight some considerations that need further reflection.

This thesis made use of several databases that were restricted to specific situations and populations. Examples include the extended set of consultations with specially trained GPs and patients with multiple persistent physical symptoms (Chapter 8 and 9) and the sample of patients with a mild to moderate depressive disorder (Chapter 10). A limitation of this focus is that it reduces the generalizability of the results to, for instance, regular primary care consultations with patients with persistent physical symptoms (Chapter 8 and 9) and all patients with a depressive disorder (Chapter 10). This underlines the strength of the population based databases that were used for others studies in this thesis (Chapter 2 and 6). Furthermore, most databases focused on patients with one primary type of symptoms, such as persistent physical symptoms or a depressive disorder. Although patients with one of these types of symptoms often also report other types of symptoms addressed in this thesis, it is important to keep in mind these studies did not focus explicitly on patients who reported the combination of depressive, anxiety and/or somatic symptoms. An exception is the NESDA database (Chapter 3, 4 and 5) [172], which included patients with depressive as well as anxiety disorders. To increase insight into the population of patients with the co-occurrence of depressive, anxiety and somatic symptoms, more studies with a transdiagnostic inclusion process are warranted.

Another limitation includes that it was difficult to differentiate between somatic symptoms sufficiently and insufficiently explained by somatic or psychiatric disorders. To determine which somatic symptoms were functional, we used self-report questionnaires (e.g. Chapter 2) as well as diagnostic codes registered by GPs in electronic records (e.g. Chapter 7). Even though a clinical assessment by a GP may more reliably indicate if a symptom is or is not sufficiently explained by diseases than the answer of a patient to a brief question without further explanation about these symptoms, both methods are not fully reliable. This problem reflects the difficulty in clinical practice to establish if a symptom is sufficiently explained by somatic or psychiatric diseases. As the presentation of diseases strongly differs across patients (take for instance the poor correlation between abnormalities on MRIs and experienced pain in patient with a spinal disc herniation) [30], it is difficult to determine if a symptom is more severe or persistent than can be expected based on a particular disease. Furthermore, due to varying opinions across clinicians about with which level of certainty a symptom can be classified as functional [30], it is challenging to formulate one uniform definition of functional somatic symptoms. Several important classification systems have shifted their focus to the presence of multiple and/or persistent somatic symptoms that are disturbing for the patient, independent of whether these symptoms are explained or unexplained by disorders [16, 43]. This approach of neglecting the presence of underlying diseases but focusing on what is observed (i.e., the symptom), which was adopted in several studies of this thesis (Chapters 3, 4, 5, 6, 8, 9, 10 and 11), is highly promising to increase uniformity in research and clinical practice.

Several chapters of this thesis concentrated on the differential characteristics of individual depressive, anxiety and/or somatic symptoms. This focus increased insight into symptom-specific characteristics, but it increased also the number of conducted tests and, therefore, the risk of type I errors [435]. We used regularization in network models to lower this risk [398]. However, it has been questioned whether this method is strict enough, especially in the study of treatment effects [436,437]. We did not use stricter corrections for multiple testing because of the exploratory nature of our research questions. Therefore, it is important to keep in mind that hypothesis-testing studies are needed to confirm some hypotheses that have been generated by our studies.

A final consideration is related to our use of individual items of rating scales to measure specific symptoms. As these scales have been designed for analyses with scale scores, they have several limitations in the analysis of individual symptoms. First, the inter-rater reliability of single items has been questioned [69,437,438]. Second, as some scales measure only the frequency of symptoms (e.g., the Four-Dimensional Symptom Questionnaire [174]), the items' clinical relevance in terms of associated distress and functional impairment remains unclear. The absence of cut-offs for clinical relevance and

variation in answering categories in some rating scales is also suboptimal [274]. Finally, as individual items vary considerably across scales [66], it is difficult to compare the results of studies based on different scales. For future studies on individual symptoms, it is essential to increase the quality of assessment, for instance with a novel scale which assesses individual symptoms with multiple items [69]. The development of such a scale offers the opportunity to adopt a multidimensional approach in which there is attention for symptoms that have empirically or historically been highlighted but are not included in current classification systems (e.g., the frustration and embarrassment which were frequently described by patients with persistent physical symptoms [Chapter 8]) [54,236,403].

Directions for research

This thesis postulated several hypotheses to explain the relation between depressive, anxiety and somatic symptoms. More prospective studies are needed to determine whether these mechanisms indeed explain the co-occurrence. In contrast to generalizing mechanisms to all patients with depressive, anxiety as well as somatic symptoms, it should be considered that it is also possible that the mechanisms explain the co-occurrence in specific individuals and contexts. We found that patients recognized this heterogeneity as their described relations between persistent physical symptoms and emotions in consultations differed across persons, symptoms and situations (Chapter 8). That explanations can be person- and symptom-specific has also been empirically confirmed. Ecological momentary assessment studies have indicated that low mood has a stronger temporal association with fatigue than stress [439], and that this association with stress is strong in some individuals but absent in others [440]. This specificity of mechanisms stresses that it is key to identify which explanations fit which patient, for which ecological momentary assessment has significant potential [441].

A second issue that should be considered is that not isolated mechanisms, but rather the cumulative effects of their dynamic interplay may lead to the co-occurrence of depressive, anxiety and somatic symptoms. This dynamic conceptualization of medicine has an intuitive fit with clinical reality [442]. For instance, it could explain that some patients are stable for a long time but relapse very rapidly after a relatively minor event in their life [443-446]. Although this complex system approach is gaining attention in the literature, empirical support remains sparse. One promising validation method is to search for the heavy-tailed data distribution that is characteristic for a complex system [295,296,447]. This distribution is in line with that depressed patients have either low or high symptom levels [448], but has to our knowledge never been studied for anxiety and somatic symptoms. Second, according to the complex systems theory, the co-occurrence of depressive, anxiety and somatic symptoms is more likely to occur in persons with

stronger cross-connections in a network between these symptom domains than persons with weaker cross-connections [449]. Studying whether the strength of cross-connections is associated with the development of the co-occurrence of depressive, anxiety and somatic symptoms, both across persons and within persons over time, is therefore an interesting validation method [444]. The principles of the complex system approach can also be applied to patients' consultation patterns, for instance by using complexity measures (Chapter 7) [295,299]. An interesting topic is if patients with a more complex (i.e., more diverse) consultation pattern have a higher risk of sudden bursts of consultations than persons with a less complex consultation pattern.

As network analysis is a novel approach in research, many topics remain open for study. Firstly, network studies that have so far been conducted have mainly focused on symptoms and, as such, often ignored the potential effects of external factors. Recently, statistical methods have been developed to combine symptoms with external factors in one network [450]. By combining symptoms as well as external factors such as biological, psychological, social and existential factors in one multi-layered hybrid model [407,408], it is possible to identify common underlying constructs, direct symptom-symptom interactions, and shared risk factors that might play a significant role in the relation between depressive, anxiety and somatic symptoms. Authors have so far also focused on networks within persons, while interactions among people could influence this [451]. Therefore, future studies could focus on the way a network of a person is affected by a higher-order system of interacting people, ranging from the impact of a head-to-head conversation with a physician to cultural influence. Furthermore, the network approach has been introduced with symptoms and external factors with negative influence as elements of the system [55,452,453]. However, positive sensations and prognostically favorable external factors are indispensable parts of daily life and the symptom's development [454,455]. Therefore, they should be included in network models too. Besides that this would provide a richer overview of the dynamics within a person, it could also help to highlight the positive sides of elements that are typically depicted as negative in medicine. For instance, depressive symptoms have been claimed to help people solve complex problems by minimizing disruption of rumination and sustaining analysis of the problem [456].

Although statistical methods for the construction of networks can help to *explain* processes underlying symptoms, it should be considered that symptoms and their underlying mechanisms constitute a personal experience and have a meaning and a purpose to people. How factors are observed by the outside world reflects different patient realities and meanings, which are highly relevant in clinical care [408,457]. To gain more insight into this *understanding* of symptoms and their underlying mechanisms, it is important to combine a quantitative focus with qualitative methods, for example by

analyzing patient's narratives [458,459]. This becomes apparent from the way patients described persistent physical symptoms and emotions in consultations (Chapter 8). Although these types of symptoms are seen as distinct categories in the medical realm, some patients completely integrated the two in their narratives. It should therefore be kept in mind that the way a typical network model is set up (i.e., with individual symptoms) may not compel with the view of each patient. In order to align with the patient in ecological momentary assessment, it would be best to discuss such assumptions beforehand and adjust the questionnaire to the patient's point of view.

Although clinical guidelines typically recommend the use of symptom management strategies, antidepressants or cognitive behavioral therapy for patients with depressive, anxiety and somatic symptoms [289,460,461], little is known about which of the options has the highest efficacy for particular patients. While we have considered the symptom-specific effects of antidepressants and psychotherapy in persons with a primary depressive disorder, future research could focus on: a) the effects of other interventions, on b) a broader spectrum of symptoms, in c) patients with co-occurring depressive, anxiety and somatic symptoms. One interesting comparison would be the relative efficacy of varying types of antidepressants. Although it is common knowledge that TCAs are more effective for pain symptoms but have more anticholinergic side effects than SSRIs [462,463], less is known about their relative effects on other specific depressive, anxiety and somatic symptoms. Studies focusing on the effects of such drug classes on more types of symptoms could help to increase insight into which interventions may be most effective for which patients with co-occurring depressive, anxiety and somatic symptoms.

A future perspective

In the historical perspective, it became apparent that numerous conceptualizations of the relation between depressive, anxiety and somatic symptoms have dominated the medical realm throughout history [1]. In recent decades, the biopsychosocial model has attempted to supersede the reductionist biomedical model, but has not fully succeeded [5]. Many authors have called for a multidimensional, multifactorial and dynamic conceptualization of medicine [8,55,446,464,465]. The complex systems approach in the network perspective may be this conceptualization. It abandons categorical classifications, allows for the consideration of factors from many different levels (e.g., biological, psychological, social, existential levels) and provides a rationale for the non-linear development of pathology [15]. Furthermore, in this discussion we explained that the approach might help to enhance patient-centered communication and personalization of treatment. As such, it may be the key to increase knowledge about the co-occurrence between depressive, anxiety and somatic symptoms, both regarding its epidemiological

and clinical aspects. The promise of the approach is reflected in the booming literature on its conceptualizations and potential applications [94]. More of such work is needed in order to investigate the basic assumptions and statistical underpinnings of the approach. Currently, however, the most important challenge lies in the translation of the conceptual model to everyday clinical practice for physicians.

A final note

We end this thesis by taking a step back. The way we view depressive, anxiety and somatic symptoms is not static. Theories changed throughout history: somatic theories originated in physically-oriented Antiques medicine, machine-like theories were created in the Industrial Age, and brain disease theories thrived together with brain investigations [1]. In this context, the complex system theory fits well with the 21st century's focus on complex systems among people via social media, economies via import and export and countries via flight paths. Similarly, where previous labels suggested a biomedical underlying mechanism ("hysteria" was derived from the Greek word for uterus), labels from the current imaging era tend to emphasize what is or is not observed ("medically unexplained symptoms" or, more recently, "persistent physical symptoms") [1]. That approaches in medicine are subject to changes teaches us that our conceptualization resembles a well substantiated mind map more than the reality. This map is an indispensable basis to get a grip on reality and to shape health care. However, we should not lean too heavily on it. Instead of imposing our medical conceptualizations and labels on patients, we should listen to their ideas and engage in a dialogue to formulate explanations together. This interplay between the patient and the physician designs the most fruitful body-mind maps.

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SUMMARY

Depressive and anxiety symptoms are highly prevalent in the general population and associated with extensive impairment in daily functioning. Patients with such symptoms often also experience somatic symptoms like headache, nausea and back pain. Somatic symptoms can be signs of physical or psychiatric disorder, but a considerable proportion, the so-called functional somatic symptoms, cannot be traced to underlying medical disease and may be the result of a complex interplay between peripheral and central processes. Although co-occurring depressive, anxiety and somatic symptoms lead to a lower quality of life and higher health costs than these symptom domains apart, much remains unknown about the mechanisms underlying their association.

Prior research was mainly based on definitions of depressive, anxiety and somatic symptom disorders as exemplified in diagnostic classification systems. As such, assessments focused on a pre-defined set of symptoms, which were summed up to one scale score. Due to a high level of heterogeneity within and overlap between such scales, this approach has been criticized. Focusing on symptom dimensions or individual symptoms could help to increase our understanding of which symptoms are important in the co-occurrence of depressive, anxiety and somatic symptoms and which symptoms respond well to specific interventions. This thesis aimed to illuminate epidemiological and clinical aspects of the co-occurrence of depressive, anxiety and somatic symptoms while focusing on symptom dimensions and individual symptoms.

Epidemiological aspects

The thesis started with exploring the symptom domains from childhood (when the symptoms first occur and their vulnerability develops) to adulthood (when most symptoms have manifested themselves). In a large community sample followed in the TRAILS study from age 10 to 26 years, we investigated patterns of co-development of depressive/anxiety versus functional somatic symptoms in Chapter 2. As previous studies had indicated heterogeneity for these trajectories across symptoms and persons, we accounted for both. We found that all possible patterns of parallel and diverging developmental patterns of the two symptom types were experienced by some persons. Still, no person experienced decreasing depressive/anxiety symptoms and increasing functional somatic symptoms. Developmental patterns did not show relevant associations with sociodemographic characteristics, negative life events and perceived parenting style. We hypothesized that one of the potential mechanisms underlying the observed developmental patterns includes progressing skills to express depressive and anxiety symptoms affectively rather than physically during adolescence. However, more research is needed to investigate this mechanism directly.

The thesis continued by studying the specificity of the co-occurrence of depressive, anxiety and somatic symptoms in adults by revealing symptom domains with the most important role in this association. We used data from NESDA, a large cohort of persons with a depressive and anxiety disorder as well as healthy controls. Chapter 3 investigated cross-sectional associations of specific depressive and anxiety disorders with dimensions of somatic symptoms. It showed that associations were strong, as patients with a depressive and/or anxiety disorder reported two to four times more often somatic symptoms than healthy controls. Major depressive disorder was most strongly associated with all dimensions of somatic symptoms, followed by generalized anxiety disorder, social phobia, panic disorder and agoraphobia, while dysthymia was not associated with any dimension of somatic symptoms. The co-occurrence was not specific with respect to the type of somatic symptom dimension. Furthermore, associations were not explained by chronic somatic diseases, sociodemographic characteristic and lifestyle factors. This study therefore showed that the co-occurrence is independent of such external factors, and that there is some specificity on the level of disorders.

Chapter 4 examined the association between somatic symptom dimensions at baseline and the course of major depressive disorder. Cardiopulmonary, gastrointestinal and general symptoms predicted the two-year persistence of major depressive disorder, but only when two or more of these dimensions were present. Musculoskeletal symptoms, in contrast, were not associated with the course of major depressive disorder. Associations were partly explained by baseline severity of depressive symptoms, but not by comorbidity with somatic and psychiatric disorders, treatment factors, lifestyle factors and disability. This indicates that somatic symptoms may have direct negative effects on depressive symptoms, which are dependent on the type and number of somatic symptom dimensions.

An approach that concentrates on individual symptoms and the emerging structure of their correlations is the network approach. Chapter 5 focused on the co-occurrence between individual depressive, anxiety and somatic symptoms in a cross-sectional network model. Individual symptoms showed highly differential numbers, strengths and patterns of associations in this network. Important bridge symptoms between the depressive/anxiety and somatic symptom domain were for example anxiety and excessive perspiration, while insomnia and muscle pain were weakly connected to the other domain. Differential associations could not be detected when depressive and anxiety symptoms were combined into a cognitive/affective and neurovegetative dimension, indicating the advantage of focusing on individual symptoms as compared to the dimensions they belong to in order to capture heterogeneity.

The thesis continued by examining symptoms of functional somatic syndromes in a cross-sectional network model in the Lifelines community sample in Chapter 6. As it

has been argued that chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome are different names for the same problem, we explored the clustering of their symptom criteria in all persons and those with functional somatic syndromes. Results indicated that the criteria showed similar associations to criteria from the same syndrome as to criteria from other syndromes. Still, symptoms clustered into a general, musculoskeletal, gastrointestinal and other dimension in all persons and a general and gastrointestinal cluster in persons with a functional somatic syndrome. This indicated that functional somatic syndromes may reflect the same underlying syndrome with different subtypes based on body systems rather than their current classification into chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome.

Clinical aspects

Next, the thesis examined characteristics of consultations for somatic symptoms and their association with psychosocial problems in adults in primary care. Chapter 7 aimed to improve the recognition of functional somatic symptoms in primary care by extracting information about prior consultation patterns from electronic records of the Family Medicine Network. We showed that diversity in reasons for encounter did not significantly predict whether a subsequent consultation was for functional somatic symptoms. As clinical observations have repeatedly indicated that this measure is useful to predict the symptoms, this suggests that clinicians pick up on other features of diversity in the presentation of patients during the consultation. The identification of functional somatic symptoms may therefore be improved by focusing on features of the patient's presentation style during the consultation.

In chapter 8, we focused on communication within extended consultations for persistent physical symptoms with specially trained GPs. Although the importance of addressing the relation of these symptoms with negative emotions is commonly emphasized, it was unclear if and how patients do this in consultations. Our qualitative analysis showed that patients spontaneously described negative emotions and their relation with somatic symptoms. Relations constituted three types: separated, in which a link between the symptom and emotion was negated; connected, in which the symptom and emotion were two connected entities; and inseparable, in which the symptom and emotion were combined within one entity. Awareness of these types of relations may help GPs to understand the starting points of patients in discussions and to collaboratively formulate explanations.

In the treatment of persistent physical symptoms, clinical guidelines frequently encourage the use of symptom management (i.e., actions that patients can undertake themselves to reduce the intensity and impact of their symptoms). As it remained elusive how these strategies arise during consultations, we explored their creation and adoption during a

series of extended consultations in primary care in the qualitative study of Chapter 9. Strategies arose from initiatives of both patients and GPs and some were formed during a collaborative process of adding new ideas and making the strategy more practical. Based on our observations, we created a conceptual model in which the adoption of strategies was enhanced by involvement of the patient in its creation as well as techniques such as tailoring the strategy to the patient's narrative and adding new motivational and practical elements to the strategy. This model underlines the importance of patient-centered care in the promotion of symptom management in primary care.

The final part of the thesis addressed the relative efficacy of interventions for depressive symptoms in adults. As previous studies had mainly used scale scores as effect parameter, we focused on the responses of individual symptoms to these interventions while differentiating between direct and indirect responses in network models. In Chapter 10, the relative efficacy of short psychodynamic supportive psychotherapy alone and combined with antidepressants for patients with mild to moderate depressive disorder was examined in a randomized controlled trial. We found that the addition of antidepressants was more effective for seven depressive symptoms and not for nine others. Of these seven symptoms, feeling entrapped, emotional lability, worry, hopelessness and low energy showed a direct response to the treatment. In contrast, blue mood and obsessive thoughts seemed to respond via improvements in other symptoms.

In Chapter 11, we conducted a large individual patient data meta-analysis to study the symptom-specific effects of cognitive behavioral therapy versus antidepressants for depression. We found that antidepressants directly effectuated greater improvements in the symptoms feelings of guilt, suicidal thoughts, psychic anxiety and general somatic symptoms compared to CBT, while depressed mood responded indirectly. Other symptoms showed similar responses to the two treatments. Additional analyses showed that information about symptom-specific efficacy could help in identifying patients who, based on their pre-treatment symptomatology, are likely to benefit more from antidepressant medication than from CBT.

Main conclusions

- Depressive and anxiety symptoms are strongly related to somatic symptoms and boundaries between these symptom dimensions are vague. Patients are willing to discuss the relation between these symptoms in consultations and invent management strategies that reduce the impact of this relation.
- The co-occurrence between depressive, anxiety and somatic symptoms may be explained by varying mechanisms, including a similar basis of the symptom dimensions and direct causal relations between them. Although it has repeatedly

been suggested that the symptom types also have shared risk factors, we were unable to identify them.

- Symptom dimensions and individual symptoms of depressive, anxiety and somatic symptoms show unique patterns of co-occurrence and responses to treatment. Specific depressive, anxiety and somatic symptoms may mediate each other's responses to interventions.

Implications for clinical care

- It is essential for physicians from all disciplines to take into account depressive, anxiety as well as somatic symptoms in their assessments and to select interventions that are effective for combinations of these symptom types.
- Collaboratively exploring the problem space and co-creating management strategies by the physician and patient during the consultation is essential to build commonly agreed explanations and plans of action.
- Physicians can use symptom profiles of patients as a source to tailor interventions to individual patients.

Implications for future research

- Trans-dimensional research is needed to avoid artificial boundaries between closely related symptoms in science.
- Longitudinal studies are warranted to disentangle mechanisms underlying the co-occurrence between depressive, anxiety and somatic symptoms while taking into account heterogeneity across symptoms and persons as well as these mechanisms' dynamics in a complex system.
- Both symptom dimensions and individual symptoms form a valuable focus in research, although individual symptoms capture the highest level of heterogeneity.

NEDERLANDSE SAMENVATTING

Depressie- en angstsymptomen komen veel voor in de algemene populatie en veroorzaken vaak ernstige beperkingen in het dagelijks functioneren. Patiënten met deze symptomen hebben vaak ook somatische symptomen zoals hoofdpijn, misselijkheid en rugpijn. Somatische symptomen kunnen een teken zijn van een lichamelijke of psychiatrische ziekte, maar een groot deel kan niet worden toegeschreven aan een dergelijke ziekte. Deze functionele somatische symptomen worden vaak gezien als het gevolg van een complex samenspel tussen perifere en centrale biopsychosociale processen. Patiënten met een combinatie van depressie-, angst- en somatische symptomen hebben een slechtere kwaliteit van leven en hogere gezondheidskosten dan mensen met één van deze typen symptomen. Toch is nog steeds veel onbekend over de specifieke patronen van de associatie tussen de symptomen en de mechanismen die hieraan ten grondslag liggen.
Eerder onderzoek was voornamelijk gebaseerd op definities van depressie-, angst- en somatische symptomen zoals beschreven in diagnostische classificatiesystemen. Metingen van de symptomen waren gebaseerd op een vooraf gedefinieerde combinatie van symptomen, wiens scores werden opgesteld tot een schaalscore. Deze schaalscores zijn bekritiseerd vanwege grote heterogeniteit binnen en overlap tussen schalen. Door in onderzoek te concentreren op symptoomdimensies of individuele symptomen zou meer inzicht kunnen worden verkregen in welke symptomen belangrijk zijn in de associatie tussen depressie-, angst- en somatische symptomen, of welke symptomen goed reageren op specifieke behandelingen. Dit proefschrift heeft tot doel om epidemiologische en klinische aspecten van de relatie tussen depressie-, angst- en somatische symptomen te onderzoeken, door te focussen op symptoom dimensies en individuele symptomen.

Epidemiologische aspecten
Het proefschrift startte met het exploreren van de symptomen van de kindertijd (wanneer symptomen voor het eerst optreden en de gevoeligheid van patiënten ontwikkelt) tot volwassenheid (wanneer de symptomen zich vaak al hebben gemanifesteerd) in Hoofdstuk 2. We gebruikten data van de TRAILS studie, waarin kinderen werden gevolgd van de leeftijd van 10 tot 26 jaar. We onderzochten hoe depressie- en angstsymptomen en functionele somatische symptomen zich gezamenlijk ontwikkelden terwijl we rekening hielden met heterogeniteit tussen symptomen en mensen. We vonden verschillende parallelle en tegenovergestelde ontwikkelingspatronen voor de twee typen symptomen. Echter, geen enkel kind ervoer functionele somatische symptomen die in ernst toenamen en depressie- en angstsymptomen die in ernst afnamen. De ontwikkelingspatronen lieten geen relevante associaties zien met sociodemografische factoren, negatieve

grote levensgebeurtenissen of de ervaren opvoedstijl. We suggereerden dat de ontwikkelingspatronen te maken zouden kunnen hebben met dat kinderen leren om emoties van depressie en angst op een affectieve in plaats van somatische manier te uiten tijdens de adolescentie, maar meer onderzoek is nodig om dit verder uit te diepen.
Het proefschrift ging verder met het onderzoeken van de specificiteit van de combinatie tussen depressie-, angst- en somatische symptomen door te bekijken welke symptoomdimensies belangrijk zijn in deze associatie in volwassenen. We gebruikten data van NESDA, een groot cohort van mensen met een depressieve of angststoornis en mensen zonder deze stoornissen. Hoofdstuk 3 onderzocht cross-sectionele associaties tussen specifieke depressieve en angststoornissen en dimensies van somatische symptomen. Het liet zien dat de associaties sterk waren, want patiënten met een depressieve en/of angststoornis rapporteerden twee tot vier keer zo vaak specifieke types van somatische symptomen als mensen zonder deze stoornissen. Een depressieve stoornis was het sterkst geassocieerd met alle typen somatische symptomen, gevolgd door een gegeneraliseerde angststoornis, sociale fobie, paniekstoornis en agorafobie, terwijl dysthymie met geen enkel type somatisch symptoom was geassocieerd. De associaties verschilden niet tussen de types somatische symptomen, en werden niet verklaard door chronische somatische ziekten, sociodemografische factoren en leefstijl factoren. Dit hoofdstuk liet daarom zien dat de associatie onafhankelijk is van zulke externe factoren, en dat er enige specificiteit op het niveau van psychiatrische stoornissen is.
Hoofdstuk 4 onderzocht of somatische symptoomdimensies het beloop van een depressieve stoornis kunnen voorspellen. We vonden dat cardiopulmonaire, gastro-intestinale en algemene symptomen een slechter beloop van de depressieve stoornis voorspelden, maar alleen wanneer twee of meer van deze dimensies aanwezig waren. Musculoskeletale symptomen voorspelden de stoornis echter niet. De gevonden associaties werden deels verklaard door de ernst van depressieve symptomen aan het begin van de studie, maar co-morbiditeit met somatische en psychiatrische ziekten, behandelfactoren, leefstijlfactoren en beperkingen in het dagelijks leven hadden geen effect op de associatie. Dit geeft aan dat somatische symptomen een direct negatief effect op depressiesymptomen zouden kunnen hebben, wat afhankelijk is van het type en aantal somatische symptoomdimensies.
De netwerkbenadering focust op individuele symptomen en hoe ze samen voorkomen. Hoofdstuk 5 onderzocht in een cross-sectioneel netwerk hoe individuele depressie-, angst- en somatische symptomen met elkaar geassocieerd waren. Individuele symptomen lieten verschillende aantallen, sterktes en patronen van associaties zien in dit netwerk. Belangrijke verbindende symptomen tussen het depressie/angst en somatische domein waren bijvoorbeeld angst en overmatige transpiratie, terwijl slaapproblemen en

spierpijn zwak geassocieerd waren met het andere domein. De verschillen in associaties konden niet gedetecteerd worden toen depressie- en angstsymptomen in de dimensies van cognitieve/affectieve symptomen en neurovegetatieve symptomen werden gecombineerd. Dit geeft het voordeel aan van de focus op individuele symptomen in plaats van symptoomdimensies om heterogeniteit te detecteren.
Hoofdstuk 6 bouwde voort op de netwerkbenadering door in een cross-sectioneel netwerk de symptoomcriteria van functionele somatische syndromen te exploreren in de Lifelines studie, gebaseerd op de algemene populatie. Het is vaak bediscussieerd of chronisch vermoeidheidssyndroom, fibromyalgie en prikkelbare darmsyndroom niet andere namen zijn voor hetzelfde probleem. Onze resultaten lieten inderdaad zien dat al hun individuele symptoomcriteria sterk met elkaar verbonden waren, zowel binnen als tussen de syndromen. Symptomen clusterden in een algemene, musculoskeletale, gastro-intestinale en 'andere' symptoomdimensie in de gehele populatie en een algemene en gastro-intestinale dimensie in mensen met de functionele syndromen. Dit suggereert dat de functionele somatische syndromen wellicht één onderliggend syndroom representeren, wat bestaat uit verschillende subtypen gebaseerd op orgaansystemen in plaats van de classificatie van symptomen voor de individuele functionele syndromen.

Klinische aspecten

Vervolgens focuste het proefschrift op karakteristieken van consulten voor somatische symptomen bij de huisarts. Hoofdstuk 7 had als doel om de herkenning van functionele somatische symptomen te verbeteren door informatie over eerdere consultatiepatronen uit een elektronisch registratiesysteem van huisartsen binnen Fame-Net te halen. We lieten zien dat diversiteit in redenen om de huisarts te bezoeken niet significant voorspelde of een volgend consult voor functioneel somatische symptomen was. Omdat klinische observaties hebben gesuggereerd dat deze diversiteit een waardevolle maat is om functionele symptomen te voorspellen, zou het kunnen dat clinici andere signalen opvangen in de symptoompresentatie van de patiënt tijdens het consult. De herkenning van functionele somatische symptomen zou daarom kunnen verbeteren als vervolgonderzoek zich richt op de stijl van symptoompresentatie tijdens het consult.
In Hoofdstuk 8 onderzochten we de communicatie in extra lange consulten voor chronische somatische klachten met speciaal getrainde huisartsen. Hoewel het als belangrijk wordt gezien om in zulke consulten de relatie tussen somatische klachten en negatieve emoties te bespreken, was het onduidelijk of en hoe patiënten dit deden. Onze kwalitatieve analyse van de consulten liet zien dat patiënten spontaan begonnen over negatieve emoties en hun relatie met somatische symptomen. De relaties die ze beschreven bestonden uit drie typen: gescheiden, waarin de emotie en het symptoom

niet met elkaar verbonden waren; connectie, waarin de emotie en het symptoom verschillende maar verbonden onderdelen waren; en onafscheidelijk, waarin de emotie en het symptoom in het licht van één geheel werden gepresenteerd. Als huisartsen zich bewust zijn van de typen relaties die door patiënten in het consult worden gebruikt, dan zouden ze wellicht beter het standpunt van de patiënt kunnen begrijpen en gezamenlijk met de patiënt een verklaring kunnen formuleren.

In de behandeling van chronische somatische symptomen wordt symptoommanagement aangeraden. Dit zijn acties die de patiënt zelf kan uitvoeren om de ernst of gevolgen van klachten te verminderen. Omdat het onduidelijk was hoe symptoommanagement strategieën ontstonden tijdens het consult, exploreerden we hun totstandkoming en of patiënten ze aannamen in series consulten in de kwalitatieve studie van Hoofdstuk 9. Strategieën ontstonden door initiatieven van zowel patiënten als huisartsen en sommigen werden gecreëerd in een gezamenlijk proces van het toevoegen van nieuwe ideeën en het aanpassen van eerdere ideeën. We formuleerden een conceptueel model waarin de aanname van een strategie meer waarschijnlijk was als de patiënt betrokken was bij de totstandkoming van de strategie, en technieken werden toegepast zoals de strategie in het verhaal van de patiënt inpassen en motiverende en praktische elementen aan de strategie toevoegen. Dit model onderstreept het belang van patiëntgerichte zorg bij het aanbieden van symptoommanagement.

Het laatste deel van dit proefschrift richtte zich op de relatieve effectiviteit van interventies voor depressiesymptomen in volwassenen. Omdat eerdere onderzoeken schaalscores als effectmaat hadden gebruikt, keken wij naar de symptoom-specifieke effecten van de interventies terwijl we differentieerden tussen directe en indirecte effecten in netwerkmodellen. In hoofdstuk 10 onderzochten we de effectiviteit van korte psychodynamische steungevende psychotherapie alleen vergeleken met deze therapie gecombineerd met antidepressiva voor patiënten met milde tot matige depressieve klachten. We vonden dat de toevoeging van antidepressiva effectief was voor zeven depressiesymptomen en niet negen andere depressiesymptomen. Van deze zeven symptomen, reageerden een gevoel gevangen te zitten, emotionele labiliteit, piekeren, gevoel van hopeloosheid en weinig energie direct op de toevoeging van antidepressiva. Een depressief gevoel en obsessieve gedachtes, daarentegen, leken indirect te reageren via verbetering in de andere symptomen.

In hoofdstuk 11 presenteerden we een grote individuele patiënt data meta-analyse naar de symptoom-specifieke effecten van cognitieve gedragstherapie versus antidepressiva. We vonden dat antidepressiva direct meer effectief waren voor de symptomen schuldgevoel, suïcidegedachtes, angst en algemene somatische symptomen, en een depressief gevoel leek indirect te reageren op de medicatie. De andere symptomen reageerden even goed op cognitieve gedragstherapie als op antidepressiva. Extra analyses lieten zien dat informatie over de symptoom-specifieke effecten van de behandelingen hielp om

patiënten te identificeren die, op basis van hun symptoomprofielen voor behandeling, waarschijnlijk meer van het ene dan het andere type interventie zouden profiteren.

Hoofdconclusies

- Depressie- en angstsymptomen zijn sterk geassocieerd met somatische symptomen en grenzen tussen deze symptoomdimensies zijn vaag. Patiënten zijn bereid om de relatie tussen de dimensies te bespreken en dragen ideeën aan om de invloed van de relatie op hun eigen leven te verminderen.
- De relatie tussen depressie-, angst- en somatische symptomen kan worden verklaard door verschillende mechanismen, waaronder een gezamenlijke basis van de symptomen en directe causale relaties tussen de symptomen. Hoewel het gesuggereerd is dat de symptomen ook gezamenlijke risicofactoren hebben, konden wij hun invloed niet aantonen.
- Symptoomdimensies en individuele symptomen laten unieke patronen van co-morbiditeit en behandelresponsen zien. Specifieke depressie-, angst- en somatische symptomen zouden elkaars respons op behandeling kunnen mediëren.

Implicaties voor de kliniek

- Het is essentieel dat clinici van alle disciplines rekening houden met depressie-, angst- en somatische symptomen in hun onderzoek en selectie van behandelingen.
- Samenwerken tijdens het exploreren van problemen en het creëren van interventies door de patiënt en clinicus is de manier om gezamenlijke verklaringen en actieplannen te formuleren.
- Clinici kunnen symptoomprofielen gebruiken om interventies te selecteren die waarschijnlijk het meest effectief zijn voor een individu.

Implicaties voor onderzoek

- Trans-dimensioneel onderzoek is nodig om kunstmatige grenzen tussen nauw verbonden symptomen te vermijden in de wetenschap.
- Longitudinaal onderzoek moet zich richten op de vraag welke mechanismen ten grondslag liggen aan de relatie tussen depressie-, angst- en somatische symptomen in specifieke individuen en voor specifieke symptomen, terwijl ze rekening houden met de dynamiek tussen deze mechanismen in een complex systeem.
- Zowel symptoomdimensies als individuele symptomen zijn een interessante focus in onderzoek, maar individuele symptomen helpen om de meeste heterogeniteit te vangen.

ABOUT THE AUTHOR

Ella Bekhuis was born in Nijmegen, the Netherlands, in 1992. After completing secondary education (VWO) at the Montesori College Nijmegen in 2010, she started her Bachelor Medicine at the University of Groningen. She did several research projects at the Interdisciplinary Center for Psychopathology and Emotion Regulation (ICPE, department of psychiatry) of the University Medical Center Groningen (UMCG). After finishing her Bachelor in 2013 (Cum Laude), these projects became part of a broader MD/PhD trajectory in which the Master program of Medicine is combined with an additional 2.5 years of scientific research. The PhD was supervised by Judith Rosmalen, Robert Schoevers and Lynn Boschloo and included collaborations with researchers and clinicians from psychiatry, general practice, psychology and statistics. Ella presented her work at various national and international conferences and was involved in the supervision of students. She spent three months at the Academic Unit for Primary care at the University of Sheffield, United Kingdom, under supervision of Chris Burton, which resulted in one quantitative and two qualitative papers about persistent physical symptoms in general practice. Ella's final clinical internships were in psychiatry at Dimence and internal medicine at the Isala hospital in Zwolle, the Netherlands. After completing her MD/PhD trajectory in 2019, Ella started working as a medical doctor in a Flexible Assertive Community Treatment (FACT) team at Dimence.

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Marrit
Catharina
Peter
Claudia
Robert
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Judith
Lynn
Monica
Chris
Close
collaborators
Johan
Rei
Tom
Rick
Janna
Dept. AUPC
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Petra
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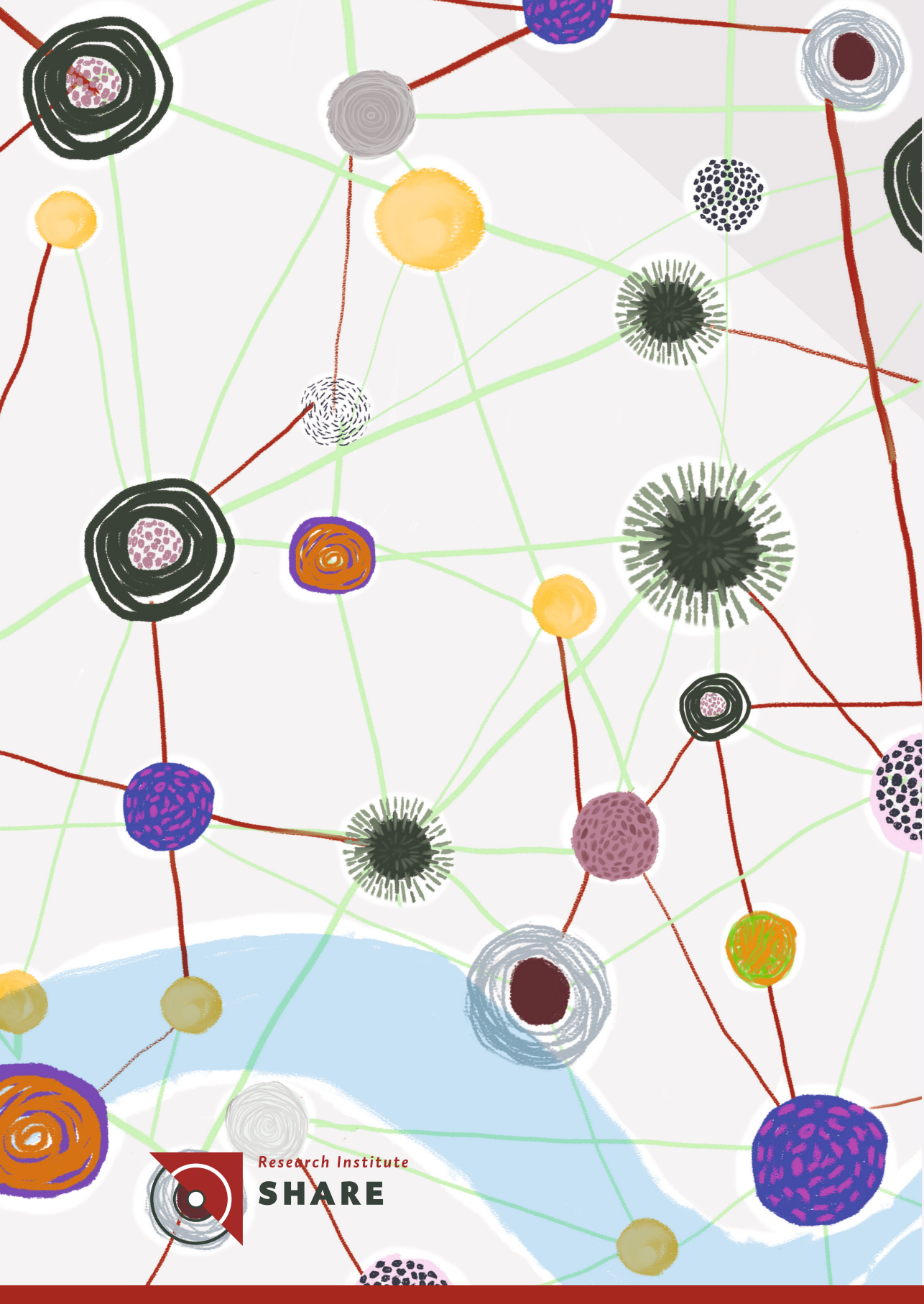
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