Medically unexplained symptoms in later life

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Cover design, lay-out and printing: Richard van Driel, Drukwerk ABC, Doornenburg,

Financial support for this dissertation was given by SeniorBeter, praktijk voor ouderen met psychische klachten, Gendt. Rijksuniversiteit Groningen and Pro Persona Nijmegen.

ISBN: 978-90-367-6647-0
ISBN: 978-90-367-6646-3 (electronical version)

rijksuniversiteit
groningen

Medically unexplained symptoms in later life

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus, prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 5 februari 2014 om 12.45 uur

door

Peter Henricus Hilderink

geboren op 8 maart 1966
te Eindhoven

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CHAPTER 1

General introduction

Based on:
Medically unexplained symptoms in older adults: a combination of physical, psychiatric and psychological factors.

P.H Hilderink, C.E.M. Benraad, T. J. W. van Driel, M.G.M Olde Rikkert. Nederlands Tijdschrift voor Geneeskunde 2008; 152 (23) 1305-1309.

Background

The experience of somatic symptoms is a normal phenomenon in the general population. Two out of three men and three out of four women report at least one medical complaint in the last two weeks [1]. This concerns symptoms such as headache, low back pain, fatigue and dizziness [2]. Most people, however, do not seek medical care for these complaints [3]. A substantial part (30-50%) of somatic symptoms presented in primary care remain medically unexplained [4-6]. In secondary medical care these percentages are even higher [7, 8]. Physical complaints become especially burdensome when they persist over time and when people persevere in seeking medical help. The burden of somatic complaints for which no medical explanation can be found is large. Patients often report a low quality of life and co-morbidity rates with anxiety and depressive disorders are high [9, 10]. Furthermore, the absence of a medical explanation gives rise to high levels of health care consumption in search for an organic origin of complaints, which subsequently places patients at risk for extensive investigations and iatrogenic damage [11].

Terminology

The best term to describe physical complaints of patients with unclear aetiology is subject to controversy. Many different terms are used, including functional somatic symptoms, psychosomatic symptoms, vague symptoms, subjective health complaints, and medically unexplained symptoms.

We have chosen to use the term Medically Unexplained Symptoms (MUS) in this thesis because this term is purely descriptive, neutral, and widely used in both clinical practice and the scientific literature [12, 13]. Nonetheless, we acknowledge that this term is still controversial, because it reflects dualistic thinking between body and mind and it may have a negative connotation as it may imply that medicine has nothing to offer for the patient [14]. From a patient perspective, however, "medically unexplained" and "functional" symptoms seem to be the most acceptable terms [15-17]. We define MUS as physical symptoms of which presence, severity or consequences cannot be explained by objectively detectable pathological abnormalities.

In the absence of physical abnormalities, symptoms are often assumed to arise as a consequence of psychological stress. This process is called somatisation in the psychological literature [18]. In the medical literature and the Dutch multidisciplinary guideline on MUS and somatoform disorders, somatisation is defined as the tendency to experience and communicate somatic distress and somatic symptoms unaccounted for by relevant pathological findings, to attribute them to physical illness, and to seek medical help for them [19].

In the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM IV-TR), MUS are considered as the core criterion for a somatoform disorder. Depending on type and combinations

of symptoms, duration, intensity, and level of distress, patients suffering from MUS may or may not be classified as having a specific somatoform disorder like somatisation disorder, pain disorder, conversion disorder, hypochondriasis, undifferentiated somatoform disorder or somatoform disorder not otherwise specified. Thus, the key step in classifying MUS as a somatoform disorder according to the DSM-IV-TR remains the exclusion of a medical cause. This classification system of somatoform disorders has been criticized as the assessment of whether symptoms are medically unexplained is unreliable, and because the concept is based on a dualistic view between body and mind [20, 21]. To exclude a somatic symptom on the basis of underlying physical illness or injury, a doctor must be consulted and a definite diagnosis must be made based on objectively detectable pathological abnormalities on examination or investigation. This central requirement is associated with significant conceptual and practical difficulties. As a result of these difficulties, many population-based surveys have omitted somatoform disorders, and health care planners have tended to ignore these disorders [14]. In DSM 5, somatoform disorders have been replaced by somatic symptom disorders. In the criteria for somatic symptom disorder, the exclusion criterion of the absence of a somatic cause has been omitted and criteria on the presence of psychological symptoms in relationship to the somatic symptoms are required now [22].

MUS and somatoform disorders in later life

Although the clinical impression is that MUS are common in all age groups, MUS in later life have received very little attention. There are several pitfalls that may contribute to this neglect of somatoform disorders and MUS in later life. These pitfalls are illustrated in the following description of three patients who visited an outpatient clinic for older persons with MUS. This outpatient clinic is based on a biopsychosocial approach, which is operationalized by consecutive diagnostic assessments by a geriatrician, a psychiatrist, and a psychologist within two weeks.

Case A

Patient A was a 75 year old widow with complaints of pain in her lower back and both legs since more than six months. As a result of this pain and reduced energy, she spent most of her time in bed. Analgesics (acetaminophen and morphine) given by her general practitioner did not sort any effect. Subsequently, the general practitioner suspected the presence of a depression and started treatment with clomipramine. This treatment initially resulted in some improvement, but six months later she was referred to our outpatient MUS clinic, because the pain had become chronic. At that time, the pain was most burdensome when standing or walking, while lying down relieved the pain slightly. She was not able to walk a hundred metres and felt extremely tired. Her daughter stressed that her mother's complaints might be related to the death of her mother's husband, who died three years ago, as the pain in her mother's legs started at that time. Physical examination by the geriatrician showed normal muscle strength, normal sensibility, and normal reflexes in her legs. Nonetheless, she was not able to walk across a line and the Romberg test was positive. She had an ataxic gait with a

forward bend posture. During the examination, the pain in her legs was located on the backside of her legs going down to her feet. Psychiatric examination confirmed an earlier depressive episode in complete remission after treatment with clomipramine. An X-ray examination of the lumbar spine showed multiple degenerative abnormalities and multiple mild and moderate dispositions between L2-L5. Although these findings were also present on an earlier examination one year ago, this had not led to further referral to exclude a lumbar stenosis. This latter diagnosis was now confirmed with a subsequent MRI examination in the orthopaedic outpatient clinic. Surgical decompression resolved her complaints almost completely.

Case B

Patient B was a 75 year old woman, who was referred to our outpatient clinic because of chronic bowel distress and an obsessive fixation on her defecation. Her complaints started about two years ago, initially with constipation and a depressed mood. She lost approximately 10 kg weight (actual weight in the past few months was 58 kg) and had trouble falling asleep. Several antidepressants (venlafaxine, nortriptyline, trazodone, sertraline) had been prescribed in therapeutic doses for sufficiently long periods, as well as augmentation strategies with risperidone and lithium. All treatment steps however failed, including inpatient treatment at a psychiatric ward of a general hospital for one month and a day care programme for three days a week. The consulted gynaecologist and internist could not find any explanation for her somatic complaints. A trial with laxatives did not yield any positive effects. On-going fixation on her bowel problems hindered compliance to the psychiatric treatment and made her husband desperate. This finally led to referral to our MUS outpatient clinic.

During the intake assessment, we saw a woman that complained merely about her defecation, while she also reported gastric problems such as belching. Psychiatric examination suggested a depressed mood with minimal facial expression and slowed movements. The Montgomery Asberg Depression Rating Scale (MADRS) score was 32, indicating a severe depression. The physical examination by the geriatrician did not provide any new information. We concluded that she suffered from a severe depression with secondary obstipation, possibly partly explained by antidepressant drug use. She was again clinically treated at a ward for geriatric psychiatry. Trazodone was switched to nortriptyline and the lithium dose was lowered in order to improve her slowed movement. MADRS scores declined rapidly to 8 in four weeks, after which she could be discharged from the hospital.

Case C

Patient C was a 65 years old woman with complaints of headache since more than six months. The pain was located at the left side of her head, and she feared a brain tumour. The pain had started a few years ago, after an acute attack of dizziness and nausea during which she vomited in public. Since then, she continuously suffered from headaches. Since she experienced syncope a few months ago, she was convinced that she had a brain tumour. As she ruminated the entire day about having a brain tumour, she was referred to our clinic. She had never

consulted a psychiatrist before. Her physical examination revealed no abnormalities; also the CT scan of her brain was completely normal. Although she was somewhat reassured by these findings, the headache remained. The assessment by the psychologist revealed that the pain had a negative impact on her sleep as well as her housekeeping and daily activities. She could be motivated to participate in cognitive behavioural group therapy. Six months later, she was completely free of headaches.

What can we learn from these cases?

Case A illustrates the main concern of most doctors: the fear of missing a somatic cause of a symptom. In their initial assessments, doctors tend to overestimate the presence of somatic explanations for a complaint. This may lead to "false-positive somatic explanations", a problem that increases in older age groups [23]. Increasing diagnostic difficulties of MUS in later life can be explained by a higher prevalence rate of co-morbid somatic disorders. The presence of one or more somatic diseases as well as the use of multiple medications with a range of potential side-effects make it difficult to determine whether complaints can be attributed to these diseases and their pharmacological treatment or not [24]. Furthermore, reference values of routine blood examinations are generally based on values found in non-elderly populations, which may also increase the risk to consider a symptom as medically explained if one or more parameters are below these reference values [25]. Finally, ageism, by the clinician as well as the patient and his or her family may incorrectly attribute somatic symptoms to the process of ageing. This latter explanation has probably played a role in case A. The degenerative abnormalities were considered normal for her age and led to the decision to withhold the patient from further examinations.

Case B illustrates the narrow relationship of somatic complaints with other psychiatric disorders, especially depressive disorders. Psychiatric co-morbidity with anxiety and depression is high in MUS patients [9, 26]. Moreover, in patients with established somatic disease, the presence of depressive symptoms is highly correlated with the number and severity of subjective somatic complaints [27]. Nonetheless, the recognition of depression and anxiety in patients with somatic symptoms remains problematic in clinical practice [28]. The high co-morbidity rates have raised doubts on clinical validity of somatoform disorders as a separate psychiatric disorder. This belief is further enforced by the fact that antidepressants are the sole pharmacological group for which the effectiveness has been proven in patients with somatoform disorders [29]. Finally, the fact that patients with a late-life depressive disorder more often present with somatic symptoms compared to younger depressed patients may also contribute to the neglect of somatoform disorders in later life [30-32]. Many old age psychiatrists regard MUS as a symptom or secondary phenomenon of depression.

The case of patient C illustrates the benefit of a multidisciplinary approach and the fact that patients with MUS may benefit from cognitive behavioural therapy. Although the effectiveness of cognitive behavioural therapy has only been proven for adult patients [8], the clinical

experiences in older patients are promising [33]. The majority of patients, however, do not receive adequate therapy. This may partly be explained by the difficulties medical doctors experience in their contacts with MUS patients [34]. Referral to cognitive-behavioural therapy may be particularly low for older patients, because older people are less often offered psychological therapy in general [35]. Referrals to other medical specialities increase with a higher age of the patient, while referrals to mental health services strongly decline beyond the age of 65 years [36]. To date, 17% of the Dutch population is above the age of 65 years, whereas in Dutch psychologist practices only 7% of the patients is 60 years or above, and only 2% of the patients is above the age of 70 years [37].

Aims and outline of this thesis

MUS in later life are neglected, both in research as well as in clinical settings, including general practice and old age psychiatry. This has resulted in limited empirical data [38] and ignorance of this subject in health care planning for older persons [14]. To organise better health care for this vulnerable group of patients, we first have to increase our knowledge on MUS in older persons. The aim of this thesis is to expand our knowledge about the presence, clinical presentation, and consequences of MUS in later life. First, information is needed on the prevalence of this problem in later life. So far no systematic review has been performed on the prevalence rates of MUS and somatoform disorders in later life. Second, the interaction of MUS and depression needs a more thorough investigation: are MUS in later life merely reflections of depression? Third, the distinction between medically unexplained and explained symptoms is problematic, especially in later life. Can a multidisciplinary approach be part of a solution for this complex problem? Finally, what are the consequences of MUS on the level of functioning and quality of life?

Prevalence

What is the prevalence of MUS and somatoform disorders in later life?

In chapter 2, we aim to estimate the prevalence of MUS and somatoform disorders in the older population based on the available literature. More specifically, we will first estimate prevalence rates for MUS and somatoform disorders according to diagnostic criteria. Secondly, we will compare prevalence rates of MUS and somatoform disorders in older age groups (≥ 65 years) with those found in middle aged (50-65 years) and younger populations (< 50 years).

MUS and depression

What is the role of co-morbidity of psychiatric disorders in elderly patients with MUS?

In chapter 3, results of the pilot study in older patients with MUS referred to our outpatient clinic are presented. Characteristics of this convenience sample are outlined, with special emphasis on the relationship of MUS with co-morbid psychiatric disorders.

What is the longitudinal relationship between pain and depression in the elderly?
In chapter 4, we further investigate the longitudinal relationship between pain and depression. Does depression predict the onset of pain, or does pain increase the risk for depression? We analysed the longitudinal relationship between depression and pain based on a 12-year longitudinal study with repeated measurements (Longitudinal Aging Study Amsterdam).

MUS and Medically Explained Symptoms (MES)

What is the somatic disease burden in older patients with MUS?
In chapter 5, the geriatric assessment of the pilot study is outlined and differences between explained, partly unexplained, and completely unexplained medically symptoms are described.

How do MUS and MES impact on quality of life across the lifespan?
In chapter 6, differences between medically explained (MES) and medically unexplained symptoms (MUS) were further analysed in order to establish whether the impact of symptoms on health-related quality of life differs between MUS and MES and to investigate if age affects this impact. Data were derived from the Prevention of Renal and Vascular End Stage Disease study (PREVEND).

Summary and final discussion

In *chapter 7*, the results of this thesis are critically reviewed and recommendations for further research and clinical practice are given.

Appendix

In this thesis, three different data sets were used derived from three studies: two population based studies and one pilot study located at a secondary care outpatient clinic.

Clinical sample

This sample consisted of a consecutive case series of patients aged 60 years or over who were referred for MUS to a multidisciplinary outpatient clinic between September 2006 and October 2007. This outpatient clinic was part of a secondary care, old-age psychiatric service of the Nijmegen Mental Health Center (currently part of ProPersona). Of the 48 patients who were consecutively referred for MUS, 37 patients gave informed consent to participate in the study. Reasons for refusal were: lack of motivation (n=4), aversion against mental health organization (n=2), hospitalization for an acute disease (n=2), moved (n=1), or unknown (n=1). One subject was excluded because of an age below 60 years. All patients underwent a standardized examination of a geriatrician, an old-age psychiatrist, and a clinical psychologist within two weeks. The geriatrician performed a full physical examination, ECG, routine blood chemistry, and a cognitive screening with the Mini Mental State Examination (MMSE). Psychiatric disorders were assessed according to the criteria of the DSM–IV-TR using the Mini International Neuropsychiatric Interview version 5.0.0 by an old-age psychiatrist.

The Longitudinal Aging Study Amsterdam (LASA)

This study is a prospective cohort study of Dutch people aged 55 to 85 years (n=3107). LASA started in 1992 and has been described and reported extensively elsewhere [39, 40]. The general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sex-stratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of men and older-old people (both men and women) was to compensate for an anticipated higher unavailability for follow-up among the older-old and men. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study [41] and was later interviewed and followed up every 3 years in LASA. Of the NESTOR–living arrangements and social networks study sample, 81.7% of the persons also participated in LASA (non-response was related to age but not to sex). All interviews were tape-recorded for quality control purposes.

For the study presented in this thesis, we used data up to 12 years of follow-up and excluded only those LASA participants in whom depressive symptoms (n=14), pain symptoms (n=1028), or both depressive and pain symptoms (n=37) were not evaluated at baseline, leaving a total study sample of 2028 participants (65.3%).

The Prevention of Renal and Vascular End Stage Disease study (PREVEND)

PREVEND is a population-based cohort study investigating micro-albuminuria as a risk factor for renal and cardiovascular disease. The recruitment of participants is described elsewhere [42]. All inhabitants of the city of Groningen between the ages of 28 and 75 years (85 421 subjects) were asked to send in a morning urine sample and to fill out a short questionnaire on demographics and cardiovascular history. A total of 40 856 subjects (47.8%) responded. After exclusion of subjects with insulin-dependent diabetes mellitus and pregnant women, all subjects with an elevated urinary albumin concentration of ≥10 mg/l (n=7768), together with a randomly selected control group with a urinary albumin concentration of <10 mg/l (n=3395), were invited for further investigations (total n=11 163). Finally, 8592 subjects completed the total screening program, making up the PREVEND study cohort. Because the PREVEND study population was enriched for albuminuria, this oversampling for albuminuria was counterbalanced in the current sub study. Albuminuria-negative participants and a random sample of albuminuria-positive participants were combined so that a population representative ratio of albuminuria-positive participants was achieved. Research assistants handed over invitations in the 2001–2002 wave to 2554 subjects to participate in this sub study, for which additional psychiatric and psychosocial data were collected. Of these 2554 subjects, 1094 (43%) completed the additional measurements. Follow-up measurements in the 2003–2004 wave were completed by a total of 976 participants (89% of the cohort with additional psychiatric and psychosocial data). This latter group was analysed with respect to MES and MUS in this thesis.

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CHAPTER 2

Prevalence of somatoform disorders and medically unexplained symptoms in old age populations in comparison with younger age groups; a systematic review.

P.H. Hilderink, R. Collard, J.G.M. Rosmalen, R.C. Oude Voshaar

Ageing Research Reviews 12 (2013) 151– 156

Abstract

Objective: To review current knowledge regarding the prevalence of somatisation problems in later life by level of caseness (somatoform disorders and medically unexplained symptoms, MUS) and to compare these rates with those in middle-aged and younger age groups.

Method: A systematic search of the literature published from 1966 onwards was conducted in the Pubmed and EMBASE databases.

Results: Overall 8 articles, describing a total of 7 cohorts, provided data of at least one prevalence rate for somatoform disorders or MUS for the middle-aged (50-65 years) or older age (≥65 years) group. Prevalence rates for somatoform disorders in the general population range from 11 to 21% in younger, 10 to 20% in the middle-aged, and 1,5 to 13% in the older age groups. Prevalence rates for MUS show wider ranges, of respectively 1.6 to 70 %, 2.4 to 87%, and 4.6 to 18%, in the younger, middle, and older age groups, which could be explained by the use of different instruments as well as lack of consensus in defining MUS.

Conclusion: Somatoform disorders and MUS are common in later life, although the available data suggest that prevalence rates decline after the age of 65 years. More systematic research with special focus on the older population is needed to understand this age-related decline in prevalence rates.

Introduction

Medically unexplained symptoms (MUS) are physical symptoms of which presence, severity or consequences cannot be conclusively explained by any detectable physical disorder [1]. MUS are common in the general population with reported prevalence rates in primary care varying between 25 and 50% [2-4]. Within the International Classification of Diseases version 10 (ICD-10) as well as the Diagnostic and Statistical Manual for Mental Disorders version IV (DSM-IV), medically unexplained symptoms are classified under the section of somatoform disorders. In order to meet the official criteria for any of these somatoform disorders, the ICD-10 places emphasis on 'a psychological cause' of bodily symptoms, whereas in the DSM-IV for most somatoform disorders a psychological cause has to be assumed and most emphasis is placed on the presence of significant impairment in social, occupational and/or other areas of functioning due to MUS. Reported prevalence rates for all forms of somatoform disorders together vary from 10-25% in primary care [5-9]. Whether somatization, the tendency to express psychological distress with somatic complaints, is more common in old age remains a matter of debate [10-12].

Patients with MUS or somatoform disorder report significant decreases in quality of life, impairment in daily functioning, increased high health care utilisation, and often undergo medical examinations and treatments unnecessarily [13-15]. In an adult population, MUS double the costs for both inpatient and outpatient health care utilisation compared to patients without MUS when adjusted for the presence of comorbid psychiatric and somatic disease [13]. Moreover, the increase of health care utilisation over a follow-up period of 5 years was higher in MUS patients than in patients without MUS [13]. Furthermore, this increase was higher than the increase associated with depressive disorder or anxiety disorders, disorders that are also associated with increased health care consumption over time [16]. Increased medical consumption is not only problematic from an economical viewpoint, but also increases the risk of iatrogenic damage due to unnecessary additional diagnostic and treatment procedures or significant doctor's delay (by not taking patients seriously anymore). These risks are probably even more relevant in later life, as older persons are frailer, have a higher a priori chance of underlying somatic diseases, and are more dependent on carers.

The past decades, several psychiatric interventions for MUS and somatoform disorders have been proven effective [17]. This optimism is tempered by the experience that numerous patients with MUS refuse "psychological treatment" [18]. Older people may be at double risk for withdrawal of adequate treatment. First, older people are less often offered psychological therapy [19]. Nevertheless, age does not seem to be a factor associated with the acceptance of psychological treatment for functional symptoms [18]. Secondly, in case of older patients, physicians are often faced with somatisation in the context of chronic somatic diseases. Higher comorbidity rates as well as higher a priori chances of underlying physical illnesses as explanation for MUS in older people may caution physicians to diagnose MUS or a somatoform disorder [20]. Therefore, data showing increased numbers of somatic explained

symptoms with increasing age and no or only a very weak correlation between MUS and age are difficult to interpret [21-23]. For example, frequent attenders, often used as a proxy for MUS, are more common among older persons than younger persons [24], but when corrected for all other significant factors, such as number of chronic diseases, age itself was not associated with frequent attending [23]. Furthermore, prevalence studies in Dutch primary care have yielded inconsistent findings for older patients, showing lower rates for somatoform disorders, but increased prevalence rates for persistent MUS [6, 25].

To our knowledge, only two reviews have published on somatoform disorders in the elderly specifically [10, 11]. The review by Sheehan & Banerjee (1999) was conducted before the majority of epidemiological studies on the prevalence of somatoform disorder in later life have been published. Nevertheless, these authors concluded that somatisation disorder in itself is rare in the older population, but that clinically relevant somatisation occurs frequently. Although the authors warn to use "masked depression" as explanation for somatisation in older persons, they acknowledge the high comorbidity between somatoform and mood disorders. The importance to disentangle somatisation from pure anxiety or depression is substantiated by another review, not specifically focussed on older persons. It shows that having numerous somatic symptoms or illness worry is associated with impairment and health care utilisation independent of anxiety and depressive symptoms [12]. A German, more recent and systematic review on the effect of aging on somatisation stated that ageing per se is not associated with an increased level of somatisation, but that the scarcity of empirical data preclude final conclusions [11]. Both reviews identified problems caused by between-study differences in the definition of somatisation problems, instruments used to measure somatisation, and finally the setting of the research population.

The objective of the present study is to estimate the prevalence of somatisation problems in the older population. More specifically, we will first estimate prevalence rates according to the level of caseness, i.e. MUS and somatoform disorders according to DSM or ICD criteria. Secondly, we will compare prevalence rates of MUS and somatoform disorders in older age groups (≥ 65 years) with those found in middle aged (50-65 years) and younger populations (< 50 years).

Methods

We performed systematic searches of the PubMed and EMBASE databases for the period 1966 through June 2011 using the keywords: medically unexplained symptoms, somatoform disorder, aged, prevalence, epidemiology. If applicable to the keyword, MeSH terms were included and then combined with the search.

We used the following criteria for inclusion of articles:

- Firstly, articles had to provide prevalence rates of somatoform disorders or MUS. Acknowledging the scarcity of empirical data, we did not apply a time-reference to the prevalence rate, but we will report the time-reference of the included studies systematically.

- Secondly, prevalence rates had to be described for different age categories, including at least one age group above 50 years of age. We defined older persons as those aged 65 years or older, as in most developed countries the chronological age 65 years coincides with retirement and is generally accepted as a cut-off for defining the elderly [26]. Acknowledging that this definition of old age is somewhat arbitrary, we also defined a middle-aged group consisting of persons aged 50-65 years as this is a period in which many chronic physical conditions start to develop.
- Thirdly, somatoform disorders had to be classified according DSM criteria and/or ICD criteria using standardized instruments. MUS are defined as physical symptoms of which presence, severity or consequences can not be explained by any detectable physical disorder. Acknowledging the lack of consensus for defining MUS, we did not apply specific restrictions with respect to definition or classification if methods were described in a reproducible manner.
- Fourthly, the study had to be conducted in the general population and/or primary care setting.

We did not apply any restrictions on the language of the article.

We performed two searches in Pubmed to identify articles about somatoform disorders and MUS, respectively. Using the keywords: medically unexplained symptoms, aged, prevalence yielded 116 hits. A second search using the keywords: somatoform disorder, aged, prevalence and epidemiology yielded 117 hits. Screening of all titles resulted in further examination of 38 abstracts and 35 full text articles, from which finally only six articles met our inclusion criteria. References were checked and provided two more useful articles. Repeating our search strategy in EMBASE did not yield any additional articles. Searches were performed independently by both PH and RC, where after results were compared and discussed. In case of disagreement RCOV was consulted for a final decision.

Statistical Methods

Although we originally intended to perform formal meta-analyses, we deemed a descriptive overview of the data more appropriate for the following reasons. Firstly, the number of articles was small. Secondly, results were heterogeneous, also after differentiating between somatoform disorders and MUS.

Results

Overall eight articles, describing a total of seven cohorts, were found that met our criteria (see table 1). In four of these seven cohorts somatoform disorders as well as MUS were assessed. The prevalence data of somatoform disorders and MUS in one cohort have been described in separate articles [27, 28]. The three other cohorts only focussed on somatoform disorders [29, 30] or on MUS [25], respectively

Age groups:
Four studies provided prevalence data for persons aged 65 years or above [6, 25, 30, 31], with one study applying an age cut-off at 60 years [29]. The age cut-off for the middle-aged persons was even less consistent, with three studies using a cut-off at 45 years [6, 25, 32] and four studies at 50 years [27, 28, 31]. Nevertheless, two of these former studies [6, 25] also reported prevalence data for those aged above 65 years or age (and were thus of interest). The other study [32] only used the cut-off of 45 years did not provide further differentiation regarding the higher age group.

Populations:
We found four population surveys conducted in three different countries: two papers described data from the same German sample (German Health Survey (GHS, n =1321), one about somatoform disorders and one about MUS [27, 28]; another paper also described a German sample (n=2552) [32] , one paper described a Norwegian sample (n= 1247) [31] and finally the last described a French sample (n=504) [30].
Three other studies, two from the Netherlands [6, 25] (n=1046 and n=225013, respectively) and one American study [29] (n=224), described prevalence rates in primary care.

Used instruments:
None of the studies included in the review used a similar diagnostic procedure. The most important differences were 1) whether or not a screening procedure was used, 2) type of diagnostic instrument that was used, and 3) the time-window that was applied.

TABLE 1: Summary of prevalence rates (%) for somatoform disorders and MUS by age

Study	Setting	Number	Diagnostic instrument		Age-group		
			Name	Time-window	< 50 years	> 50-65 years	> 65 years
Somatoform Disorders							
Hardy 1995	General population	N=504	Telephonic interview	12 months	21	20	13
Jacobi 2004	General population	N=1321	CIDI	12 months	10.7	11.7	
Leiknes 2007	General population	N=1247	CIDI	6 months	11.4 (m:7,3; w:15,1)	9.9 (m:3.8; w:16,4)	4,9 (m:3.5; w:6.5)
Hiller 2006*	General population	N=2552	SOMS-7	7 days	12.6	26.8**	
Waal de 2004*	Primary care	N=1046	SCAN	6 months	21.8	15.3	5.4
Lyness 1999	Primary care	N=224	SCID	Point prevalence			1,5 (m:1,3; v:1,6)
Medically Unexplained Symptoms							
Frohlich 2005	General population	N=1321	CIDI	12 months	28.8 (m:22,9; w:34,8)	27,2 (m:21,3; w:33,1)	
Leiknes 2007	General population	N=1247	CIDI	6 months	26.3 (m:17.0 w: 34.8)	23.4 (m:15.3 w:32,2)	18.4 (m:16,3 w:20,8)
Hiller 2006*	General population	N=2552	SOMS-7	7 days	69.7	87.1**	
Waal de 2004*	Primary care	N=1046	SCAN	6 months	27.8	22.4	7.2
Verhaak 2006*	Primary Care	N=225013	Persistent MUS***	12 months	1.6	2,4	4,6

Abbreviations: CIDI, Composite International Diagnostic Interview; SOMS-7, Screening for Somatoform Symptoms – 7 days version; SCAN, Schedules for Clinical Assessment in Neuropsychiatry, m, men, w, women.

* Age cut-off for the younger age group was set at 45 years

** This prevalence rate provides all persons of the age of 45 years or above (range 45-92 years).

*** Persistent MUS were defined as: at least four contacts with a functional symptom and without a medical diagnosis as an explanation for the symptoms during one year.

Five of the studies used a two-stage screening procedure. Four studies started with a screening questionnaire and if positive, performed a diagnostic interview for somatoform disorders [6, 27, 28, 31]. The study of Lyness used the Center of Epidemiologic Studies Depression Scale (CES-D) as screening [29]. All persons above the cut-off point of 21 were included and a random sample of persons scoring under the cut-off point, aiming to oversample the amount of depressive disorders. The diagnostic instruments that have been used varied from fully structured interviews [27-29, 31], to a semi-structured interview [6] to a self-report questionnaire [32], to chart-review [25] and finally to a telephonic interview [30] Even the two studies that used the somatoform section of the fully structured computerized Composite International Diagnostic Interview (CIDI) were not fully comparable by taking a different time-windows describing respectively 12-month [27, 28] and 6-month prevalence rates [31]. One study assessed current somatoform disorders with a duration of at least 6 months by using the semi-structured Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [6]. The SCAN leaves room for further exploration and clinical judgement by experienced mental health professionals and is often considered the gold standard for diagnosing psychiatric disorders. Another study used the Screening for Somatoform Symptoms (SOMS-7), a standardized questionnaire that asks for symptoms in the last seven days [32]. One study used a two stage telephonic interview based on the classification according to DSM IV to identify somatoform disorders in the last year [30] . Finally, the last study used data extracted from electronic records of 225013 patients of 104 general practices based on the International Classification of Primary Care (ICPC). This study focussed on chronic MUS, defined as four or more contacts for a somatic complaint, without a medical diagnosis in the period of a year. They argued that this definition is most close to clinically relevant somatoform problems [25].

Prevalence rates:
Table 1 shows prevalence rates for different age categories for somatoform disorders in the included articles. Given prevalence rates are for all different forms of somatoform disorders together. Prevalence rates in the general population range from 11 through 21% in the younger age group (below 45-50 years), 10 through 20% in the middle-aged group (45-50 to 60-65 years), and from 1.5 through 13% in the older age group (60-65 years or above). None of the studies found any differences between the younger and middle age groups, whereas the prevalence rate in the older age groups were consistently lower. Only one study found increasing prevalence rates above the age of 45 years, but this study did not report prevalence rates for persons aged 45-65 years and persons aged over 65 years separately [32].

Reported prevalence rates for MUS are even more heterogeneous with highest prevalence rates for MUS defined as at least one symptom of mild severity in the past seven days [32] and lowest prevalence rates for chronic persistent MUS in primary care [25]. Interestingly, the study reporting persistent MUS in primary care found increasing prevalence rates with age, i.e. 1.6% below the age of 45 years, 2.4% for the age group between 45-65 years and finally 4.6% for those aged 65 or above [25]. The age-effects in the other three studies were in line with those reported for somatoform disorders, i.e. no difference in prevalence rates between the

age groups below 50 years and between 50 and 65 years, but clearly lower prevalence rates in the age group above 65 years [6, 28, 31].

Discussion

Acknowledging the scarce literature on somatoform disorders and MUS in later life, our data suggest that somatoform disorders and MUS are common in older populations, although prevalence rates are lower than in younger populations. The differences between studies can partly be explained by the use of different diagnostic instruments, whereas the applied time-window may be less important. It seems plausible that semi-structured interview methods are more restrictive and therefore find lower prevalence rates than questionnaires [11]. For example, all semi-structured interviews take only symptoms into account that have led to health care utilization. Looking at the population surveys we included, we indeed found the highest prevalence rates in the study that used a questionnaire [32]. The lowest prevalence rate of 1.5%, found among American older patients in primary care by using the Structured Clinical Interview for DSM-IV disorders (SCID) in a sample with relative oversampling of depressive persons, may seem puzzling [29]. The most likely explanation is that the authors only reported prevalence rates for pain disorder and body dysmorphic disorder, whereas the more prevalent somatoform disorders like undifferentiated somatoform disorder and hypochondria were not assessed. A second, but less likely explanation is the inclusion in this study of patients from private internal medicine practices, as these patients might have had higher socio-economic backgrounds.

Although only four of the included studies did report prevalence rates for the age group above 65 years, the results suggest that prevalence rates of somatoform disorders and MUS are stable until the age of 65 years and decrease thereafter. The only exception to this finding is the study concerning persistent MUS, showing increased prevalence rates above the age of 65 years [25]. These findings are in line with studies of somatoform disorders in highly selective samples (that had to be excluded for the present review for this reason [33-35]). Using the SCREENER questionnaire to screen for psychiatric disorders in a medical outpatient clinic population, 18% of the patients below the age of 63 years had a somatoform disorder versus 11% of those aged above 63 years [33]. A study among a later life subpopulation (above the age of 55 years) of families of patients with Alzheimer's dementia or depression yielded a prevalence rate of 5% for somatoform disorder as assessed by the CIDI [34]. This is similar to later life prevalence rates in included studies that used the CIDI as diagnostic instrument that found a prevalence rate of 5% above 65 years of age [31]. Nevertheless, also some lower than expected figures have been reported. Among long-term older benzodiazepine users who visited their general practitioner, a prevalence rate of 8% for somatoform disorders was found using the PRIME-MD questionnaire[35]. This seems in line with other reported findings, although among benzodiazepine users the expected prevalence rate would be higher [36].

Nevertheless, two studies included in the review reported increasing prevalence rates for

somatoform disorders and MUS with increasing age. Both studies, however, might be biased by the limited ability to separate medically explained and unexplained symptoms, leading to an overrepresentation of somatoform complaints of which an organic cause is not excluded [11]. The first study, only differentiating between patients under and above 45 years of age, used a self-report questionnaire (SOMS-7) assessing all 53 physical symptoms reported in the DSM-IV criteria for somatoform disorders [32]. Recently, we showed that in older persons the Patient Health Questionnaire (PHQ-15), a screenings instrument used to establish symptoms that point to somatoform disorders, had a similar correlation with an index of hypochondriasis (Whiteley Index) as an index of the burden of underlying chronic somatic diseases (Cumulative Illness Rating Scale)(Benraad, et al., unpublished results) . This means the physical symptoms assessed by the DSM-IV might be less specific for somatoform disorders in older people, than in younger people. The second study used a very specific definition, which included a minimum of four visits a year at the GP for a somatoform complaint. This definition may have led to biased results, as older persons with somatoform complaints tend to be more frequent attenders than younger adults [24].

Why do prevalence rates for Somatoform disorders and MUS decrease in the elderly?
Current classification systems for somatoform disorders are not deemed appropriate for clinical use [37, 38]. The formal criteria for a somatisation disorder are quite restrictive. These criteria may be especially restrictive for elderly [4, 39]. For example, the inclusion criterion for somatization disorder is a presence of symptoms before onset of 30 years. Poor patient recall will bias and lower rates [40, 41]. Overall prevalence rates of somatoform disorders may thus be lowered artificially, further substantiated by much higher prevalence rates for suggested abridged forms of somatisation disorder [12].
Secondly, used interview methods are not validated for an elderly population, which may lead to lower estimated prevalence rates for somatoform disorders. Epidemiological studies using standardized diagnostic interviews for other mental disorders, especially depression, have consistently demonstrated lower current and lifetime prevalence estimates in later life populations compared to younger populations [42, 43]. Analyses of epidemiologic data in a population from 25-64 years based on the Diagnostic Interview Schedule (DIS) showed that older people more often attributed their symptoms to a physical condition in probe questions designed to identify the degree to which symptoms were caused by factors other than psychological. It was suggested that this response was due to the fact that the complexity of the formalized questions exceeded the cognitive capacity. "Working memory capacity" appeared to be a good predictor of this response behavior, also when corrected for co-morbid physical conditions [44]. Because working memory capacity decreases with on-going age [45], this effect might become more prominent among older persons. The attribution of symptoms to a physical condition will lead to exclusion of diagnosis of somatoform disorder and thus to lower established prevalence rates for somatoform disorders. Thirdly, not only do older patients attribute bodily symptoms to physical disorders, older persons also have more co-morbid somatic disorders, which makes doctors reluctant to exclude a somatic origin of the complaint. We previously have reported that 50% of patients referred to our outpatient

clinic for MUS had a somatic disorder that partly explained their symptoms [46]. Excluding patients with a partial, but not sufficient somatic origin of their symptoms, will lead to substantial lower prevalence rates. Indeed some studies reported to exclude patients in which there was any doubt about a somatic cause for the complaint [6]. Because of confusing terminology for somatoform disorders within the DSM-IV with implicit mind-body dualism and the unreliability of assessments of MUS, the American Psychiatric Association has proposed to rename the chapter of somatoform disorders into 'somatic symptom disorders'. The DSM-V Somatic Symptom Disorder Task Group has proposed to lump somatization disorder, hypochondriasis, undifferentiated somatoform disorder and pain disorder together in one disorder named Complex Somatic Symptom Disorder [47]. This is in line with empirical findings showing that the number of medically explained and unexplained symptoms are more informative for a dimensional diagnosis of somatization than the clustering of specific symptoms into separate somatoform disorders or functional syndromes [48-50]. As the DSM-V will focus more on the number of bodily symptoms, irrespective of explainability or unexplainability of these symptoms or their associated dysfunctional cognitions, these new criteria may better serve older people. A final explanation could be that in old age subsyndromal forms of somatoform disorders are more common than somatoform disorders meeting full DSM criteria. This could be similar to depressive disorders in later life, where minor depression is much more common than major depression [51]. This latter explanation, however, cannot fully explain the lower prevalence rates of somatoform disorders in later life as MUS, which can be considered a subsyndromal somatoform disorder, also decreases with age.

Limitations:

For proper interpretation, some limitations should be acknowledged. Firstly, empirical data are scarce. Therefore, we choose to apply the cut-off for our a priori chosen age-categories liberally in order to be able to provide a more detailed overview of the literature. Nevertheless, the general neglect of somatoform disorders and MUS in old age still raises the question whether the few studies reported can be considered representative for the community-dwelling elderly population. Overall prevalence rates of somatoform disorders and MUS in the included studies, however, were in line with the prevalence rates in studies that also including middle-aged (50-65 years) and/or older persons (aged > 65 years) but that did not report age-specific data. For example, a German study using the CIDI found an overall prevalence rate for any somatoform disorder of 11% in the general population (n=4181) aged from 18 to 65 [8]. An Italian study of the general population (n=673) reports a prevalence of 20% for all somatoform disorders using a semi-structured interview by a trained interviewer [5] and a Spanish study in primary care (n=7936) found a prevalence of 29% using the PRIME-MD questionnaire [7].

Secondly, the use of different instruments for assessing somatoform disorders limits direct comparison between studies. Although these limitations are also applicable to the younger population, research in old age psychiatry is further limited by fact that most diagnostic instruments for somatoform disorders are not validated for use in the elderly [44]. Moreover, no consensus exist on the definition of MUS, whereas the criteria for somatoform disorders

remain also highly debated and have led to widely different solutions within research projects varying from the introduction of other diagnostic entities such as abridged somatisation disorder [52] and multi-somatoform disorder [38].

Conclusion:
So far, little research has focused on somatoform disorders in the elderly. The existing evidence shows that somatoform disorders and MUS are still common in later life, although the available data suggest that prevalence rates decline after the age of 65 years. To understand why prevalence rates decrease beyond the age of 65, more systemic research with special focus on the old aged population is needed. Especially adaptation and validation of instruments to detect somatoform disorders in the elderly is needed for this purpose. To reveal the clinical relevance and natural course of subsyndromal somatoform disorders, research should focus on studying diversity, severity and chronicity of MUS rather than differentiating into separate diagnostic categories with arbitrary thresholds [53]. Because of the lack of consensus on the definition of MUS, the prevalence rates for somatoform symptoms that do not fulfil the DSM IV criteria are difficult to interpret and the clinical importance of subsyndromal somatoform disorders remains uncertain. Suggestions for future classification should consider the appropriateness for old age populations.

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CHAPTER 3

Medically unexplained physical symptoms in elderly people: A pilot study of psychiatric and geriatric characteristics.

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American Journal of Geriatric Psychiatry. 2009; 17(12):1085-1088

Abstract

Objective – To examine the somatic complaints, functional impairment and psychiatric co-morbidity in elderly patients with medically unexplained symptoms (MUS).

Method – A consecutive case series of 37 patients referred for MUS to a multidisciplinary, outpatient clinic at a secondary care mental health center in the Netherlands. All patients underwent a standardized examination by a geriatrician, psychiatrist and psychologist.

Results – For three patients a somatic explanation was found and in two their symptoms spontaneously resolved before a diagnosis could be made. Of the remaining 32 patients with MUS, depressive disorders were present in 18 (56%), anxiety disorders in 10 (31%) and substance use disorders in 6 (19%). Compared to non-depressed patients with MUS, depressed patients had more severe somatic symptoms, more psychological symptoms, and more functional impairment.

Conclusions – As we found a high co-morbidity with other psychiatric disorders in elderly patients with medically unexplained symptoms, a systematic psychiatric examination should be part of their multidisciplinary assessment.

Introduction

Medically unexplained symptoms (MUS) are usually defined as physical symptoms of which presence, severity or consequences cannot be explained by any detectable physical disorder [1]. A study among general practice visitors showed that 7% of patients aged 65 years or over were suffering from a somatoform disorders versus 22 - 28% of those aged below 65 years [2]. However, in older persons, the diagnosis of MUS is difficult for several reasons. First the increased prevalence of physical morbidity with age will lead to more pathological findings, for which the causal relationship with the presented symptoms has to be evaluated. Secondly, depressed elderly patients more often present only physical symptoms. Despite these difficulties, there are no age-specific DSM-IV criteria for somatoform disorders. These issues may result in underrecognition of somatoform disorders in elderly patients [3].

These difficulties may be overcome by a biopsychosocial approach. For this reason, we started a multidisciplinary outpatient clinic for older patients with medically unexplained symptoms. This report presents the first results with respect to the somatic complaints, functional impairment and psychiatric co-morbidity.

Method

A consecutive case series of patients aged 60 years or over who were referred for MUS to our multidisciplinary outpatient clinic from September 2006 until October 2007. This outpatient clinic was part of a secondary care, old-age psychiatric service of the Nijmegen Mental Health Center.

All patients underwent a standardized examination of a geriatrician (CB), old-age psychiatrist (PH) and clinical psychologist (DvD) within two weeks. The geriatrician performed a full physical examination, ECG, routine blood chemistry and a cognitive screening with the Mini Mental State Examination (MMSE). Psychiatric disorders were assessed according to the criteria of the DSM–IV-TR using the Mini International Neuropsychiatric Interview version 5.0.0 by an old-age psychiatrist (PH) in addition to observer rated psychiatric instruments (see below). Severity of the presenting symptom (visual analog scale (VAS) from 0, no burden, through 100, unbearable symptoms) and its functional limitations were assessed in a clinical interview by a senior clinical psychologist (DvD).

The number and severity of somatic symptoms in the past month was assessed by the well-validated Patient Health Questionnaire somatic symptom severity scale (PHQ-15) [4]. Patients had to report the burden of 15 symptoms that cover 90% of potential somatic symptoms found in patients with somatoform disorders, rated on a three-point scale (no, little or much). The item about menstrual discomfort was omitted. In an adult population, a score of 5, 10, and 15, is used as threshold for mild, medium, and high level of somatisation.

The impact of the MUS on the patients' everyday living was assessed by 7 (of the originally 15) subscales of the Sickness Impact Profile (SIP), i.e. 'household', 'social interaction', 'sleep',

'mobility', 'walking', 'alertness' and 'recreation'. The SIP has been developed to measure behavioural limitations due to physical illness.

General psychopathology was measured by the Symptom Checklist 90 item version (SCL-90), a self-report questionnaire assessing 8 domains of psychological functioning in the past week. The severity of depressive symptoms was measured by the observer-rated Montgomery Asberg Depression Rating Scale (MADRS) and the severity of hypochondriacal beliefs and attitudes with the Whiteley Index, a 14-item self-report questionnaire.

Data are presented as absolute numbers and percentages within groups in case of nominal variables, and for continuous measures as means with standard deviation (SD) or median with interquartile ranges (IQR) for normal and non-normal distributions. Patients with and without depression were compared by chi-square, two-sample t-test or Mann-Whitney U-test.

Results

Forty-eight patients were consecutively referred for MUS, of whom 37 patients gave informed consent. Reasons for refusal were: lack of motivation (n=4), aversion against mental health organization (n=2), hospitalization for an acute disease (n=2), moving homes (n=1), or unknown reasons (n=1). One subject was excluded because of age below 60 years.
Patients had a median age of 75 years (range 60 – 92) and 31/37 (84%) patients were female. Fifteen patients (41%) were married and lived with their partner; the other 22 patients lived alone. The mean MMSE score was 27.5 (SD=2.4).

In three patients, a somatic disorder was found that fully explained their symptoms, namely herpes zoster infection of the cranial nerves combined with pulmonary fibrosis (n=1), a cerebrovascular accident (n=1) and spinal canal stenosis (n=1). A further two patients reported psychosocial problems as their primary complaint. This leaves a total sample of 32 patients, who met DSM-IV criteria for a somatoform disorder: undifferentiated somatoform disorder (n=16), pain disorder (n=8), hypochondriasis (n=4), somatisation disorder (n=1), and a combination of hypochondriasis with a pain disorder (n=3). Fifteen (47%) patients had pathological findings or somatic diseases that partly explained their primary somatic complaint.

Seventeen out of the 32 patients had symptoms for over 5 years; only one patient had symptoms for less than 6 months. Twenty patients reported pain as their primary symptom (head, n=6; whole body, n=4; abdominal, n=4; mouth, n=3; back, n=2; joints, n=1). The other primary complaints were shortness of breath/coughing (n=5), dizziness (n=3), and further dysarthria, paraesthesia, anxiety/loneliness, and fatigue. The mean VAS severity score was 75 (SD=22). The impact on functioning was substantial given the mean scores on the SIP sub scale for social interaction (17, SD=15), sleep (24, SD=20), household activities (18, SD=19), mobility (16, SD=20), walking (11, SD=13), alertness (28, SD=22), and recreation (29, SD=25).

The PHQ-15 (see table 1) showed a medium severity of somatisation with a mean total score of 8.7 (SD=4.1).

TABLE 1 Prevalence of somatic complaints according to the Patient Health Questionnaire (PHQ-15) (n=31).

			Burden	
	Symptom	Prevalence % (n)	Little % (n)	Severe % (n)
1.	Abdominal pain	35 (11)	23 (7)	13 (4)
2.	Back pain	61 (19)	32 (10)	29 (9)
3.	Joint pain	75 (23)	35 (11)	39 (12)
4.	Headache	35 (11)	13 (4)	23 (7)
5.	Chest pain	35 (11)	29 (9)	6 (2)
6.	Dizziness	45 (14)	19 (6)	26 (8)
7.	Syncope	6 (2)	3 (1)	3 (1)
8.	Heart pounding	35 (11)	23 (7)	13 (4)
9.	Shortness of breath	45 (14)	19 (6)	26 (8)
10.	Sexual problems	6 (2)	3 (1)	3 (1)
11.	Intestinal problems	68 (21)	52 (16)	16 (5)
12.	Nausea	42 (13)	19 (6)	22 (7)
13.	Fatigue	52 (16)	29 (9)	23 (7)
14.	Sleeping problems	58 (18)	29 (9)	29 (9)

The mean MADRS score of 12.2 (SD=7.6) indicated mild depressive symptoms, the mean SCL-90 sum score of 171 (SD=46) a moderate level of overall psychopathology, and the mean Whiteley Index of 5.8 (SD=3.9) a moderately high level of hypochondriacal beliefs.
Twenty-two (69%) of the patients diagnosed with a somatoform disorder had one or more co-morbid psychiatric disorder (one, n=11; two, n=8, three, n=3). The most common group of co-morbid disorders were depressive disorders (n=18 (56%): major depressive disorder, n=13; dysthymia, n=5). Depressed patients had a significantly longer duration of psychiatric treatment (Mann-Whitney z= -2.22, p=.026), higher somatic symptom burden (PHQ-15: t= -2.99, df=30, p=.005), higher SCL-90 subscale scores (depression: t= -3.16, df=26, p=.004; anxiety: t= -2.48, df=26, p=.020; somatisation: t= -2.70, df=26, p=.012; insufficiency: t= -2.67 df=26, p=.013; hostility: t= -2.55, df=26, p=.017), and more functional impairment assessed with the SIP (social interactions, t= -3.15, df=28, p=.004; alertness, t= -2.80, df=28, p=.009). (see table 2) Anxiety disorders were present in 10 patients (2 patients had 2 anxiety disorders): generalizedanxiety disorder (n=4), social fobia (n=3), panic disorder (n=3), agoraphobia (n=1), specific phobia (n=1). Finally, 6 patients (19%) met criteria for substance use disorders, i.e. dependence of opioids (n=4), dependence of benzodiazepines (n=1), and finally dependence on an unknown agent (n=1).

Table 2 Comparison of patients with and without a co-morbid mood disorder.

Variables		Mood disorder		
		Yes (n=18)	No (n=14)	Statistics
• Age (years)	mean (SD)	75 (7)	75 (7)	t= -.1, df=30, p=.93
• Female sex	n (%)	15 (83%)	11 (79%)	x^2=0.1, df=1, p=.73
• MMSE	mean (SD)	27.6 (2.6)	27.1 (2.3)	t= -.5, df=27, p=.62
• Duration of psychiatric treatment (yrs)	mean (SD)	6.2 (11.1)	0.2 (0.6)	Z= -2.2, p=.026
• No. of psychotropic drugs in history	mean (SD)	3.1 (2.9)	0.6 (1.4)	Z= -3.4, p=.001
MUS characteristics:				
• Duration of MUS (years)	mean (SD)	14.7 (25.4)	16.6 (29.0)	t=.2, df=30, p=.85
• Intensity primary symptom (VAS)	mean (SD)	81 (16)	63 (29)	t= -1.8, df=18, p=.08
• PHQ-15 sumscore	mean (SD)	10.4 (3.9)	6.5 (3.5)	t= -3.0 df=30, p=.005
• Whiteley Index	mean (SD)	6.8 (4.1)	4.6 (3.2)	t= -1.7, df=30, p=.10
Current psychotropic drug use:				
• Antidepressant	n (%)	8 (44%)	6 (43%)	x^2<.1, df=1, p=.93
• Anxiolytics	n (%)	14 (78%)	8 (57%)	Fisher Exact test, p=.27
• Antipsychotics	n (%)	1 (6%)	1 (7%)	x^2<.1, df=1, p=.85
• Analgetics	n (%)	8 (47%)	3 (21%)	x^2=2.2, df=1, p=.14
Psychological functioning:				
• MADRS sum score	mean (SD)	16.7 (7.0)	6.4 (3.4)	t= -5.0, df=30, p<.001
• SCL-90 sum score	mean (SD)	198.1 (35.6)	141.8 (37.6)	t= -4.0, df=25, p< .001
o Depression	mean (SD)	43.9 (13.6)	28.7 (11.7)	t= -3.2, df=26, p=.004
o Sleep	mean (SD)	9.5 (3.5)	7.9 (4.1)	t= -1.1, df=26, p=.29
o Anxiety	mean (SD)	25.0 (9.2)	17.3 (6.9)	t= -2.5, df=26, p=.020
o Somatisation	mean (SD)	29.6 (7.5)	22.2 (7.1)	t= -2.7, df=26, p=.012
o Agorafobie	mean (SD)	11.9 (5.0)	10.3 (4.6)	t= -.9, df=26, p=.40
o Insufficiency	mean (SD)	19.1 (5.6)	14.1 (3.8)	t= -2.7 df=26, p=.013
o Hostility	mean (SD)	8.7 (3.2)	6.4 (0.9)	t= -2.5, df=26, p=.017
o Interpersonal sensitivity	mean (SD)	28.7 (7.9)	23.5 (7.2)	t= -1.8, df=26, p=.08
Impact on functioning (SIP)				
• social interactions SIP	mean (SD)	23 (16)	8 (8)	t= -3.2, df=28, p=.004
• household activities SIP	mean (SD)	22 (23)	13 (12)	t= -1.4, df=28, p=.17
• sleep SIP	mean (SD)	27 (17)	20 (23)	t= -1.0, df=28, p=.31
• mobility SIP	mean (SD)	19 (19)	13 (22)	t= -.9, df=28, p=.40
• walking SIP	mean (SD)	12 (14)	9 (13)	t= -.6, df=28, p=.55
• alertness SIP	mean (SD)	37 (21)	16 (19)	t= -2.8, df=28, p=.009
• recreation SIP	mean (SD)	37 (25)	20 (21)	t= -1.9, df=27, p=.07

Abbreviations: SD, standard deviation; MUS, medically unexplained symptoms; VAS, visual analog scale; PHQ-15, Patient
Health Questionnaire; MMSE, Mini Mental State Examination; MADRS, Montgomery Asberg Depression Rating Scale; SCL-90, Symptom Checklist-90 item version; SIP, Sickness Impact Profile.

Discussion

To our knowledge this is the first study presenting results of a standardized multidisciplinary examination of elderly patients suffering from MUS. The main finding of our study is the high prevalence of somatoform disorder with psychiatric co-morbidity of depression, anxiety and substance use disorders. For interpretation, several limitations should be acknowledged: the sample size, the multiple comparisons, the cross-sectional nature hampering causal interferences and lack of generalization to other levels of health care and health care systems by describing a secondary care, convenience sample.

Thirty-two (86%) of 37 elderly patients referred with MUS were suffering from a somatoform disorder. In only three patients we found a somatic reason for the complaints. This prevalence rate is quite low and comparable with figures that have been reported for patients referred for conversion [5]. As might have been expected in an elderly population, we found in almost half of the patients (47%) pathological findings that partly explained their primary complaint. Pain was the most common symptom. The severity and presenting physical symptoms as measured with the PHQ are comparable with patients presenting MUS in primary care [6]. In primary care, about a quarter of the patients with MUS met DSM-IV criteria for a somatoform disorder [7]. In our study, nearly all patients met DSM-IV criteria for a somatoform disorder. This is most likely explained by the fact that only patients with persistent symptoms that sustain after the 'wait and see' period will be referred and that in this patient group the burden on patients is large enough to justify classification as a somatoform disorder. The finding of only one case of somatisation disorder is in accordance with the low prevalence of this condition in the general population.

The prevalence of psychiatric co-morbidity was high (overall 69%), particularly for depressive disorders (56%). Similar figures have been reported in primary care [8]. Co-morbid depression was associated with a higher severity of the primary somatic complaint, a higher level of somatisation, and more functional impairments. The recognition of depression often is reduced by a somatic presentation and often leads to the perception of the patient as difficult [9]. Several trials showed that antidepressant drugs are effective in adult patients with MUS. To what extent this effect might be mediated by the reduction of co-morbid depressive symptoms has not been elucidated [10].

We conclude that identifying psychiatric co-morbidity in older patients with medically unexplained symptoms is highly relevant, in addition to attention for the physical causes of the complaints. Therefore, we strongly advocate a standardized multidisciplinary assessment of older patients with MUS.

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CHAPTER 4

The temporal relation between pain and depression: Results from the Longitudinal Aging Study Amsterdam.

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Psychosomatic Medicine 2012 Nov-Dec;74(9):945-51

Abstract

Objective: Pain and depression are both common in old age, but their (long-term) temporal relationship remains unknown. This study is designed to determine whether pain predicts the onset of depression and vice versa.

Methods: This is a prospective, population based cohort study with 12-year follow up and 3 years intervals in the Netherlands (Longitudinal Aging Study Amsterdam). At baseline participants were aged 55 to 85 years (n=2028). Main measurements outcomes were incident depression defined as crossing the cut-off of 16 and showing a relevant change (≥5 points) on the Center for Epidemiological Studies – Depression scale (CESD) among non-depressed participants and incident pain defined as a score of 2 or higher on the pain scale of the 5-item Nottingham Health Profile (NHP5) in pain free participants. Multiple imputation was adopted to estimate missing values.

Results: In non-depressed participants (n=1769), a higher level of pain was predictive of incident depression in multiple extended cox-regression analysis (Hazard rate [HR] = 1.13 [95% confidence interval [CI]= 1.05 – 1.22], p= .001) , which all remained significant after correction for socio-demographic characteristics , lifestyle characteristics, functional limitations and chronic diseases (HR=1.09 [95% CI=1.01 – 1.18], p=.035).

In the pain-free participants (n=1420), depressive symptoms at baseline predicted incident pain (HR = 1.02 [95% CI: 1.01 – 1.04], p= .006) , This depression measure did not independently predicted the onset of pain in the fully adjusted models.

Conclusion: As pain precedes the onset of depression, strategies to prevent depression in chronic pain patients are warranted. In contrast no effects of depression on subsequent pain were found when adjusting for covariates.

Introduction

Depression and pain are highly prevalent in older people. A comprehensive meta-analysis has reported prevalence rates of 1.8% for major depression, 9.8% for minor depression and 13.5% for clinically relevant depressive symptoms [1]. Reported prevalence rates for pain among older people vary between 25 and 88% [2]. The National UK statistics report that approximately 50% of older people are in some degree of pain or discomfort [3]. Cross-sectional studies report high comorbidity rates between pain and depression among older persons [4, 5] and the comorbidity rate increases with aging [6]. Moderate to severe pain symptoms that impair function and/or are refractory to treatment, are associated with more depressive symptoms and worsened depression outcomes. Similarly, depression in patients with pain is associated with more pain complaints and higher level of impairment [7, 8]. Although the direction of the association between pain and depression remains unclear [9, 10], a bidirectional, reciprocal association is most plausible. This means that the onset of either pain or depression is a factor that increases the likelihood of the reciprocal symptoms and/or that each syndrome is a factor that impedes recovery of the other. For clinical practice this is important, as it would entail that treatment should target both depression and pain and that systematic evaluation of pain/depressive symptoms is warranted in either disorder.

Longitudinal studies among older people consistently show that pain precedes depression and vice versa, despite the use of different and sometimes not validated measures for depression and/or pain [11-17]. Except one population based study including 4235 people aged 50 years and older [14], all studies adjusted their results for functional limitations and/or chronic diseases. Only in two studies the identified temporal pattern between pain and depression disappeared after the adjustment for covariates. In the first study, the predisposition of pain to depression disappeared after adjustment for physical functioning and chronic health conditions. Nonetheless, this study was limited as it was a population-based study with only 241 people due to a low and probably selective, attrition rate [12]. In the second study among 318 older patients referred to secondary health care, the predisposition of depression to pain already disappeared when adjusted for sociodemographic factors [16]. Probably more relevant than these two exceptions, are the following limitions:a), the lack of control in nearly all studies for pharmacological treatment of depression and pain; b), the lack of control in nearly all studies for life-style characteristics like smoking, use of alcohol and body mass index (BMI) because such characteristics may point to mediating mechanisms [10]; and c) limitations with respect to duration of follow-up or number of assessments. All studies among older adults were limited to a duration of follow-up of at most 3 years [17, 18] or a maximum of 1 or 2 follow-up measurements [11, 16]. One study among people aged 25 to 75 years, of which only 27% (629/2324) were aged 55 years or over, applied an 8-year follow-up and found that pain predicted depression and vice versa [19]. Nevertheless, this study was limited by only one follow-up measurement and neither adjusted for lifestyle characteristics nor for functional limitations or chronic diseases [19].

Objectives

To overcome these problems, we have examined the temporal relation between pain and depression over a 12-year follow-up within the Longitudinal Aging Study Amsterdam (LASA). Our objectives were to examine to what extent pain in the elderly predicts the onset of depression and to what extent depressive symptoms in the elderly population predicts the onset of chronic pain when adjusted for sociodemographic characteristics, lifestyle factors, functional limitations and the presence of chronic diseases.

Method

Study design and population

This study was conducted using data from the Longitudinal Aging Study Amsterdam (LASA), which is a prospective cohort study of Dutch people aged 55 to 85 years (n=3107). LASA started in 1992, and its methods have been described in detail elsewhere [20, 21]. The general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sexstratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of men and older-old people (both men and women) was to compensate for an anticipated higher unavailability for follow-up among the older-old and men. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study [22] and was later interviewed and followed up every 3 years in LASA; 81.7% of the NESTOR–living arrangements and social networks study sample participated in LASA, with nonresponse being related to age but not to sex. All interviews were tape-recorded for quality control purposes. The study design was approved by the ethics committee and all participants provided informed consent.

For the present study, we used data up to 12 years of follow-up and excluded only those LASA participants in whom depressive symptoms (n=14), pain symptoms (n=1028) or both depressive and pain symptoms (n=37) were not evaluated at baseline, leaving a total study sample of 2028 participants (65.3%). Of these 2028 participants, 1769 (87.2%) had no depression at baseline and 1420 (70.0%) had no pain at baseline.

Because data on pain were gathered by self-administered questionnaires which participants were asked to fill in after the face-to-face main interview, the response on the pain questionnaire was relatively low. The 1028 persons with missing pain scores had significantly higher levels of depressive symptoms compared to persons without missing pain scores (mean (SD) CESD score of 9.0 (8.1) versus 7.5 (7.6), t=5.2, df=3054, p< .001), whereas the 14 persons with missing depression scores at baseline had significantly higher levels of pain scores compared to persons without missing depression scores (mean (SD) NHP5 score of 1.9 (2.1) versus 0.7 (1.3), t=3.4, df=2040, p= .001). As shown in table 1, excluded persons because of missing data were significantly older, were less often male, had more severe cognitive impairment, were less educated, used less often alcohol, and had more chronic diseases and functional impairments.

Table 1
Comparison of in- and excluded participants at baseline

		Included (n=2028)	Excluded (n=1079)	Statistics
Age (years)	mean (SD)	68.8 (8.5)	72.5 (8.8)	t=11.3, df=3105, p< .001
Male sex	n (%)	1030 (50.8)	476 (44.1)	χ^2=12.6, df=1, p< .001
Level of education	n (%)			χ^2=95.0, df=2, p< .001
• Lower education or less		771 (38.1)	605 (56.3)	
• Secondary education		993 (49.0)	377 (35.1)	
• Higher education		261 (12.9)	92 (8.6)	
Cognitive functioning (MMSE)	mean (SD)	27.4 (2.4)	25.7 (4.2)	t=-14.0, df=3089, p< .001
Smoking (yes)	n (%)	477 (24.6)	195 (26.7)	x^2=1.3, df=1, p= .26
Use of alcohol	n (%)			χ^2=26.1, df=2, p< .001
• No use		382 (19.8)	210 (29.0)	
• Moderate use		1385 (71.7)	457 (63.2)	
• Severe use		164 (8.5)	56 (7.7)	
Body Mass Index	mean (SD)	26.6 (3.9)	27.2 (4.4)	t=3.3, df=2574, p= .001
Chronic diseases	n (%)			χ^2=110.5, df=2, p< .001
• None		851 (42.0)	346 (32.6)	
• One		716 (35.3)	377 (35.6)	
• Two or more		460 (22.7)	337 (31.8)	
Functional limitations	n (%)			χ^2=153.7, df=2, p< .001
• None		1301 (64.5)	492 (47.0)	
• One		370 (18.4)	214 (20.5)	
• Two		345 (17.1)	340 (32.5)	
Use of antidepressants	n (%)	40 (2.1)	11 (1.5)	χ^2=0.8, df=1, p= .34
Use of analgetics	n (%)	290 (15.0)	117 (16.0)	χ^2=0.4, df=1, p= .52

Abbreviation: MMSE, Mini-Mental State Examination; SD, standard deviation.

Depression

At all occasions, depressive symptoms were measured using the Center for Epidemiologic Studies Depression scale (CESD). This is a 20-item self-report scale developed to measure depressive symptoms in the community. Subjects were asked how often they had experienced each symptom during the previous week. Items were scored on a 4-point scale, ranging from 0 (rarely or none of the time) to 3 (most of or all the time). The values of these response categories were reversed for the positive affect items. The total CESD score ranges from 0 to 60. The psychometric properties of the scale were found to be good in older populations [23, 24]. The overlap with symptoms of physical illness has been shown to be very limited in a number of studies [25, 26]. A score of ≥16 has generally been used as indicative for clinically relevant

depressive symptoms [25]. In LASA, the cutoff of 16 or greater had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to DSM-IV criteria [24].
The CESD was completed every 3 years during follow-up. Incident depression was defined as a score of 16 or higher at one of the follow-up assessments in patients who scored less than 16 points at baseline combined with an increase of 5 points or more compared to their baseline symptom score. This criterion of a minimum change of 5 points was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms leading to a respondent being identified as incident depression [27].

Pain
The pain scale was derived from a subscale of the Nottingham Health Profile (NHP5) [28]. As described previously, the following 5 items were included: I am in pain when I am standing, I find it painful to change position, I am in pain when I am sitting, I am in pain when I walk, and I am in constant pain [17]. Response categories were 'no' and 'yes'. The total scale score ranges from 0 (low) to 5 (high). The reliability of the scale indexed by Cronbach's alpha was high ($\alpha = 0.82$) [17]. The pain scale was completed every 3 years during follow-up. Incident pain was evaluated in pain free persons (NHP5 sumscore = 0) and defined as a score of 2 or higher at one of the follow-up assessments. A score of 2 (clinically relevant change) was chosen to avoid random fluctuations or clinically irrelevant changes of symptoms leading to a respondent being identified as incident pain.

Covariates
Three categories of covariates were considered of interest and added block-wise to the regression analyses (see below). The first category included sociodemographic variables, medication use and cognitive functioning. The second category were life-style factors and the third category were chronic diseases and functional limitations.
The first category consisted of characteristics that were considered to be potential confounders and included sociodemographic variables (sex, age, and level of education), medication use (use of antidepressants and analgetics), and cognitive functioning. The originally 9 categories of educational level were categorized into 3 main categories, i.e. lower education or less (elementary education not completed, elementary education), secondary education (lower vocational education, general intermediate education, general secondary education), and higher education (higher vocational education, college education, university education). Use of antidepressants and analgetics was established by asking about the use of medication and by visually checking all of the participants' medications at each 3-yearly assessment. Cognitive functioning was measured with the Mini Mental State Examination (MMSE) [29]. The MMSE sumscore (range 0 – 30) was included in the analyses as a continuous variable. Persons scoring below the cut-off of 24 points (52/2028, 2.6%) were kept in the analyses. The second and third category consisted of variables, which may both confound and/or mediate the relationship between depression and pain.
The second category consisted of life-style factors, i.e. current smoking (yes/no), use of alcohol, defined as no use, severe usage (defined as 14 or more units per week for female

participants and 21 or more per week for male participants) and mild to moderate usage (those participants not scoring no alcohol or severe alcohol usage), and finally body mass index, calculated as weight in kilograms divided by height in meters squared.
The third category consisted of chronic comorbid diseases and functional limitations. The presence of 7 chronic physical diseases was measured by self-reports based on core questions and branching questions in case of positive answers. The selection of chronic diseases is based on prevalence (the most frequently occurring somatic chronic diseases in the Netherlands; roughly >5.0% in the age group 55 years and older) and functional consequences, and included 1) chronic non-specific lung disease, 2) cardiac disease, 3) peripheral arterial disease, 4) diabetes mellitus, 5) cerebrovascular accident or stroke, 6) arthritis, and 7) cancer. In a validation study, respondents' self-reports were compared to information obtained from their GPs, and proved to be sufficiently reliable [30]. For this study, the presence of chronic diseases was indicated at three levels: no disease, 1 disease or 2 or more diseases. The number of functional limitations was scored with a 3-item questionnaire and scored as none, 1, or 2 or more difficulties [31].

Analyses
Does pain predict the onset of depression? - To examine the impact of pain on the onset of depression, the analyses were restricted to participants without depression at baseline (CESD <16, n=1769). We performed Cox-regression to take the time to onset into account. All primary variables and covariates were checked for normality and collinearity, their associations with outcome variables were checked for proportionality of hazards. Collinearity refers to the possibility that two covariates are highly correlated in a way that both covariates virtually measure largely the same construct. This has been tested by bivariate correlations between covariates. Proportionality of hazards refers to the assumption that the hazards are proportional over time. Hazard functions have thus to be multiplicatively related, or in other words their ratio is assumed constant over the survival time, thereby not allowing a temporal bias to become influential on the end point. This has been tested by plotting the cumulative hazards functions for each covariate (at baseline) as well as by a complementary log-log plot.
Although Cox-regression partially corrects for dropout by censoring patients at the last available follow-up assessment, it requires at least one follow-up assessment in order to include participants in the analyses. In our case 314 participants (17.8%) dropped out before the first follow-up assessment. Participants who dropped out (n=314) were compared to included participants (n=1455) significantly older (t=9.6, df=1767, p< .001), more often male (χ^2=5.0, df=1, p= .026), had a lower level of cognitive functioning (t=-8.3, df=1763, p< .001), used less alcohol (χ^2=11.0, df=2, p= .004), and had more chronic diseases (χ^2=11.4, df=2, p= .003) and functional limitations (χ^2=29.9, df=2, p< .001). Dropouts, however, did not differ with respect to severity of depressive symptoms, pain, smoking status, BMI, use of antidepressants and use of analgetics. Furhtermore, the frequency of missing data for covariates was on average 2.0% per covariate (range 0 - 6.5%). To account for missing data, we performed multiple imputation using the Markov chain Monte Carlo method (fully conditional specification). Under the assumption of missing at random, this approach addresses biases inherent in deleting patients who do not

provide all data, and ulitimately allows for the inclusion of a larger and more representatieve sample in the analyses. We created 5 imputed data sets and all variables available (CESD score, NHP5 score and all covariates) were included in the imputation model as recommended [32]. No interaction terms were added to the imputation model and we used predictive mean matching for continuous variables. Analyses were run for each imputed dataset and the results were pooled using Rubin's [33] rules to derive one single pooled parameter etimate by taking into consideration the variance both within and between imputations. Only these pooled results were presented.

In order to examine the relationship between pain and incident depression in depth, pain was modelled in three different ways. First, we evaluated the effects of pain at baseline based on the continuous NPH5 score, ignoring pain scores during follow-up. Secondly, we calculated the mean severity of pain symptoms as the mean NHP5 score of all observations until the year of incident depression or censoring divided by the total number of observations in this interval as a proxy for a combined pain severity-chronicity score. Third, we included pain (continuous NPH5 score) as a time-dependent variable to evaluate whether pain occurs just before the onset of depression. All models were first corrected for subsyndromal depressive symptoms and covariates of the first category (potential confounders), then also for covariates of the second category (life-style factors) and finally also for covariates of the third category, that is functional limitations and chronic diseases as potential confounders and/or mediators. Covariates that may change over over time, were included as time-dependent covariates as Cox-regression allows the use of time independent (age, sex, education) and time dependent covariates (cognitive functioning, use of antidepressants, use of analgetics, smoking, use of alcohol, body mass index, functional limitations, chronic diseases).

Do depressive symptoms predict the onset of pain? – A similar set of analyses were conducted to examine the impact of depressive symptoms at baseline on the onset of pain. Cox-regression analsyes were conducted as described above, but in this case with incident pain as the dependent variable. First we restricted the analysis to participants without pain at baseline (NPH5 score = 0, n=1420). A total of 313 participants dropped out before the first follow-up (n=313). These dropouts were significantly older (t=11.4, df=1418, p<.001), less educated (x^2=15.6, df=2, p<.001) had a lower level of cognitive functioning (t=9.2, df=1416, p<.001), higher level of depressive symptoms (t=2.4,df== 2.4, df=1418, p=.017), more often smoked (x^2=3.9, df=1, p=.049), less often used alcohol (x^2=7.3, df=2, p=.026), and had more chronic diseases (x^2= 26.2,df=2, p<.001) and functional limitations (x^2=53.0, df=1, p<.001) compared to included participants (n=1107). Dropouts, however, did not differ with respect to sex, BMI, use of antidepressants and use of analgetics. Furhtermore, the frequency of missing data for covariates was on average 2.0% per covariate at baseline (range 0 - 6.2%) and up to 60.2% for body mass index at 12 years follow-up. To account for missing data, we performed a separate multiple imputation procedure for the subjects in this analysis using the same methods as described above. The imputations were done separately for both analyses as they address essentially different questions pertaining to different populations, i.e. those without baseline depression and those without baseline pain, respectively. All results presented are

based on the pooled results of the 5 imputed datasets.
To examine this relationship in depth, depressive symptoms were modelled in three different ways. First, we evaluated the effects of the severity of depressive symptoms at baseline based on the continuous CESD score, ignoring depressive symptom scores during follow-up. Secondly, we calculated the mean severity of depressive symptoms as the mean CESD score of all observations until the year of incident pain or censoring divided by the total number of observations in this interval as a proxy for a combined depression severity-chronicity score. Thirdly, we included the depressive symptom severity (continuous CESD score) as a time-dependent variable to evaluate whether an increase in depressive symptoms occurs just before the onset of pain. All models were first corrected for covariates of the first category (potential confounders), then also for covariates of the second category (life-style factors) and finally also for covariates of the third category, i.e. functional limitations and chronic diseases as potential confounders and/or mediators.

Results

Does pain increase the incidence of depression?
To predict the development of depression we first selected non-depressed participants at baseline (n=1769, 87.2%).
Of the 1769 non-depressed participants at baseline, a total of 402 (22.7%) developed depression during follow-up. The mean (SD) depression free duration of follow-up was 8.1 (3.6) years, which corresponds to an incidence rate of 28.2 per 1.000 person years.
In unadjusted Cox-regression models, incident depression was predicted by pain at baseline (Hazard Rate (HR) = 1.13 [95% CI: 1.05 – 1.22], p= .001), the combined severity-chronicity pain score (HR= 1.21 [95% CI: 1.12 – 1.32], p<.001), and by pain as a time-dependent covariate (HR = 1.15 [95% CI: 1.07 – 1.24], p< .001). The Hazard Rates count for each 1 point increase on the NPH5 scale. As shown in table 2, these associations remained significant when corrected for all three categories of covariates.

Table 2 Multivariate Cox Regression on Incident Depression

Variable	Imputed (N=1769)	
	HR (95% CI)	P Value
Pain symptoms at baseline		
• Adjusted for covariates category 1	1.05 (1.01 – 1.10)	.030
• Additionally adjusted for covariates category 2	1.08 (1.00 – 1.16)	.055
• Additionally adjusted for covariates category 3	1.09 (1.01 – 1.18)	.035
Combined severity – chronicity pain level		
• Adjusted for covariates category 1	1.13 (1.04 – 1.24)	.007
• Additionally adjusted for covariates category 2	1.14 (1.04 – 1.24)	.005
• Additionally adjusted for covariates category 3	1.17 (1.06 – 1.29)	.002
Pain symptoms (continuous at separate time-points)		
• Adjusted for covariates category 1	1.07 (0.99 – 1.16)	.088
• Additionally adjusted for covariates category 2	1.07 (0.99 – 1.16)	.092
• Additionally adjusted for covariates category 3	1.09 (1.00 – 1.19)	.047

Abbreviations: HR, hazard ratio; CI, confidence interval
Covariates category 1 include age, sex, and education (baseline), as well as Mini-Mental State Examination score, use of analgetics, use of antidepressants, subsyndromal depressive symptoms (time-dependent).
Covariates category 2 include smoking, use of alcohol, and Body Mass Index (time-dependent)
Covariates category 3 include functional limitations and chronic diseases (time-dependent)

Do depressive symptoms increase the incidence of pain?
To predict the development of pain, we first selected participants with no pain at baseline (n=1420, 70.0%).
Of the 1420 participants with no pain at baseline, a total of 346 (24.4%) developed pain during follow-up. The mean (SD) pain free duration of follow-up was 8.3 (3.6) years, which corresponds to an incidence rate of 29.3 per 1.000 person years.
In unadjusted Cox-regression analyses, incident pain was predicted by baseline depressive symptoms (HR = 1.02 [95% CI: 1.01 – 1.04], p= .006) as well as the combined severity-chronicity score of depression (HR = 1.03 [95% CI: 1.01 – 1.05], p= .011), but not by including depressive symptoms as a time-dependent covariate (HR = 1.01 [95% CI: 0.99 – 1.03], p= .160). The Hazard Rates count for each 1 point increase on the CESD scale. As shown in table 3, the effect of depression on incident pain fully disappeared after correction for confounders.

Table 3 Multivariate Cox Regression on Incident Pain

Variable	Imputed (N=1420)	
	HR (95% CI)	P Value
Depressive symptoms at baseline		
• Adjusted for covariates category 1	1.01 (1.00 – 1.03)	.121
• Additionally adjusted for covariates category 2	1.01 (1.00 – 1.03)	.134
• Additionally adjusted for covariates category 3	1.01 (1.00 – 1.03)	.137
Combined severity – chronicity depression level		
• Adjusted for covariates category 1	1.01 (0.99 – 1.04)	.265
• Additionally adjusted for covariates category 2	1.01 (0.99 – 1.04)	.274
• Additionally adjusted for covariates category 3	1.01 (0.99 – 1.04)	.290
Depressive symptoms (continuous at separate time-points)		
• Adjusted for covariates category 1	1.00 (0.98 – 1.03)	.823
• Additionally adjusted for covariates category 2	1.00 (0.98 – 1.03)	.801
• Additionally adjusted for covariates category 3	1.00 (0.98 – 1.03)	.797

Abbreviations: HR, hazard ratio; CI, confidence interval
Covariates category 1 include age, sex, and education (baseline), as well as Mini-Mental State Examination score, use of analgetics, use of antidepressants (time-dependent).
Covariates category 2 include smoking, use of alcohol, and Body Mass Index (time-dependent)
Covariates category 3 include functional limitations and chronic diseases (time-dependent)

Sensitivity analysis

We checked whether the results differed from analyses based on cases with complete data only, i.e. n=1139 and n=987 for analyses on incident depression and incident pain, respectively. Similar results were obtained when predicting incident depression, whereas with respect to incident pain, the baseline CESD score significantly predicted incident pain when corrected for socio-demographic and medication use only (HR=1.01 (95% CI: 1.00 – 1.05, p= .047).

Discussion

Main findings

Among community-dwelling older people, pain precedes the onset of clinically relevant depressive symptoms. The predictive value of pain with respect to depression is a robust finding, as not only pain at baseline was predictive of incident depression, but also the combined severity-chronicity pain score as well as by taking fluctuations in pain during follow up into account by including pain as a time-dependent variable. In contrast to our hypotheses, depressive symptoms only predicted pain in the unadjusted models.

Comparison with previous findings

The finding that pain precedes the development of depression is consistent with earlier longitudinal studies with shorter durations of follow-up in humans [11, 15-17, 19] as well as with experimental short-term animal research in which psychological and sociodemographic confounders are less important [34]. Our data add that this predictive value of pain for developping depression remains over a 12-year follow-up period when assessed at 3-yearly intervals in a large group of community dwelling older people. Moreover, this relation is not mediated by disability, and remains significant when corrected functional limitations and number of chronic diseases, which is consistent with earlier findings [17].

The negative results we found with respect to the effect of depression on the development of pain strengthens the finding of previous studies among older people showing no effect of depression on the development of pain. Our findings are in line with a review that found that 9 out of 13 studies (among younger adults) also did not find support for the predisposition of depression to pain [10], as well as with three studies among older persons. First, among 318 Chinese elderly people referred to secondary care, the predictive value of depression also became non-significant after correction for age, sex and educational level [16]. Second, a recent European population-based study among 4234 people aged 50 years and over, showed that the effect of depression on incident pain did not disappear after adjustment for sociodemographic factors, but did so after additional correction for baseline co-morbid psychopathology [11]. Unfortunately, this last study did not correct for functional limitations and/or chronic diseases. Finally, within a highly selective community sample of 529 older persons suffering from osteoarthritis, depressed mood did not led to a worsening of pain [35]. The studies among older persons that did find an effect were indeed limited to a follow-up duration up to 3 years [11, 13, 15] or were conducted in specific populations as middle-aged patients who were already suffering from musculoskeletal pain [36] or low-back pain [37] or limited to the development of low-back pain in the older population [13]. Our 12-year follow-up period is probably the major difference with previous studies and unique in this field of research. Nevertheless, as we measured depression and pain only once every three year, we can not rule out that depression impacts on the development of pain at much shorter intervals. Such short-term effects may led to analgetic drug use, change in lifestyle behaviour or inforce the development of functional impairment [18], al of which could explain our negative results in our adjusted models. Other positive findings of depression are not focussed on the incidence of pain, but on worsening of existing pain [36, 37]. Depression might have differential effects in patients with no pain compared to patients already suffering from a painfull somatic condition. Depression may amplify physical pain sensations due to changes in motivational-affective processess and cognitive-evaluative processes that can affect the processing and perception of noxious input. This might also lead to different results between chronic diseases that are rarely accompanied by pain like cerebrovascular accidents and chronic diseases that are typically accompanied by physical pain sensations like osteoarthritis [38]. Nonetheless, motivational-affective and cognitive-evaluative processes of pain experience also interfere with very low or even absence of noxious stimuli [39].

Methodological considerations

Our study is unique in having a 12-year follow-up and being able to adjust for the use of antidepressants and analgetics as well as for lifestyle variables. Nevertheless, for proper interpretation some limitations have to be acknowledged. First, selective loss to follow-up is an inevitable consequence of a longitudinal study in the elderly [40]. The selective dropout of patients with more pain symptoms and more severe depression in our study may have biased our effects. Nonetheless, completed case analyses and analyses after multiple imputation yielded comparable results. Nevertheless, the high number of excluded participants due to missing baselinedata, may limit the external generalization of our results to the more frail elderly. On the other hand, multiple imputation of the whole dataset, did not yield different results (data available on request). Second, the interval period of 3 years hampers the observation of more direct temporal correlations between pain and depression. Nevertheless, earlier studies with shorter interval periods have shown that in the elderly the presence of pain and depression were remarkably stable over time [18]. A third potential source of bias is the fact that all data relied on self-report measures of depression and pain. This might have caused an overestimation of the associations under study. However, if data indeed were contaminated due to self-report assessments, it would have lessened the chance to find differential results as we did. Furthermore, depressive symptoms were measured with the CESD, a frequently used and well-validated instrument that is sensitive to change, whereas the NHP5 pain scale is a much lesser used and less validated instrument in pain research. Especially the 5 dichotomous items may have led to a less sensitive pain measure. A fourth potential bias factor is the disregard of treatment other than antidepressants and analgetics received by the participants for depression or pain. The influence of this factor, however, is supposed to be mild because there is evidence that a large proportion of the elderly with pain or depression receive no adequate treatment [41].

Conclusion / implications

The comorbidity of depression and pain places a high burden on both the society, patients and families who it concerns and results in less favourable outcomes for both conditions. The reciprocal relationship of depresion and pain over time is thus of particular of importance for preventive medicine. We found that chronic pain in older adults places them at risk for depression. This underscores the importance of early detection of depressive symptoms in older persons experiencing pain, because older persons in general are less inclined to seek emotional help [42] and rates of underrecognition of and inadequate treatment for depression are high [43, 44]. Further research should thus examine whether specific strategies to prevent depression in chronic pain patients are effective in this at risk population. A reverse pathway of depression to pain could not be demonstrated.

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CHAPTER 5

Physical functioning in older people with somatoform disorders: A pilot study.

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Journal of the American Medical Directors Association 2013 Jan;14(1):75.e9-13.

Abstract

Objectives – The primary objective of this study was to systematically examine the physical functioning of older persons with somatoform disorders, as this has never been carried out before. Secondly, we wanted to test our hypothesis that higher somatic disease burden in patients with somatoform disorders is associated with a higher level of somatisation.

Design and Setting – Observational study of patients referred for Medically Unexplained Symptoms (MUS) to our outpatient Mental Health Centre for Older Adults. The patients were offered a standardized, multidisciplinary diagnostic procedure, including a comprehensive geriatric assessment. Inter-rater reliability between two geriatricians assessing the contribution of somatic pathology to the main somatic symptom was assessed.

Participants – A total of 37 patients referred for MUS (mean age 75 ± 6 years).

Measurements – Timed Up and Go Test (TUG) and Hand Grip Strength were used as measures for frailty; the Cumulative Index Rating Scale for Geriatrics (CIRS-G) sum score and severity index measured the burden of cumulative somatic morbidity. The Groningen Activity Rating Scale (GARS) measured functional status. The Whitely Index was used as measure for somatisation.

Results – Patients' main symptom could be completely explained by a somatic disease in 3/37 (8%) patients (kappa between geriatricians = 0.72). A total of 32 patients met the criterion for a Somatoform Disorder according to DSM-IV-TR criteria, but somatic comorbidity partially explained the main symptom in 15/32 patients. These patients were older (p=.049), had more somatic co-morbidity (p=.049), a slower gait speed (TUG, p=.035), a lower hand grip strength (p=.050) and a lower functional status (p=0.03) compared to the 17 patients without any explanation for their main somatic symptom. In contrast to our hypothesis, a higher level of somatisation was associated with less somatic disease burden.

Conclusion - Geriatric assessment has important added value in older patients referred with medically unexplained symptoms, as in half of the patients symptoms can be partially or fully explicable following careful assessment of co-morbidity and frailty.

Introduction

Medically Unexplained Symptoms (MUS) are a common phenomenon. In primary care 15-39 % of presented somatic symptoms remain unexplained [1,2]. MUS become burdensome when MUS persist over time and people persevere in seeking medical help. Psychological processes like somatisation and hypochondriasis are thought to predispose, precipitate or perpetuate the persistence of MUS. Somatisation is conceptualised as a tendency to express psychological distress with somatic complaints. In the medical literature, somatisation is often defined according to Lipowski (1998) as "the tendency to experience and communicate somatic distress and somatic symptoms unaccounted for by relevant pathological findings, to attribute them to physical illness, and to seek medical help for them" [3]. Hypochondriasis is an excessive preoccupation or worry about having a serious medical illness [4]. Although hypochondriasis can be present without having any medical symptoms, approximately 75% of the people suffering from hypochondriasis also have MUS [5]. In the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM IV-TR), a widely used classification system for psychiatric disorders, MUS are considered as the core criterion for a somatoform disorder. Nonetheless, depending on type and combinations of symptoms, duration, intensity and level of distress, patients suffering from MUS may or may not meet the criteria for a specific somatoform disorder like somatisation disorder, pain disorder, conversion disorder, hypochondriasis, or somatoform disorder not otherwise specified. It is important to note that a Somatoform Disorder can be present when a patient has partially explained somatic symptoms: the adverse effects of the somatic symptoms on everyday life are substantially more severe than expected. The burden of MUS and Somatoform Disorders is large: patients often report a low quality of life and suffer from co-morbid anxiety and depressive disorders [6]. Furthermore, MUS give rise to high levels of health care consumption in search for an organic origin of complaints, which places patients at risk for extensive and potentially iatrogenic investigations [2]. In 10-30 % of MUS, and 50-70 % of hypochondriasis, the condition becomes chronic [7].

Although empirical data are scarce, prevalence rates range from 1.5% through 18% for MUS and from 5% through 13% for Somatoform Disorders in people aged 65 years and over [8]. These figures are somewhat lower than those reported for younger people, which may be explained by diagnostic problems of MUS or Somatoform Disorders in later life. At an older age, somatisation often occurs in the context of chronic somatic diseases [9], and thus more pathological findings have to be examined in an attempt to account for the physical complaints [10]. Higher co-morbidity rates as well as higher a priori chances of underlying physical illnesses as explanation for physical complaints in older people probably cause physicians to consider these symptoms as explained [11].

To date, several etiological models for (the persistence of) MUS have been proposed [12-16]. Although consensus exists on the interplay between biological, psychological and social elements in the aetiology of MUS, models differ in the relative contribution of these factors. Psychological and social processes can be a precipitating factor, but are most often assumed to be predisposing and perpetuating factors. Biological processes, by contrast, are only included as a precipitating factor. In most models, bodily sensations that give rise to somatic symptoms

are thought to originate from both normal physiological processes (e.g. bowel peristaltic), from pathophysiological processes due to sub threshold medical conditions (e.g. elevated blood glucose levels without actual diabetes), or from clinical diseases. The contribution of pathophysiological processes is also reflected by the criterion for somatoform disorders that complaints have to be more severe than can be explained by the underlying somatic condition. Further support for the contribution of these processes can be deduced from the finding that in depressed older adults the level of somatisation increases with the number of chronic somatic conditions [17]. Thus, we might expect somatisation problems to increase parallel with an increase in somatic diseases. Therefore, more emphasis should be placed on the physical functioning of patients suffering from MUS or Somatoform Disorders, particularly in later life. The objective of the present study was 1) to describe the physical morbidity and functioning of a convenience sample of patients referred for MUS to an outpatient Mental Health Centre for Older Adults in the Netherlands and 2) to explore the association between the level of somatisation and physical performance. We hypothesized a positive association between a higher level of somatisation and lower level of physical performance.

Methods

Design

All patients, aged 60 years or over, referred for MUS to an outpatient Mental Health Centre for Older Adults in Nijmegen in the Netherlands between September 2006 and October 2007 underwent a standardized examination by a geriatrician (C.B.), old-age psychiatrist (P.H.) and clinical psychologist (DvD) within two weeks after referral. The psychiatric characteristics of this cohort have been described elsewhere [18] . In short, psychiatric disorders were assessed by an experienced old-age psychiatrist (P.H.) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV) using the Mini International Neuropsychiatric Interview version 5.0.0. The senior clinical psychologist (Dv.D.) focussed on the consequences of the somatic symptoms in everyday life, in order to prepare for and motivate patients for cognitive-behavioural treatment. The Whiteley Index (WI) was administered to assess the severity of hypochondric beliefs and attitudes as a measure of somatisation [4,19]. This self-report questionnaire includes 14 dichotomised items (yes/no) related to bodily preoccupation, disease phobia and conviction of the presence of disease. The sum score range from 0-14, with higher scores being indicative of more severe somatisation levels and hypochondric beliefs. The Dutch version has been validated in different populations with showing good test-retest reliability (0.90) and good internal consistency (Cronbach's α ranges between 0.76 and 0.80). Although a cut-off for clinically relevant levels of somatisation is not available, the WI appeared to discriminate reasonably well between hypochondriacal and non-hypochondriacal subjects [20].

Geriatric assessment

The geriatrician performed a complete geriatric assessment including an ECG, routine blood chemistry, somatic disease burden, activities of daily living and cognitive screening with

the Mini-Mental State Examination (MMSE) [21]. All correspondence of previous medical examinations was evaluated and when relevant, previous medical specialists were consulted by telephone. If considered necessary, further investigations were carried out. The duration of the primary complaint was estimated in months and patients had to rate the current intensity of their primary complaint on a visual analogue scale (VAS).

The geriatrician (C.B.) who did the geriatric assessment judged the main symptom as completely explained, partially explained or unexplained by an underlying somatic disease. As there is no objective criterion to decide whether a bodily complaint is medically explained or not, a second geriatrician (L.D.) also classified the patients' symptoms according to these three categories. This classification was based on the medical records (including findings of the first geriatrician), but blind for the final judgement of the first geriatrician. Subsequently, discrepancies were discussed between both geriatricians in order to achieve consensus. In case no consensus could be reached, a third geriatrician made the final classification for that patient (M.O.R).

Somatic Comorbidity – The Cumulative Illness Rating Scale – Geriatric (CIRS-G) was used to measure cumulative burden of diagnosed somatic diseases [22]. This scale was scored by a clinician and contains 14 domains: 13 domains of different somatic organ systems and 1 psychiatric domain, which was left out. Each item can be scored from 0-4 (range 0-52, higher score: more comorbidity). In our study we used the sum score and the 'severity index' of the CIRS-G: the total score divided by the number of domains on which the score was > 0 [23].

Frailty – As a gold standard for frailty does not exist and available frailty indices at least partly overlap with the criteria for psychiatric diseases [24,25], we administered two proxy measurements for physical frailty: the Hand Grip Strength [26], and the Timed-Up-and-Go-Test (TUG) [27]. Hand Grip Strength was measured using the Jamar Dynamometer as the best score of two consecutive attempts. The TUG is a measure that scores the time needed by a patient to get up from a chair, walk 3 metres, turn around, walk back to the chair and sit down again. Both tests have high inter-rater and test–retest reliability.

Functional status – We used the Groningen Activity Restriction Scale (GARS) to measure activities of daily living [28]. This self-assessment scale contains 18 items of ADL and IADL, with 1-4 points per item, (range 18- 72; higher score: more dependent).

Analyses

First, we evaluated the origin of patients main symptoms. We categorised patients referred for MUS in those having completely explained, partially explained and unexplained medical symptoms. Inter-rater reliability of this classification into three categories by both geriatricians was estimated by calculating the kappa.

Secondly, we compared patients suffering from somatoform disorders with partially explained or unexplained main symptoms with respect to physical functioning. Differences were tested by chi-square and by two-sample t-test or Mann-Whitney U-test. As ours was a pilot study and data-analysis was mainly explorative, we did not apply a Bonferroni correction and considered p-values of less than .05 to be significant.

Thirdly, correlations between measures of somatisation (Whiteley Index) and measures of somatic disease burden (CIRS-G, GARS) and frailty (Hand Grip Strength, TUG) were calculated by Pearson's correlation. Correlation coefficients .10 and .30 are considered small, between .30 and .50 medium and between .50 and 1.00 strong [29].

Results

Patient characteristics

A total of 48 patients were referred for Medically Unexplained Symptoms (MUS) of which 37 patients agreed to a diagnostic assessment. Reasons for refusal were: lack of motivation (n=4), aversion against mental health organization (n=2), hospitalization for an acute disease (n=2), age below 60 years (n=1), moved homes (n=1), unknown (n=1).

The 37 patients who went through the diagnostic procedure had a mean age of 74.8 years (SD=7.0 years) and 31/35 (84%) patients were female. 15 Patients (41%) were married and lived with their partner; the other 22 patients lived alone (widowed, n=18; divorced, n=2; never married, n=2). The mean MMSE score was 27.5 (SD = 2.4) indicative of good cognitive functioning.

Classification of the primary symptom

The kappa of inter-rater agreeability between the overall classification of the main somatic symptom as completely explained, partially explained, or unexplained by both geriatricians was 0.67.

The first geriatrician (CB) classified three out of these 37 patients as having a completely explained main somatic symptom. The second geriatrician (LD), who blindly evaluated the medical records, classified these same three patients as having a somatic disorder that completely explained their symptoms. In addition he scored also two other patients as such. This resulted in a kappa of 0.72 for the comparison between completely explained versus partially explained/unexplained symptoms. After discussing these two patients, consensus was reached that the underlying somatic condition only partially explained the main symptom. Of the remaining 34 patients, the main symptom spontaneously resolved in two patients, whereas the other 32 patients all met DSM-IV-TR criteria for a Somatoform Disorder (see for details also Hilderink et al., 2009) [18]. Among the 32 patients with a somatoform disorder, the kappa of inter-rater agreeability of main complaints that could be partially explained by an underlying somatic disorder versus those that were unexplained between the first (C.B.) and second (L.D.) geriatrician was 0.69. Nonetheless, consensus could quite easily been reached in discrepant cases when both geriatricians presented their arguments to each other. This consensus meeting resulted in a final classification of 15 patients with a partially explained and 17 with a unexplained main symptom.

Physical functioning in somatoform disorders in later life (n=32)

During the geriatric assessment, 20 patients reported pain as their primary symptom (head, n=6; whole body, n=4; abdominal, n=4; mouth, n=3; back, n=2; joints, n=1). The other primary complaints were shortness of breath/coughing (n=5), dizziness (n=3), and further

dysarthria, paraesthesia, anxiety/loneliness, and fatigue.

Table 1 presents the characteristics of all patients diagnosed with a Somatoform Disorder, stratified for patients with partially explained and unexplained main symptoms. The mean duration of the main symptom was almost 6 years in both groups. Patients in whom the main symptom was partially explained by a somatic condition were older (p= .049), more functionally impaired (GARS p=0.030), had higher chronic disease burden as measured by the CIRS-G total score (p=0.049), a lower gait speed (TUG p=0.035) and lower Hand Grip Strength (p=0.050) compared to patients with no explanation for their main symptom. This latter group, however, had numerically higher levels of somatisation on the Whitely Index, although the difference did not reach statistical significance (p=0.068).

Table 1 Comparison of somatic disease burden in patients suffering from somatoform disorder with and without a partially explained medical symptom (n=32)

Variables		Explanation for primary complaint		Statistics
		Unexplained (n=17)	Partially (n=15)	P
Demographics:				
• Age (years)	mean (SD)	73.0 (6.6)	77.7 (6.2)	.049
• Female sex	n (%)	13 (77)	13 (87)	0.46
MUS characteristics:				
• Duration of MUS (months)	mean (SD)	70 (71)	71 (72)	0.99
• Intensity primary symptom (VAS)	mean (SD)	7.2 (21)	7.7 (24)	0.67
Psychiatric morbidity				
• Depressive disorder	n (%)	11 (65)	7 (47)	0.31
• Anxiety disorder	n (%)	6 (35)	4 (27)	0.60
Physical functioning:				
• CIRS total score	mean (SD)	6.5 (4.2)	10.5 (6.0)	.049
• CIRS severity index	mean (SD)	1.4 (0.4)	1.8 (0.6)	.076
• Grip strength	mean (SD)	32.7 (13.7)	22.2 (11.5)	.050
• Timed up-and-go	mean (SD)	7.9 (2.9)	11.8 (5.4)	.035
• GARS	mean (SD)	23 (10)	34 (14)	.030
Level of somatisation				
• Whiteley Index	mean (SD)	6.9 (4.0)	4.6 (3.4)	.068

Abbreviations: MUS, medically unexplained symptoms; GARS, Groningen Activity Restriction Scale. CIRS-G: Cumulative Illness Rating Scale Geriatric. VAS, visual analogue scale; SD, standard deviation; p, p-value;

Associations between somatisation and parameters of physical functioning
Somatisation, as indexed with the Whitely Index, had a substantial but inverse relationship with gait speed (TUG, r= -0.44, p=.015) and a definite, but small relationship with Hand Grip Strength (r=0.27, p=.16). There was also a small inverse relationship with the CIRS severity index (r=-0.21, p=.27) and the Groningen Activity Restriction Scale (GARS, r=-0.32, p=.078). We found virtually no relationship with the CIRS-G total score (r=-0.02, p=.91).

Discussion

This is the first study on a multidisciplinary assessment of patients referred for Medically Unexplained Symptoms (MUS) in an older population. Our patients were suffering on average for 6 years with their somatic symptoms and their referring physicians referred them specifically for psychological treatment having finalised their somatic diagnostic work-up probably much earlier. Nonetheless, we showed that these patients referred to an old age psychiatry setting still importantly benefit from a comprehensive geriatric assessment. A small proportion (8%) of patients with seemingly unexplicable symptoms still could be explained, while nearly half of the formerly unexplained symptoms could be partially explained.
There are several limitations inherent in such a small pilot study on a convenience sample referred to an old age psychiatry setting. Here we would like to address the lack of statistical power and the fact that the cross-sectional nature hampers firm conclusions and causal interferences.
Nevertheless, although preliminary, our results are important. MUS and Somatoform Disorders in later life are largely neglected in geriatric literature, whereas chronic nature of the complaints, the physical functioning and frailty of this older age group may have considerable clinical consequences.
Although referred for MUS, in three (8%) out of 37 patients in our sample there did turn out to be a completely somatic explanation for the main symptom. In previous studies, misdiagnosis of MUS has mainly been focused on misdiagnosis in conversion: in a review a mean percentage of 4 % misdiagnosis was found in 22 studies published since 1970 [30, 31], which is lower than in our study.
The overall agreement between two geriatricians judging the main symptom as completely explained, partially explained or unexplained was moderate to good. We found only two studies on medical judgment of symptoms in these three categories. Our kappa is in line with these studies, which used a different methodology and were conducted in younger populations. In the first study, a kappa of 0.76 was found on agreement between two psychiatrists and one general physician using a chart review method [32]. The second study, a retrospective chart study, reported an agreement in diagnosis of only 43% between paediatricians in a panel for children who were referred for unexplained chronic pain [33].

Comparison of the groups of patients with a partially explained and unexplained main somatic symptom showed that the patients in the first group were significantly older, had more somatic co-morbidity, a lower hand grip strength, and a slower gait speed. The CIRS-G

total score for the group of patients with partially explained somatic complaints was comparable with a group of patients on an acute geriatric ward [22], but the CIRS-G 'severity index' was low and not significantly different for both groups. This indicates that, although the number of somatic diseases was higher in the partially explained group, the severity of the underlying somatic diseases was low to moderate. Overall, the comprehensive geriatric assessment data indicate that the group of persons with unexplained symptoms is a strikingly healthy population from a somatic point of view, whereas the group of persons with partially explained symptoms is less healthy and more frail. Particularly this latter group may benefit from a multidisciplinary approach including geriatric assessment.

In contrast to our hypothesis, a higher level of somatisation was associated with a better physical performance. First, the strong trend towards higher level of somatisation, as measured with Whiteley Index, was associated with a lower degree of frailty, of which the Timed Up-and-Go test reached statistical significance. Second, we did not find an association with the CIRS-G sum score, whereas the severity index of the CIRS-G was negatively associated with somatisation: more somatic conditions, be it of moderate severity, was associated with less somatisation.

There might be several explanations for this unexpected finding; physical problems in later life might result in more adequate interpretation of bodily sensations and physical problems might have validated people's help-seeking behaviour and thereby have had a dampening effect on the level of somatisation. This also offers an alternative explanation for the decreasing prevalence rates of MUS and somatoform disorders with age [8].

Conclusion

A geriatric assessment has added value in diagnosing older patients referred for MUS, even when symptoms exists for years. In half of the patients symptoms that could not be explained before, proved to be partially or fully explicable following such a comprehensive assessment. Moreover, a high somatic disease burden was found in those patients with partially explained symptoms. Longitudinal research is necessary to disentangle the relationship between somatisation and somatic disease burden in later life as this will guide therapeutic strategies, containing somatic as well as psychiatric and psychological interventions.

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CHAPTER 6

Impact of medically unexplained symptoms on health related quality of life: A comparison with medically explained symptoms and age-effects.

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Submitted

Abstract

Objective: We aimed to clarify whether medically unexplained symptoms (MUS) cause the same degree reduction in health-related quality of life (HRQoL) as medically explained symptoms (MES). Secondary aim is to describe the effects of aging on this impact.

Method: In a population based cohort (n=946, aged 28-75 years), MUS and MES were measured using the Composite International Diagnostic Interview (CIDI) and HRQoL using the EuroQol-5 Dimensions (EQ-5D). Using multiple linear regression, we regressed MUS, MES and their interaction with age on HRQoL, first adjusted for socio-demographic variables and subsequently adjusted for psychiatric comorbidity. In case of significant interaction terms, age-stratified results will be presented.

Results: Overall the association between MUS and HRQoL was stronger (B=-.247, SE =.021, p<.001) than between MES and HRQoL (B=-. 188, SE=.022, p<.001). Adjusted for psychiatric co-morbidity, these associations became almost equal (for MES: B=-.183, SE=.021, p<.001; for MUS: B=-.194, SE=.020, p<.001). Age significantly interacted with number of MUS in explaining variance in HRQoL, but not with the number of MES. The impact of MUS on HRQoL is much larger in people aged below 65 years (B=-.272, SE=.023, p<.001) versus those aged 65 years and over (B=-.149, SE=.046, p=.002). Only in the older age group, this association lost significance when adjusted for psychiatric co-morbidity (B=-.085, SE=.045, p=.062).

Conclusion: In an adult population the impact of MUS on HRQoL is larger than the impact of MES. However in later life the impact of MUS decreases suggesting that older persons cope better with MUS than younger persons.

Introduction

Physical symptoms account for the majority of consultation in primary care and at least a third of these complaints remain medically unexplained [1]. While it is recognized that physical symptoms are an important cause of illness burden in patients, it is not clear whether medically unexplained symptoms (MUS) cause the same degree of morbidity and reduction in health-related quality of life (HRQoL) as medically explained symptoms (MES). HRQol is defined as those aspects of self-perceived well-being that are related to or affected by the presence of disease or its treatment [2]. The impact of MES and MUS on HRQoL may further differ across the lifespan, taken into account that the number of MES clearly increases with age, while no or only a very weak correlation has been found between the prevalence of MUS and age [3-5].

Because of higher numbers of MES in older persons, one would expect lower HRQoL. Nonetheless, two-thirds of hospitalised older patients report good HRQoL. In this group, lower physical and psychological HRQoL was significantly associated with impaired personal activities of daily living, impaired cognition, depression, anxiety and a higher medication use [6].

MUS are defined as physical symptoms of which presence, severity or consequences cannot be explained by any detectable physical disorder [7]. Although clinicians are almost daily faced with MUS throughout the lifespan, almost no empirical data are available for MUS in later life [8]. A recent review suggests that prevalence rates of MUS are stable until the age of 65 years and decrease thereafter [9]. This might be an artefact caused by diagnostic issues differentiating between MES and MUS in later life as well as by conceptual difficulties. The concept of MUS has been criticized as it is dualistic, and its measurement is time consuming and unreliable [10, 11]. Therefore, it has been suggested that the total number of physical symptoms, including both medically explained and unexplained symptoms, is more informative in estimating health related quality of life [12-15]. Cross-sectional clinical studies indeed found a significant correlation between a high somatic symptom count, including both medically explained and unexplained symptoms, and impaired health status [1, 16]. Furthermore, one prospective cohort study showed that total somatic symptom counts predicted impaired health status over time [17]. The impact of MUS on the HRQoL in old age populations, however, has not been reported yet.

In adult populations some have suggested that MES and MUS are associated with similar levels of disability [18, 19], while others have suggested that MUS are associated with greater disability [20, 21]. In a Dutch primary care population, Quality of Life (QoL) of patients suffering from MUS was lower than that of the overall primary care population, but higher compared to depressed patients in primary care [21]. A proposed explanation for a differential impact on HRQoL between MES and MUS is the increased prevalence of affective disorders in patients suffering from MUS as compared to patients with MES as well as the fact that patients with MUS on average do have higher numbers of somatic symptoms [22]. In a predominant South Asian primary care population, patients with MUS had significantly more physical symptoms, higher levels of anxiety and depression, and lower HRQoL compared with patients with MES.

Health-related quality of life in patients was independently predicted by occupational status, educational status, anxiety, depression, and the number of physical symptoms reported. Whether symptoms were medically explained or not did not add significantly to the model after adjusting for other variables [22].

The primary aim of the present study is to examine the effect of age on the impact of MUS and MES on health-related quality of life. We hypothesize that 1) MUS are more strongly associated with impaired HRQoL than MES, 2) the differential impact of MUS and MES on HRQoL can be explained by an increased prevalence of psychiatric comorbidity in patients with MUS as compared to patients with MES, and 3) the impact of MES on HRQoL decreases with age in contrast to the impact of MUS.

Method

Population

This study has been performed in a cohort derived from Prevention of Renal and Vascular End Stage Disease (PREVEND), a population cohort study investigating micro-albuminuria as a risk factor for renal and cardiovascular disease. The recruitment of participants is described elsewhere [23], but will be summarised below. All inhabitants of the city of Groningen between the ages of 28 and 75 years (85 421 subjects) were asked to send in a morning urine sample and to fill out a short questionnaire on demographics and cardiovascular history. A total of 40 856 subjects (47.8%) responded. After exclusion of subjects with insulin-dependent diabetes mellitus and pregnant women, all subjects with a urinary albumin concentration of >10 mg/l (n=7768), together with a randomly selected control group with a urinary albumin concentration of <10 mg/l (n=3395), were invited for further investigations (total n=11 163). Finally, 8592 subjects completed the total screening program making up the PREVEND study cohort. Because the PREVEND study population was enriched for albuminuria, this oversampling for albuminuria was counterbalanced in the current substudy. Albuminuria-negative participants and a random sample of albuminuria-positive participants were combined so that a population representative ratio of albuminuria-positive participants was achieved. Research assistants handed over invitations in the 2001–2002 wave to 2554 subjects to participate in a substudy, for which additional psychiatric and psychosocial data were collected. Of these 2554 subjects, 1094 (43%) completed the additional measurements.

Follow-up measurements in the 2003–2004 wave were completed by a total of 964 participants (89% of the cohort) with additional psychiatric and psychosocial data (see below). The recruitment of these participants that formed the cohort for the current study has been extensively described elsewhere [24]. The study was approved by the local medical ethics committee and all subjects gave written informed consent to participate.

Physical symptom count:

Physical symptom count was based on the somatization section of the Composite International Diagnostic Interview (CIDI), a fully structured psychiatric interview assessment with adequate test–retest reliability and validity [25]. A fully computerized version of the CIDI 2.1 12-month

was applied, suitable for self-administration. Trained interviewers were present for questions and for participants who needed computer help. The probing scheme of the self-administered version is completely identical to the interviewer-administered version; the difference between both versions is that the questions are not read out loud by the interviewer but instead are read on the screen by the participant him/herself.
In short, the CIDI somatization section surveys the occurrence of 43 symptoms in the past year. Symptoms are considered present when they meet severity criteria, i.e. provoke a healthcare visit. If these criteria are met, the interview assesses in a hierarchical fashion whether a medical doctor diagnosed a symptom as due to physical illness or injury, or whether a symptom was caused by the use of medication, drugs or alcohol. If these inquiries are negative for these medical explanations, the symptom is scored as a functional symptom. In those cases in which the diagnosis involved a functional syndrome (such as irritable bowel syndrome, chronic fatigue syndrome or fibromyalgia), the symptom was recoded as a functional symptom.

Health related quality of life:
Self-rated health-related quality of life was measured using the descriptive section of the EuroQol-5 Dimensions (EQ-5D) [26]. The EQ-5D consists of a descriptive system that records the level of self-reported problems on each of the five dimensions of the classification (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each dimension the respondent is asked to choose between three options: no problem, some/moderate problems, or extreme problems/unable. Health states defined by the five-dimensional descriptive system, can be converted into a weighted health state index by applying scores from value sets elicited from general population samples which leads to a mean weighted health index ranging from 0 (dead) to 1(optimal health) [27, 28].

Covariates:
Age, sex, educational level (operationalized as the number of years of education beyond the age of 12), marital status (married or not married) and psychological distress (measured with the Dutch translation of the 12-item General Health Questionnaire [GHQ-12])[29]. The presence of depression and anxiety disorders was assessed by the corresponding sections of the CIDI 2.1, 12 month version. For depression, all diagnoses of single or recurrent depression and dysthymia were included. For anxiety disorder, panic disorder with and without agoraphobia, social phobia and generalised anxiety disorder were included.

Statistical analyses:
Demographics and clinical characteristics will be described for participants with and without MUS and/or MES as well as for older and younger patients based on an age cut-off at 65 years [9]. Differences between groups were examined using independent samples t-tests or ANOVA for normally distributed, continuous variables, nonparametric Mann Whitney U tests or Krusskall Wallis for skewed continuous variables, and χ^2 tests for categorical variables.
The impact of the number of MUS and number of MES on HRQoL was assessed with multiple linear regression models with HRQoL as the dependent variable and adjusted for

socio-demographic variables (age, sex, educational level, marital status). In case of a significant interaction term between age and the number of MUS or age and the number of MES, analyses were separately presented for participants aged below 65 years and those aged 65 years and older based on previous found differences in prevalence rates for MUS between these age groups.

In model 1, the impact of the number of MES on HRQoL was examined. In model 2, the impact of the number of MUS on HRQoL was examined. In model 3, the number of MES and number of MUS were simultaneously entered, together with their interaction. In case of a non-significant interaction term, the interaction term was removed from the final model. In order to examine the impact of psychiatric comorbidity, all models were subsequently adjusted for the presence of any depressive or anxiety disorder within the past 12 months. In case the B decreased by 10% or more after adjustment for psychiatric comorbidity, it was considered an explanatory factor.

All analyses were conducted in SPSS version 18 (Chicago, Ill.) with p-values <.05 considered statistically significant.

Results

For 946/964 (98.1%) of the eligible participants, the EQ-5D and the CIDI physical symptom scores were available. Mean age of these participants was 55.2 (SD 11.1) years, 51.8% was female, and 55.5% was married. The mean number of years of education beyond the age of 12 years was 8.1 (SD= 4.5) years. Overall, 7.1% of the participants suffered from a depressive disorder and 5.1% from an anxiety disorder.

Table 1 presents the characteristics separately for participants without physical symptoms, for participants suffering from MES, for participants suffering from MUS, and finally for participants suffering from both MES and MUS within the past year. MES were associated with older age, while MUS were not. Psychological distress differed significantly between the four groups, with highest levels in participants with MUS and MES, followed by those with MUS alone, those with MES alone, and finally lowest levels in participants without physical symptoms.

The number of physical symptoms for MUS were highest in the group of participants suffering from both type of symptoms. HRQoL also differed across the four groups, although post-hoc tests did not show any difference between persons with only MES versus those with only MUS. HRQoL was highest in the group with neither MUS nor MES, followed by the group with MUS only and MES only, whereas it was lowest in participants suffering from both, MES and MUS.

Table 1. Characteristics of people with no somatic symptoms, MES, MUS or MES and MUS together.

Variables	No MES or MUS (n=284)	MES (n=162)	MUS (n=270)	MES and MUS (n=230)	Statistics
Socio-demographics:					
• Age (mean (SD)) [1,3,4,6]	53.1 (10.6)	57.9 (11.5)	53.7 (10.0)	57.5 (11.7)	F=12, df=3, p<.001
• Female sex (n (%))	106 (37.3)	86 (53.1)	153 (56.7)	145 (63.0)	x^2=38.2 df=3, p<.001
• Married (n (%))	156 (54.9)	94 (58.0)	144 (53.3)	131 (57.0)	x^2=1.7, df=3, p=.76
• Years education (mean (SD)) [1,3,4,6]	8.8 (4.5)	7.3 (4.3)	8.7 (4.5)	6.7 (4.5)	F=12, df=3, p<.001
Psychiatric morbidity					
• Depressive disorder (n (%))	7 (2.5)	8 (4.9)	26 (9.6)	26 (11.3)	x^2= 19.2, df=3, p<.001
• Anxiety disorder (n (%))	4 (1.4)	5 (3.1)	19 (7.0)	20 (8.7)	x^2=17.7, df=3, p<.001
• GHQ (mean (SD))[1,2,3,4,5]	0.9 (1.9)	1.8 (3.0)	2.5 (3.3)	2.7 (3.5)	F=20, df=3, p<.001
Physical symptoms					
• Number of MES (median (IQR)) [1,3,4,5,6]	n.a	1,0 (2.0)	n.a	2.0 (2.0)2.4 (2.2)	x^2=3.1 df=1 p=.077
• Number of MUS (median (IQR)) [2,3,4,5,6]	n.a	n.a	1.0 (1.0)	2.0 (2.0)	x^2=11.5, df=1, p<.001
Health related Quality of Life					
• Dutch EQ-5D (mean (SD)) [1,2,3,5,6]	0.95 (0.09)	0.83 (0.21)	0.84 (0.19)	0.77 (0.22)	F=45, df=3, p<.001

[1] Significant difference post-hoc test (p<.05) between no MES or MUS versus MES

[2] Significant difference post-hoc test (p<.05) between no MES or MUS versus MUS

[3] Significant difference post-hoc test (p<.05) between no MES or MUS versus MES and MUS

[4] Significant difference post-hoc test (p<.05) between MES versus MUS

[5] Significant difference post-hoc test (p<.05) between MES versus MES and MUS

[6] Significant difference post-hoc test (p<.05) between MUS versus MES and MUS

Abbreviations: MUS, medically unexplained symptoms; MES, medically explained symptoms; p, p-value; GHQ, General Health Questionnaire; EQ5-D, EuroQol-5 Dimensions; n, number; SD, standard deviation; IQR, Interquartile Range; n.a, not applicable.

Table 2 presents characteristics of participants by age (<65 versus 65 years and over). Older participants were more often married, lower educated and had lower prevalence rates of anxiety disorders compared to their younger counterparts. The proportion of persons with MES was significantly higher in the older age group, as well as the mean number of MES. However, no differences between age groups were found for MUS in both the prevalence of participants with MUS as well as the mean number of MUS.

Table 2 Comparison between participants under the age of 65, and 65 and over.

Variables	Age <65 (n=734)		Age ≥65 (n=212)		Statistics
Demographics:					
• Female sex	n (%)	393 (53.5)	97	(45.8)	x^2=4.0 df=1 p=.046
• Years education	mean (SD)	8.79 (4.46)	5.53	(3.91)	t=10, df =379 p<.001
• Married	n (%)	389 (53.0)	136	(64.2)	x^2=8.2 df=1 p<.001
Psychiatric morbidity					
• Depressive disorder	n (%)	58 (7.9)	9	(4.2)	x^2=3.3 df=1 p=.068
• Anxiety disorder	n (%)	46 (6.3)	2	(0.9)	x^2=9.7 df=1 p=.002
• GHQscore	mean (SD)	2.1 (3.1)	1.6	(2.7)	t= 2.3 df=388 p=.019
Health related Quality of Life:					
• Dutch EQ-5D	mean (SD)	.86 (.19)	.84	(.19)	t=1.7 df=944 p=.10
Medical symptoms					
• One year number MES	mean (SD)	.80 (1.6)	1.4	(1.8)	t=-4.5 df=316 p<.001
• One year number MUS	mean (SD)	1.2 (2.0)	1.2	(1.9)	t=.37 df=944 p=.75
• Number persons with MES	n (%)	270 (36.8)	122	(57.5)	x^2=29.2 df=1 p<.001
• Number persons with MUS	n (%)	385 (52.5)	115	(54.2)	x^2=.21 df=1 p=.65

Abbreviations: MUS, medically unexplained symptoms; MES, medically explained symptoms; n,number; SD standard deviation. GHQ, General Health Questionnaire EQ5-D EuroQol-5 Dimensions.

Within the whole study population, linear regression analyses adjusted for socio-demographic characteristics, showed that the association between MUS and HRQoL was stronger (B=-.247; p<.001) than that between MES and HRQoL (B=-. 188; p<.001). When additionally adjusted for presence of depression and anxiety disorders, the strength of the association of MES and MUS with HRQoL became almost equal: for MES: B=-.183 (p<.001); for MUS: B=-.194 (p<.001). Age significantly interacted with number of MUS in explaining variance in HRQoL (interaction term: β=.405, t=2.7, p<.01), but not with the number of MES (Interaction term: β=-.14, t=-.96, p=.34).

When additionally adjusted for presence of depression and anxiety disorders, this interaction term remains significant for MUS (interaction term: β=.31, t=2.1, p=.04) and not significant for MES (interaction term β=-.16, t=-1.1, p=.27). Based on the significant interaction term between age and MUS, analyses will be presented separately for younger and older patients.

Table 3 Association between MES / MUS and health related quality of life by multiple linear regression analysis*

	Adjusted for socio-demographic characteristics				Adjusted for socio-demographic characteristics &psychopathology				
	B (SE)	**ß**	**p-value**	**R^2**	**B (SE)**	**ß**	**p-value**	**R^2**	**∆B**
Age lower than 65 years (n=738)									
Model 1				.11				.23	
• No. of MES	-.229 (.028)	-.29	<.001		-.211 (.026)	-.27	<.001		7.9 %
Model 2				.20				.26	
• No. of MUS	-.293 (.024)	-.42	<.001		-.238 (.024)	-.34	<.001		19.5 %
Model 3**				.25				.32	
• No. of MES	-.191 (.026)	-.24	<.001		-.185 (.025)	-.24	<.001		3.1 %
• No. of MUS	-.272 (.023)	-.39	<.001		-.220 (.023)	-.32	<.001		19.1 %
Age 65 years or over (n=217)									
Model 1				.20				.33	
• No. of MES	-227 (.044)	-.34	<.001		-.194 (.041)	-.29			14.5 %
Model 2				.17				.28	
• No. of MUS	-.195 (.047)	-.28	<.001		-.126 (.046)	-.18	.007		35.4 %
Model 3**				.24				.34	
• No. of MES	-.194 (.045)	-.29	<.001		-.177 (.042)	-.27	<.001		10.3 %
• No. of MUS	-.149 (.046)	-.21	.002		-.085 (.045)	-.12	.062		42.9 %

* Linear regression analyses with health related quality of life (EQ-5D) as the dependent variable and adjusted for age, sex, educational level, marital status; separately presented with and without adjustment for depression (CIDI) and anxiety (CIDI).

Abbreviations: MUS, medically unexplained symptoms; MES, medically explained symptoms; SE, standard error

Table 3 summarizes the associations between the health related quality of life and the number of MES and the number of MUS in the past 12 months for younger (age < 65 years) and older participants separately.

Model 1 and 2 present the association of MES and MUS with HRQoL without additional adjustment for each other, whereas in model 3 both the number of MES and number of MUS are included. The beta's found in model 1 and 2 hardly differ from those found in model 3, indicating no mutual confounding for MES and MUS.

As indicated by the significant interaction term described above, the results in table 3 clearly

show that the impact of MUS on HRQoL is lower in the older age group compared to the younger age group, whereas no difference is noted with respect to MES.
Overall, the effect size B for MES or MUS was reduced in each model when adjusting for the presence of depression and anxiety. In the younger age group, only the effect size B for MUS decreased with more than 10%, whereas in the older age groups the effect size B for both MES and MUS decreased by more than 10%. Furthermore, the explanatory effect of depression and anxiety in the older age groups were twice as large for MUS as compared to MES.

Discussion

This study demonstrated that the impact of MUS on the HRQoL is larger than the impact of MES on the HRQoL and becomes nearly equal when adjusted for psychiatric co-morbidity. In contrast to our hypothesis, the impact of MES on HRQoL was not dependent on age, whereas MUS had relatively less impact on HRQoL in later life compared to younger persons. Interestingly, in people aged below 65 years, the impact of MUS on HRQoL is larger than the impact of MES, whereas opposite findings were found in the older age group. The presence of anxiety and depressive disorders partly explained the association between MUS and HRQoL and in the older age group the impact of MUS on the HRQoL even lost significance. In later life, comorbid affective disorders also partly explained the association between MES and HRQoL albeit to a lower extent. Differences between MES and MUS across age groups remained similar when adjusted for psychiatric co-morbidity,

The stable prevalence rates of MUS across the lifespan we found in our study, contrast with many studies reporting on decreasing levels of MUS with increasing age [9, 30, 31]. Nonetheless, the only study describing prevalence rates for MUS above the age of 65 that applied similar methodology by using the CIDI, reported only a mild decrease of MUS above the age of 65 [32]. Interestingly, the impact of MUS on HRQoL decreases with increasing age. This is in line with findings in patients with chronic pain. For example, in a Norwegian community-based study, older persons more often suffered from chronic pain compared to younger and middle aged persons, but they showed better adjustment to their pain and reported higher quality of life scores [33]. Comparably, an outpatient clinical sample of patients suffering from non-malignant chronic pain showed that older patients displayed less disability and preoccupation with somatic symptoms, despite longer duration of pain and multiple medical illnesses compared to their younger counterparts [34]. In a tertiary care pain clinic older patients were more likely to present with identifiable biomedical pathology for their chronic pain, and were less likely to have discernible psychological factors contributing to their complaints compared with younger patients [35]. Several explanations may account for the decrease in impact of MUS with increasing age. Firstly, it could be survivor bias due to a higher mortality rate of MUS patients with poor HRQoL, possibly reflecting unidentified organic causes. This explanation seems unlikely, although data on mortality within MUS patients because of "missed organic causes" are scarce. In a neurological study with a 18-month follow up, missed diagnoses were found in 0.4% [36]. Moreover, mortality rates in MUS patients in a liaison psychiatry practice were even

lower than mortality rates in control group of patients referred for other reasons [37]. Another explanation would be a cohort effect, in which differences between generations explain the reduced effect of MUS on HRQoL in older persons. For example, people that were exposed by World War II and less welfare in the early 20th century might have lower expectations of their health and well-being than the younger generations of babyboomers and following generations [38]. Longitudinal studies are needed to examine possibly cohort effects. The fact that we do not see the same difference in impact of MES on HRQoL between age groups makes a cohort effect less likely.

Another and more plausible explanation is better adaptation and better acceptance of medical symptoms with increasing age. Literature focusing on the perspective of pain in the elderly suggests that older patients have a tendency to expect and accept pain, are more reluctant to complain, and have a stronger will to "keep on going"[39, 40]. For example, the majority of older people with chronic peripheral joint pain do not consult a doctor, because they see joint pain and stiffness as an inevitable part of ageing. They view themselves as healthy despite painful joints [41]. Similarly, in oncology patients with comparable pain intensity and interference, older and younger cancer patients described different adaptations to cancer pain. Older patients adapted by employing accommodative strategies. Younger patients less often used such strategies and more often struggled with accepting the losses associated with cancer pain [42]. Several studies have shown that better acceptance is directly related with a higher level of HRQoL. For example, in hemophilia-related joint pain patients, pain acceptance and HRQoL were correlated and increased pain acceptance was related with higher HRQoL at follow-up [43]. Also, in people with diabetes, HRQoL was strongly related to their levels of illness acceptance [44]. Finally, we found a large explanatory role for comorbid affective disorders in the older age group. This supports the commonly accepted view of a higher level of somatisation and of affective-somatic symptoms in depressed older patients compared to their younger counterparts [45-47]. It is hard to differentiate whether these somatic symptoms originate from somatization or because of accentuation of symptoms of concomitant physical illness [48].

Methodological considerations

A major strength of the present study is the large age-range, which enables the study of age-effects applying similar methodology. Nonetheless, for proper interpretations, some methodological issues should be taken into account. Firstly, generalizability of our results is complex. On the one hand, one may consider the attrition rate of the different recruitment steps in our study at least moderate. On the other hand, a population-based approach is valuable with respect to research on MUS and somatisation. In clinical practice, patients with MUS and/or somatoform disorders present in different echelons and different settings in the health care system, which is largely dependent on the local situation. Therefore, studies on clinical samples of patients with somatisation are even more difficult to generalise. Secondly, the prevalence of depression and anxiety disorders was low in the older age group and significantly lower compared to the younger age group. Therefore, the conclusion that depression and anxiety almost fully accounts for the variation in HRQoL of MUS in later life is based on the effects of depression and anxiety in a few older persons. Thirdly, we measured

both MUS and MES using the same instrument, enabling comparisons between both types of symptoms and their associations with HRQoL. The fact that MUS and MES were assessed with a computerized interview might be seen as a limitation. However, symptoms were only counted if participants had visited a medical doctor and only classified as being functional if it was reported that a medical doctor had indicated that all enquiries were negative for medical explanations. Moreover, we collected detailed information on a large number of MUS and performed our analyses on a continuous variable for the number of MUS instead of using an arbitrary cut-off score. Finally, recall bias may have attenuated the reliability of the CIDI to measure MUS and MES and this recall bias is likely to be associated with age [49]. We limited our analyses to symptoms that occurred in the last 12 months by which we have limited the effect of recall bias.

Conclusion

In an adult population, the impact of MUS on HRQoL is larger than the impact of MES. This difference is not explained by co-morbid depression and anxiety. However, with increasing age the impact of MUS decreases and in older persons becomes even lower than the effect of MES on HRQoL. Further research has to reveal why the impact of MUS on HRQoL decreases with age in contrast to the impact of MES on HRQol.

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CHAPTER 7

Summary and general discussion

Summary and general discussion

The aim of this thesis was to expand our knowledge about the presence, clinical presentation, and consequences of medically unexplained symptoms (MUS) in later life. Whereas for the adult population there is a substantive body of literature on MUS and somatoform disorders, studies on this subject in later life are scarce. In this final chapter, the results of previous chapters will be summarized and integrated, and methodological considerations will be discussed. Finally, implications and recommendations for intervention strategies and future research will be considered.

Three main themes can be distinguished in the studies described in this thesis: the prevalence of MUS and somatoform disorders in later life, the co-morbidity of MUS with depression, and finally the relationship between MUS and medically explained symptoms (MES). These themes will subsequently be outlined in this chapter, keeping in mind the key question to be answered in this thesis: Does age affect prevalence, clinical presentation, or impact of MUS on health-related quality of life (HRQoL).

Prevalence of MUS and somatoform disorders in later life

In **chapter 2**, we reviewed studies on prevalence of MUS and somatoform disorders, and concluded that the available data suggest that prevalence rates of MUS and of somatoform disorders decline after the age of 65 years. Possible explanations for this decline include inappropriate classification models, invalid measurement instruments, a higher attribution of bodily symptoms to physical conditions in later life, and finally the possibility of more subsyndromal forms of somatoform disorders in later life. Our findings in this thesis are in line with these explanations. For example, somatic symptoms in later life are believed to be part of the phenomenology of late life depressions [1]. This might lead to lower rates of somatoform disorders in elderly if somatic symptoms are interpreted as reflections of depression instead of separately classified as MUS or a somatoform disorder. In **chapter 3**, we found that co-morbid depression was present in more than half of the patients with MUS who are referred to an old age psychiatric secondary care setting. Further research is needed to establish whether the decline of somatoform disorders in later life is indeed an effect of inadequate classification. In **chapter 5**, we showed that in about half of the older patients with MUS who visited an outpatient clinic for old age psychiatry, somatic pathology partly explained the severity of their symptoms. In younger adults with MUS, proportion of symptoms which is partially explained will probably be lower because of the lower burden of chronic physical diseases [2]. In patients with comorbid chronic physical diseases, doctors and researchers are more reluctant to define a somatic complaint as unexplained [3]. In general, doctors in primary care are more likely to err symptoms as explained rather than medically unexplained, with age being the most important risk factor for false positive diagnosis of medically explained symptoms [4]. Patients themselves also tend to attribute symptoms as medically explained in order to be taken more seriously by their general practitioner [5, 6]. When patients with a partial but not

sufficient somatic origin of their symptoms are excluded from a diagnosis of somatoform disorders, this will lead to substantial lower prevalence rates. In **chapter 6**, however, we found no effect of age on the prevalence rate of MUS within the age range from 25 to 75 years in a population-based cohort. The number of MUS within the last year was measured with the Composite International Diagnostic Interview (CIDI). We did find that the impact of MUS on HRQoL decreased in the later life group. Since the impact on daily functioning is an explicit criterion of the DSM classification system, this decreasing impact of MUS on HRQoL might result in lower prevalence of somatoform disorders. If true, it supports the hypothesis that in older persons more subsyndromal forms of somatoform disorders might exist. All these factors mentioned above might contribute to lower prevalence rates of MUS and somatoform disorders in later life.

MUS and depression

In **chapter 3**, we found a high rate of co-morbid depressive mood disorders (56%) in older patients with somatoform disorders. Co-morbid depression was associated with a higher severity of the primary somatic complaint, a higher level of somatisation, and more functional impairments. Several limitations hamper the interpretation of these results, including the small size and the sampling frame of this secondary care, convenience sample, located at a public mental health service. Nevertheless, our findings are in line with studies that also revealed comorbidity rates for depression and anxiety in patients with MUS in about half of cases [7, 8]. In primary care, reported comorbidity rates vary between 25 and 70% [3, 9, 10]. Whether these co-morbidity rates increase with age is not clear yet. To our knowledge, only one study specifically addressed the issue of comorbidity by age [2]. Co-morbidity rates between MUS and depression or anxiety did not increase with age in that study. Nonetheless, this study was limited to an age range from 25 to 65 years [7].

The high comorbidity with depression might be due to either an effect of depression on somatic symptoms, or an increase of depression due to somatic symptoms. In **chapter 4**, we found that among community-dwelling older people, pain precedes the onset of clinically relevant depressive symptoms whereas no effects of depression on subsequent pain were found. The higher incidence of depression in persons with pain was not mediated by disability, and remained significant when adjusted for functional limitations and number of chronic diseases. Patients with chronic pain thus not only have high levels of co-morbidity with depression, but are also at risk of developing new depressive episodes. This is especially relevant as the prognosis of both pain and depression worsens when both occur simultaneously [11-13].
Is this close relation between somatic complaints and depression age specific? In **chapter 6,** we found that comorbid affective disorders explained more variance of the association between MUS and HRQoL in the older age group than in the younger age group. This result suggests that a higher level of somatisation and somatic-affective symptoms are more strongly associated in depressed older patients compared to their younger counterparts. More somatic presentation of depression in later life was demonstrated in a recent meta-analysis comparing

the phenomenology of major depression between older and younger adult patients [1].
The question arises whether age-related factors modify the presentation of depression or whether it is just a higher prevalence of co-morbid somatic illnesses that leads to more somatic symptoms in late-life depression. However, persistent differences in phenomenology of depression were also demonstrated in earlier studies after adjustment for somatic comorbidity [14, 15]. Thus, aging appears to increase the number of somatic complaints in depression, while a high prevalence of depression is observed in older patients with MUS. The results in this thesis support that later in life, the relation between depression and somatic symptoms intensifies, leading to increasing diagnostic difficulties [16].

MUS and MES

Clearly a major difference between younger and older patients with MUS is the higher co-occurrence with MES in later life. Numbers of MES increase with aging due to increasing numbers of chronic diseases [17]. When the age groups of 30-44 and above 75 years of age are compared, neurological and pulmonary disorders double, musculoskeletal disorders more than triple, hearing problems quadruple, and vision problems increase even 50-fold [2]. The diagnostic difficulties caused by these higher numbers of MES have already been mentioned. In **chapter 5**, we identified a sufficient somatic explanation in only a small proportion (8%) of older patients referred for MUS, while nearly half of the formerly unexplained symptoms could be partially explained. There are many explanatory models for MUS based on biological, psychological, and social elements [18-20]. In some of these models, biological factors are described as a precipitating factor for somatisation [21, 22]. Physiological changes (such as in pathophysiological processes) are then presumed to trigger a higher focus of attention on normal physiological sensations thus leading to MUS [23,18]. However, in our convenience sample of older patients with MUS, a higher number of somatic diseases was associated with less somatisation. An explanation for this unexpected finding might be that more physical problems in later life might result in more adequate interpretation of bodily sensations and physical problems. Alternatively, older patients might simply better cope with bodily sensations. The findings in **Chapter 6** are in line with these ideas. The number of MES increased with age while their impact on HRQoL remained stable. In contrast, the number of MUS remained stable and their impact on HRQoL decreased with higher age. This suggests better adaptation strategies for somatic sensations that are medically unexplained in later life. This is in line with other findings of relatively stable HRQoL despite increasing somatic burden with aging and within chronic somatic diseases [24, 25] and an increasing positive emotional attitude towards physical health with increasing age [26, 27]. In summary, results described in this thesis suggest that the higher frequency of somatic pathology influences the prevalence and impact of MUS in later life. Firstly, a relatively high proportion of symptoms are only partially unexplained due to higher levels of comorbid somatic diseases. Secondly, the impact of MUS on experienced HRQoL decreases in later life.

What are the consequences of the new diagnostic system in DSM-5?

The validity of somatoform disorders as defined in DSM IV have been hotly debated [28-30]. Some have even argued that somatoform disorders should be merged with depression or anxiety disorder categories because doubt exists about somatoform disorders as a distinct mental illness [31, 32]. Others have argued that somatization, depression and anxiety are different disorders, contributing independently to illness behaviour [21, 33]. Main shortcomings in routine clinical care are the "mind-body dualism" based on a unreliable classification of complaints as medically explained or not [34, 35] and the rather random categorisation into different somatoform disorders [36]. The used terminology of the DSM-IV is also of little use in primary care, because it fails to include milder forms of somatization which results in low rates of agreement between general practitioners diagnoses of somatization and diagnoses derived from DSM-IV [28, 37]. The somatic symptom workgroup for DSM-5 aimed to overcome these problems, and proposed major changes [29, 31, 38]. In May 2013, the adaptations made in the DSM-5 were presented at the American Psychiatric Association congress in San Francisco. The chapter on somatoform disorders of the DSM has indeed been radically changed. Somatoform disorders as defined in DSM-IV are replaced by Somatic Symptom Disorders(SSD) in DSM-5 [39]. SSD includes the former somatisation disorder, undifferentiated somatoform disorder, and pain disorder. The major change in comparison with DSM IV is that the diagnostic criteria are no longer based on the presence of MUS, but centre around one or more somatic symptoms that are distressing or result in significant disruption of daily life. This change eliminates the diagnostic problem of distinguishing between medically explained and unexplained symptoms [40]. Secondly, positive psychological diagnostic criteria are added to the diagnostic criteria. These include excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following: (1) Disproportionate and persistent thoughts about the seriousness of one's symptoms; (2) Persistently high level of anxiety about health or symptoms; and (3) Excessive time and energy devoted to these symptoms or health concerns. It is assumed that inclusion of this positive criterion will increase the predictive validity and clinical utility of the diagnosis [41-43].

What do these changes mean for the interpretation of the studies described in this thesis, and for the diagnosis and care for older patients? Clearly, problems in determining whether a complaint is medically explained or not have become irrelevant for the diagnosis. In **chapter 5**, we showed that this diagnostic problem is especially prominent in older patients and may result in a large number of partially explained symptoms. The overall agreement between the two geriatricians judging the main symptom as completely explained, partially explained, or unexplained was moderate to good, but far from perfect. Eliminating this diagnostic uncertainty probably increases the validity of the disorder in older persons. Higher prevalence rates of SSD are found in patients suffering from functional syndromes, such as fibromyalgia and irritable bowel syndrome, and in patients with chronic somatic diseases [44, 45]. Because the latter are especially present in later life, it can be assumed that this will result in increasing numbers of SSD in older populations. Some argue that the new DSM-5 SSD increases the risk

of mislabelling many people as mentally ill [44, 46]. When we consider the results in this thesis, we think that the low prevalence rates of somatoform disorders in later life are at least partly an artefact due to the diagnostic difficulties of the DSM-IV. Thus, the higher prevalence of SSD in patients with comorbid chronic medical conditions is an improvement over DSM-IV diagnostic categories, because these patients were probably falsely excluded. An advantage of this broader scope can thus be that psychiatric assessment and treatment can be applied to patients who until now often stayed entangled in somatic diagnostic processes. Studies show positive results for Cognitive Behavioural Treatment (CBT) for both MUS as well as functional syndromes like fibromyalgia and irritable bowel syndrome [47]. Also mild to medium effect sizes for CBT are shown in patients with chronic pain and fatigue or for distress due to general medical conditions [48]. Whether the symptoms are medically explained or not is thus not crucial for the effectiveness of CBT. A possible disadvantage of abandoning the concept of MUS may be that differences between MES and MUS are no longer noticed. Although the total number of symptoms is strongly correlated with impact on the HRQoL [49-51], we found that MUS and MES did independently correlate with HRQoL (**chapter 6**). Differences between the impact of MES and the impact of MUS on the HRQoL were found for different age groups, with a lower impact of MUS but not MES on HRQoL in later life. These differences can lead to new insights in the process of acceptance of and adaptation to MUS, and may guide the development of successful treatment strategies.

Methodological considerations

In general, research on MUS and somatoform disorders is hampered by many methodological difficulties. The number of epidemiological studies is limited due to the fact that a thorough evaluation of both somatic and psychiatric pathology is needed for a correct classification of symptoms as medically unexplained. In **chapter 2**, we found that most of the epidemiological studies used a two-stage strategy to overcome this problem [3, 52-55]. A screening instrument is administered in the wider population, followed by a more structured interview method for MUS in selected or high-risk populations. Data on older populations are even rarer because elderly are often excluded from epidemiological studies. Also in intervention studies focussed on somatoform disorders such as CBT and pharmacological treatment, persons over the age of 65 years are often excluded [56-58]. Currently, no randomised controlled studies have been conducted among older patients suffering from MUS. Longitudinal studies in older cohorts also have to cope with an inevitable loss to follow-up [59]. Available studies are often of a cross-sectional nature which hampers firm conclusions and causal interferences [60]. The required intensive assessments for MUS result in small sample sizes in clinical studies. Generalisation of the results can therefore be difficult, especially since most patients with MUS are seen in primary care. If patients with MUS are referred to specialised care, this is usually to medical specialists in a general hospital rather than to psychiatrists [32]. Future research should also concentrate on other settings, such as primary care, specialist outdoor clinics and geriatric outdoor settings. Another problem is that the use of different definitions for MUS and somatisation complicates the interpretation of the results. For example, in **chapter 4** we

have described the longitudinal relationship between chronic pain and depression. Chronic pain is often mentioned in relation to unexplained symptoms [61], but surely chronic pain is not synonymous with MUS [62]. Moreover, the definition of MUS is not strictly formulated. The new diagnostic category of SSD within the DSM-5 will hopefully bring more uniformity in definitions. Finally, the use of different instruments for measurement of somatisation is problematic, and none of the instruments is well-validated in older populations [63]. New instruments for screening and a structured interview for SSD need to be developed for or validated in older populations.

Clinical implications

In this thesis, we focused on MUS in later life. When integrating the results from the present thesis with the changes in the field of MUS, several clinical implications can be outlined. We did not find more somatization in older compared to younger age groups; on the contrary, prevalence rates of somatoform disorders in later life decrease. Nevertheless, special attention for the older age group is still required. The combined presence of MES and MUS, and the high prevalence of depression in this age group warrant a close collaboration between psychological, psychiatric, and somatic disciplines. First of all for diagnostic purposes: a psychiatric assessment in this high-risk population is recommended, because recognition of depression is hampered by a somatic presentation in primary care [16, 64]. We need to realise that most MUS patients are not referred to psychiatrists, but receive medical investigations and treatments in somatic health care settings [65, 66]. Therefore, prevalence rates for MUS in secondary care settings might be higher than in primary care [67]. Multidisciplinary approaches are being developed for the various functional syndromes, with special outdoor clinics for syndromes such as chronic pain, fibromyalgia, and tinnitus [68-70]. For older persons, this multidisciplinary approach should include a geriatric, psychiatric and psychological approach, which can be combined in a MUS outdoor clinic for older persons. These outdoor clinics can be situated within a psychiatric as well as a general hospital setting. The general hospital probably will be most suitable, because of lower stigmatisation for patients [71].

This multidisciplinary approach should not be restricted to the diagnostic process. Instead, treatment should also intervene on somatic, psychiatric, and psychological levels simultaneously to optimize the level of functioning and to improve quality of life. Psychiatric assessment and treatment should concentrate on psychological symptoms of SSD and co-morbid psychiatric disorders, especially depressive disorders. In younger adults CBT is effective for a wide range of physical symptoms and MUS [47, 72] and pharmacological treatment with antidepressants are effective for MUS and various functional syndromes [73]. There are no trials in which cognitive-behavioural therapy and antidepressants have been compared [47, 73]. Because many MUS are partially explained by an organic cause in older patients, optimization of the somatic condition can also improve quality of life. For example: a patient presents with chronic dizziness and fear of falling started after a fall. Psychiatric evaluation might reveal an anxiety disorder with agoraphobia after a somatic event. Geriatric evaluation might

reveal low blood pressure and impaired mobility. Revision of blood pressure medication and physiotherapy can improve mobility and self-confidence, after which treating avoidance behaviour as part of CBT is more readily accepted and probably more effective. If these outdoor clinics are situated in secondary care, collaboration with general practitioners is crucial for relapse prevention in case of successfully treated patients, and to prevent iatrogenic damage and to support patients with partially recovered functioning or chronic MUS [74, 75].

Future research

To our knowledge, this thesis contains the first systematic research on medically unexplained symptoms in later life. Our studies have resulted in more research questions. Our review on prevalence rates for MUS and somatoform disorders in later life revealed that very few studies were available. None of the available studies focussed specifically on later life. Thus, more epidemiological studies on somatisation in older populations are warranted. With the coming of the DSM-5, prevalence rates of SSD will be established. It will be of special interest to examine whether prevalence rates for DSM-5 SSD will be higher than those for DSM-IV somatoform disorders. Validation of measurement instruments for SSD is needed in elderly populations. Longitudinal studies are essential to establish the course of MUS in later life, their effects on incident depression, their impact on quality of life, and the associated costs.

To date, no studies are available on the treatment of older patients with MUS. Since we advocated a multidisciplinary approach, we recommend to evaluate the effect of interventions on quality of life and well-being as outcome measurements. CBT and pharmacological interventions should be compared for their effectiveness in older MUS patients. Research on adaptive sickness cognitions in later life may be interesting, because this may feed new therapeutic strategies and adaptations of cognitive interventions for MUS patients in general. Moreover, the treatment of co-morbid somatic and psychiatric disorders should be evaluated and compared in condition with and without augmentation with specific treatment programmes for MUS. Finally, it is important to know whether a multidisciplinary approach can reduce total health care costs. A multidisciplinary assessment is expensive, but may reduce costly referrals to other secondary health care services. Another aspect that deserves further study is the effect of the organisation of care on treatments effectivity and health care costs. Such studies could compare the proposed secondary care multidisciplinary approach with a collaborative care model with a focus in primary care, and even a very parsimonious model restricted to primary care extended with reattribution techniques, self-help groups and consultation letters [76-78].

Hopefully the studies in this thesis may contribute to more attention for patients with MUS in later life in both daily clinical practice and future research.

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NEDERLANDSE SAMENVATTING

Het onderzoek in dit proefschrift is voortgekomen uit ervaringen in de klinische praktijk. Ouderen presenteren zich regelmatig met lichamelijke klachten zonder dat er bij uitvoerig lichamelijk onderzoek lichamelijke oorzaken worden gevonden die deze klachten volledig kunnen verklaren. Ouderen richten zich met deze klachten vaak in eerste instantie tot de huisarts of een somatisch georiënteerde specialist. Wanneer deze geen afwijkingen vindt, zijn oudere patiënten moeilijk te motiveren psychologische aspecten nader te laten onderzoeken door een psychiater of psycholoog. Patiënten ervaren een dergelijke doorverwijzing vaak als een afwijzing. Om dit probleem het hoofd te bieden is er een polikliniek opgericht voor onderzoek en behandeling van Somatisch Onvoldoende verklaarde Lichamelijke Klachten (SOLK) bij ouderen in Nijmegen waar patiënten achtereenvolgens worden gezien door klinisch geriater, psychiater en psycholoog.

Onze kennis over SOLK is nagenoeg volledig gebaseerd op onderzoek bij jongere volwassenen. Zo weten we dat SOLK bij deze leeftijdsgroep veel voorkomen: tussen 30-50% van de klachten waarvoor patiënten hun huisarts bezoeken zijn klachten zonder duidelijke lichamelijke oorzaak. Als de klachten aanhouden en patiënten hulp blijven zoeken, kan dat frustraties opleveren voor zowel patiënten als hulpverleners. Mensen met SOLK ervaren vaak een hoge lijdensdruk en rapporteren vaak een lage kwaliteit van leven. Tevens is er een hoge co-morbiditeit met depressie en angstproblemen. In hoeverre SOLK voorkomen bij ouderen en hoe dit samenhangt met de kwaliteit van leven voor ouderen is nauwelijks bekend.

In **hoofdstuk 1** illustreren we drie oudere patiënten die de specifieke problemen bij SOLK op latere leeftijd goed weergeven. Vermoedelijk dat juist deze specifieke problemen bijdragen aan de geringe aandacht voor SOLK in deze leeftijdsgroep.

Voorbeeld 1 betreft een 75 jarige vrouw met pijn aan haar benen. Diverse medisch specialisten vonden geen oorzaak voor haar klachten; de medische verslaglegging spreekt over "leeftijd gerelateerde klachten" of "slijtage". De huisarts dacht vervolgens aan een (gemaskeerde) depressie, maar behandeling hierop gericht sloeg niet aan. Hierop werd zij verwezen naar onze polikliniek in verband met onverklaarde pijn aan haar benen. Bij aanvullend onderzoek door de klinisch geriater werd alsnog een lichamelijke oorzaak gevonden, namelijk een vernauwing van haar wervelkanaal. Dit voorbeeld illustreert hoe moeilijk het is om verklaarde en onverklaarde klachten bij ouderen uit elkaar te houden. Met enige regelmaat worden lichamelijke klachten ten onrechte aan normale veroudering toegewezen.

Voorbeeld 2 betreft een 75-jarige vrouw met langdurige maag- en darmklachten. Zij is tevens bekend met recidiverende, depressieve stemmingen. Ondanks verschillende behandelingen door zowel een psychiater als door internist en gynaecoloog blijven de klachten bestaan. Op onze polikliniek stellen we een depressieve stoornis vast. Wanneer we deze strak volgens de richtlijnen behandelen verbetert niet alleen haar stemming, maar verdwijnen ook haar de lichamelijke klachten. Dit voorbeeld geeft aan dat depressies en SOLK nauw met elkaar zijn verweven op latere leeftijd en soms moeilijk uit elkaar te houden zijn.

Voorbeeld 3 betreft een 65-jarige vrouw met chronische hoofdpijn. Nadat ze publiekelijk onwel geworden is, is ze aanhoudend angstig een hersentumor te hebben. Ze wordt hierdoor zo gehinderd, dat ze haar huis niet meer uit durft. Aanvullend onderzoek door de geriater en een scan van haar hoofd stelt patiënte enigszins gerust, maar de hoofdpijn blijft. Mevrouw is te motiveren om deel te nemen aan een psychotherapeutische groepsbehandeling om te leren beter met haar angst en lichamelijke klachten om te gaan. Hierop verdwijnt niet alleen haar angst, maar ook haar hoofdpijn. Dit voorbeeld geeft de voordelen aan van een multidisciplinaire aanpak door klinisch geriater, psychiater en psycholoog.

De doelstelling van dit promotieonderzoek was om meer kennis te verwerven over het vóórkomen, de klinische presentatie en de gevolgen van SOLK bij ouderen. Het onderzoek richtte zich op de volgende deelvragen. Hoe vaak komen SOLK voor op oudere leeftijd. Wat is de relatie tussen SOLK en depressie. Wat is de samenhang van SOLK met medisch verklaarde lichamelijke klachten en wat is de relatie van SOLK met de kwaliteit van leven bij ouderen.

Voorkomen van SOLK op latere leeftijd

In **hoofdstuk 2** bestudeerden we aan de hand van de bestaande literatuur hoe vaak SOLK op latere leeftijd voorkomen. In het meest gebruikte psychiatrische classificatiesysteem (DSM IV) vormen SOLK en ziekteangst de kernsymptomen van de somatoforme stoornissen. Naast de aanwezigheid van SOLK zijn er tevens aanvullende criteria gesteld alvorens te kunnen spreken van een somatoforme stoornis. Somatoforme stoornissen kunnen daarom gezien worden als een ernstiger vorm van SOLK en derhalve is in ons onderzoek gekeken naar het vóórkomen van zowel SOLK als somatoforme stoornissen bij ouderen. De gevonden resultaten werden vergeleken met het vóórkomen van SOLK en somatoforme stoornissen op jongere leeftijden. In totaal konden we slechts 8 studies vinden die het vóórkomen van SOLK of somatoforme stoornissen op latere leeftijd beschreven. Er waren grote onderlinge verschillen tussen de diverse onderzoeken. Zo werden sommige onderzoeken uitgevoerd in de algemene bevolking, terwijl anderen zich richten op huisarts patiënten. Bij de diverse onderzoeken werden verschillende meetinstrumenten en tijdsintervallen gebruikt om het vóórkomen van SOLK te beschrijven. Desondanks duiden de gevonden resultaten erop dat de aantallen SOLK en somatoforme stoornissen stabiel zijn tot het 65e levensjaar, waarna er een afname plaatsvindt. Uitzondering hierop waren chronische SOLK klachten in de huisartsen praktijk. Deze bevindingen riepen bij ons de vraag op of SOLK op latere leeftijd nu daadwekelijk minder voorkomen, of dat het een gevolg is van complexe diagnostiek op hoge leeftijd zoals geïllustreerd in voorbeeld 1 en 2 in hoofdstuk 1. Een andere mogelijkheid zou zijn dat op oudere leeftijd juist mildere vormen van aan lichamelijk symptomen gebonden stoornissen voorkomen.

SOLK en depressie bij ouderen

In **hoofdstuk 3** bekeken we een klinische steekproef van 37 achtereenvolgende patiënten die waren verwezen naar de polikliniek voor ouderen met SOLK in Nijmegen. Pijn bleek de

meest voorkomende presenterende klacht te zijn. We vonden dat veel van deze ouderen, die verwezen waren voor SOLK, ook last bleken te hebben van andere psychiatrische stoornissen. Vooral stemmingsstoornissen maar ook angststoornissen en afhankelijkheid van medicijnen kwamen veel voor. Bij de ouderen met SOLK die ook een depressie hadden, was er sprake van meer lichamelijke klachten en meer beperkingen in het dagelijks functioneren dan bij niet depressieve SOLK patiënten. Vanwege de sterke samenhang tussen depressie en SOLK hebben we in **hoofdstuk 4** nader onderzocht of langdurig bestaande pijn de kans vergroot op het krijgen van een depressie, en vice versa of chronische depressie de kans op het optreden van pijn vergroot. Dit hebben we onderzocht aan de hand van gegevens van een grote groep van 2028 ouderen tussen de 55 en 85 jaar bij wie over een periode van 12 jaar iedere 3 jaar gegevens waren verzameld over onder andere het hebben van pijn en depressieve symptomen. Uit de gegevens bleek dat mensen met chronische pijn een grotere kans hebben op het ontwikkelen van een nieuwe depressie dan mensen zonder chronische pijn. Dit verhoogde risico bleef bestaan als werd gecorrigeerd voor reeds bekende factoren die ook invloed kunnen zijn op het ontstaan van een depressie, waaronder algemene socio-demografische variabelen (geslacht, opleiding en huwelijkse staat), leefstijl karakteristieken (roken, alcoholgebruik en lichaamsgewicht) en het voorkomen van chronische ziekten of het hebben van beperkingen in het dagelijks functioneren. De omgekeerde relatie, een vergrote kans op het krijgen van pijn in ouderen met een chronische depressie werd niet gevonden, wanneer werd gecorrigeerd voor reeds bekende risicofactoren voor een depressie.

SOLK en de samenhang met medisch verklaarde lichamelijke klachten bij ouderen

In **hoofdstuk 5** bekeken we in hoeverre ook verklaarde lichamelijke klachten voorkomen bij ouderen met SOLK. In de reeds eerder genoemde steekproef van 37 oudere SOLK patiënten werd onderzoek gedaan naar de lichamelijke gesteldheid van deze patiënten. Hierbij werd een inschatting gemaakt van het aandeel van de eventueel aanwezige objectieve afwijkingen in de gepresenteerde klacht. Hiertoe vond bij iedere patiënt een uitgebreid en gestandaardiseerd onderzoek plaats door een klinisch geriater. Er werd een indeling gemaakt in volledig verklaarde, gedeeltelijk verklaarde of volledig onverklaarde klachten. Juist omdat dit bij ouderen zo moeilijk is, beoordeelde een tweede klinisch geriater onafhankelijk van de eerste geriater tevens de mate waarin de klacht(en) verklaard konden worden door een lichamelijke oorzaak aan de hand van het medisch dossier.

In 3 van de 37 patiënten werd alsnog een lichamelijke verklaring voor de klacht gevonden. Bij twee patiënten bestond een sterke relatie met psychosociale problemen en herstelde de klacht spontaan. Van de overige 32 patiënten met SOLK bleek dat in ongeveer de helft van de gevallen sprake was van lichamelijke afwijkingen die de klachten gedeeltelijk konden verklaren, maar niet geheel. De overeenkomst tussen de beide klinisch geriaters was redelijk goed. In vergelijking met ouderen met geheel onverklaarde klachten zijn ouderen met gedeeltelijk verklaarde klachten lichamelijk in slechtere conditie, en hebben zij meer chronische ziektes en meer beperkingen bij het dagelijks functioneren. Het hebben van gedeeltelijk verklaarde

lichamelijke klachten leidde niet tot meer lichamelijke bezorgdheid vergeleken met geheel onverklaarde klachten.

SOLK en de relatie met kwaliteit van leven

In **hoofdstuk 6** hebben we zowel de relatie onderzocht tussen SOLK en de kwaliteit van leven als tussen medisch verklaarde klachten en de kwaliteit van leven in een groep van 946 volwassenen met een leeftijd tussen de 28 en de 75 jaar. Hierbinnen hebben we gekeken of deze relaties vergelijkbaar zijn bij jong-volwassenen en ouderen. SOLK bleken de kwaliteit van leven sterker negatief te beïnvloeden dan medisch verklaarde klachten. Als we echter corrigeren voor psychiatrische co-morbiditeit, die bij SOLK meer voorkomt, dan wordt de relatie met de kwaliteit van leven voor SOLK en verklaarde lichamelijke klachten even groot. Wij vonden ook dat leeftijd van invloed is op de relatie tussen SOLK en kwaliteit van leven. Boven de 65 jaar hangen SOLK veel minder sterk samen met de kwaliteit van leven dan bij jong-volwassenen. Enkel bij ouderen verdween deze relatie volledig na correctie voor de aanwezigheid van psychiatrische co-morbiditeit. Deze bevindingen suggereren dat ouderen beter om weten te gaan met SOLK dan jongere volwassenen.

Conclusies

In **hoofdstuk 7** hebben we de verschillende bevindingen uit dit proefschrift in een breder perspectief geplaatst en gekeken wat de verdere implicaties zijn voor de dagelijkse praktijk en toekomstig onderzoek. De studies in dit proefschrift hebben aangetoond dat SOLK ook op latere leeftijd voorkomen. De klinische presentatie en herkenning wordt gecompliceerd door de intensievere samenhang met depressies en door het gelijktijdig vóórkomen van medisch verklaarde lichamelijke klachten op latere leeftijd. De effecten van SOLK op de kwaliteit van leven lijken lager te zijn bij ouderen dan bij jongeren. Enerzijds kan dit wijzen op een betere aanpassing aan lichamelijke klachten met het stijgen van de leeftijd. Anderzijds kan het wijzen op het voorkomen van mildere vormen van SOLK op latere leeftijd. De studies laten verder zien dat een multidisciplinaire diagnostische aanpak waardevol kan zijn bij deze categorie patiënten. Toekomstig onderzoek moet uitwijzen of een dergelijke multidisciplinaire aanpak daadwerkelijk leidt tot een effectievere behandeling voor de klachten van deze patiënten binnen de geestelijke gezondheidszorg. Uiteraard moeten hierbij aansluitend behandelstudies worden uitgevoerd om psychologische- en/of medicamenteuze behandeling van SOLK bij ouderen te kunnen onderbouwen. Tevens zal bekeken moeten worden of een dergelijke aanpak kostenbesparend werkt ten opzichte van de huidige praktijk of ten opzichte van een alternatieve aanpak, zoals bijvoorbeeld, een vaak aanbevolen strategie van periodieke consulten door de huisarts om verdere medische consumptie af te remmen.

Dit proefschrift legt de complexiteit bloot van SOLK op latere leeftijd. Hiermee willen we een aanzet geven voor meer aandacht voor ouderen met SOLK, zowel in de dagelijkse klinische praktijk als in toekomstig onderzoek.

DANKWOORD

Het proefschrift is klaar en dit is het moment om eens terug te kijken naar de afgelopen periode. Toen een jaar of acht geleden het idee ontstond van het opzetten van onderzoek was er nog niet echt sprake van een duidelijk doel. Het ging meer om het maken van een reis, gedreven door ervaringen uit de dagelijkse praktijk wilden we ons verder ontwikkelen en onderzoek leek daartoe een goed middel. Het is een lange interessante reis geworden en ik wil een aantal "reisgenoten" en "passanten" bij deze bedanken voor hun bijdrage.

Allereerst mijn medereizigers vanaf het eerste uur, Dorine van Driel en Carolien Benraad. We kunnen veilig stellen dat zonder de samenwerking vanaf het eerste begin ik nu niet op dit punt zou zijn aangeland. Het vroeg veel pionierswerk om in een, wat onderzoek betreft nog geheel onontgonnen gebied, samen op zoek te gaan en onze onderzoeksplannen om te zetten in daden. We vormden vanaf het begin een drie-eenheid waar steeds een ander het voortouw nam. En terugkijkend kunnen we stellen dat we het toch zo gek nog niet hebben gedaan. Al zag het daar in het begin, gezeten tussen grote stapels door ons verzamelde patiënten gegevens, nog niet direct naar uit. Carolien dank dat je op het goeie moment de mankracht wist op te trommelen om die stapels om te zetten naar datasets. Dorine dank voor het klankbord en de sparringpartner die je gedurende het hele traject bent geweest! Ik ben jullie zeer dankbaar en vind het ook fijn dat jullie mij terzijde zullen staan bij de afronding.

Mijn promotor prof dr. R. Oude Voshaar, beste Richard mijn dank voor jouw bijdrage is groot. Vanaf het moment dat jij aansloot bij mijn onderzoek kwam het geheel in een stroomversnelling. Door jouw attitude en opvatting over hoe te leren onderzoek te doen, van aanvankelijk samen tot uiteindelijk alleen zelf doen, kreeg ik zelf ook het geloof in dat het een haalbaar traject kon worden. Ook Marco wil ik bedanken voor het afstaan van de tijd met Richard, als we weer eens samen een avond flink aan het doorwerken waren op de computerkamer van jullie mooie penthouse in Nijmegen. En Richard, hoewel je zelf een duizelingwekkend tempo hanteert in je eigen carrière heb ik me nooit opgejaagd gevoeld, maar steeds gestimuleerd, uitgedaagd, geïnspireerd en gesteund. Je benaderbare houding voor grote of kleine zaken, dat is pas bijzonder!
Mijn promotor Prof dr. J. Rosmalen, beste Judith, bedankt voor je scherpe, maar zeer constructieve en altijd snelle commentaar op mijn stukken. Met je kennis van onverklaarde lichamelijke klachten en het Groningse onderzoek vormde je een perfecte aanvulling en het kan geen toeval zijn dat vanaf het moment dat jij aansloot bij het traject de publicaties elkaar in rap tempo opvolgden.
De leden van de beoordelingscommissie, prof. dr. M. Stek, prof. dr. J. Slaets en prof. dr. S. Visser hartelijk dank voor het beoordelen en kritisch lezen van mijn proefschrift.

Prof dr. J. Buitelaar, prof dr. A. Speckens en prof dr. M. Olde Rikkert. Beste Jan, Anne en Marcel, dank dat jullie in het begin van dit traject bereid waren te luisteren naar, en structuur brachten in, de nog grove onderzoeks-ideeën. Ook bedankt voor jullie soepele opstelling toen gedurende het traject dingen toch anders gingen lopen. Speciale dank Marcel voor je hulp bij het zetten van de eerste stap, door me bij te staan met je kritische, constructieve feedback bij het schrijven van het eerste artikel.

Al mijn co-auteurs wil ik bedanken voor hun bijdrages, commentaren en soms ook het mogen gebruiken van bestaande datasets. Rose Collard, Rose bedankt dat je me hebt geholpen verder wegwijs te worden met SPSS zodat ik de bij de cursus opgedane kennis direct met feedback kon toepassen, dank voor je geduld en altijd snelle reacties.
Prof dr. Aartjan Beekman wil ik danken voor het gebruik van de data van het LASA onderzoek en je interesse in het onderzoek. Je houding was steeds zeer coöperatief en gericht om optimaal gebruik te maken van de nog verborgen bevindingen in deze opgeslagen datasets.

Directie en afdeling ProCES van Pro Persona wil ik danken voor het faciliteren van het doen van onderzoek naast mijn klinische bezigheden door het toekennen van onderzoekuren. Verder mijn leidinggevenden gedurende de afgelopen jaren, met name Jan van Haandel, Rene van de Water en Maarten Meulbroek. Jullie waren altijd bereid mee te denken en te luisteren als er een plan kwam om de patiëntenzorg te veranderen. Zoals bij het opzetten van een poli voor ouderen met Onverklaarde Lichamelijke Klachten. Jullie hielpen dit vorm te geven en te ondersteunen met secretaresses, doktersassistente etc. Hartelijke dank, ondanks mijn gemopper soms over krapte in bezettingen.

Overige medewerkers en collega's van ProPersona zoals alle secretaresses die voor mij lijsten met gegevens moesten verzamelen, arts-assistenten die hielpen gegevens te bewerken, collega's die tijdens mijn onderzoekuren niet op mij konden terugvallen en altijd geïnteresseerd bleven vragen hoe ver het stond met mijn onderzoek.

Mijn vrienden Rolf Blankemeijer en Jan-Willem de Klein; Rolf je hebt onbedoeld mede de aanzet gegeven tot het doen van dit promotieonderzoek. Door je altijd prikkelende stellingen zag ik in wat een voorrecht het is om tijd aan onderzoek te kunnen besteden en je begrijpt dat ik nu dus wacht op jouw proefschrift. Jan-Willem samen doelen stellen om naar toe te werken was stimulerend. Ik vrees wel dat de in het vooruitzicht gestelde sabbatical en bijbehorende reis als beloning voor onze trajecten nog even op zich zal laten wachten. Maar we kunnen vast wel een goede plaats vinden om eens te proosten op de goede afloop van beide trajecten, wellicht in Dublin? Richard van Driel, wat een heerlijk gevoel dat ik volledig op jou kon vertrouwen voor de vormgeving van dit proefschrift.

Marianne sinds jij in mijn leven bent gekomen heb ik voor alles meer energie gekregen en dat heeft ook zeker gegolden voor dit proefschrift. Waar sommigen vreesden dat door mijn privé beslommeringen het schip zou stranden, voelde ik juist volle wind in de zeilen en hernieuwde energie om mijn doel te bereiken, zeker ook door jouw aanmoedigingen om door te zetten. Tot slot Merel, Britt en Demi die altijd zorgen voor een goed thuisfront met voldoende afleiding.

Peter

CURRICULUM VITAE

Peter Hilderink werd geboren op 8 maart 1966 in Eindhoven. Hij behaalde in 1984 zijn eindexamen van het atheneum-B met extra vak Latijn aan de Gemeentelijke Scholengemeenschap Woensel te Eindhoven. Aansluitend studeerde hij geneeskunde aan de Rijksuniversiteit Utrecht waar hij in 1992 zijn artsexamen behaalde. Hij deed hiertoe een aantal buitenlandse stages waaronder een stage in het Diaconessen ziekenhuis te Paramaribo. Na afronding van zijn geneeskunde studie vervulde hij zijn dienstplicht als bataljonsarts van het 108 Verbindingsbataljon te Garderen. In 1994 werkte hij als arts assistent niet in opleiding (AGNIO) op de PAAZ van het Lichtenberg Ziekenhuis te Amersfoort. Hierna startte hij met de opleiding tot psychiater in Tilburg (opleider prof dr. P.P.G. Hodiamont). Gedurende deze opleiding ontwikkelde zich de interesse in de ouderenpsychiatrie. In 2000 heeft hij de opleiding tot psychiater afgerond en was hij aansluitend werkzaam op de Geriatrische Afdeling Psychiatrisch Ziekenhuis (GAPZ) van GGZ Midden-Brabant te Tilburg. In 2002 maakte hij de overstap naar Nijmegen om te gaan werken bij het GGZ Nijmegen, inmiddels Pro Persona. Sindsdien werkt hij binnen de diverse afdelingen van het cluster ouderenpsychiatrie van Pro Persona. Tevens is hij sinds 2005 vaste consulent psychiatrie voor de Sint Maartenskliniek te Nijmegen. In 2007 was hij medeoprichter van Mentalis, polikliniek voor ouderen met angst- depressie- en onverklaarde lichamelijke klachten, een samenwerkingsverband tussen Pro Persona en het Universitair Medisch Centrum Nijmegen St Radboud. In 2010 richtte hij samen met Dorine van Driel (klinisch psycholoog) een zelfstandige psychiatrische praktijk op voor ouderen in gemeente Lingewaard (SeniorBeter) waar hij ook parttime werkt.

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Medically unexplained symptoms in later life

1. Dat de prevalentie van Somatisch Onvoldoende verklaarde Lichamelijke Klachten (SOLK) na het 65e jaar afneemt komt ten dele doordat lichamelijke klachten op latere leeftijd eerder worden toegeschreven aan een co-morbide depressie of somatische aandoening (dit proefschrift).

2. Bij een oudere die zich presenteert met een chronisch onverklaarde lichamelijke klacht is een verhoogde alertheid op aanwezigheid van psychiatrische stoornissen noodzakelijk (dit proefschrift).

3. Zowel een goed psychiatrisch onderzoek alsook een gedegen evaluatie door een klinisch geriater draagt bij tot betere zorg voor ouderen met persisterende SOLK (dit proefschrift).

4. Chronische pijn bij ouderen leidt tot verhoogde kans op het krijgen van een nieuwe depressieve episode (dit proefschrift).

5. Een mindere impact van SOLK op de kwaliteit van leven bij ouderen in vergelijking met jongere volwassenen zou kunnen betekenen dat ouderen zich beter kunnen aanpassen aan het krijgen van lichamelijke klachten (dit proefschrift).

6. Onverklaard maakt onbemind.

7. De gezondheid van de patiënt is vaak omgekeerd evenredig met het aantal dokters betrokken bij zijn behandeling.

8. Een goed hoofd en een goed hart vormen altijd een geweldige combinatie (Nelson Mandela).

9. Het gaat om de reis, niet om de bestemming (Confusius).