APPEARANCE OF DEPRESSION IN LATER LIFE

Johanna Maria (Annette) Hegeman

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Author: Johanna Maria (Annette) Hegeman

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APPEARANCE OF DEPRESSION IN LATER LIFE

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Johanna Maria Hegeman

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Promotor
Prof. dr. R.C. van der Mast

Copromotoren
Dr. H.C. Comijs, GGZ inGeest/VUmc
Dr. R.M. Kok, Parnassia

Promotiecommissie
Prof. dr. J. Gussekloo
Prof. dr. W.P. Achterberg
Prof. dr. M.L. Stek, GGZ inGeest/VUmc
Prof. dr. R.C. Oude Voshaar, UMCG

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Chapter 1

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Introduction

Case report

Mrs. A., a 71-year-old woman, was referred by her general practitioner (GP) to the internal medicine outpatient clinic of our hospital because of complaints of weight loss and tiredness that had persisted for several months. Her medical history included recurrent bronchitis, heart failure due to valvular heart disease, diabetes mellitus type II, and hypertension; she had no psychiatric history. Mrs. A. is married to a dairy farmer and, two years ago, their oldest son took over their dairy farm and she and her husband moved to another residence.

A thorough diagnostic work-up by the internist revealed no somatic explanation for her complaints. Subsequently, she was referred to a neurologist because of additional memory complaints, visual hallucinations and psychomotor slowing. No neurodegenerative disorder (Lewy body dementia) or cerebral vascular accident was found. Before referral to mental health care was effectuated, the clinical picture further deteriorated and she was admitted to the internal ward with fever and dehydration. Moreover, she refused to eat and drink and her weight dropped from 72 to 49 kilogram. She was diagnosed with a staphylococcus bacteremia and hypernatremia. After starting enteral tube feeding Mrs. A. developed a refeeding syndrome with hypokalemia and hypophosphatemia.

Nursing on the internal ward was not possible due to her behavioral problems (e.g. partial mutism, aggressive behavior, being paranoid); for this reason, and also for further psychiatric examination, she was transferred to our medical-psychiatric unit. Heteroanamnestic information revealed that all this behavior started months ago with depressive cognitions and her belief that, although persons close to her looked like her intimates, they certainly were not. Psychiatric examination showed a severe major depressive disorder with a Capgras delusion (delusional misidentification syndrome). Further, the somatic morbidity resulted in a temporary delirium. Treatment with a tricyclic-antidepressant and an antipsychotic was not effective and involuntary electroconvulsive therapy (ECT) was started. After four ECT sessions improvement was noticed and complete recovery occurred after additional ECT sessions. One year after her complaints had started, Mrs. A. could be discharged home in good health, but with minor cognitive side-effects due to the ECT.

This case report of an older woman is an example of late-life depression that had not been recognized properly, probably due to a more somatic presentation of depression. This resulted in a delay of adequate treatment with serious somatic morbidity and loss of mental wellbeing, as well as unnecessarily high healthcare costs.

Depression is defined as the presence of either a sad mood or loss of interest most of the day during a period of at least two weeks, accompanied by at least four of the following

symptoms: disturbances in weight and/or appetite, sleep disturbances, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive or inappropiate guilt (e.g. delusional), loss of concentration or indecisiveness, and recurrent thoughts of death, suicidal ideation or suicide attempts.[1] In general, late-life depression is characterized by a chronic course with a high recurrence rate.[2-4] Depression in late life often co-occurs with age-related chronic somatic diseases.[5, 6] Despite the fact that depression is a common mental disorder in late life, it often remains a hidden burden.[7, 8] As illustrated by our case report, this stresses the importance of adequate recognition and treatment of late-life depression. For Mrs. A., as well as for her GP and other physicians, it would have been helpful to have had more insight into how depression presents in late life.

The work presented in this thesis aims to expand our knowledge on the appearance of depression in later life.

Presentation of late-life depression

In fact, over the decades it has been suggested that depression in later life presents in different ways compared with depression earlier in life. However, until now, studies examining the link between age and the phenomenology of depression have shown conflicting results. Some studies suggested that depression in late life was mainly characterized by motivational symptoms such as loss of interest, loss of energy and psychomotor retardation.[9-12] Also, contradictory data have shown that depression in later life is associated with the absence of suicidality, as well as with an increase in suicidality.[13, 14] Furthermore, it was found that in late-life depression a depressed mood was less often present, whereas anxiety, somatic symptoms, somatization and hypochondriasis were more often present compared to early-life depression.[15-18] In contrast, other studies found similar symptoms of depression in older compared to younger age,[19-21] and three narrative reviews confirmed that there was insufficient evidence for a different clinical picture of depression in older people.[22-24] Thus, in general, these attempts to establish or negate a different phenomenology of late-life depression remain inconclusive.

At the same time, it is well established that depression is a clinically heterogeneous disorder, irrespective of age.[25, 26] Due to the diverse clinical picture (such as found within a DSM diagnosis of depression) this tends to result in 'blurred' research without a clear outcome.[25] Therefore, nowadays, research focuses on the variation of symptoms within the DSM diagnosis of a depressive disorder in order to find symptom pattern-related etiological pathways and individualized treatment options.[27, 28] A method used to detect certain symptom patterns is to define *symptom dimensions* that represent the severity of several symptoms grouped together in a specific *symptom domain*. Further, symptom dimensions together describe the clinical picture of an individual's depression in a *symptom profile*.

Symptom dimensions that underlie the Inventory of Depressive Symptomatology Self-Report (IDS-SR) have been identified in younger persons, but may differ from symptoms dimensions in older persons. [26, 29]

Somatic symptoms and somatic (co)morbidity in late-life depression

Several reasons for a different presentation of late-life depression have been suggested. First, socio-cultural factors, such as less expression of sadness in the older cohort of people who are not accustomed to complaining about their depressed mood. [22, 30-32] Instead, reporting somatic symptoms of depression to their physician may be much more familiar and easier to them. Second, the overlap of somatic symptoms of depression and common comorbid somatic diseases in late-life may result in a more somatic presentation of depression, due to incorrect attribution of somatic symptoms of physical illness to a diagnosis of depression. Third, depression and sickness behavior are thought to share similar inflammatory pathways and partially overlapping symptoms, such as motivational and somatic symptoms of depression. [33] Nevertheless, depression can be distinguished from sickness behavior by the presence of depressed mood, suicidality, and feelings of worthlessness or guilt. [33] However, it is precisely these symptoms that are considered less pronounced in late-life depression. Fourth, age-related differences in etiology such as bereavement, cognitive impairment and age-related underlying biological pathways (e.g. vascular pathology, inflammation and dysregulation of the hypothalamic-pituitary-adrenocortical axis) may explain a different phenomenology of depression in older compared to younger persons. [34-40] In this way, a falsely found more somatic presentation of depression, as well as under-recognition of a somatically masked depression, may be the consequence in later life. Therefore, it is of interest to investigate how age-related somatic comorbidity affects the presentation of depression.

The common co-occurrence of chronic somatic diseases and depression in late life may have an impact not only on the presentation but also on the course of depression. [5, 41] However, until now, very few studies have examined the influence of specific chronic somatic diseases on the course of depression in late life. Nevertheless, there is growing evidence that overall somatic disease burden has a negative impact on the course of depression. [5, 42] Similarly, shared underlying pathways of depression and comorbid chronic somatic diseases may result in a more chronic course of depression. [43] Also, depressive feelings usually accompany loss of health and pain and, as a result, can lead to the persistence of a pre-existing depression. [44-47] Further, probably due to a blurred presentation of depression in the presence of somatic comorbidity, underrecognition and undertreatment of depression may occur resulting in its persistence.

Cardiovascular diseases and loneliness in late-life depression

Loneliness may be an important phenomena in depression that influences health outcome.[48] Loneliness is defined as the unpleasant feeling of 'missing' that occurs when a social network is deficient in a subjective way.[49] This subjective experience is valued as loneliness when the social network is incongruent with one's wishes or standards.[49] Weiss distinguished between emotional loneliness, arising in the absence of a close emotional attachment, and social loneliness, defined as not taking part in a social network.[50]. There is a strong mutual relation between loneliness and depression in later life.[51-54] It is known that late depression is related to an increase in somatic morbidity and mortality, of which cardiovascular disease is the most examined and most well known.[43, 55, 56] However, it remains unclear whether the same is true for loneliness. Therefore, it is of interest to study loneliness and depression simultaneously as possible determinants of cardiovascular disease in order to unravel whether it is depression, or loneliness, or both, that is of importance.

Background and outline of the thesis

As described above, within the heterogeneous appearance of depression, age-related heterogeneity may occur in late life. For instance, late-life depression may present with more somatic symptoms and less depressed mood compared to depression earlier in life. However, the frequent co-occurrence of depression and chronic somatic diseases in late life with partial overlap of symptoms of depression, physical illness and sickness behavior, probably blurs the presentation of late-life depression. On the other hand, somatic comorbidity may have an impact on symptoms of depression itself. Therefore, it is important to further clarify the clinical picture of late-life depression to be able to adequately recognize late-life depression and to relate various symptom patterns within late-life depression to specific etiology, course and treatment options.

In our study, we had the opportunity to use baseline and longitudinal (two-year follow-up) data from the Netherlands Study of Depression in Older Persons (NESDO).[6] The NESDO is an ongoing prospective cohort study that aimed to examine determinants, long-time course and consequences of depression in late life. Between 2007 and 2010, 378 older persons with a depressive disorder according to the DSM-IV criteria and within the last six months before baseline assessment, and 132 non-depressed older persons, were included in the NESDO baseline sample (total sample n=510, aged 60-93 years).[6] Participants were recruited from primary healthcare practices and mental healthcare institutes to create a sample that represents all different stages of depression. Participating primary healthcare practices are from the regions of Amsterdam, Leiden and Groningen, and participating mental healthcare institutes are the GGZ inGeest, the VUMC in Amsterdam, the LUMC and GGZ Rivierduinen and Parnassia in Leiden, the UMCG and Lentis in Groningen, the GGNet

in Apeldoorn, and the UMC Radboud and GGZ Nijmegen in Nijmegen. Excluded were persons with a Mini-Mental State Examination (MMSE) score <18, a primary diagnosis of dementia, a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, or insufficient command of the Dutch language. During a four-hour baseline assessment consisting of written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples, a wide range of information was obtained with respect to health outcomes, demographic, psychosocial, clinical, biological and genetic characteristics. Data obtained from the baseline assessment were used in our cross-sectional studies. Every six months, the severity of depressive symptoms was monitored with the Inventory of Depressive Symptomatology Self Report (IDS-SR) that was sent to all participants that were still in the study. Between 2009 and 2012, a second extensive face-to-face assessment was performed. Because of attrition, 285 of the 378 depressed older persons at baseline participated in the two-year follow-up. Data obtained from the two-year follow-up assessment were used in our longitudinal study. More detailed information on the study design and attrition during follow-up is described elsewhere.[5, 6]

In this thesis we aimed to address the following questions:

- Are depressed older persons different from depressed younger persons with respect to the presentation of symptoms of depression? In Chapter 2, we describe the results of a meta-analysis that combines data from studies examining the relation between age and the phenomenology of depression on a symptom level.
- Which symptom dimensions of depression can be defined at old age using the IDS-SR? Are these symptom dimensions different from the IDS-SR symptom dimensions at younger age? In Chapter 3 we explore symptom dimensions of the IDS-SR at old age in comparison with the IDS-SR dimensions found at younger age.
- Is a more prominent somatic presentation of depression in late life the consequence of the presence of somatic diseases? To answer this question, in Chapter 4 we aimed to disentangle the effect of somatic diseases and age on the presentation of late-life depression.
- Is the course of late-life depression affected by somatic comorbidity? Since we hypothesized that an unfavorable course of depression would be associated with specific chronic somatic diseases and the burden of cumulative chronic somatic diseases, Chapter 5 presents a longitudinal examination of the influence of various common chronic somatic diseases separately, as well as cumulatively, on the course of depression.

- Is loneliness differently associated with cardiovascular disease in depressed older persons compared to non-depressed older persons? In Chapter 6 we examine this question taking into account that both depression and loneliness are thought to be related to cardiovascular disease and, therefore, strengthening of the association may occur.

In Chapter 7, the results of this thesis are summarized, clinical implications are discussed and some suggestions are made for future research.

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Chapter 2

Phenomenology of depression in older compared with younger adults: meta-analysis

J.M. Hegeman
R.M. Kok
R.C. van der Mast
E.J. Giltay

British Journal of Psychiatry 2012; 200:275-281

Abstract

Background

Late-life depression may differ form early-life depression in its phenomenology.

Aims

To investigate the effect of age on the phenomenology of major depression.

Method

A systematic search was conducted in Pubmed, Embase and PsycINFO for all studies examining the relation between age and phenomenology of major depression, according to the RDC, DSM and ICD criteria. Studies were included only if the age groups were compared at the single-item level using the 17-, 21- or 24-item versions of the Hamilton Rating Scale for Depression; a meta-analysis was done for each item of the 17 item scale.

Results

Eleven papers met the inclusion criteria. Older depressed adults, compared to younger depressed adults, demonstrated more agitation, hypochondriasis and general as well as gastrointestinal somatic symptoms, but less guilt and loss of sexual interest.

Conclusions

The phenomenology of late-life depression differs only in part from that of early-life depression. Major depression in older people may have a more somatic presentation, whereas feelings of guilt and loss of sexual function may be more prevalent in younger people.

Introduction

Late-life depression is a common psychiatric disorder at old age. It often has a poor long-term prognosis more frequently showing a chronic course and a higher relapse rate compared to depression at younger age.[1] In addition, late-life depression is linked to more medical co-morbidity (e.g. cognitive impairment and cardiovascular diseases) and a high risk of mortality.[2-4] A different phenomenology has been suggested for late-life compared to early-life depression. Possible reasons for a different presentation of late-life depression are the overlap of somatic symptoms of depression and physical disease in old age, and socio-cultural factors such as the minimal expression of sadness in the current cohort of old people not used to complaining about depressed mood.[5] Also, age-related biological and psychological factors may underlie a different phenomenology of late-life and early-life depression. In 3 narrative reviews insufficient evidence was found to support a different presentation of depression in older people.[5-7] However, conceptual and methodological limitations of the reviewed studies, and the inherent subjectivity and bias proneness of narrative reviews, might have played a role in this conclusion. Therefore, this meta-analysis of studies examines the phenomenology of depression at the single-item level of the Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or abbreviated to HAM-D.

Methods

Study selection

A systematic literature search was performed in PubMed, EMBASE and PsycINFO. The following (key)words were used: depress*, depressive, major depression, dysthymic disorder, geriatric patients, geriatric psychiatry, elder*, elderly, geriatric, aged, old age, old, oldest old, middle aged, adult, adults, early onset, late onset, onset age, age of onset, age at onset, phenomenol*, symptom*, clinical presentation, clinical features, atypical, melanchol* and dimension*. These were combined with the Medical Subject Headings (MeSH) depression, depressive disorder, signs and symptoms and age factors. The search was run on the 18 July 2011. No limitations in the search strategy were inserted. Reference lists from all relevant literature were hand searched for additional relevant articles overlooked by the database search. Then, titles and abstracts of the articles were screened to identify possible relevant articles. Finally, the remaining articles were full-text reviewed (by J.H.) with respect to our inclusion and exclusion criteria. In case of doubt, articles were discussed in a consensus meeting with three authors (J.H., R.K., R.M.).

Studies were excluded if no comparison was made between old age and younger age regarding the phenomenology of major depression; if studies did not present primary data (e.g. letters, comments and reviews were excluded); and if the study population consisted mainly of persons with bipolar disorder, schizoaffective disorder or dementia.

Samples could be drawn from an in-patient, out-patient, primary healthcare or general population. As depression is a heterogeneous disorder irrespective of age, strict diagnostic criteria were used. Participants had to be diagnosed with major depression according to either the RDC, ICD-9, ICD-10, DSM-III, DSM-III-R or DSM-IV criteria. The cut-off age for late-life depression had to be defined between 50 and 70 years or, alternatively, correlation coefficients between age and item scores had to be presented. To increase homogeneity, we only included studies in which symptoms of depression were measured using the HAM-D and both age groups were compared at the single-item level for the HAM-D-17, HAM-D-21 or HAM-D-24. Furthermore, the HAM-D is the most commonly used observer-rated and validated instrument for rating depression in both younger and older adults.[8] Where articles reported data on overlapping cohorts, the studies with the largest sample size or with the most complete information were included.

Mean scores and standard deviations as well as frequencies of the 17 items of the HAM-D-17 for all HAM-D scales, mean total HAM-D scores (and standard deviations), and number of participants were extracted from the articles. Form studies reporting frequencies of high- or low-severity scores on individual HAM-D items, as well as presence of the item, the frequency of any presence at all was extracted. Correlations were extracted when articles provided only correlations between age and single-item scores. When only subsets of the 17 HAM-D items were presented, the authors of more recent studies (published after 1995) were contacted and requested to provide missing data. Where mean scores or correlations were presented separately for men and women or for early-onset and late-onset late-life depression, these were transformed into one weighted combined mean score (SD) or correlation coefficients using appropriate formula.

Quality assessment

Quality assessment of observational studies in meta-analyses is not usual and there is no consensus regarding the method used.[9,10] In the present study, the quality of the included studies was assessed by two authors (J.H., E.G.) using a checklist with the following 5 criteria: (a) both age groups were selected from the same source population; (b) population characteristics and inclusion and exclusion criteria were described; (c) (semi)structured diagnostic instruments were used; (d) difference in overall disease severity between younger and older patients controlled for, or no statistically significant difference in depression severity reported; and (e) a complete set of 17 HAM-D items was usable or transformable for

meta-analysis. For two criteria weighting was applied, resulting in quality criteria a through c being coded as 0 or 1, and criteria d and e as 0, 1 or 2 points, and these criteria were summed to yield a sum score ranging from 0 to 8 points. If no information was provided as to whether a specific quality criterion was met, it was coded as 0 points. The cut-off for high or low quality was defined at a score of 5 or more, based on the 60% cut-off point commonly used in quality assessments.[11] Discrepancies between the reviewers were resolved through discussion (J.H., E.G.).

Statistical analyses

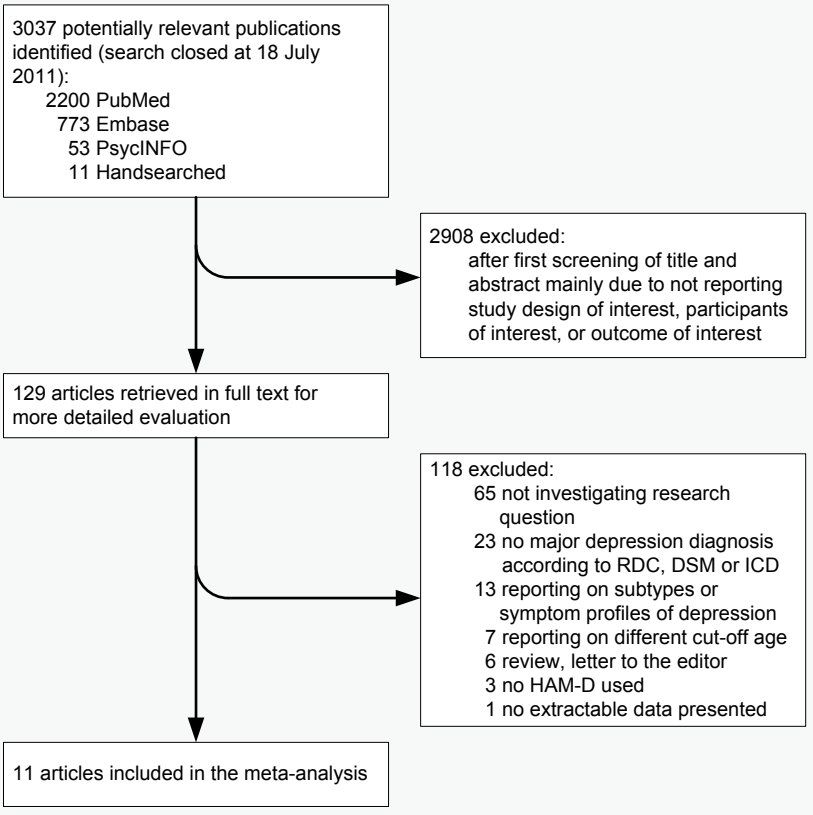
Data management, calculation of effect sizes and quantitative data synthesis were performed using the Comprehensive Meta-Analysis software version 2.0.021 (www.meta-analysis.com). Odds ratios were calculated for each HAM-D-17 item separately and were used for all mean comparisons. A higher odds ratio means that the particular HAM-D item showed higher prevalence rates and/or higher severity in older *v*. younger patients. Because considerable heterogeneity was expected, all analyses were performed with the random-effects model that reduces the risk of a type I error (as fixed models typically result in narrower confidence intervals). To assess heterogeneity between the studies we calculated the I^2, which is an indicator of heterogeneity in percentages, and used a value ≥50% to indicate meaningful heterogeneity.[12] In addition, *Q* statistics were calculated. A statistically significant *Q* rejects the null hypothesis of homogeneity and indicates a heterogeneous distribution of effect sizes between studies, meaning that systematic differences, possibly influencing the results, are present. For each HAM-D-17 item two summary estimates were calculated: an estimate based on the studies with usable data (see Fig. 2); and an estimate based on the studies with a quality score of ≥5 points, to estimate the effect of bias and potential confounding. A p-value below 0.01 was considered statistically significant, because of multiple testing for every HAM-D item.

Results

Selected studies

The search yielded 3037 articles, including 2200 in PubMed, 773 in Embase, 53 in PsycINFO and 11 hand-searched articles. Exclusion of duplicates and irrelevant references after a first screening of the titles and abstracts left 129 potentially relevant articles for further evaluation (Fig. 1). Most articles were excluded because they did not report the outcome of interest (65 studies), mainly as follows: comparing the phenomenology of early onset *v*. late onset late-life depression (20 studies), or examining neurocognitive function rather than

Figure 1. Flow chart of study selection.



depressive symptomatology in relation with age (14 studies). Of the 23 excluded articles not concerning a diagnosis of major depression, 21 reported on depressive symptoms, one reported on minor depression and one on dysthymic disorder.

Finally, 11 articles were included in this meta-analysis comparing early and late-life major depression. Because some articles did not present all individual items of the HAM-D, three sets of authors were contacted.[13-16] In one case we received the unreported HAM-D items.[13] In the second case,[14,15] the authors were also asked whether two different articles presented data on the same study population. Although our question was not answered we extracted the data, choosing the article with the largest study population. As the HAM-D items 'weight loss' and 'anxiety' were not presented in this larger study, we extracted these data from the article with the smaller sample size.[14,15] Data from a third article by this group were

Table 1. Characteristics of the 11 included studies.

Study	Assessment instrument, Criterion	Population	Sample size, n			Age, years						Exclusion Criteria	HAM-D score: mean (SD)			
						Mean age			Cut-off age	Mean age at onset						
			EL	LL	All	EL	LL	All		EL	LL		EL	LL	All	Q[a]
Brown *et al* (1984)	SADS, RDC	IP	28	63	91	39	64		50	34	60	Bipolar disorder, schizophrenia, schizoaffective disorder, secondary depression	32.0 (7.5)	31.3 (7.8)		7
Small *et al* (1986)	NR, DSM-III	OP	38	39	77	35	67		55			Psychosis, actively suicidal	22.1 (5.0)	22.7 (6.1)		4
Brodaty *et al* (1991)	Semi-structured interview, DSM-III	IP/OP	181	61	242	37	69		60			Primary diagnosis of alcohol or drug abuse, not fluent in English, insufficient cognition	18.8 (7.6)	21.2 (9.6)		5
Koenig *et al* (1993)	DIS, RDC	Medical IP	26	44	70				<40-70+[b]			NR				5
Wallace *et al* (1995)	Structured interview, DSM-III	IP			257			39				Medical or pharmacological condition that might invalidate dexamethasone suppression test				5
Brodaty *et al* (1997)	Structured interview, DSM-III-R	OP	208	77	285	38	69		60			Bipolar disorder, depression secondary to organic disorder, diagnosis other than major depression episode	20.8 (6.5)	25.2 (7.1)		5
Stage *et al* (2001)	Structured interview DSM-III/III-R/IV	IP	228	233	461			55	55			Other mental or neurological disorders, acute infections, pregnancy, severe systemic diseases			23.1 (4.4)	6
Tan *et al* (2001)	Structured interview, DSM-IV	IP/OP	28	42	70	38	73		60	35	69	Neurological disorder, dementia, mute	23.8 (5.2)	26.5 (6.3)		8
Brodaty *et al* (2005)	Structured interviews, DSM-III-R/IV	IP/OP	242	40	282				60			Depression secondary to physical illness or substance abuse	19.1 (6.5)	22.2 (8.0)		5
Shahpesandy (2005)	NR, ICD-10	NR	60	46	106	45	71		65			NR				1
Gournellis *et al* (2010)	SCID-IV, DSM-IV	IP	30	69	99	45	70		60	45	56	MMSE<23, depression secondary to somatic condition, non-psychotic depression	29.3 (5.7)	30.3 (6.0)		8
All studies					2011											

DIS, Diagnostic Interview Schedule; EL, Early-Life Depression; HAM-D, Hamilton Rating Scale for Depression; IP, in-patient; LL, late-life depression; MMSE, Mini-Mental State Examination; NR, not reported; OP, out-patient; RDC, Research Diagnostic Criteria; SADS, Schedule for Affective Disorders and Schizophrenia; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders.

a. Quality assessment score.
b. Participants were aged <40 or >70 years.

also included in this meta-analysis because the study population was without any doubt a different group.[17] In the third case, the author was unobtainable for further information concerning not reported or not transformable HAM-D scores and methodological issues.[16] For this latter article, Z scores and p-value statistics were used for the reported HAM-D items.

Late-life depression v. early-life depression

Table 1 presents the characteristics of the included studies; the total number of patients was 2011. On average, older patients had significantly more severe depression (seven studies with standardized difference in means: 0.33, 95% CI 0.13-0.52, p=0.001).[13-15,17-20] However, four studies did not report the overall HAM-D severity scores for older and younger patients.[16,21-23] In fact, depression severity was particularly higher in older patients in the three studies of Brodaty *et al.*[14,15,17] Apart from this, another study included a population with psychotic depression only,[13] in which both age groups were severely affected. Small *et al* reported only on guilt.[19] With regard to quality assessment, we rated 9 articles[13-15,17,18,20-23] as being of high quality and 2 articles[16,19] as being of lower quality.

Figure 2 presents the pooled odds ratios for the relation between age and symptoms of depression according to the HAM-D-17. Random effect modelling, with a 95% confidence interval (CI) and p<0.01, showed that older people with major depression, compared to younger people, demonstrated more agitation (OR=1.84, 95% CI 1.39-4.45, p<0.001), general

Figure 2. Forest plot of overall odds ratios (and their 95% confidence intervals as the extremes of the diamonds) comparing early-life and late-life occurrence of every HAM-D-17 item in a random-effects meta-analysis of 11 studies, ordered according to the magnitude of the effect size. Red diamonds indicate the items more prevalent and/or severe in older patients, and the blue diamonds the items more prevalent and/or severe in younger patients.

HAM-D-17 item	Statistics for each study					Sample size		Odds ratio and 95% confidence interval
	Odds ratio	Lower limit	Upper limit	Z value	P value	N studies	N participants	
Hypochondriasis	3.132	2.240	4.378	6.679	< 0.001	9	1678	
Somatic–general	2.007	1.382	2.916	3.657	< 0.001	7	1154	
Agitation	1.842	1.388	2.445	4.229	< 0.001	6	1048	
Somatic–gastrointestinal	1.580	1.266	1.971	4.052	< 0.001	7	1154	
Weight loss	1.554	0.989	2.441	1.914	0.056	7	1333	
Insomnia–late	1.513	1.082	2.117	2.417	0.016	7	1154	
Anxiety–somatic	1.476	1.023	2.129	2.079	0.038	8	1439	
Loss of insight	1.305	0.858	1.984	1.243	0.214	7	1154	
Retardation	1.157	0.585	2.288	0.418	0.676	7	1154	
Work and activity	1.145	0.664	1.975	0.487	0.626	7	1154	
Insomnia–middle	1.141	0.833	1.564	0.824	0.410	7	1154	
Anxiety–psychic	1.127	0.779	1.630	0.636	0.525	7	1333	
Insomnia–early	1.125	0.887	1.427	0.972	0.331	6	1048	
Depressed mood	0.921	0.555	1.529	–0.318	0.750	7	1154	
Guilt	0.524	0.424	0.646	–6.020	< 0.001	9	1473	
Sexual interest	0.512	0.373	0.703	–4.138	< 0.001	7	1154	
Suicidality	0.450	0.213	0.952	–2.088	0.037	6	1048	

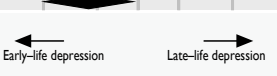
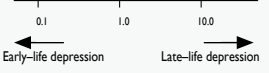


Figure 3. Forest plot for the 6 statistically significant HAM-D-17 items ($P<0.01$) for the comparison between early-life and late-life depression.

HAM-D-17 item	Sample size	Statistics for each study					Odds ratio and 95% confidence interval
	N	Odds ratio	Lower limit	Upper limit	*Z* value	*P* value	
Hypochondriasis							
Brown *et al* (1984)	91	2.250	0.995	5.089	1.948	0.051	
Brodaty *et al* (1991)	242	5.398	2.824	10.318	5.101	< 0.001	
Koenig *et al* (1993)	70	1.020	0.322	3.231	0.034	0.973	
Wallace *et al* (1995)	257	2.688	1.693	4.269	4.192	< 0.001	
Stage *et al* (2001)	461	2.018	1.439	2.830	4.066	< 0.001	
Tan *et al* (2001)	70	7.497	2.960	18.989	4.249	< 0.001	
Shahpesandy (2005)	106	3.336	1.594	6.978	3.198	0.001	
Brodaty *et al* (2005)	282	5.127	2.353	11.172	4.113	< 0.001	
Gournellis *et al* (2010)	99	3.447	1.555	7.643	3.046	0.002	
Overall	**1678**	**3.132**	**2.240**	**4.378**	**6.679**	**< 0.001**	
Somatic–general							
Brown *et al* (1984)	91	1.000	0.446	2.242	0.000	1.000	
Koenig *et al* (1993)	70	1.508	0.411	5.538	0.619	0.536	
Wallace *et al* (1995)	257	1.516	0.968	2.376	1.817	0.069	
Tan *et al* (2001)	70	6.824	2.709	17.188	4.074	< 0.001	
Stage *et al* (2001)	461	1.870	1.335	2.619	3.638	< 0.001	
Shahpesandy (2005)	106	3.336	1.594	6.978	3.198	0.001	
Gournellis *et al* (2010)	99	1.734	0.794	3.788	1.381	0.167	
Overall	**1154**	**2.007**	**1.382**	**2.916**	**3.657**	**< 0.001**	
Agitation							
Brown *et al* (1984)	91	2.562	1.130	5.812	2.252	0.024	
Koenig *et al* (1993)	70	1.128	0.425	2.990	0.242	0.809	
Wallace *et al* (1995)	257	1.683	1.072	2.641	2.263	0.024	
Stage *et al* (2001)	461	2.097	1.494	2.943	4.280	< 0.001	
Tan *et al* (2001)	70	3.272	1.345	7.963	2.613	0.009	
Gournellis *et al* (2010)	99	0.978	0.449	2.128	–0.057	0.955	
Overall	**1048**	**1.842**	**1.388**	**2.445**	**4.229**	**< 0.001**	
Somatic–gastrointestinal							
Brown *et al* (1984)	91	1.296	0.577	2.908	0.628	0.530	
Koenig *et al* (1993)	70	13.255	0.657	267.586	1.686	0.092	
Wallace *et al* (1995)	257	1.472	0.940	2.306	1.689	0.091	
Stage *et al* (2001)	461	1.494	1.070	2.087	2.354	0.019	
Tan *et al* (2001)	70	1.103	0.463	2.626	0.222	0.825	
Shahpesandy (2005)	106	2.457	1.194	5.057	2.441	0.015	
Gournellis *et al* (2010)	99	2.216	1.010	4.860	1.986	0.047	
Overall	**1154**	**1.580**	**1.266**	**1.971**	**4.052**	**< 0.001**	
Guilt							
Brown *et al* (1984)	91	0.713	0.317	1.600	–0.821	0.412	
Small *et al* (1987)	77	0.403	0.141	1.151	–1.697	0.090	
Brodaty *et al* (1991)	242	0.967	0.521	1.795	–0.107	0.915	
Koenig *et al* (1993)	70	0.545	0.154	1.933	–0.939	0.348	
Wallace *et al* (1995)	257	0.446	0.283	0.705	–3.458	0.001	
Stage *et al* (2001)	461	0.477	0.340	0.669	–4.280	< 0.001	
Tan *et al* (2001)	70	2.842	0.301	26.862	0.911	0.362	
Shahpesandy (2005)	106	0.403	0.196	0.829	–2.468	0.014	
Gournellis *et al* (2010)	99	0.482	0.220	1.055	–1.826	0.068	
Overall	**1473**	**0.524**	**0.424**	**0.646**	**–6.020**	**< 0.001**	
Sexual interest							
Brown *et al* (1984)	91	0.322	0.141	0.734	–2.696	0.007	
Koenig *et al* (1993)	70	0.211	0.073	0.609	–2.875	0.004	
Wallace *et al* (1995)	257	0.588	0.374	0.922	–2.311	0.021	
Stage *et al* (2001)	461	0.804	0.576	1.122	–1.284	0.199	
Tan *et al* (2001)	70	0.452	0.188	1.087	–1.773	0.076	
Shahpesandy (2005)	106	0.470	0.230	0.961	–2.070	0.038	
Gournellis *et al* (2010)	99	0.455	0.208	0.998	–1.964	0.050	
Overall	**1154**	**0.512**	**0.373**	**0.703**	**–4.138**	**< 0.001**	



(OR=2.01, 95% CI 1.38-2.92, p<0.001) and gastrointestinal somatic symptoms (OR=1.58, 95% CI 1.27-1.97, p<0.001) and hypochondriasis (OR=3.13, 95% CI 2.24-4.38, p<0.001), but less guilt (OR=0.52, 95% CI 0.42-0.65, p<0.001) and less loss of sexual interest (OR=0.51, 95% CI 0.37-0.70, p<0.001) (Fig. 3). A sensitivity analysis of the 9 articles of high quality revealed that the significant differences persisted for all 6 HAM-D-17 items.[13-15,17,18,20-23] Another sensitivity analysis excluding studies with more severe depression in older people *v.* younger people revealed similar results.[14,15,17] Again, removing the study with patients with psychotic depression only,[13] did not notably affect the sizes of the odds ratios, although these were no longer significant for loss of sexual interest and general and gastro-intestinal somatic symptoms.

Heterogeneity between studies was not significant for the items agitation (Q=6.44, p=0.26), gastrointestinal (Q=5.17, p=0.52) somatic symptoms, guilt (Q=8.10, p=0.43) and loss of sexual interest (Q=10.12, p=0.12), suggesting a homogeneous distribution of effect sizes between the studies. However, for the items hypochondriasis (Q=17.90, p=0.02) and general somatic symptoms (Q=13.17, p=0.04) the I^2 value was just above the 50%, which has a minor effect as we used random-effect models. No study was identified as a consistent outlier for most of the 17 HAM-D items.

Discussion

The results of this meta-analysis show a partly different phenomenology of late-life depression compared with early-life depression. Older people with major depression demonstrated more agitation, general and gastrointestinal somatic symptoms and hypochondriasis, but less guilt and less loss of sexual interest, compared with younger people with major depression. The difference between the two groups did not reach statistical significance for late insomnia, somatic anxiety and suicidality, which might be due to the small numbers of subjects (type II error). In general, these results indicate that major depression in older people may have a more somatic presentation, whereas feelings of guilt and loss of sexual function may be symptoms that are more specific for depression at a younger age.

Our results are largely consistent with some earlier studies examining this subject in a different way than comparison at the single-item level of HAM-D. For example, older people with major depression were found more likely to have somatic symptoms and less likely to have guilt, suicidal and cognitive symptoms.[24] Another study found that older people were more likely to have agitation and late insomnia,[25] whereas younger people were more likely to have increased appetite, weight gain and decreased libido. Similarly, in a study examining exclusively psychotic depression,[26] an increase of agitation and a decrease of suicidality

and guilt was found in old age compared with younger age. Husain *et al* used the 30-item Inventory of Depressive Symptomatology - Clinician Rated and found clinically meaningful differences.[27] In their study, older people with non-psychotic major depression had more gastrointestinal symptoms and middle and late insomnia, less irritability and hypersomnia, and were less likely to hold negative cognitions of the self or the future. Others, [28-30] however, found no differences in the phenomenology of late-life and early-life depression. For instance, no differences in symptomatology of major depression were found in an inpatient psychiatric population using the Duke Depression Evaluation Schedule for the Elderly.[31] In addition, Corruble *et al*,[32] using the Montgomery-Äsberg Depression Rating Scale (MADRS), found similar results in a comparison of the phenomenology of major depression at age ≥60 years *v.* <60 years. In a sensitivity analysis we added the seven items that roughly corresponded to the HAM-D items, which did not lead to different conclusions (data not shown). In three reviews without quantitative data analysis it was argued that no clinically relevant differences were found.[5-7] However, although the studies in these earlier narrative reviews almost overlap with our studies, some recent articles were not included. Also, these differences in interpretation may relate to the advantages of a meta-analysis over a narrative review that is more prone to subjectivity and bias. Remarkably, in contrast to earlier studies, we did not find differences between older and younger age in the HAM-D items 'loss of insight', 'work and activity' and 'psychomotor retardation', which are closely related to the concept of apathy.[33-35] Also, in spite of what has been suggested by others,[5,36,37] no difference was found in depressed mood.

The question arises whether age-related factors modify the presentation of depression or just lead to overlap of somatic symptoms of depression and medical illness, both complicating the diagnosis of late-life depression. For example, not only decrease of sexual desire and sexual function with ageing, but also the lack of a living partner, might explain our finding that older patients had less sexual dysfunction caused by depression compared with younger patients.[38] The expression of more somatic symptoms and less guilt in older patients might be explained by the tendency of the current cohort of older people to express somatic instead of psychological complaints.[39] Alternatively, it might be that the phenomenology of late-life depression is related to specific risk factors; for instance, in the oldest old people, psychomotor retardation and loss of energy were associated with vascular or neurodegenerative risk factors whereas symptoms such as thoughts of death, as well as sleep and appetite disturbances, were more strongly related to an inflammatory risk factor.[40] However, another study on this subject reported conflicting results.[41] Besides, it is difficult to distinguish apathy and cognitive impairment as distinct clinical entities from depression at old age because of overlap of symptoms. Again, it follows that depression may have been overestimated in these studies, suggesting a different phenomenology based on

wrong assumptions.[42,43]

Several methods have been proposed to resolve the issue of overlap of somatic symptoms of depression and physical illness, complicating the diagnosis of late-life depression. For example, in an inclusive approach all somatic symptoms are included regardless of being primarily due to a medical illness, whereas in an exclusive approach somatic symptoms of depression are excluded and only psychological symptoms are counted for a diagnosis of depression. Next, in an aetiological approach a somatic symptom is only counted if not caused by a medical illness and in a substitutive approach the somatic symptoms are replaced by non-somatic alternatives.[44] Although the HAMD-17 is criticized for its use in patients with physical illness due to including too many somatic items, the use of this scale is even justified to diagnose post-stroke depression and depression in Parkinson's disease.[45,46] Moreover, some somatic symptoms were highly sensitive for post-stroke depression.[45]

Strenghts and limitations

The present study has some limitations. First, older patients had on average a higher level of severity of depression compared to younger patients, which may account for the slightly different phenomenology in older patients. Although statistically significant, these differences in depression severity were small and therefore not regarded as clinically relevant. In addition, sensitivity analysis excluding studies with significantly more severe depression in older people revealed similar results,[14,15,17] suggesting that our results are not likely explained by differences in depression severity. Alternatively, overlapping somatic symptoms of depression and co-morbid age-related physical disorders may explain the higher scores on depression severity scales in the older population. Second, we could not adjust for co-morbid physical disorders in older *v.* younger people. Lack of this information means that we cannot be certain if our findings are related to somatic co-morbidity. In fact, all but one study included in-patients, and perhaps older patients with a more somatic presentation were hospitalized more often than younger depressed patients in order to exclude an underlying somatic illness. In previous studies,[21,27] however, differences in the phenomenology of major depression persisted after adjustment for somatic comorbidity. One of these studies was included in our meta-analysis and used an inclusive approach for rating HAM-D items.[21] Third, as studies mainly reported on in-patients it follows that generalization of our findings to an out-patient or the general population is limited. Fourth, a conceptual limitation is the use of strict RDC, DSM and ICD diagnostic criteria for major depression and the HAM-D. Obviously, if distinctive features of late-life depression indeed exist, they would be missed if not included in the HAM-D. Moreover, if depression in older people presents with many symptoms that differ from the DSM or ICD criteria, then these patients might not be diagnosed as having depression and would not have been included

in these studies. Finally, this meta-analysis focused on comparing depression at older and younger age, irrespective of age of first onset. It follows that we did not address the question of whether the age at onset of the first depressive episode is related to a specific symptom profile of early- or late-onset late-life depression. However, the studies of Gournellis *et al* and Brodaty *et al* compared both early *v.* late-life depression and early onset *v.* late onset in late-life depression.[13-15] Gournellis *et al* found differences related to both age at onset and current age in which the group of older patients with early-onset depression had an in-between position concerning the extent of differences in hypochondrial ideation and gastrointestinal symptoms compared to a group of older patients with late-onset and a group of younger patients with early-onset depression.[13] In the studies of Brodaty *et al*,[14,15] differences were found related to current age only, but not for age at onset. Furthermore, as late-life depression probably encompasses patients with recurrent depressive episodes and treatment-refractory depression, it is possible that differences in the phenomenology between late-life and early-life depression might be more marked when studies only include patients with first episode depressive episodes. Ideally, these would be prospective cohort studies because recall bias of age at onset is one of the problems of such studies.[47] However, older patients with recurrent depressive episodes might also have a 'new onset' distinctive depressive episode, for example related to (vascular) changes in the ageing brain.

Strengths of this meta-analysis include the thorough search resulting in over 2000 patients from 11 studies, the quality of the review process, and the consistent findings across studies with generally low heterogeneity. Moreover, we are not aware of previous meta-analyses examining the relation between age and the phenomenology of major depression.

Clinical implications

In summary, the results of this study suggest only in part a different phenomenology of major depression in older people compared with younger adult patients. These findings are relevant for clinical practice, because we should be aware that major depression in older people may present in a more somatic way. This may help our understanding of the phenomenology of late-life depression related to certain risk factors and age at onset, in order to improve recognition and early detection, and refine prevention and treatment of depression in older people.

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Chapter 3

Symptom dimensions and subscales of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons

J.M. Hegeman*
K.J. Wardenaar*
H.C. Comijs
M.W.M. de Waal
R.M. Kok
R.C. van der Mast

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* These authors contributed equally as shared first authors

Abstract

Background

Using symptom dimensions may be more effective than using categorical subtypes when investigating clinical outcome and underlying mechanisms of late-life depression. Therefore, this study aims to identify both the factor and subscale structure of late-life depression underlying the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons.

Method

IDS-SR data of 423 participants in the Netherlands Study of Depression in Older Persons (NESDO) were analyzed by exploratory (EFA) and confirmatory factor analysis (CFA). The best-fitting factor solution in a group of older persons with a major depressive disorder diagnosis in the last month (n=229) was replicated in a control group of older persons with no or less severe depression (n=194). Multiple group (MG-CFA) was performed to evaluate generalizability of the best-fitting factor solution across subgroups, and internal consistency coefficients were calculated for each factor.

Results

EFA and CFA show that a 3-factor model fits best to the data [comparative fit index (CFI)=0.98; Tucker Lewis Index (TLI)=0.99; and root mean square error of approximation (RMSEA)=0.052], consisting of a 'mood', 'motivation' and 'somatic' factor with adequate internal consistencies (alpha coefficient 0.93, 0.83 and 0.70, respectively). MG-CFA shows a structurally similar factor model across subgroups.

Conclusion

The IDS-SR can be used to measure three homogeneous symptom dimensions that are specific to older people. Application of these dimensions that may serve as subscales of the IDS-SR may benefit both clinical practice and scientific research.

Introduction

In many aspects, late-life depression is a heterogeneous disorder that has a negative effect on the quality of life in older persons. Unfortunately, research has been unable to identify underlying etiological mechanisms of (late-life) depression which could serve as a target for novel treatments.[1] This might (in part) be due to the common use of the overly restrictive diagnostic DSM-IV categories, which are problematic for reasons related to e.g. comorbidity, arbitrary boundaries and diagnostic heterogeneity.[1-4] Moreover, the applicability and validity of the DSM-IV diagnoses, including depression, might be even more problematic in older persons. The DSM classification tends to focus on younger persons and takes little account of changes in symptomatology that may be seen with aging, such as less expression of sadness and a more pronounced role of somatic symptoms.[5-7] Consequently, using solely DSM-IV diagnoses in older persons may lead to undiagnosed late-life depression.[8,9]

A promising approach to improve recognition of late-life depression, and the search for underlying mechanisms, would be to focus more on the variations in symptomatology in older persons with depression. To reveal such variations in symptomatology in late-life depression, different methodological approaches can be used. A *categorical* approach using latent class analysis aims to define *subtypes* of late-life depression based on clustering of persons with similar characteristics. Such research has revealed several clusters of older depressed persons, which differed mainly by overall symptom severity as well as the nature of the depressive symptoms, such as somatic symptoms and suicidal thoughts.[10,11]

However, it is argued that a *dimensional* approach may offer additional benefits compared with a categorical approach. A *symptom dimension* can be defined as a continuous spectrum of severity on a specific symptom domain of late-life depression. In a *symptom profile* various symptom dimensions are used together to describe an individual's clinical picture. Advantages of a dimensional approach, as opposed to a categorical approach, include its high diagnostic specificity in combination with its continuous nature, which increases statistical power to detect small effects.[12] In addition, dimensions do more justice to the continuous distribution of psychopathology in the general population as no fixed threshold is set between ill and non-ill, preventing the exclusion from analyses of individuals with sub-threshold, but clinically relevant, symptoms. Conveniently, symptom dimensions and symptom profiles offer a way to circumvent categorical co-morbidity.[13] Therefore, using *symptom dimensions* may be more effective than using categorical *subtypes* when investigating underlying mechanisms of late-life depression.[1,13-15]

A practical method for defining dimensions of late-life depression is to use existing depression measures that are widely administered. Factor analytical studies of these psychiatric measures to identify symptom domains are available for the adult psychiatric

population,[14] but are less frequent for older persons with late-life depression.[16,17]

A widely-used instrument that covers both the key symptoms of depression and somatic/vegetative symptoms is the Inventory of Depressive Symptomatology Self Report (IDS-SR), originally developed to measure severity of overall depression (www.ids-qids.org).[18] Factor analytical studies of the IDS-SR in younger persons revealed different numbers of symptom domains with considerable overlap.[18-21] Recently, in younger persons a 3-factor model was found to have optimal fit, including a 'mood/cognition', an 'anxiety/arousal' and a 'sleep' symptom domain.[22] However, as age-related features may cause heterogeneity in the phenomenology of late-life depression, symptom dimensions found in younger persons cannot be generalized to older persons.

Therefore, the present study explores the factor structure of the IDS-SR at old age using an integrated approach of exploratory and (multiple group) confirmatory factor analyses (EFA and CFA) in two different samples of older persons (total n=423). Also, the question as to whether the resulting factors could serve as more specific subscales of the IDS-SR to measure symptom dimensions is being examined.

Methods

Participants

Data were obtained from the baseline assessment of the Netherlands Study of Depression in Older Persons (NESDO). The NESDO is a multi-site naturalistic cohort study, aimed to examine the course and consequences of depressive disorders in older persons. The study design of the NESDO is described in detail elsewhere.[23] From 2007 until 2010, 378 depressed (diagnoses within the last 6 months according to the DSM-IV criteria) and 132 non-depressed persons aged 60-93 years were recruited from mental healthcare and primary healthcare settings to create a sample reflecting all different stages of the disease (total n=510). Excluded were persons with a Mini Mental State Examination score (MMSE) under 19, a primary diagnosis of dementia and insufficient command of the Dutch language. The study protocol of NESDO was approved by the ethical review boards of all participating study centers.

All participants with complete data on the IDS-SR were included in our analyses (n=423) and divided into two non-overlapping study groups: persons with a DSM-IV diagnosis of major depressive disorder (MDD) diagnosis during the last month (Group 1: n=229), and a control group consisting of healthy older persons and older persons with a minor depressive, dysthymic or anxiety disorder, according to the DSM-IV (Group 2: n=194). Group 1 was used to explore the factor structure of the IDS-SR and Group 2 was used to independently replicate this factor solution.

In Group 1, of all 275 participants in NESDO with a MDD diagnosis during the last month, 46 (16.7%) were excluded because of missing responses on the IDS-SR, leaving a total of 229 participants. For the same reason, of the 235 participants in Group 2, 41 (17.4%) were excluded, resulting in a total of 194 participants. We decided not to impute missing data, as new sources of bias cannot be ruled out, and the sample size would still remain adequate. Participants with incomplete data on the IDS-SR were more often women (p=0.002) and had marginally fewer years of education (p=0.022) compared to included participants of the pooled sample.

Instruments

Demographic information was assessed with standard questions concerning age, gender and years of education. The Composite International Diagnostic Interview (CIDI; WHO version 2.1; lifetime version) was used to assess the presence of a depressive disorder (major depression, dysthymia and minor depression) or anxiety disorder (panic disorder, agoraphobia, social phobia and generalized anxiety disorder) according to the DSM-IV criteria in the month prior to the measurement day.

All participants were administered the Dutch translation of the IDS-SR.[18] In the IDS-SR, items are scored on a four-point scale, with each item equally weighted and summed to a total score. A higher total score indicates more serious depression with a maximum score of 84. The item pairs 11-12 and 13-14 were each rescored into one variable: '11/12: change of appetite' and '13/14: change of weight', respectively. This was done because each subject can only endorse one possibility of each item pair (e.g. either increased or decreased appetite).

Statistical analyses

Exploratory factor analysis

To investigate the factor structure of the IDS-SR, in Group 1 we performed exploratory factor analysis (EFA) on a matrix of polychoric correlations. To determine the number of factors, the resulting Eigen Values were compared with Eigen Values extracted from 1000 random data sets that paralleled the original data set (same N, same number of variables). In this *parallel analysis*, the number of factors was determined by finding the last factor with an Eigen Value that was higher than the 95th percentile random Eigen Value (using the SPSS syntax, provided by O'Connor, 2000).[24] The extracted factors were rotated to simple structure using an oblique rotation method (PROMAX), allowing for inter-correlated factors. The EFA was conducted with Mplus 5.1.[25] Random Eigen Value were generated with SPSS 17.0.

Confirmatory factor analysis

CFA was used to evaluate the fit of the EFA model in Group 2. In the input model, all factors

were allowed to co-vary freely. On each factor, all factor loadings were set to be free, except for one item per factor that had its loading fixed to 1 to set the scale of the model. Because the items were categorical and had a skewed distribution, fit was determined with a Weighted Least Squares (WLSMV) estimator, based on polychoric correlation matrices using a diagonal weight matrix with standard errors, and mean- and variance adjusted chi-square test statistics that use a full weight matrix.[25] Because WLSMV is intended for categorical data, it estimates the threshold locations between adjacent categories of each indicator variable instead of single intercepts, which are only informative for continuous indicator variables.[25] Several fit indices were used to evaluate model fit: the Comparative Fit Index (CFI), the Tucker Lewis Index (TLI) and the Root Mean Square Error of Approximation (RMSEA). A CFI and TLI >0.90 indicates adequate fit (>0.95 indicates good fit). An RMSEA <0.08 indicates adequate fit (<0.06 indicates good fit), with values approaching zero indicating better fit.

Multiple group confirmatory factor analyses

To evaluate the generalizability of the model across different population-strata, multiple group CFA (MG-CFA) was performed with gender and age (<70 years/≥70 years). Different MG-CFA models with increasing constraint were fit to the data in sample 2. First, models were fit without restrictions across groups (e.g. men and women) to test fit of the basic model structure. Second, models were fit with the constraint of equal thresholds across groups. Third, models were fit with thresholds and factor loadings constrained across groups. Fourth, models were fit with thresholds, factor loadings and (co)variances constrained across groups. To determine whether model constraints resulted in a significant change of model fit, the DIFFTEST procedure of Mplus was used. When using WLSMV, a regular χ^2-difference test is not possible because the distribution of the difference does not follow a normal χ^2 distribution. The DIFFTEST procedure was developed to enable difference testing with WLS estimated nested models.[26] A significant difference in model fit when constraints are applied ($p<0.05$) indicates that the model parameters differ across subsamples. All MG-CFAs were conducted with Mplus version 5.[25]

Internal Consistency

Internal consistency coefficients (alpha's) were computed for each of the factors, using the computation method for ordinal data based on polychoric correlations (computed with EQS; Multivariate software Inc, Encino, CA, USA) between the items (following Zumbo et al., 2007; Gadermann *et al*, 2012).[27,28] An alpha ≥0.70 was considered to indicate adequate internal consistency.

Results

Demographic and psychiatric characteristics

The demographic and psychiatric characteristics of both study groups are presented in Table 1. In Group 1, all participants had MDD and 107 participants (46.7%) also had an anxiety disorder. In Group 2, 22 participants (11.3%) had a dysthymic or minor depressive disorder and 16 participants (8.2%) had an anxiety disorder. The mean total IDS-SR score in Group 1 was 32.7 (SD=12.4) and in Group 2 was 14.4 (SD=11.8), indicating a considerable difference in overall depression severity.

Table 1. Demographic and psychiatric characteristics of the two study groups.

Sample	Group 1 (n=229)	Group 2 (n=194)
Mean age in years (SD)	70.2 (7.2)	70.4 (7.2)
Age range (years)	60-80	60-93
Women (%)	141 (61.6%)	121 (62.4%)
Mean years of education (SD)	10.5 (3.4)	11.8 (3.7)
Depressive disorders in past month, n (%)		
Dysthymia	69 (30.1%)	5 (2.6%)
Minor depression	1 (0.4%)	17 (8.8%)
Major depression	229 (100%)	0
Anxiety disorders in past month, n (%)		
Panic with agoraphobia	21 (9.2%)	4 (2.1%)
Social phobia	38 (16.6%)	6 (3.1%)
Panic without agoraphobia	9 (3.9%)	0
Agoraphobia	20 (8.7%)	0
Generalized anxiety disorder	24 (10.5%)	6 (3.1%)
IDS-SR total score, mean (SD)	32.7 (12.4)	14.4 (11.8)

IDS-SR = Inventory of Depressive Symptomatology-Self Report

Exploratory factor analyses

Parallel analysis in Group 1 suggested the retention of 3 factors (see Table 2). After rotation, the model consisted of one factor with mostly mood items (9 items, ´Mood´), a factor with mostly motivational items (5 items, ´Motivation´), and a factor with somatic symptom items

Table 2. Factor-loadings in a 3-factor model of the IDS-SR in group 1 with MDD in last month (n=229).

IDS-SR item		Somatic	Mood	Motivation
25	Aches and pains	**0.64**	-0.11	-0.17
26	Sympathetic arousal	**0.59**	0.05	-0.08
3	Early morning awakening	**0.56**	0.03	0.13
22	Interest in sex	**0.41**	-0.02	-0.29
1	Initial insomnia	**0.35**	0.24	0.15
2	Middle insomnia	**0.34**	0.16	0.14
11/12	Appetite disturbance	**0.29**	0.14	-0.07
13/14	Weight disturbance	**0.30**	-0.08	-0.03
5	Feeling sad	0.05	**0.83**	-0.01
6	Feeling irritable	-0.04	**0.74**	0.05
7	Feeling anxious or tense	0.34	**0.60**	0.14
8	Reactivity of mood	0.02	**0.58**	-0.11
10	Quality of mood	0.01	**0.51**	0.00
29	Interpersonal sensitivity	-0.09	**0.51**	-0.10
17	Future pessimism	0.09	**0.48**	-0.20
27	Panic/phobic symptoms	0.30	**0.45**	-0.07
18	Suicidal thoughts	0.13	**0.39**	-0.16
16	Self-criticism and blame	0.02	0.28	**-0.43**
23	Psychomotor retardation	0.01	0.20	**-0.45**
4	Sleeping too much	-0.29	-0.03	**-0.46**
19	Interest in people/activities	-0.11	0.24	**-0.65**
20	Energy/fatiguability	0.25	-0.16	**-0.72**
30	Leaden paralysis/physical energy	0.44	-0.03	-0.43
21	Pleasure or enjoyment (not sex)	0.12	0.41	-0.36
15	Concentration/decision making	0.00	0.30	-0.37
28	Constipation/diarrhoea	0.26	-0.12	-0.30
24	Psychomotor agitation	0.22	0.17	-0.23
9	Diurnal variation of mood	-0.03	0.11	-0.12
EFA Eigen Value		8.003	1,979	1,598 (1,470)*
Random Eigen Value		1,784	1,638	1,548 (1,473)*

Factor Analysis based on polychoric correlations. IDS-SR = Inventory of Depressive Symptomatology-Self Report; the primary loading for each item is printed **bold**. MDD = Major Depressive Disorder.
*) Eigen Values for the next highest factor.

(8 items, ´Somatic´). Six items (items 9, 15, 21, 24, 28 and 30) loaded on more than one item and were therefore not included in the subsequent factor model. The Somatic and Mood factors were positively correlated (r=0.48). Both of these factors were negatively correlated with the Motivation factor (r=-0.31 and r=-0.53), indicating that the third factor represents 'presence of motivation' instead of 'lack of motivation'. These factor-correlations indicated sufficient differentiation between the factors.

Confirmatory factor analyses

The CFA results are shown in Table 3. CFA in the complete sample 2 (n=194) showed that the EFA-identified factor structure fit the data well (CFA=0.98, TLI=0.99, RMSEA=0.052).

Table 3. Confirmatory factor analyses of a 3-factor structure for the IDS-SR in a sample of older persons (n=194).

Analysis	Equality Constraints*:	CFI	TLI	RMSEA	Tested model differences	Δχ2(Δdf)**	p-value
Complete Sample	-	0.98	0.99	0.052	-	-	-
Males only	-	0.96	0.96	0.097	-	-	-
Females only	-	0.98	0.99	0.056	-	-	-
Multiple Group CFA: Gender	Unconstrained	0.96	0.96	0.070	-	-	-
	1.Thresholds	0.95	0.96	0.072	1 vs. unconstrained	33.25 (20)	0.03
	2.Thresholds + FL	0.96	0.97	0.064	2 vs. 1	11.50 (13)	0.57
	3. FL + thresholds + (co)variances	0.97	0.97	0.062	3 vs. 2	2.93 (3)	0.40
<70 years	-	0.98	0.99	0.062	-	-	-
≥70 years	-	0.97	0.97	0.079	-	-	-
Multiple Group CFA: Age	Unconstrained	0.96	0.97	0.070	-		
	1. Thresholds	0.96	0.97	0.062	1 vs. unconstrained	19.83 (23)	0.65
	2. Thresholds + FL	0.97	0.98	0.065	2 vs. 1	11.72 (12)	0.47
	3. FL + thresholds + (co)variances	0.97	0.97	0.061	3 vs. 2	79.18 (2)	0.06

CFI = Comparative Fit Index; TLI=Tucker Lewis Index; RMSEA=Root Mean Square Error of Approximation;

*) Constraints in CFA with polychoric correlations and model estimation with weighted least squares (WLSMV) for categorical non-normal data: Multiple Group CFA with equality constraints on item thresholds (instead of intercepts), factor loadings (FL) and (co)variances.

**) Difference testing based on the DIFFTEST procedure for nested models with WLSMV (Mplus 5).

Multiple group CFA

MG-CFA with gender-groups showed that model fit significantly changed when the item thresholds were constrained to be equal in men and women (p=0.03) (see Table 3). Subsequent constraints of the factor loadings and (co)variances across men and women did not further change model fit. These results indicated that only the thresholds of the items differed substantially across men and women. Inspections of the thresholds in the unconstrained model indeed revealed that some items had higher threshold of endorsement in men (e.g. feeling sad [item 5], interpersonal sensitivity [item 29]) and some items had higher thresholds in women (e.g. reactivity of mood [item 8]). However, for many item thresholds, gender differences were minimal (e.g. appetite change [item 12/13]). These results indicated that response tendencies of individual items can differ to a certain extent across gender. For the MC-CFA with age groups, Group 2 was split at the 50th age percentile into a '<70 years' group and a '≥70 years' group. Constraining the thresholds, factor loadings and (co)variances to be equal across these groups did not affect model-fit, indicating that these model-parameters could be generalized across the two different age-strata.

Internal consistency

All three factors had adequate internal consistencies, although the Mood and Motivation factors performed better than the Somatic factor. The internal consistencies were largely similar across gender and age-groups, except for the Somatic factor, which had and alpha of 0.60 in the >70 group.

Table 4. Internal consistency coefficients for the IDS-SR factors.

	IDS-SR factor		
Sample	Mood	Motivation	Somatic
Complete	0.93	0.83	0.70
Men	0.93	0.81	0.70
Women	0.93	0.84	0.72
Age ≤70	0.94	0.84	0.78
Age >70	0.92	0.83	0.60

Coefficients are alphas for ordinal data, based on polychoric correlations between the items in each factor. IDS-SR=Inventory of Depressive Symptomatology-Self Report.

Discussion

The present study aimed to define a factor model and specific subscales representing symptom dimensions of the IDS-SR in older persons. EFA resulted in a 3-factor solution of the IDS-SR, representing a distinct mood, motivation and somatic factor. The 3-factor solution, as found in a sample of older persons with MDD, was replicated with additional CFA in a sample of healthy and less severely depressed older persons. MG-CFA showed that the identified model was structurally similar across gender and age-groups, but response tendencies of some individual items can differ to a certain extent across gender. This should be taken into account when using symptom dimensions as subscales. Subsequent calculation of the ordinal alpha coefficients indicated that the factors could potentially serve as subscales of the IDS-SR in older persons with major depression, and in older persons who are less severely depressed, anxious, or healthy.

Regarding other depression measures, factor analytical studies in older persons showed both overlap and differences in the factor solutions compared to each other, and to our study.[16,17,29-34] In general, the present finding of a distinct mood symptom domain (including feelings of sadness) is in line with other studies,[33] whereas other symptoms, such as suicidal thoughts or anxiety, vary across the different mood symptom domains.[16,17,31]

In most cases, a separate symptom domain of somatic symptoms, or categorized as vegetative symptoms, was recognized in older persons. For example, our results are in line with factor analytical studies of the Hamilton Anxiety Rating Scale (HAM-A) in older persons with dysthymia[33] and of the HAM-D in physically ill older persons with major depression[31], both revealing a distinct somatic symptom domain. Similarly, factor analysis of the MADRS in an older population with major depression showed a 3-factor structure with a distinct symptom domain of vegetative symptoms,[17] whereas an 'anxiety-vegetative' symptom domain was found in an older population with major depression and mild cognitive impairment[16]. Again, a somatic symptom domain was found for the Center for Epidemiological Studies Depression Scale (CES-D) in an older general population, besides symptom domains concerning depressed affect, positive affect and interpersonal problems.[34] Our results also show, in line with previous research that somatic symptoms seem to manifest themselves independently from other symptom domains in older patients. However, the relatively low observed internal consistency of the somatic subscale compared to the other subscales may be a consequence of a less homogeneous content due to overlap of the somatic symptoms of depression and medical comorbidity. Also, internal consistency of the somatic subscale was markedly decreased in the age group ≥70 years, indicating that the properties of the somatic factor as a subscale changes with age.

Regarding our motivation symptom domain, the items 'energy/fatiguability' and 'interest

in people/activities' resemble apathy symptoms, which is in line with the withdrawal-apathy-vigor factor of the 30-item Geriatric Depression Scale (GDS).[35] At the same time, the factor dysphoric mood showed little overlap with our finding, but other symptom domains of the GDS, such as hopelessness, cognitive impairment and anxiety, were not found in our study.[29] Furthermore, factor analyses of the SCL-90-R Depression and Additional Symptom Scale in a community-based sample of older women revealed a depletion symptom domain corresponding to our motivation symptom domain, but feelings of guilt and self-blame were related to a depressive symptom domain.[32] A separate motivation symptom domain was not found for the MADRS as only the item 'lassitude' of this scale reflects apathy.[16,17,33]

As hypothesized in the Introduction, the factors identified in our population of older persons differed from those found earlier in younger persons.[22] In younger persons a 'mood/cognition' and 'anxiety/arousal' factor were found, whereas in our study among older persons a 'mood' factor and separate factors concerning motivation and somatic symptoms were found. The 'mood/cognition' factor found in younger persons differed mainly from our 'mood' subscale by including motivation items and cognitive items such as interest in people/activities, energy/fatiguability, concentration/decision making and self-criticism and blame. Anxiety items were exclusively related to the mood factor in older persons in contrast to younger persons. The item 'psychomotor retardation' was included in the 'motivation' factor in older persons, whereas in younger persons it was included in the 'anxiety/arousal' factor. Importantly, these results of identical studies in a younger and older population may indicate that late-life depression is made up of different symptom domains compared to early-life depression, and may thus have partly different underlying aging-related aetiologies. For example, it has been found that psychomotor retardation and motivational symptoms were related to vascular and neurodegenerative risk-indicators, whereas suicidal thoughts, sleep and appetite disturbances were related to inflammatory risk-indicators.[36] Other factor analytical studies of the IDS-SR in a younger population resulted in factor solutions that show partial overlap with our mood and somatic symptom domains, but again did not comprise a distinct motivation factor.[18,19] Similarly, a meta-analyses of the factor structures of the CES-D, HAM-D, Beck Depression inventory (BDI) and Zung Self-Rating Depression Scale (SRDS) in a younger population revealed a mood and somatic factor for all four instruments; but, again, a separate motivation factor was not found and the somatic factor of the CES-D was not in line with ours.[14] Therefore, the presently observed distinction between mood and motivation related symptoms could be typical for older persons.

Although the ongoing debate as to whether age affects the phenomenology of depression remains inconclusive,[5] our results seem to support the view that age does have an impact. Moreover, in a recent meta-analysis, a partly different phenomenology was found in late-life compared to early-life depression, with older adults showing less guilt and more somatic symptoms.[6] In addition, not only age at the current depressive episode but also

age at onset of a first episode may affect the phenomenology of late-life depression.[37] In contrast to our finding of an age-specific dimensional structure of depression, no age-specific subtypes were found using a categorical approach with latent class analysis in a population of middle-aged and older depressed persons.[38]

An important issue in diagnosing late-life depression is the overlap of somatic symptoms of depression and symptoms of age-related medical illness. The GDS was developed to measure depression in older adults, in part by leaving out somatic symptoms to prevent overestimation of depression severity due to comorbid somatic illnesses.[39] Furthermore, it was shown that the MADRS was more appropriate in a medically ill older population compared to the HAM-D.[31] However, in order to effectively compare the phenomenology of depression between older and younger persons, it is more informative to use a measure that is broadly used in all age groups. Clearly, such an instrument should cover all main aspects of depression including depressive somatic symptoms, which is the case for the IDS-SR. Finally, the question arises whether a distinct somatic dimension partly represents age-related medical illnesses. It is reported that the role of somatic symptoms in old-age depression may be unbiased by age-related medical illnesses.[40,41] However, to answer this question, future research should compare healthy depressed older people and depressed older people with somatic comorbidity.

This study has several strengths. First, due to the substantial sample size, we were able to conduct EFA and CFA in independent samples and had enough data to conduct MG-CFA to check generalizability of the identified model across subgroups. Second, our results are generalizable to an extensive older population, as our sample reflects all different stages of depression, different healthcare settings, and a broad range of old age.

Some limitations also need mentioning. First, the results of this study cannot be generalized to depressed older persons with dementia or severe cognitive impairment since these persons were excluded. Second, the extent of the differences between excluded participants due to missing IDS-SR data and the included participants indicates that there may have been some selection bias. Third, the MG-CFA showed that item thresholds differ across men and women, although for most items only minimally. This indicates that gender-specific norms have to be developed.

In summary, this study identifies three homogeneous factors of the IDS-SR in older persons reflecting a mood, motivation and somatic symptom dimension. These symptom dimensions may potentially serve as subscales of the IDS-SR. The use of these symptom dimensions in clinical practice and future research may improve diagnostic specificity as well as the search for determinants of early onset *v.* late onset late-life depression. Finally, the results of our study provide insight into the phenomenology of depression in older persons compared to younger persons, as a qualitatively different factor structure of late-life depression was found.

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Supplementary Material

Results of the four subsequent Exploratory Factor Analyses

Table S1. Factor-loadings in a 1-factor model of the IDS-SR in group1 (n=229).

IDS-SR items	Depression
05 Feeling sad	**0.73**
21 Pleasure or enjoyment (not sex)	**0.66**
07 Feeling anxious or tense	**0.62**
17 Future pessimism	**0.59**
27 Panic/phobic symptoms	**0.58**
30 Leaden paralysis/physical energy	**0.57**
08 Reactivity of mood	**0.55**
19 Interest in people/activities	**0.55**
06 Feeling irritable	**0.54**
20 Energy/fatiguability	**0.53**
16 Self-criticism and blame	**0.52**
15 Concentration/decision making	**0.50**
18 Suicidal thoughts	**0.50**
23 Psychomotor retardation	**0.47**
26 Sympathetic arousal	**0.47**
22 Interest in sex	**0.45**
25 Aches and pains	**0.44**
29 Interpersonal sensitivity	**0.44**
24 Psychomotor agitation	**0.42**
10 Quality of mood	**0.37**
01 Initial insomnia	**0.32**
03 Early morning awakening	**0.30**
11/12 Appetite disturbance	**0.30**
28 Constipation/diarrhoea	0.27
02 Middle insomnia	0.24
13/14 Weight disturbance	0.14
09 Diurnal variation of mood	0.12
04 Sleeping too much	0.10

IDS-SR = Inventory of Depressive Symptomatology Self Report; the primary loading for each item is printed in bold font.

Table S2. Factor-loadings in a 2-factor model of the IDS-SR in group1 (n=229).

IDS-SR items	Mood	Somatic
19 Interest in people/activities	**0.81**	-0.26
16 Self-criticism and blame	**0.62**	-0.09
20 Energy/fatiguability	**0.59**	-0.04
23 Psychomotor retardation	**0.59**	-0.12
21 Pleasure or enjoyment (not sex)	**0.58**	0.12
05 Feeling sad	**0.56**	0.24
15 Concentration/decision making	**0.54**	-0.03
04 Sleeping too much	**0.52**	-0.49
06 Feeling irritable	**0.45**	0.14
29 Interpersonal sensitivity	**0.45**	0.01
08 Reactivity of mood	**0.44**	0.16
17 Future pessimism	**0.43**	0.22
30 Leaden paralysis/physical energy	**0.40**	0.22
27 Panic/phobic symptoms	**0.36**	0.29
18 Suicidal thoughts	**0.35**	0.20
10 Quality of mood	**0.31**	0.10
24 Psychomotor agitation	**0.31**	0.15
03 Early morning awakening	-0.20	**0.61**
01 Initial insomnia	-0.07	**0.48**
07 Feeling anxious or tense	0.26	**0.46**
26 Sympathetic arousal	0.13	**0.43**
02 Middle insomnia	-0.10	**0.41**
25 Aches and pains	0.12	**0.40**
11/12 Appetite disturbance	0.07	0.29
22 Interest in sex	0.23	0.28
13/14 Weight disturbance	0.05	0.23
28 Constipation/diarrhoea	0.18	0.12
09 Diurnal variation of mood	-0.19	0.08

IDS-SR = Inventory of Depressive Symptomatology Self Report; the primary loading for each item is printed in bold font.

Table S3. Factor-loadings in a 3-factor model of the IDS-SR in group1 (n=229).

IDS-SR items	Mood	Motivation	Somatic
05 Feeling sad	**0.82**	0.03	-0.05
06 Feeling irritable	**0.69**	0.01	-0.12
07 Feeling anxious or tense	**0.59**	-0.13	0.23
08 Reactivity of mood	**0.59**	0.06	-0.04
29 Interpersonal sensitivity	**0.49**	0.13	-0.14
17 Future pessimism	**0.44**	0.12	0.11
10 Quality of mood	**0.39**	0.04	-0.03
27 Panic/phobic symptoms	**0.39**	0.08	0.21
21 Pleasure or enjoyment (not sex)	0.37	0.30	0.11
18 Suicidal thoughts	**0.33**	0.11	0.13
20 Energy level/fatiguability	-0.15	**0.62**	0.24
19 Interest in people/activities	0.22	**0.61**	-0.14
04 Sleeping too much	-0.06	**0.51**	-0.32
23 Psychomotor retardation	0.16	**0.43**	-0.02
16 Self-criticism and blame	0.20	**0.43**	-1.00
15 Concentration/decision making	0.25	0.33	-0.01
24 Psychomotor agitation	0.12	0.20	0.20
09 Diurnal variation of mood	0.04	0.14	-0.04
03 Early morning awakening	0.03	-0.23	**0.58**
25 Aches and pains	-0.09	0.11	**0.56**
26 Sympathetic arousal	0.06	0.04	**0.50**
30 Leaden paralysis/physical energy	-0.03	0.35	0.41
22 Interest in sex	-0.02	0.19	**0.41**
01 Initial insomnia	0.28	-0.24	0.32
13/14 Weight disturbance	-0.10	-0.01	**0.31**
02 Middle insomnia	0.17	-0.20	**0.30**
28 Constipation/diarrhoea	-0.12	0.20	0.27
11/12 Appetite disturbance	0.11	-0.02	0.27

IDS-SR = Inventory of Depressive Symptomatology Self Report; the primary loading for each item is printed in bold font.

Table S4. Factor-loadings in a 4-factor model of the IDS-SR in group1 (n=229).

IDS-SR items	Motivation/ Cognition	Mood	Somatic	Sleep
19 Interest in people/activities	**0.73**	0.08	-0.12	-0.12
20 Energy/fatiguability	**0.67**	-0.21	0.26	-0.09
15 Concentration/decision making	**0.52**	0.11	-0.10	0.08
23 Psychomotor retardation	**0.52**	0.07	-0.02	-0.07
21 Pleasure or enjoyment (not sex)	**0.46**	0.23	0.03	0.09
16 Self-criticism and blame	**0.43**	0.19	0.07	-0.16
04 Sleeping too much	**0.35**	0.04	-0.07	-0.45
17 Future pessimism	0.31	0.30	-0.01	0.17
05 Feeling sad	0.15	**0.74**	-0.09	0.05
10 Quality of mood	-0.23	**0.70**	0.15	-0.34
06 Feeling irritable	0.06	**0.65**	-0.10	-0.03
07 Feeling anxious or tense	-0.03	**0.54**	0.14	0.16
08 Reactivity of Mood	0.19	**0.48**	-0.10	0.08
29 Interpersonal sensitivity	0.21	**0.40**	-0.13	-0.02
27 Panic/phobic symptoms	0.17	**0.33**	0.15	0.09
18 Suicidal thoughts	0.16	**0.31**	0.09	0.03
25 Aches and pains	-0.02	0.00	**0.65**	-0.04
26 Sympathetic arousal	-0.01	0.12	**0.50**	0.04
30 Leaden paralysis/physical energy	0.27	0.05	**0.48**	-0.12
03 Early morning awakening	-0.17	0.04	**0.41**	0.27
22 Interest in sex	0.29	-0.10	**0.32**	0.14
01 Initial insomnia	-0.04	0.15	0.08	**0.39**
02 Middle insomnia	0.01	0.03	0.07	**0.38**
11/12 Appetite disturbance	0.16	-0.03	0.10	**0.27**
09 Diurnal variation of mood	-0.05	0.21	0.13	**-0.29**
04 Sleeping too much	0.35	0.04	-0.07	**-0.45**
13/14 Weight disturbance	-0.02	-0.08	0.27	0.07

IDS-SR = Inventory of Depressive Symptomatology Self Report; the primary loading for each item is printed in bold font.

Chapter 4

Depression in later life: a more somatic presentation?

J.M. Hegeman
M.W.M. de Waal
H.C. Comijs
R.M. Kok
R.C. van der Mast

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Abstract

Background

Depression later in life may have a more somatic presentation compared with depression earlier in life due to chronic somatic disease and increasing age. This study examines the influence of the presence of chronic somatic diseases and increasing age on symptom dimensions of late-life depression.

Methods

Baseline data of 429 depressed and non-depressed older persons (aged 60-93 years) in the Netherlands Study of Depression in Old Age were used, including symptom dimension scores as assessed with the mood, somatic and motivation subscales of the Inventory of Depressive Symptomatology-Self Report (IDS-SR). Linear regression was performed to investigate the effect of chronic somatic diseases and age on the IDS-SR subscale scores.

Results

In depressed older persons a higher somatic disease burden was associated with higher scores on the mood subscale (B=2.02, p=0.001), whereas higher age was associated with lower scores on the mood (B=-2.30, p<0.001) and motivation (B=-1.01, p=0.006) subscales. In depressed compared with non-depressed persons, a higher somatic disease burden showed no different association with higher scores on the somatic subscale (F(1,12)=9.2, p=0.003, partial η^2=0.022).

Limitations

Because the IDS-SR subscales are specific for old age, it was not feasible to include persons aged <60 years to investigate differences between earlier and later life.

Conclusions

It seems that neither higher somatic disease burden nor higher age contribute to more severe somatic symptoms in late-life depression. In older old persons aged ≥70 years, late-life depression may not be adequately recognized because they may show less mood and motivational symptoms compared with younger old persons.

Introduction

Depression later in life may have a more somatic presentation compared with depression earlier in life,[1] thereby complicating the recognition of depression.[2] For instance, a recent meta-analysis found that depressed older persons showed more hypochondriasis and somatic symptoms of depression, whereas feelings of guilt and loss of sexual interest were more related to early-life depression.[3]

There are several explanations for a possibly more somatic presentation of depression in late-life. For example, the symptoms of (more frequent) somatic diseases in older age may be mistaken for somatic symptoms of depression. Also, several studies found an association between late-life depression and somatic comorbidity, whereas others found a weakening association between depression and somatic diseases with increasing age, despite an increase in the prevalence of somatic diseases.[4-7] Alternatively, with increasing age depression might be characterized by more somatic symptoms due to various underlying age-related biological pathways in late-life depression compared with depression earlier in life.[8-13]

Using the Inventory of Depressive Symptomatology Self Report (IDS-SR) among older people, we earlier identified a mood, motivation and somatic subscale reflecting three homogeneous symptom dimensions.[14] These IDS-SR symptom dimensions appeared to be specific for old age, as only two symptom dimensions including 'mood/cognition' and 'anxiety/arousal' were found at a younger age.[15]

The present study aims to investigate the effects of both somatic comorbidity and increasing age on the presentation of late-life depression according to the mood, motivation and somatic subscales of the IDS-SR.[14,16] To unravel the possible misattribution of symptoms of chronic somatic diseases and aging to depression, we examined the effects of chronic diseases and aging on IDS-SR symptom severity in depressed and non-depressed older people. We hypothesized that, with a higher number of chronic somatic diseases and higher age, there would be a more prominent somatic presentation of late-life depression as reflected in higher scores on the IDS-SR somatic subscale. However, we expected that a higher number of chronic somatic diseases and higher age would not affect the presentation of late-life depression with respect to mood and motivation symptoms according to the corresponding IDS-SR symptom subscales.

Methods

Study sample

Data were used from the baseline assessment of the Netherlands Study of Depression in Old Persons (NESDO), conducted among people aged ≥60 years. NESDO is a multi-site naturalistic cohort study examining the determinants, long-time course and consequences of depressive disorders at old age. The design of the NESDO is described in detail elsewhere.[17] In short, between 2007 and 2010 participants were enrolled from mental healthcare and primary healthcare settings to create a sample reflecting all different stages of depression. Excluded were persons with a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, and insufficient command of the Dutch language. Also excluded were persons with a Mini-Mental State Examination score (MMSE) <18 or a primary diagnosis of dementia.

The baseline NESDO sample consists of 378 depressed (diagnosis within the last 6 months according to DSM-IV criteria) and 132 non-depressed persons aged 60-93 years (total sample n=510). The present study included 303 persons diagnosed with a depressive disorder according to the DSM-IV criteria within the last month before baseline assessment, and 132 non-depressed persons, all with complete data on the IDS-SR. Persons with missing total scores on all three subscales were excluded. For this reason, 3 persons from the 303 depressed group and 3 persons from the 132 non-depressed group were excluded, leaving 300 depressed and 129 non-depressed persons (total=429) for the present analysis. The persons with missing scores on all three subscales did not differ from the included persons with respect to gender (p=0.313) and number of years of education (p=0.057). Both depressed and non-depressed persons were included to examine differences in the presentation of depressive symptoms due to somatic diseases and higher age in their own right, and in relation to depression.

The study protocol was approved by the ethical review boards of all the participating centers and informed consent was signed by all participants.

Measures

Socio-demographics

Demographic information was collected with standard questions concerning age, gender and years of education. Age was used as a categorical variable with a cut-off age of 70 years, being close to both the median and mean age of the whole sample. Thus, the 'younger old' are defined as people aged <70 years and the 'older old' as people aged ≥70 years.

Depressive symptoms and neuropsychiatric characteristics

The presence of a depressive disorder (major depression, dysthymia and minor depression) according to the DSM-IV criteria within the last month before the baseline assessment was measured with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; lifetime version).[18] The Dutch translation of the IDS-SR[16] was used to compute total scores of the three old-age specific IDS-SR subscales.[14] The IDS-SR items of the mood, somatic and

Figure 1. Items of the IDS-SR subscales.

Mood subscale	
Item 5	Feeling sad
Item 6	Feeling irritable
Item 7	Feeling anxious or tense
Item 8	Reactivity of mood
Item 10	Quality of mood
Item 17	Future pessimism
Item 18	Suicidal thoughts
Item 27	Panic/phobic symptoms
Item 29	Interpersonal sensitivity
Somatic subscale	
Item 1	Initial insomnia
Item 2	Middle insomnia
Item 3	Early morning awakening
Item 11/12	Appetite disturbance
Item 13/14	Weight disturbance
Item 22	Interest in sex
Item 25	Aches and pains
Item 26	Sympathetic arousal
Motivation subscale	
Item 4	Sleeping too much
Item 16	Self criticism and blame
Item 19	Interest in people/activities
Item 20	Energy/fatiguability
Item 23	Psychomotor retardation

Mood subscale: 9 items, maximum score=27; Somatic subscale: 8 items, maximum score=24; Motivation subscale: 5 items, maximum score=15.
Abbreviations: IDS-SR, Inventory of Depressive Symptomatology-Self Report.

motivation subscales were scored on a four-point scale (range 0-3 points) (Figure1). These age-specific subscales of the IDS-SR can be used in older persons with no or different stages of depression and have shown adequate properties across different age and gender groups in late-life.[14]

Global cognitive functioning was assessed with the MMSE.[19]

Clinical characteristics

A self-report questionnaire was used to assess the presence of chronic somatic diseases as follows: participants were asked whether they had chronic non-specific lung disease, cardiovascular diseases, diabetes mellitus, stroke, intestinal disorders, arthritis or arthrosis, cancer, thyroid gland diseases, or any other disease. Obtaining information on the presence of chronic somatic diseases using a self-report questionnaire has shown to be adequate compared with obtaining information from the general practitioner.[20] The total number of chronic somatic diseases was obtained by counting the number of self-reported chronic somatic diseases (count 0-8), excluding hypertension, and dichotomized into 0 or 1, and 2 or more chronic somatic diseases. The cut-off of 2 chronic somatic diseases is close to the mean number of chronic somatic diseases (1.9) in the whole sample, and distinguishes between no/lower somatic disease burden and a higher somatic disease burden.

The current smoking status was derived from the Fagerstrom test for Nicotine Dependence. Alcohol use was defined as the amount of glasses consumed per day and assessed with the Alcohol Use Disorders Identification Test; the results were categorized into 0, 1-2, and >2 glasses a day.[21]

Statistical analyses

Data were analysed using SPSS version 20.0. First, differences in demographic, and neuropsychiatric and clinical characteristics, between depressed and non-depressed older persons were evaluated using a t-test for continuous variables, chi-square tests for categorical variables, and non-parametric tests for not normally distributed variables. All analyses were carried out two-sided with a significance level of $p<0.05$.

We performed three-way independent analyses of covariance (ANCOVA) to obtain adjusted mean scores for each IDS-SR subscale in eight distinctive groups defined by the presence of depression, the number of chronic somatic diseases, and age, as follows: depressed persons aged <70 years with 0 or 1 chronic somatic diseases, depressed persons aged <70 years with ≥2 chronic somatic diseases, depressed persons aged ≥70 years with 0 or 1 chronic somatic diseases and with ≥2 chronic somatic diseases, non-depressed persons aged <70 years with 0 or 1 chronic somatic diseases, non-depressed persons aged <70 years with ≥2 chronic somatic diseases, non-depressed persons aged ≥70 years with 0

or 1 chronic somatic diseases and with ≥2 chronic somatic diseases. The dependent variable was the score on the IDS-SR subscale and the three independent variables were depression, chronic somatic diseases, and age. Potential confounding variables including gender, years of education, alcohol use, smoking status, and MMSE were added as covariates. We did not adjust for overall depression severity because age-related or chronic somatic disease-related differences in the scores of the IDS-SR subscales are also part of the total severity score. Controlling for the severity of depression therefore involves circularity, which could result in overadjustment. A full factorial design was used in which the significance ($p<0.10$) of the two-way interaction terms of depression and chronic somatic diseases, depression and age, and chronic somatic diseases and age, and a three-way interaction term involving depression, chronic somatic diseases and age, were examined in the whole sample. Eta squared ($\eta^2 >0.01$ ~ small effect size, $\eta^2 >0.06$ ~ medium effect size, and $\eta^2 >0.14$ ~ large effect size) and F ratios were used as a measure of effect size.

In case of significant interaction, the sample was stratified and multiple linear regression analyses were performed for each IDS-SR subscale in order to examine the influence of chronic somatic diseases and age, respectively, on the presentation of depressive symptoms. Potentially confounding variables including gender, years of education, alcohol use, smoking status, and MMSE were added to the regression model.

Results

Table 1 presents the demographic, neuropsychiatric and clinical characteristics of the depressed and non-depressed persons. Depressed persons had fewer years of education, a lower median MMSE score, a higher number of chronic somatic diseases, were more often smokers and used less alcohol, compared with non-depressed persons. Some of the depressed persons had more than one depressive disorder within the last month before baseline assessment. Figure 2 presents the adjusted mean scores of the three IDS-SR subscales for subgroups defined by depression, the number of chronic somatic diseases and age (see also Table S1 Supplementary material).

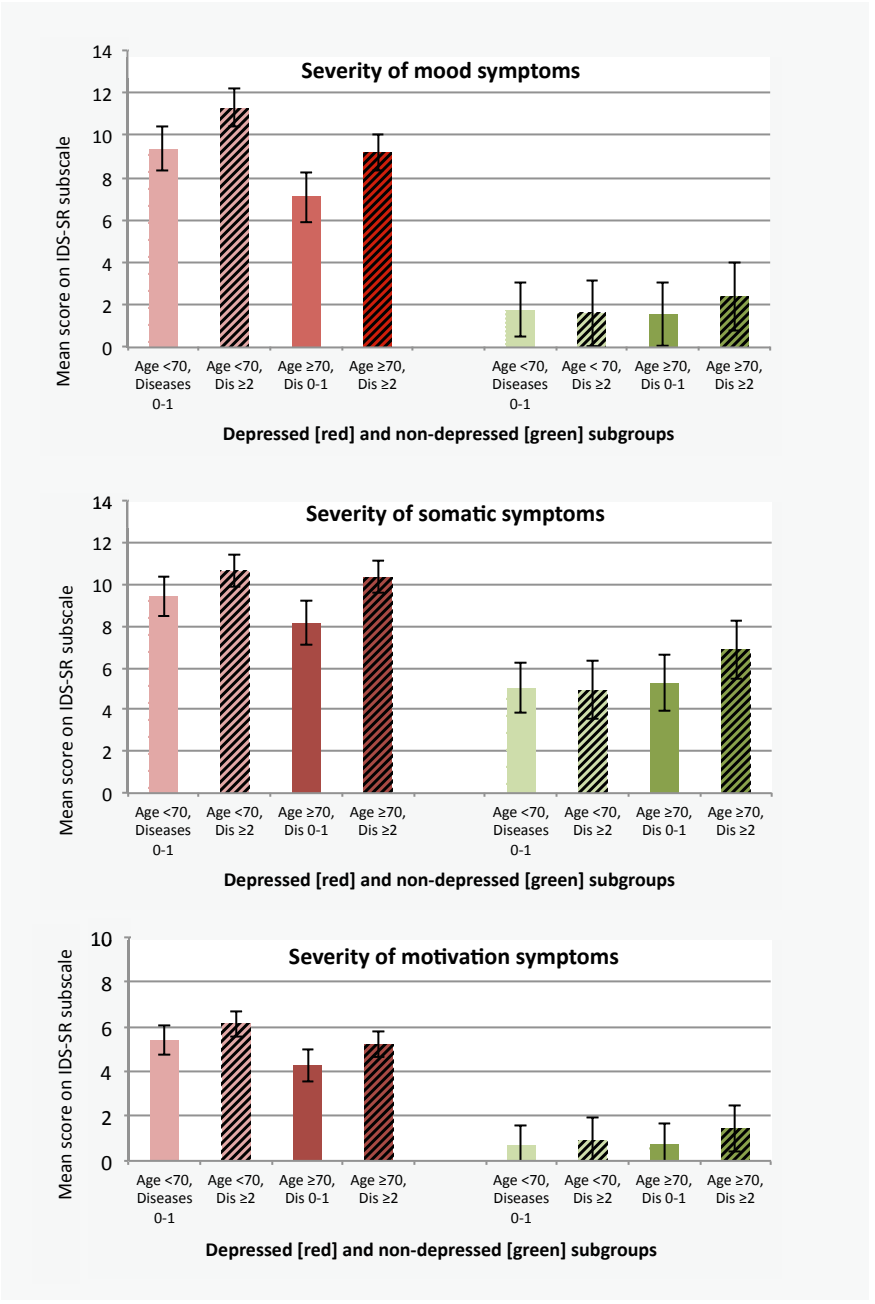
A significant interaction was found between depression and the number of chronic somatic diseases for the mood subscale ($F(1,12)=3.47$, $p=0.063$, partial $\eta^2=0.008$); this indicates that, in depressed compared with non-depressed persons, a higher somatic disease burden had a different association with scores on the IDS-SR mood subscale. However, no significant interaction was found between depression and the number of chronic somatic diseases for the somatic ($F(1,12)=1.49$, $p=0.223$, partial $\eta^2=0.004$) and motivation ($F(1,12)=0.43$, $p=0.512$, partial $\eta^2=0.001$) subscales. This indicates a similar association in depressed and non-

Table 1. Comparison of demographic, neuropsychiatric and clinical characteristics between depressed and non-depressed persons.

Sample (n=429)	Depressed (n=300)	Non-depressed (n=129)	p-value
Demographic characteristics			
Mean age in years (SD)	70.5 (7.3)	70.0 (7.3)	
Age range in years	60-90	60-93	
Age 70, n (%)	146 (48.7)	56 (43.4)	
Women, n (%)	193 (64.3)	79 (61.2)	
Mean years of education (SD)	10.4 (3.5)	12.5 (3.5)	
Neuropsychiatric characteristics			
Depressive disorders in past month, n (%)			
Minor depression	20 (6.7)	-	
Dysthymia	94 (31.3)	-	
Major depression	272 (90.7)	-	
IDS-SR, mean total score (SD)	32.2 (12.4)	7.8 (6.4)	<0.001
Mood subscale, mean total score	9.8 (5.0)	1.2 (2.0)	<0.001
Somatic subscale, mean total score	10.1 (4.2)	4.9 (3.1)	<0.001
Motivation subscale, mean total score	5.4 (3.1)	0.7 (1.2)	<0.001
MMSE, median score (IQR)	28.0 (2)	29.0 (2)	<0.001
Clinical characteristics			
Mean number of chronic somatic diseases (SD)	2.1 (1.5)	1.5 (1.1)	<0.001
Number of chronic somatic diseases present, n (%)			<0.001
0-1	116 (38.7)	74 (57.4)	
≥2	184 (61.3)	55 (42.6)	
Chronic somatic disease present, n (%)			
Diabetes mellitus	36 (12.0)	18 (14.0)	0.576
Chronic Non Specific Lung Disease	48 (16.0)	9 (7.0)	0.012
Thyroid disease	32 (10.7)	7 (5.4)	0.083
Cardiovascular diseases	66 (22.0)	27 (20.9)	0.805
Stroke	35 (11.7)	3 (2.3)	0.002
Arthritis or arthrosis	146 (48.7)	59 (45.7)	0.577
Oncological diseases	57 (19.0)	24 (18.6)	0.924
Intestinal disorders	71 (23.7)	11 (8.5)	<0.001
Current smoker, n (%)	82 (27.5)	10 (7.8)	<0.001
Alcohol use, glasses/day, n (%)			<0.001
0	122 (40.9)	17 (13.3)	
1-2	152 (51.0)	84 (65.6)	
>2	24 (8.1)	27 (21.1)	

Abbreviations: SD, standard deviation; IQR, interquartile range; MMSE, Mini-Mental State Examination; IDS-SR, Inventory of Depressive Symptomatology-Self Report; Means (standard deviations) and overall p-values with independent t-tests for normally distributed continuous variables; medians (interquartile range) and overall p-values with nonparametric Mann-Whitney tests for skewed distributed continuous variables; number of persons (percentages) and overall p-values with x2 tests for categorical variables.

Figure 2. Adjusted mean scores of the three IDS-SR subscales for subgroups defined by depression, age and the number of chronic somatic diseases. Whiskers represent 95% confidence intervals of sample mean.



depressed persons between chronic somatic diseases and symptom severity of the somatic subscale ($F(1,12)=9.20$, $p=0.003$, partial $\eta^2=0.022$), with a small effect size. The same applies to the association between somatic disease burden and symptom severity of the motivation subscale ($F(1,12)=4.94$, $p=0.027$, partial $\eta^2=0.012$). Furthermore, a significant interaction was found for depression and age for the mood ($F(1,12)=7.57$, $p=0.006$, partial $\eta^2=0.018$), somatic ($F(1,12)=5.42$, $p=0.020$, partial $\eta^2=0.013$), and motivation ($F(1,12)=5.16$, $p=0.024$, partial $\eta^2=0.013$) subscales demonstrating that, in depressed compared with non-depressed persons, age had a different association with symptom severity of all three subscales. The ANCOVAs for all three IDS-SR subscales, including all interaction terms, are shown in the supplementary material (Tables S1 and S2).

Table 2. Multivariate regression of age and chronic diseases on scores of IDS-SR subscales in depressed and non-depressed persons.

	Depressed				Non-depressed			
Predictors	*B*	SE	*β*	*p*-value	*B*	SE	*β*	*p*-value
Severity of symptoms of mood subscale								
Diseases	2.02	0.58	0.197	0.001	0.64	0.37	0.162	0.082
Age	-2.30	0.56	-0.231	<0.001	0.48	0.36	0.120	0.189
Severity of symptoms of somatic subscale								
Diseases	1.61	0.49	0.185	0.001	1.01	0.54	0.164	0.065
Age	-0.70	0.48	-0.082	0.145	1.28	0.53	0.208	0.018
Severity of symptoms of motivation subscale								
Diseases	0.85	0.38	0.101	0.025	0.44	0.22	0.180	0.047
Age	-1.01	0.37	-0.163	0.006	0.17	0.21	0.069	0.435

Adjusted for gender, years of education, MMSE, current smoker and alcohol use. Abbreviations: IDS-SR, Inventory of Depressive Symptomatology-Self Report.

Because significant interactions were found, the subsequent analyses were stratified according to depression status (Table 2). In Table 2, the *B* coefficient for chronic somatic diseases reflects the difference in mean subscale scores of persons with higher somatic disease burden compared with persons with lower somatic disease burden. Similarly, the *B* coefficient for age equals the difference in mean subscale scores found in 'older old' persons compared with 'younger old' persons. Table 2 shows that, with respect to the mood

subscale, depressed persons with higher somatic disease burden presented more severe mood symptoms compared with depressed persons with lower somatic disease burden, whereas older old depressed persons showed less severe mood symptoms compared with younger old depressed persons. In non-depressed persons, the presence of chronic somatic diseases and age were not associated with the severity of mood symptoms. With respect to the somatic subscale, the presence of chronic somatic diseases was associated with symptom severity of the somatic subscale in depressed but not in non-depressed persons. Age was not associated with symptom severity of the somatic subscale in depressed persons. However, in non-depressed persons, higher age was associated with higher somatic symptom severity. According to the motivation subscale, higher somatic disease burden was associated with more severe motivational symptoms in both depressed and in non-depressed persons. At the same time, older old depressed persons showed less severe symptoms on the motivation subscale compared with younger old depressed persons, whereas age was not associated with the severity of motivational symptoms in non-depressed persons.

Discussion

This study examined the influence of somatic comorbidity and age on the presentation of late-life depression. Remarkably, our results demonstrate a reverse effect of the presence of chronic somatic diseases compared with the effect of higher age on the presentation of late-life depression on all three subscales. That is, for all three subscales late-life depression was characterized by higher symptom severity when a higher burden of somatic diseases was present, and by less symptom severity with higher age. However, the association between age and symptom severity of the somatic subscale did not reach significance. Thus, late-life depression was not only characterized by more somatic symptoms but also by more severe mood and motivational symptoms in the presence of higher somatic disease burden, whereas the expected more prominent somatic presentation of late-life depression in the older old compared with younger old depressed persons was not found.

In the non-depressed group, no such association in the opposite direction of chronic somatic diseases compared with age was consistently found for the three subscales. Non-depressed persons showed no clinically relevant symptom severity on the mood and motivation subscale, whereas chronic somatic diseases and age were positively associated with symptom severity of the somatic subscale. This finding that non-depressed persons showed more somatic symptoms with more somatic disease burden or higher age might be interpreted as somatic symptoms that appear with the occurrence of chronic somatic

diseases and aging. However, as no significant difference was found between depressed and non-depressed persons in symptom severity of the somatic subscale related to the presence of chronic somatic diseases, the more prominent somatic presentation of late-life depression found in the presence of higher somatic disease burden might be the consequence of misattribution of symptoms of chronic somatic diseases to depression. This latter finding concurs with our previous study showing a relatively low internal consistency of the somatic subscale compared with the other subscales and that internal consistency of the somatic subscale was decreased in the age group >70 years; this indicates a less homogeneous content of the somatic subscale due to overlap of somatic symptoms of depression and chronic diseases.[14] Furthermore, the slightly higher symptom severity of the motivation subscale, found in the presence of higher somatic disease burden in depressed and non-depressed persons, might represent sickness behavior, even though the effect on symptom severity on the mood scale for non-depressed persons did not reach significance.

Our results are partly in line with others investigating the relation between somatic diseases, age and the phenomenology of depression as measured with a single item level of the Inventory of Depressive Symptomatology Clinician Rating (IDS-C_{30}) in depressed persons aged 18-72 years.[22,23] Although the age range of the studies of Hussain *et al*. and Yates *et al.* only partly reflected our age range and did not include the older old, some results were consistent with our study, i.e. in the presence of somatic comorbidity more symptoms of the somatic subscale (e.g. sympathetic arousal, and aches and pains) were found and, with increasing age, less symptoms of the mood subscale (e.g. irritability and negative cognitions) were found.[22,23]

In our study, the lower score found on the motivation subscale in the older old compared with the younger old depressed persons is in contrast to the generally found increase of apathy in older depressed persons.[24] However, besides the motivational symptoms resembling apathy, the motivational subscale also includes the item 'sleeping too much' as well as a depressive cognitive item. Therefore, it can be questioned whether scores on the motivational subscale adequately represent apathy severity. Furthermore, in an earlier meta-analysis on age-related differences in the phenomenology of depression, it was found that older depressed persons compared with younger depressed persons showed less feelings of guilt,[3] which is in line with our current finding. Alternatively, perhaps the increase of apathy generally found in older depressed persons is particularly associated with cognitive dysfunctioning rather than with higher age.

As suggested previously, late-life depression often remains unnoticed;[2] this is an important issue that may be further clarified by our results. The present finding that the older old compared with younger old depressed persons show less symptoms on the IDS-SR mood and motivational subscale implies that, particularly in older old persons aged ≥70 years, late-

life depression may not be recognized properly. A possible explanation for this is a cohort effect of the current older generation not being accustomed to expressing psychological symptoms.[25] Furthermore, inconsistent results are reported on the topic of specific age-related pathophysiological pathways in late-life depression, such as the inflammatory and vascular depression hypothesis.[26-28] Age-specific pathophysiological pathways might explain differences in the phenomenology of depression at old age. However, until now, this issue has rarely been examined except for executive and cognitive dysfunction in relation to (cerebral) vascular diseases and vascular risk factors. For example, in an older old depressed population, thoughts of death, sleep and appetite-related symptoms of depression were found to be related to inflammatory factors, whereas motivation symptoms were related to vascular and degenerative risk factors.[29] Moreover, our result of fewer mood symptoms in older old depressed persons is unlikely to be the consequence of a wrongly diagnosed depression instead of apathy as a syndrome of its own, as no increase was found in symptoms on the motivation subscale, including items resembling apathy.

Diagnosing late-life depression may also be complicated by incorrect attribution of somatic symptoms of somatic diseases to depression. Suggested solutions are an inclusive or exclusive approach that includes or excludes all somatic symptoms of depression when diagnosing late-life depression.[30-32] These latter solutions are limited to somatic symptoms only, whereas the present study shows that somatic diseases are also related to more severe mood and motivational symptoms. In contrast to the somatic and motivational subscale, a significant difference was found in the association between severity of mood symptoms and a higher somatic disease burden in depressed compared with non-depressed persons. Accordingly, the higher symptom severity of the mood subscale found in depressed persons with higher somatic diseases burden, might reflect a strengthening of the symptoms of the depression itself and not only of mood symptoms that co-exist with somatic diseases. Therefore, an exclusive approach specifically related to all somatic symptoms seems an appropriate solution to examine the severity of late-life depression. Indeed, it may be difficult to establish whether a symptom is a result of a physical illness, sickness behavior, the aging process, or depression. Therefore, an etiological or substitutive approach, excluding or replacing only somatic symptoms specifically caused by a somatic disease, respectively, does not seem practical.[33-38] Thus, our results imply that severity of depression may be overestimated in the presence of somatic comorbidity, but only with respect to the somatic and motivational symptom domain.

This study has some limitations. The IDS-SR subscales used are specific for old age and differ from the previous IDS-SR subscales used in younger age.[15] Therefore, we could not include persons aged <60 years in this study to compare them with older adults regarding the associations of somatic diseases and IDS-SR symptom dimensions. Similarly, we could

not investigate the effect of younger age compared with older age on the presentation of depressive symptoms according to the symptom dimensions of the IDS-SR. A major strength of this study is the large study sample consisting of depressed and non-depressed persons. Therefore, differences in the effects of chronic somatic diseases and age on depressive symptomatology between depressed and non-depressed could be examined to distinguish between symptoms wrongly attributed to depression and symptoms of the depression itself. Moreover, in this study a depressive disorder was diagnosed using the CIDI and not by applying a cut-off score on a symptom severity scale. Therefore, incorrectly diagnosed depression due to misattribution of somatic symptoms of chronic somatic diseases to depression, was less likely to occur. Furthermore, the study sample reflects different stages of depression and healthcare settings, thereby increasing the generalizability of the results.

In conclusion, it appears that neither higher somatic disease burden nor higher age contribute to more severe somatic symptoms of late-life depression. Our results imply that severity of late-life depression may be overestimated in the presence of somatic comorbidity, but only with respect to the somatic and motivational symptom domain due to misattribution of symptoms of somatic diseases and sickness behavior. In fact, higher somatic disease burden does contribute to higher severity of mood symptoms of late-life depression. Finally, particularly in the older old aged ≥70 years, late-life depression may not be recognized properly as this group tend to show less mood and motivational symptoms.

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Supplementary Material

Table S1. Mean scores (SE) of IDS-SR subscales (Figure 1).

Depressed				Non-depressed			
<70		≥70		<70		≥70	
0-1 Diseases	≥2 Diseases	0-1 Diseases	≥2 Diseases	0-1 Diseases	≥2 Diseases	0-1 Diseases	≥2 Diseases
Mean score (SE) mood subscale of the IDS-SR							
9.36 (0.52)	11.28 (0.45)	7.08 (0.60)	9.19 (0.44)	1.76 (0.65)	1.63 (0.80)	1.57 (0.76)	2.40 (0.82)
Mean score (SE) somatic subscale of the IDS-SR							
9.40 (0.47)	10.64 (0.40)	8.13 (0.54)	10.34 (0.39)	5.03 (0.60)	4.91 (0.71)	5.26 (0.68)	6.87 (0.73)
Mean score (SE) motivation subscale of the IDS-SR							
5.40 (0.33)	6.13 (0.29)	4.26 (0.38)	5.20 (0.28)	0.70 (0.43)	0.93 (0.51)	0.75 (0.49)	1.44 0.54)

Adjusted for gender, years of education, MMSE, current smoker and alcohol use.

Table S2. Associations between scores of IDS-SR subscales and number of somatic diseases, age and depression.

	F (df)	p-value	partial η^2
Mood subscale			
Depression	228.5 (1,12)	<0.001	0.358
Age	4.4 (1,12)	0.037	0.011
Diseases	6.8 (1,12)	0.010	0.016
Depression*age	7.6 (1,12)	0.006	0.018
Depression*diseases	3.5 (1,12)	0.063	0.008
Age*diseases	0.4 (1,12)	0.522	0.001
Depression*age*diseases	0.2 (1,12)	0.663	<0.001
Somatic subscale			
Depression	87.9 (1,12)	<0.001	0.177
Age	0.2 (1,12)	0.700	<0.001
Diseases	9.2 (1,12)	0.003	0.022
Depression*age	5.4 (1,12)	0.020	0.013
Depression*diseases	1.5 (1,12)	0.223	0.004
Age*diseases	2.8 (1,12)	0.096	0.007
Depression*age*diseases	0.2 (1,12)	0.632	0.001
Motivation subscale			
Depression	185.2 (1,12)	<0.001	0.316
Age	1.6 (1,12)	0.202	0.004
Diseases	4.9 (1,12)	0.027	0.012
Depression*age	5.2 (1,12)	0.024	0.013
Depression*diseases	0.4 (1,12)	0.512	0.001
Age*diseases	0.3 (1,12)	0.569	0.001
Depression*age*diseases	0.04 (1,12)	0.834	<0.001

Adjusted for gender, years of education, MMSE, current smoker and alcohol use.

Chapter 5

Effect of chronic somatic diseases on the course of late-life depression

J.M. Hegeman
E.M. Fenema
H.C. Comijs
R.M. Kok
R.C. van der Mast
M.W.M. de Waal

Under revision

Abstract

Objective

To examine the influence of specific chronic somatic diseases and overall somatic diseases burden on the course of depression in older persons.

Methods

This was a prospective cohort study with a two-year follow-up. Participants were depressed persons (n=285) from the Netherlands Study of Depression in Older Persons (NESDO). The presence of chronic somatic diseases was based on self-report. Diagnosis of depression was assessed with the Composite International Diagnostic Interview and severity of depression was measured with the Inventory of Depressive Symptomatology Self Report (IDS-SR).

Results

Cardiovascular diseases (odds ratio [OR]=1.67, 95% confidence interval [CI] 1.02-2.72, p=0.041), musculoskeletal diseases (OR=1.71, 95% CI 1.04-2.80, p=0.034) and the number of chronic somatic diseases (OR=1.37, 95% CI 1.16-1.63, p<0.001) were associated with having a depressive disorder at 2-year follow-up. Furthermore, chronic non-specific lung diseases, cardiovascular diseases, musculoskeletal diseases, cancer or cumulative somatic disease burden were associated with a chronic course of depression.

Conclusion

Somatic disease burden is associated with a poor course of late-life depression. The course of late-life depression is particularly unfavorable in the presence of chronic non-specific lung diseases, cardiovascular diseases, musculoskeletal diseases and cancer.

Introduction

In late life, the course of depression is often unfavorable and characterized by chronicity or recurrence.[1] An important factor contributing to the persistence of depression at old age may be the presence of somatic comorbidity.[1] It is known that somatic diseases and depression often co-exist.[2,3] Moreover, there is conclusive evidence for the negative somatic consequences of depression (e.g. somatic morbidity and overall mortality risk) particularly in late life.[4-9] Also, almost any chronic somatic disease increases the risk for the development of a depressive disorder.[3,7,10-14] Furthermore, there is emerging evidence for the persistence of a depressive disorder in the presence of somatic disease burden in older persons.[15-19]

However, very few studies have examined the influence of specific somatic diseases on the course of depression in older persons. In the presence of cardiovascular disorders, recurrence of depression may occur more often across the life span,[14] and depressive symptoms tend to persist in older persons with peripheral vascular diseases.[20] Moreover, in older persons with both type 2 diabetes and a co-morbid disease, persistence of depressive symptoms appeared to be increased, but not in patients with diabetes alone.[11] However, all these studies either included only the somatically ill, or the general population in which depression was not formally diagnosed. Therefore, evidence for the effect of specific chronic somatic diseases on the course of late-life depression remains largely inconclusive.

Several mechanisms have been proposed to clarify the relation between depression and a possible adverse course in the presence of somatic comorbidity. Depression and some somatic diseases are thought to share underlying biological pathways (e.g. inflammation, thrombo-embolism and dysregulation of the hypothalamic-pituitary-adrenocortical axis), which may result in poorer depression outcome in the presence of comorbid somatic disease.[21-25] Furthermore, the well-known relation of late-life depression with disability and pain secondary to somatic diseases, may account for a poorer outcome of late-life depression.[13,26-31] Alternatively, depression in older persons is difficult to diagnose in the presence of somatic illness due to overlap of symptoms of depression, somatic disease and sickness behavior, which may result in under-recognition and under-treatment of late-life depression.[32-36]

The present study aimed to investigate the effect of chronic somatic diseases (clustered into six specific categories) on the course of depression in depressed older persons. We hypothesized that specific chronic somatic diseases, and the burden of cumulative chronic somatic diseases, would be associated with an unfavorable course of depression.

Methods

Participants

Data were used from the Netherlands Study of Depression in Old Persons (NESDO),[37] an ongoing cohort study on the determinants, long-time course and consequences of depressive disorders among older people aged ≥60 years. An extensive description of the study design of NESDO is provided elsewhere.[37] In summary, from 2007 to 2010, participants were included from mental healthcare and primary healthcare settings to create a sample reflecting all different stages of depression. Excluded were persons with a Mini-Mental State Examination score (MMSE) <18, a primary diagnosis of dementia, a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, or insufficient command of the Dutch language. Severity of depressive symptoms was monitored with the Inventory of Depressive Symptomatology Self Report (IDS-SR) that was sent to all participants every six months. Two years after the baseline measurements, a second face-to-face assessment was performed between 2009 and 2012. The Medical Ethical Committee approved the study and written informed consent was obtained from all participants.

The baseline NESDO sample consists of 378 older persons with a depressive disorder, according to DSM-IV criteria, within the last 6 months before baseline assessment and 132 non-depressed older persons. Due to attrition, of the 378 depressed older persons at baseline only 285 participated in the 2-year follow-up; this latter group was included in the present study. Comijs *et al.* (2015) provided attrition rates for the 2-year results from the NESDO. In short, attrition rates were higher in persons who were depressed at baseline and had more severe psychopathology, lower cognitive functioning, or were recruited from an outpatient or inpatient mental healthcare setting compared to primary care.[19]

Measures

Socio-demographics

Age, gender and years of education were assessed with standard questions.

Depression

The presence of a depressive disorder (major depression, dysthymia and minor depression) according to the DSM-IV criteria within 6 months before the baseline assessment and at the 2-year follow-up assessment was measured with the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The IDS-SR was used to assess depression severity at baseline, at 2-year follow-up, and at every 6 months in between. The IDS-SR score ranges from 0-84 and classifies depression severity into: no depression (score <14), mild depression

(score 14-25), moderate depression (score 26-38), severe depression (score 39-48), and very severe depression (score >48). Comijs *et al.* (2015) distinguished five different courses of depression: 1) 'remission' of depression defined as an IDS score <14 for at least the last two observations; 2) 'recurrent' depression defined as an IDS score <14 for at least one of the observations; 3) 'chronic mild to moderate' depression defined as all IDS scores of 14-38; 4) 'chronic moderate to severe' depression defined as all IDS scores of 26-84; and 5) chronic depression with 'variable severity' defined as all IDS scores of 14-84.[19]

Chronic somatic diseases and somatic disease burden

A self-report questionnaire was used to assess the presence of frequently occurring chronic somatic diseases in older persons.[38] Participants were asked whether they had a chronic non-specific lung disease (asthma, chronic bronchitis and pulmonary emphysema), peripheral vascular disease, cardiac disease, diabetes mellitus, stroke, osteoarthritis, rheumatoid arthritis, fibromyalgia, ulcer, Crohn's disease, colitis ulcerosa, irritable bowel syndrome, hepatitis, liver cirrhosis, cancer, thyroid gland disease, or any other chronic somatic disease. Self-report on the presence of chronic somatic diseases in older persons was found sufficient when compared to information obtained from the general practitioner, except for peripheral vascular disease.[38] Therefore, the accuracy of self-reported peripheral vascular disease was improved by combining it with the ankle-brachial pressure index (ABI). The ABI is defined as the blood pressure in the lower legs divided by the blood pressure in the arms, and a value <0.9 indicates the presence of peripheral atherosclerosis.[39] In the analyses, self-reported pain in the calves during walking was included as peripheral vascular disease when ABI was ≤0.9. Chronic somatic diseases were clustered into six disease categories, broadly in accordance with the International Classification of Diseases, version 10 (ICD-10): 1) chronic non-specific lung diseases including asthma, chronic bronchitis and pulmonary emphysema; 2) cardiovascular diseases including cardiac diseases, peripheral vascular disease, stroke as well as diabetes mellitus; 3) musculoskeletal diseases including osteoarthritis, rheumatoid arthritis and fibromyalgia; 4) gastrointestinal diseases including ulcer, Crohn's diseases, colitis ulcerosa, irritable bowel syndrome, hepatitis and liver cirrhosis; 5) thyroid diseases; and 6) cancer. The total number of self-reported chronic somatic diseases was used as a measure of overall somatic disease burden.

Statistical analyses

Analysis of attrition rates in the NESDO sample was made for the presence of somatic diseases using Chi-square tests. Descriptive statistics were used to describe the socio-demographic, clinical and neuropsychiatric characteristics of depressed older persons at

baseline. Logistic regression analyses were applied to investigate the associations between baseline comorbid chronic somatic disease categories and outcome of depression at 2-year follow-up, with adjustment for age, gender and years of education. For each of the chronic somatic diseases with a sample size of ≥30 persons, similar analyses were performed. Then, logistic regression was performed to investigate the association between baseline overall somatic disease burden and outcome of depression at 2-year follow-up, with adjustment for age, gender and years of education. To examine the associations between baseline comorbid chronic somatic disease categories and the number of chronic somatic diseases with the five designated courses of depression, multinomial logistic regression analyses were applied adjusted for age, gender and years of education. We did not adjust for depression severity at baseline because the defined depression course types were based on the severity scores during the 2 years of follow-up. The course of depression designated 'remission' was used as the reference group. No further multinomial logistic regression analyses were performed for the various chronic somatic diseases within the somatic disease categories due to expected insufficient power. A non-linear association between the number of chronic somatic diseases and outcome of depression at 2-year follow-up was examined by adding a quadratic term or square root into the regression models. The SPSS version 20.0 was used to perform the statistical analyses.

Results

Table 1 presents the baseline socio-demographic and clinical characteristics of the study sample. The attrition rate in the NESDO sample was significantly higher in depressed persons with comorbid chronic non-specific lung diseases compared to depressed persons without these diseases (p=0.027), whereas attrition rates showed no significant difference for depressed persons with and without any of the other disease categories or with the number of chronic somatic diseases. The reasons for attrition in depressed persons with comorbid chronic non-specific lung diseases (n=21) were death (n=5), no interest (n=5), and unable to participate due to mental (n=8) or physical reasons (n=3).

Table 2 presents the odds ratios (ORs) of having a depressive disorder at 2-year follow-up in depressed older persons with comorbid chronic somatic diseases at baseline. The presence of cardiovascular and musculoskeletal diseases, and the number of somatic diseases, were significantly associated with having a depressive disorder at 2-year follow-up.

Figure 1 shows the relative amount of the five courses of depression for each of the chronic somatic disease categories. Table 3 shows the results from the multinomial logistic

Table 1. Socio-demographics and clinical characteristics of depressed older persons.

Characteristics	Baseline sample (n=285)
Sociodemographic	
Age in years, mean (sd)	70.6 (7.5)
Female gender, n (%)	187 (65.6)
Education in years, mean (sd)	10.6 (3.4)
Clinical characteristics	
Major depression, past 6 months, n (%)	199 (69.8)
Dysthymia past 6 months, n (%)	4 (1.4)
Minor depression past month, n (%)	11 (3.9)
Major depression and dysthymia past 6 months, n (%)	71 (24.9)
IDS-SR total score, mean (sd)	29.7 (12.8)
MMSE, median (IQR)	28.0 (1.0)
Number of chronic diseases,	
mean (sd)	2.1 (1.5)
range	0-8
0, n	34
1, n	78
2-3, n	120
≥ 4, n	52

Abbreviations: sd, standard deviation; IQR, interquartile range; IDS-SR, Inventory of Depressive Symptomatology Self Report.

regression for chronic somatic diseases at baseline and the course of depression at 2-year follow-up with remission (n=50) as reference outcome. In total, 29 persons could not be included in the multinomial logistic regression analyses due to missing data on the type of course of depression. Compared to the included persons, they had significantly less years of education (p=0.043), but did not differ in age, gender, number of chronic diseases or specific somatic diseases. Depressed older persons with chronic non-specific lung diseases had an odds ratio of 3.39 (95% CI 1.01-11.38, p=0.048) for having a moderate to severe chronic depression. Similarly, cardiovascular and musculoskeletal diseases were significantly associated with a moderate to severe chronic course of depression in the 2-year follow-up. Furthermore, cardiovascular diseases, cancer and overall somatic disease burden were significantly associated with a chronic course with variable severity. For each additional

chronic somatic disease, the chance of having a moderate to severe chronic depression increases with 92% (OR=1.92, 95% CI 1.41-2.61, p<0.001). No significant associations were found for the quadratic term or square root of the number of chronic somatic diseases suggesting that there was no non-linear association between the number of chronic somatic diseases and depression status at 2-year follow-up.

Table 2. Associations between chronic somatic diseases and a depressive disorder at 2-years follow-up (n=285).

Chronic somatic disease at baseline		Odds of having a depressive disorder at 2-year follow-up[a] (n=138)		
	n (%)	Odds ratio (95% CI)	Wald test	p
Chronic non-specific lung disease	37 (13.0)	1.46 (0.73-2.95)	1.140	0.286
Asthma	15 (5.3)	-	-	-
Chronic bronchitis	20 (7.0)	-	-	-
Pulmonary emphysema	7 (2.5)	-	-	-
Cardiovascular disease	104 (36.3)	1.67 (1.02-2.72)	4.196	0.041
Cardiac disease	61 (21.5)	1.57 (0.89-2.78)	2.372	0.124
Stroke	30 (10.5)	1.94 (0.89-4.25)	2.743	0.098
Peripheral vascular disease	10 (3.5)	-	-	-
Diabetes	35 (12.3)	1.70 (0.82-3.50)	2.043	0.153
Musculoskeletal disease	149 (52.5)	1.71 (1.04-2.80)	4.497	0.034
Osteoarthritis	142 (50.0)	1.55 (0.94-2.53)	2.999	0.083
Reumatoid arthritis	13 (4.6)	-	-	-
Fybromyalgia	12 (4.2)	-	-	-
Gastrointestinal disease	69 (24.3)	1.63 (0.94-2.84)	3.013	0.083
Ulcer	40 (14.0)	1.55 (0.78-3.07)	1.378	0.207
Intestinal diseases	34 (12.0)	2.12 (1.00-4.52)	3.778	0.052
Liver disease or liver cirrhosis	6 (2.1)	-	-	-
Thyroid	32 (11.3)	1.45 (0.68-3.09)	0.914	0.339
Cancer	62 (24.3)	1.25 (0.71-2.21)	0.740	0.435
Number of chronic somatic diseases (continuum)	-	1.37 (1.16-1.63)	13.375	<0.001

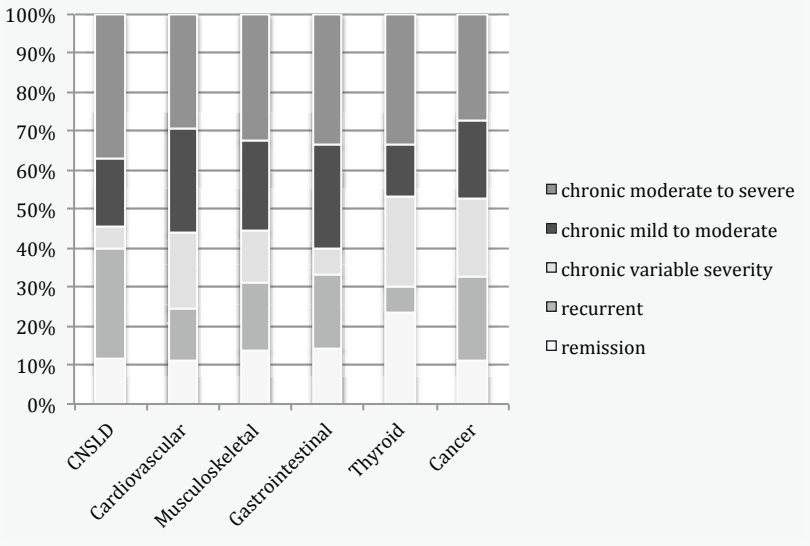
Notes: Adjusted for age, gender and years of education. Degrees of freedom (df) = 1 for all tests.
a. Using logistic regression, separate models for each chronic somatic disease.

Table 3. Multinomial logistic regression for chronic somatic diseases at baseline and the course of depression at 2-years follow-up with remission (n=50) as reference outcome.

Baseline	Recurrent (n=48)			Chronic variable severity (n=31)			Chronic mild to moderate (n=66)			Chronic moderate to severe (n=60)		
Chronic somatic disease categories (n)	OR (95% CI)	Wald test	p	OR (95% CI)	Wald test	p	OR (95%)	Wald test	p	OR (95% CI)	Wald test	p
CNSLD (n=35)	3.19 (0.91-11.17)	3.278	0.070	0.82 (0.14-4.81)	0.048	0.826	1.18 (0.31-4.48)	0.061	0.805	3.39 (1.01-11.38)	3.893	0.048
Cardiovascular (n=89)	1.22 (0.47-3.20)	0.164	0.685	4.62 (1.70-12.51)	9.041	0.003	2.15 (0.91-5.10)	3.028	0.082	2.94 (1.23-7.05)	5.849	0.016
Musculoskeletal (n=137)	1.61 (0.69-3.77)	1.218	0.270	2.11 (0.81-5.49)	2.347	0.126	1.71 (0.77-3.77)	1.733	0.188	3.77 (1.62-8.74)	9.525	0.002
Gastrointestinal (n=63)	1.26 (0.46-3.40)	0.508	0.653	0.59 (0.16-2.15)	0.660	0.423	1.38 (0.55-3.48)	0.386	0.497	2.28 (0.91-5.73)	0.469	0.078
Thyroid (n=30)	0.22 (0.04-1.15)	3.214	0.073	1.55 (0.46-5.24)	0.492	0.483	0.36 (0.10-1.37)	2.244	0.134	0.90 (0.30-2.70)	0.033	0.904
Cancer (n=55)	2.74 (0.92-8.16)	3.292	0.070	4.50 (1.44-14.08)	6.663	0.010	1.51 (0.51-4.44)	0.559	0.455	2.70 (0.94-7.73)	3.426	0.064
Number of chronic somatic diseases (continuum)	1.17 (0.84-1.63)	0.903	0.342	1.79 (1.27-2.52)	11.086	0.001	1.22 (0.90-1.66)	1.687	0.194	1.92 (1.41-2.61)	17.126	<.001

Notes: CNSLD: chronic non-specific lung diseases. OR: Odds Ratio. CI: Confidence Interval. Adjusted for gender, age and years of education. Degrees of freedom = 1 for all tests. Separate models for each chronic somatic disease category.

Figure 1. The course of depression at 2-years follow-up for chronic somatic diseases at baseline.



CNSLD, chronic non-specific lung diseases

Discussion

The present study shows that the presence of somatic comorbidity is associated with an unfavorable course of late-life depression. More specifically, depressed older persons with cardiovascular diseases, musculoskeletal diseases or cumulative somatic disease burden are more likely to have a depressive disorder 2 years later. Furthermore, depressed older persons with chronic non-specific lung diseases, cardiovascular diseases, musculoskeletal diseases, cancer or cumulative somatic disease burden are more likely to have a chronic course of depression. Thyroid and gastrointestinal diseases had no significant impact on the course of late-life depression.

In line with our findings, the Longitudinal Aging Study Amsterdam (LASA) also found that in older persons aged 55-85 years the overall somatic disease burden was associated with the persistence of depression;[15] however, in LASA depression was not formally diagnosed. Our results are also partly in line with the Netherlands Study of Depression and

Anxiety (NESDA).[40] In that study, investigation of a younger adult population (aged 18-65 years) showed that musculoskeletal diseases and diabetes had a negative impact on the course of depression at 2-year follow up; however, there was no impact of overall somatic disease burden on the course of depression.[40] In contrast to our findings, a recent review found no higher risk for recurrence of depression in the presence of somatic comorbidity.[41] However, the results of that review should be interpreted with caution as only a few studies were included since most of them examined recurrence of depression in a somatically ill population only. Moreover, because none of the studies included an older population their results cannot accurately be compared with ours. Another study found that the course of depression did not differ for depressed persons with and without insulin-dependent diabetes, whereas persistence of depression was more often found in depressed persons with a history of myocardial infarction.[42] In the latter study, although most of the participants with comorbid somatic disease were aged ≥40 years, the extent to which the cohort was an older population was not reported.

In summary, our results are not directly comparable with other studies investigating the course of depression in the presence of specific chronic somatic diseases due to different methodological and sample characteristics.

A major strength of the present study is that the study sample consisted of both somatically ill and healthy depressed older persons enrolled from a primary healthcare population, and from an outpatient and an inpatient mental healthcare population. To our knowledge, no other study has examined the course of depression in older persons with and without specific chronic somatic diseases in which depression was formally diagnosed and severity of depression was measured regularly.

This study has also some limitations. Our earlier study found that severity of late-life depression may be overestimated in the presence of somatic comorbidity due to misattribution of symptoms of chronic somatic diseases to depression.[32] This applies to the five different courses of depression, as defined by severity scores on the IDS-SR. For the IDS-SR we earlier identified a mood, motivation and somatic symptom dimension at old age, and found that symptoms of the somatic and motivation dimension partly overlapped with symptoms of chronic somatic diseases and sickness behavior.[14,43] Therefore, some overestimation of severity of the chronic course types will occur. Also, in our present study, attrition was significantly higher in depressed persons with comorbid chronic non-specific lung diseases mainly due to death and mental problems. It is likely that depressed persons with chronic non-specific lung diseases that were lost to follow-up had a poorer course of depression. This probably results in underestimation of the negative effect of chronic non-specific lung diseases on the course of depression during follow-up and the presence of depression at 2-year follow-up. Our finding that chronic non-specific lung diseases and

cancer have a negative impact on the course, but not on the presence of depression at 2-year follow-up, may be explained by an effect on depressive symptom severity only. This is in line with our previous finding that worsening of mood symptoms of depression occurs in the presence of a higher somatic disease burden.[14] However, for cancer and cardiovascular disease, it cannot be excluded that the association with a chronic course with variable severity may in part reflect symptoms of sickness behavior, cancer or cardiovascular disease.[29] Also, the low prevalence rates of chronic non-specific lung diseases and thyroid disease may have led to insufficient power to provide more conclusive answers, especially with respect to the course of depression at 2 years follow-up. We carefully considered withdrawing the chronic non-specific lung diseases and thyroid diseases from the multinomial logistic regression as it turned out that prevalence rates were low. However, a significant association was found between chronic non-specific lung diseases and a moderate to severe chronic course type of depression at 2 years follow-up. For this reason, we considered this a meaningful and valid result. At the same time, we acknowledge that the non-significant association between thyroid diseases and course types at 2 years follow-up is most probably inconclusive.

Finally, the presence of chronic somatic diseases was based on self-report only and was not assessed by a physician. However, with the exception of osteoarthritis, self-report on chronic somatic diseases in depressed older persons was shown to be consistent with information obtained from medical records.[38] For osteoarthritis, older persons may have pain and stiffness in the joints due to osteoarthritis but may not always consult a general practitioner, indicating that self-report on osteoarthritis is sufficient. Furthermore, it is reported that including information on the use of medication,[40] or receiving treatment for a certain somatic disease, did not further improve the accuracy of self-reported chronic somatic diseases.[38]

In conclusion, our results indicate that chronic non-specific lung diseases, cardiovascular diseases, musculoskeletal diseases and cancer have a negative impact on the course of late-life depression, and that a cumulative negative impact occurs with increasing overall somatic disease burden. The awareness of a negative impact of somatic comorbidity on the course of depression stresses the importance to improve treatment in older persons who are frequently confronted with both depression and chronic somatic diseases. Although cognitive behavioral therapy[44] and antidepressants[45,46] are effective in treating depression in the presence of somatic comorbidity, it is important to treat somatic comorbidity at the same time. It is shown that an integrated care-management model in primary health care for depressed persons with comorbid diabetes or coronary heart disease resulted in a greater improvement in the quality of life and outcome of depression and chronic somatic diseases, compared to usual care.[47,48] Finally, improving the treatment of depression in the presence of somatic comorbidity is important not only for reasons such as mental wellbeing, quality

of life, disability and mortality, but also to help limit the increasing healthcare costs in an aging population. [49-52]

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Chapter 6

Loneliness and cardiovascular disease and the role of late-life depression

J.M. Hegeman*
N. Schutter*
H.C. Comijs
T.J. Holwerda
J. Dekker
M.L. Stek
R.C. van der Mast

Submitted

* These authors contributed equally as shared first authors

Abstract

Objective

Loneliness and depression have a strong reciprocal influence and both predict adverse health outcomes. In contrast to depression, little is known about the relation between loneliness and cardiovascular disease. This study examines the association between loneliness and cardiovascular disease in depressed and non-depressed older males and females.

Methods

Cross-sectional data of 477 depressed and non-depressed persons in the Netherlands Study of Depressed Older Persons (NESDO) were used. Logistic regression analysis was performed to examine the relation between loneliness and cardiovascular disease. Depression was added to the fully adjusted regression model to examine whether depression is an explanatory factor in the relation between loneliness and cardiovascular disease. Interaction terms were introduced in the regression model to investigate whether depressed and non-depressed males and females differed in their association between loneliness and cardiovascular disease.

Results

Loneliness and cardiovascular disease were not associated in the total group depressed and non-depressed persons after adjustment for confounders. No significant interaction term was found for loneliness and depression in their relation to cardiovascular disease. The interaction term between gender and loneliness (dichotomous: p=0.005; continuous: p=0.003) yielded a significant association with cardiovascular disease. Subsequent stratification revealed an association between loneliness and cardiovascular disease in females (continuous: odds ratio [OR]=1.13, 95% confidence interval [CI] 1.06-1.21, p<0.001; dichotomous: OR=2.64, 95% CI 1.50-4.65, p=0.001), but not in males. The association remained significant after adjustment for confounders, but it lost significance after adding depression in the model.

Conclusion

Loneliness and cardiovascular disease were associated only in females, but the presence of depression explained this association.

Introduction

Loneliness is a psychological experience that results from a lack of belonging.[1] It is considered to be an expression of negative feelings due to missing relationships.[1] Not only is loneliness one of the main indicators of social and mental wellbeing,[1,2] it is also related to increased morbidity and mortality in later life.[3-5] In both middle-aged and older persons, loneliness has been associated with higher blood pressure.[6-9] Also, some lonely persons are more likely to be obese and to suffer from a metabolic syndrome.[10,11] However, the mechanisms of negative health outcomes in relation to loneliness are largely unknown. It is possible that lifestyle factors (e.g. smoking, overweight, and low physical activity) and biological mechanisms (e.g. stress-induced endocrine and immune responses) play a role.[11,12] As these lifestyle factors are risk factors for cardiovascular disease it is conceivable that, in the presence of loneliness, a risk profile for cardiovascular disease is more often present and, therefore, cardiovascular diseases may partly explain the adverse health outcome of loneliness. However, although the association between loneliness and cardiovascular diseases has rarely been examined,[13] an association has been reported between loneliness and incident coronary heart disease in females, but not in males.[14]

Lonely older people often suffer from depressive symptoms, and loneliness and depression have a strong reciprocal influence in middle-aged and older persons.[15-17] Moreover, a two-fold mortality risk was found in depressed older persons when loneliness was present.[18] In contrast to loneliness, it is known that depression and cardiovascular diseases are closely related.[19-23] For instance, major depressive disorder is an independent risk factor for mortality following myocardial infarction.[20] In middle-aged and older females, recurrent major depressive disorder was found to be a predictor for cardiovascular disease.[24] Depression is also related to incident stroke[25] and to peripheral artery disease[26]. Consequently, the strong increase in mortality found in the co-occurrence of loneliness and depression might be explained by cardiovascular disease.[18]

This study investigates whether loneliness is associated with cardiovascular disease, in both depressed and non-depressed older males and females. More specifically, we explore whether depression explains the association between loneliness and cardiovascular disease, and whether such an association differs between depressed and non-depressed older males and females.

Methods

Participants

For this study, data were used from the baseline assessment of the Netherlands Study of Depressed Older Persons (NESDO). The NESDO started in 2007 and is an ongoing prospective cohort study on the determinants, long-term course and consequences of depressive disorders among older people aged ≥60 years recruited from different regions (e.g. urban and rural areas) in the Netherlands.[27] In the baseline NESDO sample 378 depressed and 132 non-depressed older persons were included from mental healthcare and primary healthcare settings to create a sample reflecting all different stages of depression. Excluded were persons with a primary diagnosis of dementia according to the clinician, a psychotic or bipolar disorder, a Mini Mental State Examination score (MMSE) ≤18 (out of 30 points), or insufficient command of the Dutch language. Non-depressed controls were recruited from primary healthcare settings; inclusion criteria for the controls were: no lifetime depression, no dementia or other serious psychiatric condition, and good command of the Dutch language. The study protocol of NESDO was centrally approved by the Ethical Review Board of the VUMC and also by the local ethical review boards of each participating center.[27] During a four-hour baseline assessment (including written questionnaires, interviews, a medical examination, a cognitive computer task and the collection of blood and saliva samples), a wide range of information was gathered about health outcomes and demographic, psychosocial, clinical, biological and genetic determinants.

Measurements

Loneliness

Loneliness was measured with the original 11-item De Jong Gierveld loneliness scale. The De Jong Gierveld loneliness scale is a valid instrument to measure overall loneliness.[28,29] Items in the De Jong Gierveld loneliness scale are scored on a 5-point scale. In this study, items were rescored into a dichotomous value: responses indicating loneliness are assigned a score of 1 and responses indicating no loneliness are assigned a score of 0. The maximum total score of the De Jong Gierveld loneliness scale is 11, with a cut-off score of 3 to distinguish between lonely and not lonely individuals.[28]

Cardiovascular disease

The presence of cardiovascular disease was assessed using a self-report questionnaire. That is, participants were asked whether they have, or have ever had angina, a heart infarct, cardiac arrhythmia, heart failure, any other heart condition (e.g. valvular heart disease), a stroke, or pain in the calves during walking. The use of a self-report questionnaire to assess

the presence of chronic somatic diseases was found accurate compared to information gathered from a general practitioner, with the exception of self-reported peripheral vascular disease.[30] Therefore, self-reported pain in the calves was combined with the ankle-brachial index (ABI) to more accurately assess the presence of peripheral vascular disease (PVD).[31,32] The ABI has shown to be effective in measuring PVD and is defined as the ratio of the ankle and brachial blood pressure that predicts PVD if the score is ≤0.9.[32] In addition, including information about the use of medication did not further improve the accuracy of self-reported information on the presence of somatic illnesses.[33]

Depression

The Composite International Diagnostic Interview (CIDI; WHO version 2.1) was used to assess the presence of a depressive disorder (major depression, dysthymia and minor depression) according to the DSM-IV-Classification within six months before the baseline assessment.

Covariates

Demographic characteristics such as age, gender, years of education and partner status were collected using standard questions. Social network was measured with the Close Person Inventory that counts the number of meaningful relationships (e.g. friends and relatives) and was dichotomized using a cut-off of 6 persons.[34] Current smoking status was assessed by simple questions. The Alcohol Use Disorders Identification Test (AUDIT) was used to assess alcohol use, defined as the amount of glasses a day.[35] Physical activity was measured with the International Physical Activity Questionaire (IPAQ) that calculates the total metabolic equivalent of task (MET) minutes a week.[36] MET minutes represent the energy cost for daily activities compared to the energy cost for a person at rest.

Statistical analyses

T-test and chi-square tests were used to detect differences between the lonely and non-lonely participants with respect to depression status, cardiovascular disease and all covariates. For non-normally distributed variables, Mann-Whitney tests were used. Multiple imputation techniques were applied due to missing values for the covariates social network size (1.6% missing) and physical activity (17.6% missing). To detect relevant confounders, logistic regression analyses were performed in which all potential confounders were entered one by one in the models to examine whether a ≥10% change occurred in the odds ratio (OR) of the association between loneliness and cardiovascular disease.

Logistic regression analysis was used to examine the association between loneliness as dichotomous determinant and the presence of cardiovascular disease as outcome variable. The model was adjusted for relevant confounders. In the fully adjusted model,

depression was introduced, to investigate whether depression was an explanatory factor in the association between loneliness and cardiovascular disease. Depression was considered an explanatory factor if a ≥10% change occurred in the OR of the association between loneliness and cardiovascular disease. Next, the interaction term between loneliness and depression was introduced in the fully adjusted model to examine whether the association between loneliness and cardiovascular disease was different for depressed compared to non-depressed participants. In case this interaction was significant ($p<0.05$), analyses were repeated for the two subgroups (depressed and non-depressed) separately. We also introduced an interaction term for loneliness and gender, to explore whether there is a gender-specific association between loneliness and cardiovascular disease. In case a significant interaction term was found, regression analyses were repeated in males and females separately. Further, all regression analyses were repeated with overall loneliness severity as a continuous determinant.

Results

Loneliness scores were available for 477 participants (6.5% missing). Persons with missing data were not different from included persons with respect to mean age (70.9 *v.* 70.6 years, p=0.82), female gender (63.6% *v.* 65.0%, p=0.88), partner status (married or has a partner: 48.5% *v*. 58.9%, p=0.24), physical activity (total MET minutes/week: 2578 *v.* 2665, p=0.88), and the presence of depression (81.8% *v.* 73.6%, p=0.30) or cardiovascular disease (33.3% *v.* 27.9%, p=0.51). Table 1 summarizes the sociodemographic and clinical characteristics of the study sample according to their loneliness status. The mean age (SD) of the total study sample was 70.6 (7.3) years and 64.9% was female. Lonely participants were significantly older, were more often males and without a partner, had fewer years of education and a smaller social network, and were more often depressed. Furthermore, lonely participants had more often a cardiovascular disease, and were more often smokers and less often engaged in physical exercise. However, lonely participants drank less alcohol.

Logistic regression analyses in which all potential confounders were entered one by one in the models revealed that partner status, physical activity level and social network size were confounders in the association between loneliness and cardiovascular disease. Therefore, these variables were introduced as covariates in the subsequent analyses. We also included age as a covariate to adjust for age-effects.

We performed logistic regression analyses with the presence of cardiovascular disease as outcome. First, we ran this analysis with loneliness as a dichotomous variable and adjusted for the confounders mentioned above. These analyses showed no significant association

Table 1. Characteristics of the study population (n=477).

	Lonely (n=289)	Not lonely (n=188)	p-value*
Age, mean (SD)	71 (7.2)	70 (7.3)	<0.001
Female gender, n (%)	186 (64.4)	124 (66.0)	<0.001
Years of education, mean (SD)	10.4 (3.5)	11.7 (3.6)	<0.001
Depressive disorder in past 6 months, n (%)	265 (91.7)	86 (46.7)	<0.001
Partnerstatus, n (%) with partner	138 (47.8)	143 (76.1)	<0.001
Social network, n (%)			<0.001
< 6	180 (62.7)	61 (32.6)	0.001
≥ 6	107 (37.3)	126 (67.4)	<0.001
Current smoker, n (%)	75 (26.0)	25 (13.4)	<0.001
Alcohol use: AUDIT score (SD)	2.44 (3.4)	3.48 (3.1)	0.032
Physical activity MET-min./week (SD)	2392 (2511)	3099 (2866)	<0.001
Cardiovascular disease, n (%)	91 (31.5)	42 (22.5)	0.032

* Normally distributed variables were tested with t-tests (continuous variables) or chi-square tests (categorical) and non-normally distributed variables were tested with Mann-Whitney tests.

Abbrevations: SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; MET, metabolic equivalent of task.

Table 2. Association between loneliness (dichotomous) and cardiovascular disease.

	OR (95% CI)	p-value
Crude		
Loneliness	1.59 (1.04-2.42)	0.03
Adjusted		
Loneliness*	1.27 (0.80-2.03)	0.32
Loneliness**	1.16 (0.69-1.93)	0.58
Loneliness x depression**	0.74 (0.23-2.36)	0.61

*Adjusted for age, partner status, physical activity, social network size.

**Adjusted for the above mentioned variables, plus depression.

between loneliness and cardiovascular disease (Table 2). Next, we added the interaction term between depression and loneliness to the fully adjusted model. However, this interaction terms was not statistically significant (Table 2). These logistic regression analyses were repeated with loneliness as a continuous variable. Again, no significant association between loneliness and cardiovascular disease was found after adjustment for confounders (Table 3). Also the interaction term between depression and loneliness showed no significant association with cardiovascular disease (p=0.09).

The interaction term between gender and loneliness yielded a significant association for loneliness as dichotomous variable (OR=3.61, 95% confidence interval [CI] 1.47-8.83, p=0.005) and for loneliness as a continuous variable (OR=1.20, 95% CI 1.06-1.35, p=0.003). Therefore, we repeated the logistic regression analyses in the males and females separately (Table 4). A significant association between loneliness (dichotomous and continuous) and cardiovascular disease was found in females, but not in males. After adjustment for confounders, the association remained significant for loneliness as a dichotomous and continuous variable, but it lost significance when depression was added to the model. Further, in females, a significant interaction term of depression and loneliness was found with loneliness as a continuous variable (p=0.03), but not with loneliness as a dichotomous variable. Stratification by depression did not reveal significant associations between loneliness as a continuous variable and cardiovascular disease in the depressed (OR=1.04, 95% CI 0.95-1.13, p=0.46) and non-depressed (OR=1.31, 95% CI 0.96-1.79, p=0.09) females.

Table 3. Association between loneliness (continuous) and cardiovascular disease.

	OR (95% CI)	p-value
Crude		
Loneliness	1.07 (1.01-1.13)	0.02
Adjusted		
Loneliness*	1.04 (0.98-1.10)	0.25
Loneliness**	1.03 (0.96-1.10)	0.48
Loneliness x depression*	0.85 (0.71-1.03)	0.09

*Adjusted for age, partner status, physical activity, social network size.

**Adjusted for the above mentioned variables, plus depression.

Table 4. Associaton of loneliness (dichotomous and continuous) and cardiovascular disease in males and females.

	Males (n=167)		Females (n=309)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Crude				
Loneliness (dichotomous)	0.96 (0.88-1.05)	0.38	2.64 (1.50-4.65)	0.001
Adjusted				
Loneliness *	0.93 (0.83-1.03)	0.18	1.96 (1.05-3.63)	0.03
Loneliness **	0.91 (0.81-1.03)	0.13	1.75 (0.88-3.50)	0.11
Crude				
Loneliness (continuous)	0.71 (0.36-1.40)	0.33	1.13 (1.06-1.21)	<0.001
Adjusted				
Loneliness *	0.62 (0.29-1.31)	0.21	1.10 (1.01-1.18)	0.02
Loneliness **	0.57 (0.26-1.27)	0.17	1.08 (0.99-1.18)	0.08

*Adjusted for age, partner status, physical activity, social network size.

** Adjusted for the above mentioned variables, plus depression.

Discussion

In this study, the relation between loneliness and cardiovascular disease was examined in a depressed and non-depressed older population. Significant associations were found between loneliness and cardiovascular disease. However, when relevant confounders were added to the model, the association between loneliness and cardiovascular disease did not remain significant. This suggests that multiple factors (e.g. physical activity, social network size, partner status) that co-occur with loneliness, but not loneliness itself, influence the presence of cardiovascular disease. Nevertheless, in females only, the association between loneliness and cardiovascular disease remained significant after adjustment for relevant confounders, but it lost significance after adjustment for depression. In conclusion, a significant association between loneliness and cardiovascular disease was only found in females, but the presence of depression explained this association.

Our results are not in line with other studies examining the association between loneliness and cardiovascular disease, with the exception of one study.[37] In this latter study,

no obvious association between coronary insufficiency and feelings of loneliness was found in a population aged 70-90 years.[38] To our knowledge, few studies found loneliness to be associated with cardiovascular disease[13,14,38] and none of these studies considered the potential explanatory role of depression. For instance, one study found greater loneliness to be associated with increased probability of having a coronary condition, even after adjustment for lifestyle factors;[13] however, that study did not correct for a diagnosis of depression. Another study examined incident coronary heart disease in a longitudinal study of a community sample of male and females and found loneliness to be associated with an increased risk of incident coronary heart disease among females.[14] Models were adjusted for various confounders but not for the diagnosis of depression. Furthermore, in contrast to our study, loneliness was assessed with only one item from the Center for Epidemiologic Studies of Depression scale. Since the mean age in this latter study was 44 years, it is not directly comparable to our study with a much older population. In fact, we did find an association between loneliness and cardiovascular disease in females, and not in males. However, in our study, we found that the presence of depression explained this association. Another study analyzed the relationship between loneliness and cardiovascular mortality and found a feeling of loneliness to be associated with cardiovascular mortality, especially among males.[38] However, they used a single question to assess loneliness, and depression was not assessed in their study. In summary, the present study shows that when examining the association between loneliness and cardiovascular disease in older adults, it is important to adjust for the presence of depression, especially in females. The fact that other studies did not take the presence of depression into account, might in part explain the difference in the findings.

In contrast to loneliness, the association between depression and cardiovascular disease has been confirmed more often.[20-22] Importantly, these studies did not take into account the strong mutual relation between depression and loneliness. In our study, however, there was no evidence that loneliness might explain the previously found association between depression and cardiovascular disease. Therefore, our findings do not support the hypothesis that cardiovascular disease might explain the previously found increased mortality and morbidity associated with loneliness. This is in line with the results of others: for example, a prospective cohort study found no decline of health and longevity in lonely older persons.[39] Other studies found that social isolation, but not loneliness, was associated with mortality.[3,40]

A major strength of the present study is a study population recruited from different healthcare settings that consisted of depressed and non-depressed older persons. This allowed to rule out the possibility of a confounded relation between loneliness and cardiovascular disease based on depression. To our knowledge, no other study has examined loneliness and formally diagnosed depression together in relation to cardiovascular disease.

The present study also has some limitations. First, it was not possible to include the length of time that loneliness was experienced because this information was not available. However, it is possible that only loneliness experienced on the long-term predicts cardiovascular disease. This could imply that a lack of such an association in our study might be due to a shorter duration of loneliness in our participants; longitudinal research is needed to confirm this. Secondly, some participants could not be included due to missing values on the loneliness scale. However, because no differences were found in relevant variables between persons with missing values on the loneliness scale and included persons, it is unlikely that our results are biased due to selection.

In conclusion, until now there is lack of agreement among studies regarding the association between loneliness, cardiovascular risk factors, cardiovascular disease and mortality. Our results suggest that loneliness in its own right is not related to cardiovascular disease in depressed and non-depressed older adults. Apparently, the higher morbidity and mortality that is associated with loneliness do not seem to originate in an association with cardiovascular disease.[3,4] Depression and other factors (e.g. partner status, physical activity level and social network size) associated with loneliness may be involved in the association with morbidity and mortality.

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Chapter 7

Summary and general discussion

Summary and general discussion

Background

The work in this thesis focuses on investigation of the appearance of depression in later life. Although a different presentation of late-life compared to early-life has been suggested for many decades, it remains unclear whether this really is the case. Explanations for a possibly different clinical presentation of late-life depression include the co-occurrence of depression and age-related somatic diseases. Our studies focus on the impact of age and somatic diseases on the appearance of late-life depression. Somatic diseases in older age may affect both the symptom profile and the course of depression. On the other hand, symptoms of somatic diseases may be mistaken for somatic symptoms of a depression. In this thesis, we aimed to establish whether there is an age-related presentation of depression and to further unravel the appearance of late-life depression in relation to somatic comorbidity.

Summary of the results

Presentation of late-life depression

As a starting point, we performed a meta-analysis on age-related differences in the phenomenology of depression **(Chapter 2)**. In line with our expectations, the study showed that some symptoms of early-life and late-life depression differed, but not all of them. For example, compared to early-life depression, late-life depression presented with more agitation, general and gastrointestinal somatic symptoms and hypochondriasis, and with less feelings of guilt and less loss of sexual interest. However, because older people often lack a partner and often have decreased sexual desire and functioning, this might explain why loss of sexual interest was less often reported in late-life depression. Moreover, we could not rule out that some of the differences in the occurrence of the 'somatic' symptoms of depression were 'untrue' differences, due to the overlap of somatic symptoms of depression and age-related somatic comorbidity at old age.

The study in **Chapter 3** aimed to establish symptom dimensions and corresponding subscales of late-life depression underlying the Inventory of Depressive Symptomatology Self-Report (IDS-SR) in older depressed and non-depressed persons. We found that, in older people, the IDS-SR measures three homogeneous symptom dimensions reflecting a mood, a somatic and a motivational symptom domain. The *mood symptom dimension* contains the IDS-SR items: feeling sad, feeling irritable, feeling anxious or tense, reactivity of mood, quality of mood, future pessimism, suicidal thoughts, panic or phobic symptoms, and interpersonal sensitivity. The *somatic symptom dimension* consists of the IDS-SR items: initial and middle insomnia, early morning awakening, appetite disturbance, weight disturbance, interest in sex, aches and pains, and sympathetic arousal. Finally, the *motivational symptom*

dimension includes the IDS-SR items: sleeping too much, self-criticism and blame, interest in people/activities, energy/fatiguability and psychomotor retardation. We showed that these symptom dimensions can be used as IDS-SR-subscales and are generalizable to a broad older population, as our sample reflects the different stages of depression, as well as healthy controls, different healthcare settings, and a wide range of older ages. Importantly, the IDS-SR subscales are specific for older people, as they differ from the previously found symptom dimension used in younger persons.[1] The use of these dimensions to distinguish different symptom profiles within late-life depression may benefit both clinical practice and related research.

Our meta-analysis revealed a more somatic presentation of late-life compared to early-life depression. However, the question as to whether it was an 'untruly' found more somatic presentation due to misattribution of symptoms of age-related somatic diseases to depression was not answered in that study. **Chapter 4** describes the results of our study on the influence of somatic diseases and age on the presentation of late-life depression using the three IDS-SR subscales as described above. Both depressed and non-depressed older persons were included to differentiate between the presentation of depressive symptoms due to somatic diseases and higher age in their own right, and in relation to depression. We found that neither a higher somatic disease burden nor higher age contributed to more somatic symptoms of late-life depression itself. This finding is in contrast with other studies suggesting a more somatic presentation of depression in later life; however, these studies did not take into account the possible misattribution of symptoms of comorbid somatic diseases to depression.[2-4] Further, our finding that depressed older old persons aged ≥70 years tend to show less mood symptoms is in line with other studies that compared older and younger depressed persons with age cut-offs between 65-75 years.[2,5,6] Remarkably, we found a decrease in symptom severity of the motivational symptom dimension with higher age, in contrast to the high prevalence of apathy in our depressed cohort found by others.[7] However, our motivational symptom dimension included the symptoms sleeping too much, self-criticism and blame, interest in people/activities, energy/fatiguability and psychomotor retardation, which apparently does not represent the concept of apathy as defined by Marin and Starckstein.[8] Actually, our finding of less symptoms of the motivational symptom dimension in depressed older old persons aged ≥70 is partly in line with our meta-analyses and other studies that found less feelings of guilt in later life.[9-12] Alternatively, the generally found increase of apathy in late-life depression may be the consequence of a decline in cognitive functioning rather than of increasing age.

Our finding of less mood symptoms in our older group of depressed persons (i.e. aged over 70 years) raises the question as to whether this is a result of not *experiencing* or not *reporting* a sad mood. The few articles that have discussed this issue reported conflicting

opinions. It is possible that the current cohort of older persons is not accustomed to, or is ashamed to express a sad mood and, instead, expresses somatic symptoms of depression.[13,14] Another prossibility is that older persons more often consider a sad mood to be a normal part of their aging life. On the other hand, it is argued that depressed older persons may present with medically unexplained somatic symptoms, hopelessness or apathy, due to not experiencing a sad mood.[6] In fact, a prospective cohort study on this topic found that, compared to younger persons, older persons reported less sadness as measured with the CIDI. Remarkably, the younger cohort, 13 years later, reported sadness in the same way as the older cohort did before.[15] This suggests that the age-related differences found in reporting depressive symptoms cannot be explained by a cohort effect. At the same time, it was found that older depressed persons often do not report any depressive symptoms to their GP, in contrast to what was reported in a research interview.[16] However, our findings are not based on information gathered from a GP, but on reported depressive symptoms of the IDS-SR which were measured in an interview during the NESDO baseline assessment. Therefore, our finding of less reported mood and motivational symptoms based on the IDS-SR obtained from an interview seems even more valid, as in daily practice older depressed persons might spontaneously report even less mood and motivational symptoms to their GP, than found in the present study.

Somatic (co)morbidity in late-life depression

The study in **Chapter 5** aimed to further clarify the relation between depression and somatic diseases with respect to the impact of chronic somatic diseases on the course of late-life depression. In line with previous studies, we confirmed that the overall somatic disease burden is associated with the presence of depression at 2-years follow-up.[17,18] Also, a chronic severe course of depression was more often found with increasing overall disease burden. In particular, the presence of both cardiovascular disease and musculoskeletal disease was associated with a depression at 2-year follow-up and with a chronic severe course of depression. Furthermore, a chronic course of depression with variable severity was more often found in the presence of chronic non-specific lung diseases and cancer. Thyroid and gastrointestinal diseases were not associated with a chronic or recurrent course of depression at 2-year follow-up.

Chapter 6 presents the results of our study examining the presence of cardiovascular diseases in relation to both loneliness and late-life depression. Loneliness and cardiovascular diseases were associated only in females, but the presence of depression explained this association. Unexpectedly, we found no relationship between loneliness itself and cardiovascular diseases, neither in the presence nor absence of depression. Until now, few studies have examined the relation between loneliness and cardiovascular diseases. These

studies, except for one,[19] were not in line with our results.[20-22] However, in those studies depression was not adjusted for, whereas our study showed that depression can be a confounder for the relation between loneliness and cardiovascular disease.

Methodological considerations

This thesis comprises the results of a meta-analysis that was based on 11 studies including more than 2000 participants, as well as the results of four studies that used data from the NESDO and included 510 participants. The design of the NESDO studies was observational, most were cross-sectional studies and one study had a longitudinal design. A cross-sectional observational design is suitable to answer our research questions on the presentation of depression and to define symptom dimensions of the IDS-SR in later life. However, due to its cross-sectional design no conclusions can be drawn about possible causal relationships between these associations, e.g., between loneliness and cardiovascular disease in depressed and non-depressed older persons. Of course, it may be even more valuable to examine this research question in a long-term cohort study covering several decades. After all, a long-term exposure to loneliness or depression seems inevitable when it comes to a possible risk factor for (cardio)vascular disease at older age. For instance, a 40-year longitudinal study showed that depression at younger age was a risk factor for death from stroke at older age.[23] However, in line with our finding, a 20-year longitudinal study that followed older persons from age 70 until 90 years did not find an increase of mortality or morbidity in the presence of loneliness.[24]

In this thesis we had the opportunity to use data from the NESDO sample consisting of both healthy and somatically ill older persons, as well as formally diagnosed depressed and non-depressed older persons, enrolled from primary health care, outpatient mental health care and inpatient mental health care. Therefore, we were able to examine symptoms that were related both to somatic diseases and depression. Furthermore, to our knowledge, no other study has examined the course of formally diagnosed depression in older persons with and without specific chronic somatic diseases. The few studies that have examined specific somatic diseases in relation to depression were mostly performed among a somatically ill population only, or investigated depressive symptoms in a general population.[25,26] However, some critical questions and remarks are also warranted. Firstly, it is possible that, in some cases, depression has been wrongly diagnosed due to misattribution of symptoms of somatic diseases to depression. In that case, bias might have occurred which, however, seems unlikely. In NESDO, depression was formally diagnosed using the CIDI, which only counts a symptom as diagnostic for the presence of depression if it is not caused by a physical illness. Also, our finding of less severity on the mood and motivational dimension with increasing age was found in the depressed subgroups with both a lower and higher

somatic disease burden. Secondly, because the IDS-SR subcales were established in an older population, it was not possible to compare symptom profiles of depression between older persons and younger persons below the age of 60 years. Thirdly, another unavoidable issue of a cohort study among an older population is the expected high attrition rate due to death or disability. In the NESDO, one-fifth of all participants were lost during the 2-year follow-up. Death and cognitive problems were the most important reasons for attrition in the depressed group, whereas having no interest or time were the most important reasons for the non-depressed group. Only the depressed group was included in our study on the course of depression at 2-year follow-up. Despite the fact that attrition was (as expected) higher in the depressed group compared to the non-depressed group, attritrion was not regarded as high compared to other cohort studies in older populations.[17]

Clinical implications of our study

The findings of our study may have contradictory clinical implications. Our results imply a more somatic presentation of depression with higher age, because a decline of mood and motivational symptoms goes together with a relative increase of somatic symptoms. This may result in *underrecognition* of late-life depression in clinical practice because (non-psychiatric) physicians may not suspect depression as an explanation for the presented somatic complaints. On the contrary, in case a depression rating scale is being used, an *overestimation* of late-life depression may be the result due to misattribution of symptoms of somatic diseases (and sickness behavior) to depression.

Back to the case report

A masked appearance of depression due to a more somatic clinical picture also applied to Mrs. A. At that time, it was unclear whether she had either not experienced or had not reported a sad mood. However, her family had noticed her negative thoughts and a sad mood; this helped us to eventually diagnose a depression. For Mrs. A., only after she had somewhat recovered from her depression could she adequately answer our questions and confirm that she had indeed experienced a sad mood. Earlier, she had not mentioned being sad to her GP or other physicians. Instead, she presented with somatic complaints that later proved to be part of a depression and, therefore, her depression remained unrecognized.

Indeed, it is known that late-life depression is often not adequately recognized by non-psychiatric physicians.[27,28] Awareness that older depressed persons often do not spontaneously report a sad mood or depressive cognitions, may improve recognition of depression in later life. Therefore, we emphasize the importance of physicians asking patients (and their next-of-kin) about a low mood and depressive cognitions, especially in case of medically unexplained somatic symptoms.[29,30]

Another important finding emerging from our work is that the course of depression is even more unfavorable in the presence of somatic comorbidity. This situation also applied to Mrs. A., who had recurrent bronchitis, heart failure, diabetes mellitus type II and hypertension, as well as a severe course of her depression. Moreover, there were many negative somatic consequences of her depression, resulting in (temporary) functional loss and high costs due to a long hospitalization. Therefore, our finding of an unfavorable course of depression with a higher somatic disease burden emphasizes the need for integrated somatic-psychiatric care for older depressed persons, in whom somatic comorbidity is relatively common.

Assessment of depression and depression severity

At the same time, we found that overestimation of depression severity may occur in the presence of somatic comorbidity when using a depression rating scale (e.g. the IDS-SR). Depression scales are used for the screening of depression (with cut-off points) and the rating of depression severity in both clinical practice and research. The overestimation of depression may particularly apply to those rating scales that include somatic symptoms of depression, such as the IDS-SR, the Hamilton Depression Rating Scale or the Beck Depression Inventory.[31,32] In the early 1980s, the Geriatric Depression Scale (GDS, 1982) and the Hospital Anxiety and Depression Scale (HADS, 1983) were developed and minimize the impact of somatic symptoms. These rating scales may partly overcome the problem of attributing symptoms of somatic diseases to late-life depression. However, with respect to the IDS-SR, more research is needed to define adjusted (higher) cut-offs of the IDS-SR in older persons, specifically for somatically ill older individuals.

Research implications of our study

In older depressed persons, a higher symptom severity of all three IDS-SR subscales was found in the presence of a higher somatic disease burden. However, this was due to misattribution of symptoms of somatic diseases with respect to the somatic and motivational symptom dimension, whereas a truly higher symptom severity was found for the mood dimension. Therefore, for research purposes, the use of the IDS-SR subscales requires adjustment of the symptom severity scores for somatic comorbidity, but only for the motivational and somatic symptom dimension. If *overall* depression severity as measured with the IDS-SR is adjusted for somatic comorbidity, overadjustment will probably occur. Obviously, when depression rating scales are used for screening purposes they should be followed by a diagnostic research interview to formally diagnose depression according to the criteria of the DSM.

Several solutions have been proposed to solve the issue of attributing symptoms of somatic diseases to a depressive disorder when diagnosing depression according to the diagnostic criteria of the DSM in medically ill (older) people. However, until, now, none of

them are satisfactory.[33] For instance, we think that an *exclusive approach* that ignores the somatic symptoms of depression is inappropriate at old age, since we found that precisely non-somatic symptoms of depression were less pronounced in late-life depression.[34] Also, the overestimation of symptoms of the motivational dimension is not resolved using an exclusive approach. In medically ill older persons, a high specificity and low sensitivity was found based on an exclusive approach, with half of the depressed persons being missed.[34] On the other hand, an *inclusive approach* that uses all the somatic symptoms, even if symptoms originate from a somatic disease, showed a high sensitivity but may result in poor specificity.[34] A *substitutive approach* replaces the somatic symptoms (but not the motivational symptoms) by other depressive symptoms to improve the distinction between depression and somatic diseases.[35,36] Furthermore, *an etiological approach* that counts symptoms towards depression if they are judged not to be caused by a somatic disease, is not easy to carry out.[37-39] Moreover, it is known that we cannot always reliably approximate the origin of a symptom.[34] Therefore, we recommend the use of an *inclusive approach* to ensure recognition of depression in late life.[34] In contrast, an etiological approach is required to formally diagnose depression according to the criteria of the DSM-IV.[40] Admittedly, when using an inclusive approach one must be aware that the diagnostic criteria of the DSM can (possibly) be fulfilled by symptoms of sickness behavior and/or a somatic disease. At old age, however, because unrecognized depression may result in an adverse health outcome it is important to rule depression out. An additional requirement, i.e., that the presence of a sad mood, depressive cognitions (e.g. feelings of worthlessness or guilt) or suicidality is essential, might be a suitable intermediate solution because these symptoms may distinguish depression from sickness behavior and/or somatic diseases.[37,41]

Future research on the appearance of depression in later life

In this thesis, because we aimed to contribute to the unravelling of the heterogeneous presentation of depression, we focused on age-related heterogeneity. The impact of age of onset on the age-related differences found in the presentation of late-life depression was not studied in this work and still needs further examination. Future research should also aim at investigating underlying mechanisms of (age-related) symptom variations within late-life depression (such as biological, psychological and sociological pathways) and how they modify the appearance of depression.[42]

More studies are also needed to improve the recognition of late-life depression, as improved recognition may enhance the outcome of depression and somatic health. Finally, our findings were based on symptoms reported on a depression scale. However, further investigation is needed with respect to experienced symptoms that may not be (or are less spontaneously) reported to a physician, compared to the use of a questionnaire at old age.

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Nederlandse samenvatting

Nederlandse samenvatting

Achtergrond

Het onderzoek in dit proefschrift richt zich op de presentatie van depressie op oudere leeftijd. Al decennia lang wordt gesuggereerd dat symptomen van depressie op oudere leeftijd verschillen van symptomen van depressie op jongere volwassen leeftijd, maar het is nog steeds onduidelijk of dit werkelijk zo is. Een van de mogelijke verklaringen voor een andere presentatie van depressie op oudere leeftijd is het tegelijkertijd optreden van depressie en leeftijdsgerelateerde lichamelijke ziekten. Het kan zijn dat lichamelijke ziekten zowel de presentatie als het beloop van depressie op oudere leeftijd beïnvloeden. Het is ook denkbaar dat klachten van een lichamelijke aandoening ten onrechte worden toegeschreven aan een depressie. Het doel van dit proefschrift is om vast te stellen of depressie op oudere leeftijd er anders uitziet dan op jongere leeftijd en om de presentatie en beloop van depressie in relatie tot somatische comorbiditeit verder te ontrafelen.

Resultaten

Presentatie van depressie op oudere leeftijd

Allereerst verrichtten we een meta-analyse naar de invloed van leeftijd op de symptomen van depressie (**hoofdstuk 2**). Zoals we verwachtten toonde de meta-analyse aan dat de symptomen van depressie op oudere leeftijd gedeeltelijk verschillen van depressie op jongere volwassen leeftijd. Depressieve ouderen vertoonden ten opzichte van depressieve jongere volwassenen meer agitatie, meer lichamelijke klachten en vaker angst voor lichamelijke ziekten, maar minder schuldgevoelens en verlies van seksuele interesse. Ouderen hebben echter in vergelijking met jongere volwassenen vaker geen partner en een lagere seksuele interesse, wat het minder voorkomen van verlies van seksuele interesse kan verklaren. Daarnaast is het niet uitgesloten dat we ten onrechte een meer lichamelijke presentatie van depressie op oudere leeftijd vonden, omdat we geen onderscheid konden maken tussen lichamelijke klachten voortvloeiend uit een depressie of een - op oudere leeftijd vaker voorkomende - lichamelijke aandoening.

In de studie in **hoofdstuk 3** hebben we onderzocht welke onderliggende symptoomdimensies en corresponderende subschalen de Inventory of Depressive Symptoms - Self Report (IDS-SR) omvat. Wij vonden drie symptoomdimensies voor de IDS-SR: één dimensie met stemmingsklachten, één met lichamelijke klachten en één met motivationele klachten. De symptoomdimensie met stemmingsklachten omvat de IDS-SR items: somber voelen, prikkelbaar voelen, angstig of gespannen voelen, reactiviteit van de stemming, kwaliteit van de stemming, pessimistische toekomstverwachting, gedachten aan dood of suïcide, paniek of fobische klachten, en gevoeligheid voor interpersoonlijke afwijzing. De lichamelijke

symptoomdimensie bestaat uit de IDS-SR items: in slaap vallen, slaap gedurende de nacht, vervroegd wakker worden, verstoorde eetlust, gewichtsverandering, belangstelling voor seks, pijnklachten en andere lichamelijke klachten. Als laatste, de motivationele symptoomdimensie omvat de IDS-SR items: teveel slapen, zelfverwijt, interesse in andere mensen en activiteiten, energie en gevoel van traagheid. Wij toonden aan dat de gevonden symptoomdimensies als IDS-SR subschalen te gebruiken zijn en generaliseerbaar zijn naar een brede ouderenpopulatie. Immers, onze studiepopulatie omvatte alle stadia van depressie en een gezonde controlegroep, was afkomstig uit de eerste lijn en de geestelijke gezondheidzorg, en bestreek een brede leeftijdsrange. De gevonden subschalen bij depressieve ouderen verschillen van de eerder gevonden subschalen bij jongeren. De gevonden IDS-subschalen kunnen gebruikt worden om symptoomvariaties van een depressie – symptoomprofielen genoemd – bij ouderen in kaart te brengen, wat nuttig kan zijn voor de klinische praktijk en kan helpen om toekomstig wetenschappelijk onderzoek naar depressie te verfijnen.

Onze meta-analyse liet een meer somatische presentatie van depressie zien op oudere leeftijd ten opzichte van jongere leeftijd. Het is echter mogelijk dat symptomen van (leeftijdsgerelateerde) lichamelijke ziekten ten onrechte waren toegeschreven aan de depressie. Hoofdstuk 4 beschrijft het antwoord op de vraag of er werkelijk een meer somatische presentatie van depressie is op latere leeftijd, aan de hand van de drie, hierboven beschreven, IDS-SR subschalen. We onderzochten zowel depressieve als niet-depressieve ouderen om te kunnen ontrafelen welke symptomen voortkwamen uit chronische lichamelijke ziekten of veroudering zelf, en welke symptomen bij de depressie hoorden. We vonden geen toename van lichamelijke symptomen van de depressie zelf bij het ouder worden, ook niet bij een hogere ziektelast. Deze bevinding is tegenstrijdig met resultaten uit eerdere onderzoeken. In deze eerdere onderzoeken werd echter geen rekening gehouden met het ten onrechte toeschrijven van symptomen van lichamelijke ziekten aan depressie. Uit onze studie kwam verder naar voren dat depressieve ouderen boven de 70 jaar *minder* stemmingsklachten laten zien. Dit komt overeen met de resultaten van eerdere studies die oudere en jongere depressieve ouderen vergeleken en afkappunten voor de leeftijd hanteerden tussen de 65-75 jaar. Onze bevinding van een lagere ernstscore op de motivationele symptoomdimensie van de IDS bij een leeftijd boven de 70 jaar is opmerkelijk, gezien de eerder gevonden hoge prevalentie van apathie in ons cohort depressieve ouderen. De IDS motivationele symptoomdimensie omvat echter de items teveel slapen, zelfverwijt, interesse in andere mensen en activiteiten, energie en gevoel van traagheid en komt daarmee niet precies overeen met het concept apathie zoals gedefinieerd door Marin en Starckstein. Daarentegen is onze bevinding dat depressieve ouderen boven de 70 jaar minder symptomen van de motivationele symptoomdimensie laten zien wel in

overeenstemming met onze meta-analyse en andere studies die minder schuldgevoelens vonden op latere leeftijd. Het is denkbaar dat de vaak gevonden toename van apathie bij depressie op latere leeftijd vooral een gevolg is van cognitieve achteruitgang en niet zozeer samenhangt met het ouder worden zelf.

Depressie en somatische (co)morbiditeit op oudere leeftijd

In hoofdstuk 5 bestudeerden we het effect van de aanwezigheid van chronische ziekten op het beloop en herstel van depressie tijdens twee jaar follow-up, en wel van de volgende chronische ziekten: longziekten, hart- en vaatziekten (inclusief diabetes mellitus), ziekten van het bewegingsapparaat (inclusief slijtage en reuma), maagdarmziekten, kanker en schildklierziekten. Zoals eerder onderzoek al aantoonde, bevestigde ons onderzoek dat een hogere somatische ziektelast geassocieerd is met de aanwezigheid van een depressie 2 jaar later. Ook bleek dat er vaker een chronisch ernstig beloop van de depressie tijdens deze twee jaar werd gevonden bij een hogere somatische ziektelast. Vooral de aanwezigheid van hart- en vaatziekten of een ziekte van het bewegingsapparaat bleek geassocieerd te zijn met een depressie na twee jaar follow-up en met een chronisch ernstig beloop van de depressie. Verder bleek dat een chronisch wisselend beloop van depressie vaker voorkwam bij depressieve ouderen met een longziekte of kanker. Schildklier- en maagdarmziekten waren niet geassocieerd met een chronisch of recidiverend beloop van depressie.

Hoofdstuk 6 beschrijft de resultaten van onze studie naar de aanwezigheid van hart- en vaatziekten in relatie tot eenzaamheid en depressie op latere leeftijd. Wij vonden alleen bij oudere vrouwen een samenhang tussen eenzaamheid en hart- en vaatziekten. Deze samenhang bleek echter te berusten op de aanwezigheid van depressie, en niet op eenzaamheid zelf. Tot op heden zijn slechts enkele studies gedaan naar de relatie tussen eenzaamheid en hart- en vaatziekten, en de resultaten hiervan zijn - behoudens één studie – niet overeenkomstig onze bevindingen. In deze eerdere studies werd echter niet gecorrigeerd voor depressie, terwijl het bekend is dat eenzaamheid en depressie veelvuldig naast elkaar voorkomen. Daarbij komt dat depressie geassocieerd is met somatische morbiditeit en mortaliteit, waarvan de relatie met hart- en vaatziekten het best onderzocht is. In het onderzoek naar de invloed van eenzaamheid op de gezondheid dient eveneens de invloed van depressie meegenomen te worden, omdat dit de resultaten kan vertekenen.

Implicaties voor de klinische praktijk

De bevindingen uit ons onderzoek kunnen tegenstrijdige consequenties hebben voor de klinische praktijk. Onze bevinding dat bij het ouder worden *minder* symptomen uit de stemmings- en motivationele symptoomdimensies van een depressie voorkomen, impliceert (relatief) een meer somatische (of gemaskeerde) presentatie van depressie.

Dit kan tot gevolg hebben dat depressie op oudere leeftijd minder goed herkend wordt door artsen die onvoldoende bedacht zijn op een depressie als mogelijke verklaring voor lichamelijke symptomen. Daarom is het van belang dat artsen een sombere stemming of depressieve cognities goed in kaart brengen, vooral als ouderen onvoldoende begrepen lichamelijke klachten laten zien.

Daar tegenover staat dat een overschatting van depressie kan plaatsvinden wanneer een depressievragenlijst zoals de IDS-SR wordt afgenomen. Symptomen van een chronische lichamelijke aandoening (en ziektegedrag) kunnen dan onterecht worden toegeschreven aan een depressie. Depressievragenlijsten worden gebruikt voor het meten van de ernst van depressie en voor screening op de aanwezigheid van een depressie. Als een depressievragenlijst (zoals de IDS-SR) wordt gebruikt voor screening, dient aansluitend een klinische diagnostische evaluatie of een gestandaardiseerd interview te worden verricht om een depressie te diagnosticeren volgens de criteria van de Diagnostic and Statisical Manual of Mental Disorders (DSM).

Slotopmerkingen

Deze studie heeft tot het belangrijke inzicht geleid dat een depressie op oudere leeftijd er anders uitziet dan op jongere leeftijd. Toekomstig onderzoek moet uitwijzen wat de onderliggende mechanismen zijn van de gevonden leeftijdsgerelateerde symptoomvariaties. Welke biologische, psychologische en/of sociologische factoren spelen hierbij een rol, en op welke manier beïnvloeden ze de presentatie van depressie? Ook de rol van de leeftijd waarop een eerste depressie optrad, dient in toekomstig onderzoek verder onderzocht te worden. Daarnaast vonden wij dat het negatieve beloop van depressie bij ouderen nog ongunstiger wordt in aanwezigheid van een hogere ziektelast. Dit onderstreept het belang van een effectief geïntegreerd somatisch-psychiatrisch behandelaanbod voor deze kwetsbare groep ouderen.

Curriculum Vitae

Curriculum Vitae

Annette Hegeman werd geboren op 11 juli 1967 in Almelo, waar zij in 1985 haar diploma behaalde van het voorbereidend wetenschappelijk onderwijs aan het Pius-X College. Van 1985 tot 1993 studeerde zij Geneeskunde aan de Rijksuniversiteit Utrecht. In 1990 deed zij haar wetenschappelijke stage bij de Icelandic Cancer Society in Reykjavik, onder supervisie van Dr. Helga Ögmundsdóttir.

Na het behalen van het artsdiploma op 29 april 1993, werkte zij als arts-assistent interne geneeskunde en chirurgie (niet-in-opleiding) in het St. Jozef Ziekenhuis (heden: Groene Hart Ziekenhuis) in Gouda. Vervolgens werkte zij een half jaar als arts-assistent op de eerste hulp van het Halifax Royal Infirmary in Groot-Brittannië.

Van 1994 tot 1997 volgde zij de opleiding tot huisarts aan de Universiteit van Amsterdam. Na enkele jaren werkzaam te zijn geweest als waarnemend huisarts en in haar eigen praktijk De Opmaat in Almere, werkte zij als arts-assistent psychiatrie (niet-in-opleiding) bij GGZ Buitenamstel (heden: GGZ inGeest), locatie van Hilligaertstraat, om zich te oriënteren op een specialisatie in de psychiatrie. Van 2004 tot 2008 werd zij opgeleid tot psychiater door Piet Verhagen en Dr. Harold van Megen bij GGZ Meerkanten te Ermelo (heden: GGZ Centraal).

Sinds 2008 werkt zij als psychiater in het St. Antonius Ziekenhuis in Utrecht. Zij is daarnaast Balintgroep begeleider voor intervisie van huisartsen in de regio Utrecht. Eind 2008 startte zij haar promotieonderzoek bij Roos van der Mast, hoogleraar ouderenpsychiatrie in het LUMC. Tussen 2006 en 2011 was zij bestuurslid van de Afdeling Consultatieve- en Ziekenhuispsychiatrie van de Nederlandse Vereniging voor Psychiatrie (NVvP). Vervolgens was zij in 2013 en 2014 lid van de werkgroep versterking ziekenhuispsychiatrie van de NVvP. In de periode 2013-2015 was zij voorzitter van de vakgroep psychiatrie in het St. Antonius Ziekenhuis. Momenteel is zij medisch hoofd van de afdeling Psychiatrie & Psychologie in het St. Antonius Ziekenhuis.

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