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

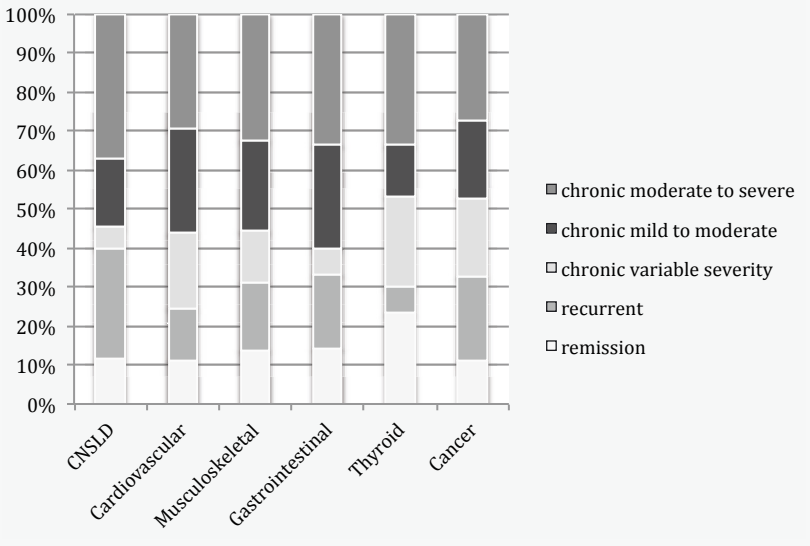
Notes: Adjusted for age, gender and years of education. Degrees of freedom (df) = 1 for all tests.
a. Using logistic regression, separate models for each chronic somatic disease.

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]

References

1. Beekman AT, Deeg DJ, Smit JH et al. Predicting the course of depression in the older population: results from a community-based study in The Netherlands. J Affect Disord 1995; 34:41-49.

2. Scott KM, Bruffaerts R, Tsang A et al. Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. J Affect Disord 2007; 103:113-120.

3. Yohannes AM, Willgoss TG, Baldwin RC et al. 2010. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. Int J Geriatr Psychiatry 2010; 25:1209-1221.

4. Cuijpers P, Vogelzangs N, Twisk J et al. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry 2013; 202:22-27.

5. Penninx BW, Milaneschi Y, Lamers F et al. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med 2013; 11:129.

6. Beekman AT, Penninx BW, Deeg DJ et al. Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). J Affect Disord 1997; 46:219-231.

7. Nayak R, Rajpura J. Assessing Depression among Older Persons with Arthritis: A Nationwide Health Status Survey. ISRN Rheumatol 2013; doi: 10.1155/2013/968343.

8. Bremmer MA, Hoogendijk WJ, Deeg DJ et al. Depression in older age is a risk factor for first ischemic cardiac events. Am J Geriatr Psychiatry 2006; 14:523-530.

9. Wouts L, Oude Voshaar RC, Bremmer MA et al. 2008. Cardiac disease, depressive symptoms, and incident stroke in an elderly population. Arch Gen Psychiatry 2008; 65:596-602.

10. van Ede L, Yzermans CJ, Brouwer HJ. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. Thorax 1999; 54:688-692.

11. Pouwer F, Beekman AT, Nijpels G et al. Rates and risks for co-morbid depression in patients with Type 2 diabetes mellitus: results from a community-based study. Diabetologia 2003; 46:892-898.

12. van 't Land H, Verdurmen J, ten Have M et al. The association between arthritis and psychiatric disorders; results from a longitudinal population-based study. J Psychosom Res 2010; 68:187-193.

13. Bisschop MI, Kriegsman DM, Deeg DJ et al. The longitudinal relation between chronic diseases and depression in older persons in the community: the Longitudinal Aging Study Amsterdam. J Clin Epidemiol 2004; 57:187-194.

14. Kendler KS, Gardner CO, Fiske A et al. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Arch Gen Psychiatry 2009; 66:857-863.

15. Beekman AT, Deeg DJ, Geerlings SW et al. Emergence and persistence of late life depression: a 3-year follow-up of the Longitudinal Aging Study Amsterdam. J Affect Disord 2001; 65:131-138.

16. Geerlings SW, Beekman AT, Deeg DJ et al. Physical health and the onset and persistence of depression in older adults: an eight-wave prospective community-based study. Psychol Med 2000; 30:369-380.

17. Licht-Strunk E, van der Windt DA, van Marwijk HW et al. The prognosis of depression in older patients in general practice and the community. A systematic review. Fam Pract 2007; 24:168-180.

18. Cole MG, Bellavance F. Depression in elderly medical inpatients: a meta-analysis of outcomes. CMAJ 1997; 157:1055-1060.

19. Comijs HC, Nieuwesteeg J, Kok R et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. BMC Psychiatry 2015; doi: 10.1186/s12888-015-0401-5.

20. Smolderen KG, Aquarius AE, de Vries J et al. Depressive symptoms in peripheral arterial disease: a follow-up study on prevalence, stability, and risk factors. J Affect Disord 2008; 110:27-35.

21. Capuron L, Neurauter G, Musselman DL et al. Interferon-alpha-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. Biol Psychiatry 2003; 54:906-914.

22. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. Biol Psychiatry 2004; 56:819-824.

23. Bremmer MA, Beekman AT, Deeg DJ et al. Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord 2008; 106:249-255.

24. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? Biol Psychiatry 2004; 55:1-9.

25. Vogelzangs N, Duivis HE, Beekman AT et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry 2012; 2:e79.

26. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003; 54:216-226.

27. Beekman AT, Geerlings SW, Deeg DJ et al. The natural history of late-life depression: a 6-year prospective study in the community. Arch Gen Psychiatry 2002; 59:605-611.

28. Gore M, Brandenburg NA, Dukes E et al. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage 2005; 30:374-385.

29. Harrington CB, Hansen JA, Moskowitz M et al. It's not over when it's over: long-term symptoms in cancer survivors: a systematic review. Int J Psychiatry Med 2010; 40:163-181.

30. Verhaak PF, Dekker JH, de Waal MW et al. Depression, disability and somatic diseases among elderly. J Affect Disord 2014; 167:187-191.

31. Turvey CL, Schultz SK, Beglinger L et al. A longitudinal community-based study of chronic illness, cognitive and physical function, and depression. Am J Geriatr Psychiatry 2009; 17:632-641.

32. Hegeman JM, de Waal MW, Comijs HC et al. Depression in later life: A more somatic presentation? J Affect Disord 2014; 170C:196-202.

33. Hegeman JM, Kok RM, van der Mast RC et al. Phenomenology of depression in older compared with younger adults: meta-analysis. Br J Psychiatry 2012; 200:275-281.

34. Maes M, Berk M, Goehler L et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med 2012; doi: 1741-7015/10/66.

35. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007; 29:147-155.

36. Furedi J, Rozsa S, Zambori J et al. The role of symptoms in the recognition of mental health disorders in primary care. Psychosomatics 2003; 44:402-406.

37. Comijs HC, van Marwijk HW, van der Mast RC et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. BMC Res Notes 2003; doi: 10.1168/1756-0500-4-524.

38. Kriegsman DM, Penninx BW, van Eijk JT et al. Self-reports and general practitioner information on the presence of chronic diseases in community-dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. J Clin Epidemiol 1996; 49:1407-1417.

39. Fowkes FG, Murray GD et al (Ankle Brachial Index Collaboration). Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008; 300:197-208.

40. Gerrits MM, van Oppen P, van Marwijk HW et al. The impact of chronic somatic diseases on the course of depressive and anxiety disorders. Psychother Psychosom 2013; 82:64-66.

41. Kok GD, Bockting CL, Burger H et al. Double trouble: does co-morbid chronic somatic illness increase risk for recurrence in depression? A systematic review. PLoS One 2013; 8:e57510.

42. Wells KB, Rogers W, Burnam MA et al. Course of depression in patients with hypertension, myocardial infarction, or insulin-dependent diabetes. Am J Psychiatry 1993; 150:632-638.

43. Hegeman JM, Wardenaar KJ, Comijs HC et al. The subscale structure of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons. J Psychiatr Res 2012; 46:1383-1388.

44. Beltman MW, Voshaar RC, Speckens AE. Cognitive-behavioural therapy for depression in people with a somatic disease: meta-analysis of randomised controlled trials. Br J Psychiatry 2010; 197:11-19.

45. Rayner L, Price A, Evans A et al. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis. Palliat Med 2011; 25:36-51.

46. Taylor D, Meader N, Bird V et al. Pharmacological interventions for people with depression and chronic physical health problems: systematic review and meta-analyses of safety and efficacy. Br J Psychiatry 2011; 198:179-188.

47. Katon WJ, Lin EH, Von Korff M et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010; 363:2611-2620.

48. Watson LC, Amick HR, Gaynes BN et al. Practice-based interventions addressing concomitant depression and chronic medical conditions in the primary care setting: a systematic review and meta-analysis. J Prim Care Community Health 2013; 4:294-306.

49. Krishnan KR, Delong M, Kraemer H et al. Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry 2002; 52:559-588.

50. Kessler RC, Birnbaum H, Bromet E et al. Age differences in major depression: results from the National Comorbidity Survey Replication (NCS-R). Psychol Med 2010; 40:225-237.

51. Lyness JM. Depression and comorbidity: objects in the mirror are more complex than they appear. Am J Geriatr Psychiatry 2008; 16:181-185.

52. Simon GE, Chisholm D, Treglia M et al. Course of depression, health services costs, and work productivity in an international primary care study. Gen Hosp Psychiatry 2002; 24:328-335.