VU Research Portal

A six-year prospective study of the prognosis and predictors in patients with late-life depression

Jeuring, Hans W; Stek, Max L; Huisman, Martijn; Oude Voshaar, Richard C; Naarding, Paul; Collard, Rose M; van der Mast, Roos C; Kok, Rob M; Beekman, Aartjan T F; Comijs, Hannie C

Link to publication in VU Research Portal

A Six-Year Prospective Study of the Prognosis and Predictors in Patients With Late-Life Depression

Hans W. Jeuring, M.D., Max L. Stek, M.D., Ph.D., Martijn Huisman, Ph.D.,
Richard C. Oude Voshaar, M.D., Ph.D., Paul Naarding, M.D., Ph.D.,
Rose M. Collard, Ph.D., Roos C. van der Mast, M.D., Ph.D., Rob M. Kok, M.D., Ph.D.,
Aartjan T.F. Beekman, M.D., Ph.D., Hannie C. Comijs, Ph.D.

Objectives: *To examine the six-year prognosis of patients with late-life depression and to identify prognostic factors of an unfavorable course.* **Design and Setting:** *The Netherlands Study of Depression in Older Persons (NESDO) is a multisite naturalistic prospective cohort study with six-year follow-up.* **Participants:** *Three hundred seventy-eight clinically depressed patients (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision criteria) and 132 nondepressed comparisons were included at baseline between 2007 and 2010.* **Measurements:** *Depression was measured by the Inventory of Depressive Symptomatology at 6-month intervals and a diagnostic interview at 2- and 6-year follow-up. Multinomial regression and mixed model analyses were both used to identify depression-related clinical, health, and psychosocial prognostic factors of an unfavorable course.* **Results:** *Among depressed patients at baseline, 46.8% were lost to follow-up; 15.9% had an unfavorable course, i.e., chronic or recurrent; 24.6% had partial remission; and 12.7% had full remission at six-year follow-up. The relative risk of mortality in depressed patients was 2.5 (95% confidence interval 1.26–4.81) versus nondepressed comparisons. An unfavorable course of depression was associated with a younger age at depression onset; higher symptom severity of depression, pain, and neuroticism; and loneliness at baseline. Additionally, partial remission was associated with chronic diseases and loneliness at baseline when compared with full remission.* **Conclusions:** *The long-term prognosis of late-life depression is poor with regard to mortality and course of depression. Chronic diseases, loneliness, and pain may be used as putative targets for*

optimizing prevention and treatment strategies for relapse and chronicity. (Am J Geriatr Psychiatry 2018; 26:985–997)

Key Words: Depression, old age, risk factors, prognosis, outcome

Highlights

- The long-term prognosis of late-life depression is poor in terms of mortality and course.
- Depression in later life is a chronic and disabling disorder, in which treatment is probably still suboptimal.
- An unfavorable course is associated with a younger age at onset of depression, higher baseline depression, chronic pain, neuroticism and loneliness.
- Patients with a partial remission might benefit from interventions targeting chronic diseases and loneliness.
- Considering the poor prognosis and high dropout among depressed older patients in this study, much could be gained by improving prevention and treatment strategies.

INTRODUCTION

Late-life depression is a complex and heterogeneous disorder, often accompanied by an unfavorable prognosis.[1] It has been associated with a chronic course,[2] a higher risk of subsequent development of cognitive impairment or dementia,[3] and premature death.[4] Although late-life depression can be treated effectively, relapse and recurrence, as well as chronicity, are a major problem in daily practice. Studies on the long-term prognosis of late-life depression are required to inform clinicians and to identify prognostic factors that may contribute to the improvement of treatment strategies and relapse prevention.

An unfavorable prognosis of late-life depression has been demonstrated in both community samples[5–8] and clinical samples.[9–14] Beekman et al.[6] studied the six-year course of community-dwelling older adults with late-life depression, using both diagnostic interviews and self-reports, and found that 32% had a severe chronic course and 44% an unfavorable but fluctuating course, whereas only 23% showed remission.[6] In our previous two-year follow-up study of the Netherlands Study of Depression in Older Persons (NESDO), we found that nearly 50% of the clinically depressed patients still had a depression diagnosis, and 61% had a chronic course of depressive symptoms.[13] It is known that depression in older adults is more likely to have a chronic or chronic-relapsing course

compared to younger adults.[2,15] Since meta-analyses of treatment studies have demonstrated equal efficacy of antidepressants among all ages,[16] suboptimal maintenance treatment may be an explanation for the less favorable prognosis in older adults. Also, some specific depressive syndromes occur more often in later life, such as depression-executive dysfunction syndrome with apathy,[17] which has particularly been linked to a poor outcome.[18,19]

Currently, there has been an increasing interest in identifying distinct long-term trajectories of depressive symptoms using latent class analyses. Hybels et al.[12] identified four trajectory classes in a clinical sample of depressed older adults after three years of follow-up, including a quick recovery class (43%), a persistent moderate symptom class (27%), a persistent high symptom class (15%), and a slow recovery class (15%).[12] Higher perceived stress and lower social support were associated with the persistent high symptom class.[12] These trajectories have proven to be useful in obtaining a better insight into the course of late-life depression; for example, by distinguishing a fast recovery class from a slow recovery class.[12,20] However, its use for clinicians may be limited, for they rely on a depression diagnosis for the management of depression, not on depressive symptoms only.

Multiple factors from different domains of functioning contribute to the onset and prognosis of depression.[21] For clinical purposes, prognostic factors

may be assigned to a depression-related clinical domain, a health and lifestyle domain, and a psychosocial domain. Several factors from these domains have been associated with an unfavorable course of depression, including comorbid anxiety,[22] sleep problems,[23] chronic diseases,[13,15] functional limitations,[24] pain,[25] loneliness,[26] lack of social support,[12] childhood trauma,[27] and neuroticism.[28] Whether these factors are also associated with the prognosis of depression in the long-term remains to be explored.

The aim of the present study was twofold. First, the long-term prognosis of late-life depression was examined in terms of both main reasons for attrition and course types in clinically depressed patients over six years. Second, prognostic factors of long-term course types were identified. We hypothesized that the long-term prognosis of late-life depression is poor, with a high mortality rate and an unfavorable course, including recurrence and chronicity, in most patients.

METHODS

Study Design

The Netherlands Study of Depression in Older Persons (NESDO) is a multisite prospective cohort study designed to examine the course and consequences of depressive disorders in older adults (≥60 years). Sampling procedures have been previously described in detail.[29] In short, data collection of the baseline measurement took place between 2007 and 2010. Depressed patients were recruited in five regions in the Netherlands from both mental healthcare facilities and general practitioners. Nondepressed comparisons were recruited from general practitioners and were included if they had no lifetime diagnosis of depression. Participants were excluded when they had a dementia diagnosis or were suspected to have dementia based on clinicians' judgment. Follow-up assessments by means of a face-to-face interview were performed two years[13] and six years after baseline using the same measurement instruments as at baseline. Additionally, postal assessments were performed every 6 months, including a questionnaire on self-reported depressive symptoms. Well-trained research assistants conducted the interviews. All interviews were audiotaped and quality controlled. The

research coordinator regularly evaluated interviews on the basis of their audiotapes. Question wording and probing behavior of interviewers was frequently monitored by checking a random selection of about 10% of all taped interviews. Written informed consent was obtained from all participants. NESDO study protocol had been approved centrally by the ethical review board of the VU University Medical Center and subsequently by the ethical review boards of the Leiden University Medical Center, University Medical Center Groningen, and Radboud University Medical Center Nijmegen.

Sample

At baseline, NESDO included 378 depressed patients with major depressive disorder (N = 265), dysthymia (N = 6), double depression (N = 94) (major depression and dysthymia), or minor depression (N = 13) according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria[30] and 132 nondepressed comparisons aged greater than or equal to 60 years.[13] Depressed patients did not differ from nondepressed comparisons with respect to mean age and sex, but depressed patients had less education, were more often divorced or widowed, and had lower cognitive functioning. From the 510 respondents at baseline, 401 were retained in the two-year follow-up assessment, with an overall attrition rate of 21.4%.[13]

Measurements

Depression

The DSM-IV-TR diagnoses of major depression, dysthymia, and minor depression were assessed with the Composite Interview Diagnostic Instrument (CIDI, WHO, Version 2.1) on follow-up at two and six years.[30] Severity of depressive symptoms was measured by a postal assessment every 6 months as a continuous variable with the Inventory of Depressive Symptomatology (IDS),[31] which is a 30-item self-report scale that was developed to assess all core criterion diagnostic depressive symptoms. The IDS scores range between 0 and 84, with higher scores indicating more severe depression. An IDS score less than 14 was defined as no depression.[32] The scale has acceptable psychometric properties in depressed outpatients[31] and depressed

inpatients.[32] Cronbach's alpha for the IDS in our sample was 0.83.

Course Types

The course types were categorized according to the two-year and six-year measurements into: a) full remission; b) partial remission; c) recurrent; and d) chronic using both the symptom severity level (according to the IDS) and diagnosis of depression (according to the DSM-IV-TR). Full remission was defined as the absence of a depression diagnosis at six-year follow-up, combined with an IDS score less than 14 at six-year follow-up (at measurement cycles 12 and 13, thereby covering 6 months). Partial remission was defined as the absence of a depression diagnosis at 6-year follow-up, but with an IDS score greater than or equal to 14 at 6-year follow-up (at measurement cycles 12 and 13). The absence of a depression diagnosis at two years but the presence of a diagnosis at six years was labeled as "recurrent." The presence of a depression diagnosis at both two- and six-year follow-up was labeled as "chronic." The last two categories (recurrent and chronic) were based on the diagnosis of depression according to the CIDI only.

Prognostic Factors

Demographics were assessed using standard questions and included sex, age, and education level (years). The following *depression-related clinical factors* were included: previous episode of depression, age of onset of depression, and comorbid anxiety diagnosis (y/n). These were assessed by the CIDI, severity of depressive symptoms was assessed by the IDS,[31] severity of anxiety symptoms was assessed by the Beck Anxiety Inventory (BAI),[33] global cognitive functioning was assessed by the Mini-Mental State Examination (MMSE),[34] apathy was assessed by the Starkstein Apathy Scale (SAS),[35] sleep problems were assessed by the Women's Health Initiative Insomnia Rating Scale (WHIIRS),[36] and use of antidepressants and frequent use of benzodiazepines were assessed by inspection of the medication. The following health and *lifestyle factors* were also included: Chronic physical diseases were self-reported and assessed by the LASA Physical Activity Questionnaire (LAPAQ),[37] functional

limitations were assessed by the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0),[38] metabolic syndrome was assessed by the original Adult Treatment Panel III (ATP-III) criteria,[39] chronic pain was assessed by the Graded Chronic Pain Scale (GCPS),[40] body mass index was measured in kg/m², physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) and dichotomized (low versus moderate/high),[41] smoking was assessed by asking current smoking behavior (y/n), and alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT).[42] The following *psychosocial factors* were included: Neuroticism was assessed by the NEO Five-Factor Inventory (NEO-FFI),[43] childhood trauma was assessed by the Netherlands Mental Health Survey and Incidence Study (NEMESIS) questionnaire,[44] partner status (y/n) was asked, loneliness was assessed by the Rasch-Type Loneliness Scale (RTLS),[45] social support was assessed by the Close Person Inventory and dichotomized (poor [< 2 confidants] versus good [≥ 2 confidants]),[46] and recent life events were assessed by the Brugha questionnaire.[47]

Statistical Analyses

First, descriptive analyses were used to describe attrition and its determinants in the patient group (Appendix S1, eTable S1). For both the patient group and nondepressed comparison group, attrition rates were calculated by dividing the proportion of respondents that were lost to follow-up with the total number of respondents at baseline. Subsequently, bivariate and multivariate logistic regression analyses were used to identify determinants of attrition (Appendix S1, eTable S2). Second, study sample characteristics were described according to the "course of late-life depression," in which the "recurrent" and "chronic" groups were combined to ensure equal group sizes for the purposes of subsequent statistical analyses (Table 1).

A correlation matrix was derived for the independent variables to rule out multicollinearity. A Pearson correlation cutoff of 0.70 was used to determine whether substantial correlation was present and whether variables had to be left out of subsequent analysis. No correlation greater than 0.70 was found between all independent variables. The highest correlations observed were between BAI and neuroticism (0.52) and BAI and WHODAS 2.0 (0.45). Also, the

TABLE 1. Characteristics of N = 201 Depressed Patients at Baseline and According to Their Course Type of Late-Life Depression at Follow-Up

Prognostic factors	Baseline Total N = 201	Six-year follow-up, course types		
		Full remission N = 48	Partial remission N = 93	Recurrent or Chronic N = 60
Demographics				
Women, N (%)	137 (68.2)	28 (58.3)	66 (71.0)	43 (71.7)
Age, years, mean (SD)	69.0 (6.5)	68.4 (5.9)	69.5 (6.8)	68.5 (6.5)
Education, years, mean (SD)	10.9 (3.5)	10.8 (3.1)	10.8 (3.4)	11.0 (4.0)
Depression-related clinical factors				
Previous episode depression, yes, N (%)	175 (90.2)	41 (87.2)	80 (90.9)	54 (91.5)
Age of onset of depression, mean (SD)	46.3 (19.7)	48.4 (18.3)	49.1 (18.5)	40.5 (21.4)
Severity depressive symptoms, mean (SD)	29.7 (12.5)	26.0 (13.6)	28.5 (10.2)	34.5 (13.6)
Comorbid anxiety diagnosis, yes, N (%)	79 (39.3)	17 (35.4)	30 (32.3)	32 (53.3)
Severity anxiety symptoms, mean (SD)	16.8 (10.7)	14.3 (10.6)	15.6 (9.2)	20.6 (12.1)
Global cognitive functioning, mean (SD)	28.1 (1.6)	28.1 (1.5)	28.3 (1.4)	27.8 (2.0)
Apathy, mean (SD)	16.8 (5.3)	15.3 (5.2)	17.1 (5.4)	17.5 (5.2)
Sleep problems, mean (SD)	10.9 (5.2)	11.0 (5.7)	10.6 (5.1)	11.3 (5.1)
Use of antidepressants, yes, N (%)	145 (72.9)	37 (78.7)	58 (63.0)	50 (83.3)
Frequent use of benzodiazepines, yes, N (%)	73 (36.3)	20 (41.7)	29 (31.2)	24 (36.3)
Health and lifestyle factors				
Chronic diseases, mean (SD)	2.1 (1.5)	1.5 (1.0)	2.1 (1.5)	2.5 (1.8)
Functional limitations, mean (SD)	25.0 (12.3)	23.5 (11.9)	23.4 (11.2)	28.6 (13.7)
Metabolic syndrome, original ATP III criteria, yes, N (%)	61 (30.3)	11 (22.9)	32 (34.4)	18 (30.0)
Chronic pain, yes, N (%)	111 (55.5)	23 (47.9)	48 (51.6)	40 (67.8)
Body mass index, mean (SD)	26.1 (4.3)	25.1 (3.7)	26.3 (4.2)	26.6 (4.8)
Physical activity, low, N (%)	47 (24.1)	13 (28.3)	15 (16.7)	19 (32.2)
Smoking, yes, N (%)	47 (23.4)	10 (20.8)	24 (25.8)	13 (21.7)
Alcohol use, median (IQR)	2 (4)	2 (4)	3 (5)	0 (3)
Psychological and social factors				
Neuroticism, mean (SD)	39.1 (6.2)	37.1 (5.9)	38.5 (4.9)	41.7 (7.4)
Childhood trauma index, mean (SD)	1.0 (1.2)	0.9 (1.1)	1.0 (1.1)	1.2 (1.3)
Partner, no, N (%)	95 (47.3)	20 (41.7)	48 (51.6)	27 (45.0)
Loneliness, mean (SD)	6.6 (3.5)	4.8 (3.3)	7.0 (3.4)	7.5 (3.3)
Social support, poor, N (%)	96 (48.0)	23 (48.9)	44 (47.3)	29 (48.3)
Recent life events, mean (SD)	1.8 (1.3)	1.6 (1.3)	1.9 (1.4)	1.8 (1.3)

Notes: SD: standard deviation; ATP III: Adult Treatment Panel III; IQR: interquartile range.

correlations between the independent variables at baseline and the dependent variable IDS at baseline, as well as at two- and six-year follow-up, were retrieved. At baseline, none of the variables was correlated with IDS at greater than 0.70. The highest correlations observed were between IDS and WHODAS 2.0 (0.69), IDS and BAI (0.56), and IDS and neuroticism (0.54).

Bivariate multinomial regression analyses were performed to investigate the association between each prognostic factor and "course of late-life depression" using "full remission" as a reference group (Table 2). An additional analysis was performed using "partial remission" as a reference group for the comparison with a chronic/recurrent (unfavorable) course. To overcome the study's statistical power problem, multivariate analyses were performed using linear mixed models, with the longitudinally measured IDS as a dependent variable (Table 3). First, group-wise multivariate analyses were conducted for each of the three separate domains. Subsequently, the final multivariate model contained all prognostic factors that were associated with IDS at $p < 0.05$ from the group-wise multivariate analyses. The goodness of fit for all multivariate models was evaluated with the −2 log likelihood (−2LL) method by comparing the fitted fixed-effects models to the model with no predictors (null model). We evaluated changes in the −2LL between the null model and each fitted fixed-effects model. Analyses were performed using IBM SPSS 22.0.

TABLE 2. Prognostic Factors Associated With Long-Term Course Types of Late-Life Depression From Bivariate Analyses Using Multinomial Logistic Regression

Prognostic factors	Partial Remission (reference: full remission)				Recurrent or Chronic (reference: full remission)				Recurrent or Chronic (reference: partial remission)			
	OR	95% CI	Wald χ^2	p value	OR	95% CI	Wald χ^2	p value	OR	95% CI	Wald χ^2	p value
Demographics												
Women	1.75	(0.84–3.62)	2.25	0.13	1.81	(0.81–4.03)	2.09	0.15	1.04	(0.51–2.12)	0.01	0.93
Age	1.03	(0.97–1.08)	0.89	0.35	1.00	(0.94–1.06)	0.01	0.95	0.98	(0.93–1.03)	0.88	0.35
Education	1.00	(0.90–1.11)	0.00	0.99	1.02	(0.92–1.14)	0.15	0.70	1.02	(0.93–1.12)	0.22	0.64
Depression-related clinical factors												
Previous episode depression, yes	1.46	(0.48–4.50)	0.44	0.51	1.58	(0.45–5.54)	0.51	0.47	1.08	(0.34–3.48)	0.02	0.90
Age of onset of depression	1.00	(0.98–1.02)	0.04	0.84	0.98	(0.96–1.00)	4.11	0.043	0.98	(0.96–0.99)	6.59	0.010
Severity depressive symptoms	1.02	(0.99–1.05)	1.36	0.24	1.06	(1.02–1.10)	11.27	0.001	1.04	(1.01–1.07)	8.07	0.005
Comorbid anxiety diagnosis, yes	0.87	(0.42–1.81)	0.14	0.71	2.08	(0.96–4.54)	3.41	0.065	2.40	(1.23–4.68)	6.60	0.010
Severity anxiety symptoms	1.01	(0.98–1.05)	0.46	0.50	1.06	(1.02–1.10)	7.68	0.006	1.04	(1.01–1.08)	6.99	0.008
Global cognitive functioning	1.08	(0.87–1.34)	0.45	0.50	0.90	(0.72–1.13)	0.83	0.36	0.84	(0.69–1.02)	3.16	0.076
Apathy	1.07	(1.00–1.14)	3.36	0.067	1.08	(1.00–1.17)	4.24	0.040	1.01	(0.95–1.08)	0.20	0.66
Sleep problems	0.99	(0.92–1.06)	0.17	0.68	1.01	(0.94–1.09)	0.12	0.73	1.03	(0.97–1.10)	0.73	0.39
Use of antidepressants, yes	0.46	(0.20–1.04)	3.45	0.063	1.35	(0.51–3.58)	0.37	0.55	2.93	(1.32–6.52)	6.94	0.008
Use of benzodiazepines, yes	0.63	(0.31–1.31)	1.53	0.22	0.93	(0.43–2.02)	0.03	0.86	1.47	(0.75–2.90)	1.25	0.26
Health and lifestyle factors												
Chronic diseases	1.42	(1.08–1.87)	6.15	0.013	1.65	(1.23–2.21)	10.99	0.001	1.16	(0.94–1.43)	1.95	0.16
Functional limitations	1.00	(0.97–1.03)	0.00	0.95	1.04	(1.00–1.07)	4.34	0.037	1.04	(1.01–1.07)	6.29	0.012
Metabolic syndrome, yes	1.77	(0.80–3.92)	1.95	0.16	1.44	(0.60–3.44)	0.68	0.41	0.82	(0.41–1.64)	0.32	0.57
Chronic pain, yes	1.16	(0.58–2.33)	0.17	0.68	2.29	(1.04–5.03)	4.25	0.039	1.97	(0.99–3.90)	3.83	0.050
Body mass index	1.08	(0.98–1.18)	2.57	0.11	1.10	(1.00–1.21)	3.50	0.061	1.02	(0.95–1.10)	0.23	0.63
Physical activity, low	0.51	(0.22–1.19)	2.45	0.12	1.21	(0.52–2.80)	0.19	0.66	2.38	(1.09–5.17)	4.75	0.029
Smoking, yes	1.32	(0.57–3.05)	0.43	0.51	1.05	(0.42–2.66)	0.01	0.92	0.80	(0.37–1.72)	0.34	0.56
Alcohol use	1.05	(0.95–1.16)	0.78	0.38	0.89	(0.77–1.03)	2.43	0.12	0.85	(0.75–0.97)	5.90	0.015
Psychological and social factors												
Neuroticism	1.04	(0.98–1.10)	1.53	0.22	1.14	(1.06–1.22)	12.90	<0.001	1.09	(1.03–1.16)	8.98	0.003
Childhood trauma index	1.11	(0.81–1.52)	0.39	0.53	1.26	(0.90–1.76)	1.83	0.18	1.14	(0.87–1.50)	0.88	0.35
Partner, no	0.67	(0.33–1.35)	1.25	0.26	0.87	(0.41–1.88)	0.12	0.73	1.30	(0.68–2.50)	0.64	0.43
Loneliness	1.20	(1.08–1.34)	10.78	0.001	1.26	(1.11–1.42)	13.58	<0.001	1.05	(0.94–1.16)	0.75	0.39
Social support, poor	0.94	(0.46–1.89)	0.03	0.86	0.98	(0.46–2.10)	0.00	0.95	1.04	(0.54–2.00)	0.02	0.90
Recent life events	1.24	(0.95–1.63)	2.45	0.12	1.17	(0.88–1.57)	1.13	0.29	0.95	(0.74–1.20)	0.21	0.65

Notes: Degrees of freedom for Wald χ^2 statistic: 1.

TABLE 3. Prognostic Factors Associated With Higher Symptom Levels of Depression During Six Years From Bivariate and Multivariate Linear Mixed Models Analyses

Prognostic factors	Bivariate models			Multivariate models, group-wise			Multivariate model, final		
	β (SE)	p value	df	β (SE)	p value	df	β (SE)	p value	df
Demographics									
Women	2.24 (1.60)	0.16	198						
Age	−0.03 (0.12)	0.79	199						
Education	0.04 (0.22)	0.87	199						
a) Depression-related clinical factors				**Group-wise model a**					
Previous episode depression, yes	7.70 (2.52)	0.003	191	−0.18 (2.19)	0.93	165			
Age of onset of depression	−0.16 (0.04)	<0.001	193	−0.08 (0.03)	0.017	165	−0.06 (0.03)	0.040	166
Severity depressive symptoms	0.55 (0.05)	<0.001	198	0.40 (0.06)	<0.001	167	0.32 (0.07)	<0.001	168
Comorbid anxiety diagnosis, yes	3.73 (1.51)	0.014	198	0.88 (1.23)	0.48	165			
Severity anxiety symptoms	0.51 (0.06)	<0.001	189	0.22 (0.07)	0.002	168	0.11 (0.07)	0.11	170
Global cognitive functioning	−0.57 (0.46)	0.22	201						
Apathy	0.69 (0.14)	<0.001	188	0.30 (0.12)	0.011	166	0.15 (0.12)	0.20	166
Sleep problems	0.57 (0.14)	<0.001	190	−0.09 (0.13)	0.48	165			
Use of antidepressants, yes	−0.52 (1.70)	0.76	196						
Use of benzodiazepines, yes	−0.25 (1.56)	0.87	198						
b) Health and lifestyle factors				**Group-wise model b**					
Chronic diseases	2.70 (0.45)	<0.001	198	1.43 (0.43)	0.001	187	0.68 (0.39)	0.084	165
Functional limitations	0.41 (0.05)	<0.001	192	0.25 (0.06)	<0.001	187	−0.05 (0.06)	0.46	168
Metabolic syndrome, yes	3.92 (1.61)	0.015	199	−0.68 (1.52)	0.66	188			
Chronic pain, yes	7.80 (1.39)	<0.001	198	4.22 (1.32)	0.002	188	2.60 (1.21)	0.033	167
Body mass index	0.81 (0.17)	<0.001	201	0.46 (0.17)	0.009	189	0.23 (0.14)	0.12	167
Physical activity, low	−1.41 (1.79)	0.43	193						
Smoking, yes	0.92 (1.77)	0.60	198						
Alcohol use	−0.47 (0.21)	0.025	196	−0.14 (0.18)	0.43	186			
c) Psychological and social factors				**Group-wise model c**					
Neuroticism	0.89 (0.11)	<0.001	188	0.73 (0.11)	<0.001	185	0.24 (0.12)	0.043	167
Childhood trauma index	1.56 (0.64)	0.015	198	0.81 (0.55)	0.15	184			
Partner, no	1.15 (1.50)	0.44	198						
Loneliness	1.18 (0.21)	<0.001	188	0.70 (0.20)	0.001	185	0.39 (0.18)	0.036	166
Social support, poor	−0.19 (1.50)	0.90	197						
Recent life events	0.53 (0.56)	0.35	198						

Notes: β: regression coefficient; SE: standard error; df: degrees of freedom, rounded to ones; p values for the regression coefficients were generated with t tests. Multivariate group-wise analyses contain factors that were associated with p < 0.05 in bivariate analyses for each domain (a–c). The final multivariate model contains all factors that were associated with p < 0.05 in the multivariate group-wise analyses (a–c). Goodness of fit: model a ($\chi^2[7] = 2370.073$, p < 0.001), model b ($\chi^2[6] = 607.702$, p < 0.001), model c ($\chi^2[3] = 956.429$, p < 0.001), final model ($\chi^2[10] = 2042.444$, p < 0.001).

RESULTS

Attrition of NESDO

Figure 1 contains the flowchart of NESDO. From the 510 respondents at baseline, 299 participated in the six-year follow-up assessment with an overall attrition rate of 41.4%. The attrition rate between two- and six-year follow-up was 25.4%. The attrition rates for the patient and comparison groups differed at 46.8% and 25.8%, respectively. The most important reasons for attrition in the patient group were mortality (16.4%) and mental reasons (15.1%), mainly cognitive impairment, whereas the most important reason for attrition in the nondepressed comparison group was refusal (9.1%). A total of 70 participants (13.7%) died during six-year follow-up, including 62 depressed patients and 8 nondepressed comparisons. The relative risk of mortality among depressed patients was 2.47 times (95% confidence interval [CI] 1.26–4.81) higher versus nondepressed comparisons ($\chi^2[1] = 8.84$, p = 0.003).

Among depressed patients, attrition was the same for men and women ($\chi^2[1] = 0.78$, p = 0.38) (Appendix S1, eTable S1). In bivariate analyses (Appendix S1, eTable S2), determinants of attrition in the patient group were higher age (odds ratio [OR] 1.08, 95% CI 1.05–1.11), less education (OR 0.93, 95% CI 0.87–0.98), a higher age at onset of depression (OR 1.01, 95% CI
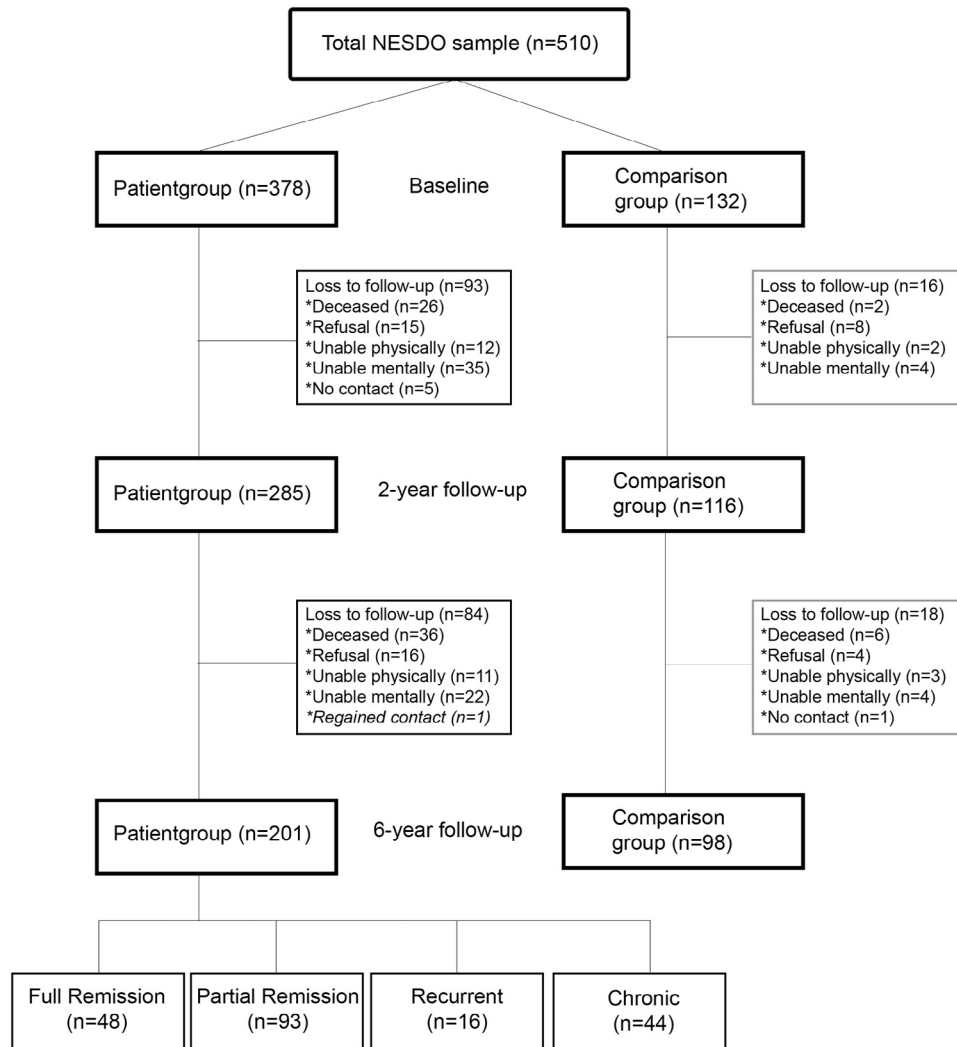
1.00–1.02), worse cognitive functioning (OR 0.79, 95% CI 0.71–0.88), and less physical activity (OR 2.01, 95% CI 1.28–3.15). In multivariate analyses, age (OR 1.06, 95% CI 1.03–1.09) and global cognitive functioning (OR 0.83, 95% CI 0.75–0.95) remained significantly associated with attrition in the patient group.

Prognosis of Late-Life Depression

Among the total 378 depressed patients at baseline, 177 (46.8%) were lost to follow-up, 60 (15.9%) had recurrent or chronic depression, 93 (24.6%) had partial remission, and only 48 (12.7%) had full

remission at six-year follow-up. Of those with full remission at six years, 43.8% reached this after two years.

Table 1 shows the characteristics of 201 clinically depressed patients who were able to participate in the study over the full six years according to their course type. This sample consisted of 137 (68.2%) women, and the mean age of the sample was 69.0 (standard deviation 6.5) years. Sixty (29.9%) depressed patients had an unfavorable course type (8.0% recurrent, 21.9% chronic), 93 (46.3%) had partial remission, and 48 (23.9%) had full remission. The mean IDS score at 6-month intervals, according to the prognosis of

FIGURE 2. Inventory of Depressive Symptomatology (IDS) mean score at 6-month intervals according to the prognosis of depressed patients after six-year follow-up.
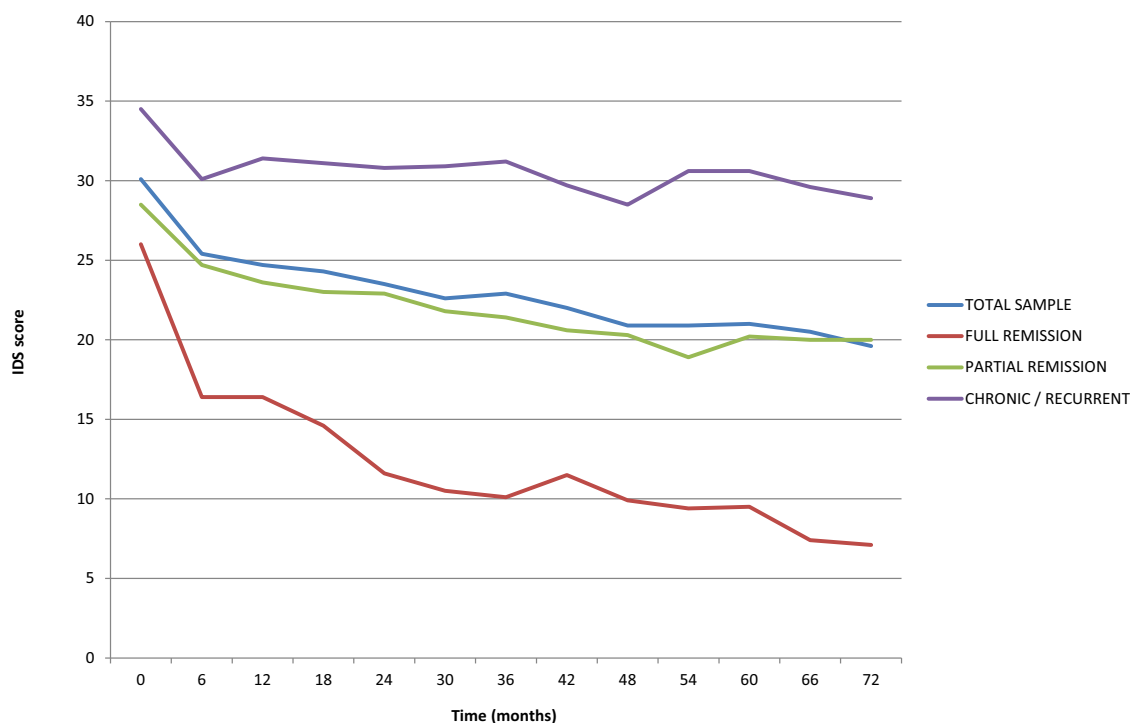
depressed patients after six-year follow-up, is shown in Figure 2.

Prognostic Factors

In Table 2, results from bivariate analyses demonstrate that the depression-related clinical factors (younger age at onset of depression, higher severity of depression, higher severity of anxiety, and more apathy), the health and lifestyle factors (chronic diseases, functional limitations, and chronic pain), and the psychosocial factors (neuroticism and loneliness) were all associated with an unfavorable course type as compared to full remission. As compared to full remission, partial remission was only associated with chronic diseases and loneliness and not with any of the depression-related clinical factors. As compared to partial remission, an unfavorable course type was associated with a younger age at onset of depression, higher severity of depression, a comorbid anxiety disorder, higher severity of anxiety, use of antidepressants,

functional limitations, less physical activity, less alcohol use, and neuroticism.

From multivariate longitudinal analyses (Table 3), a younger age at onset of depression, higher severity of depression, chronic pain, neuroticism, and loneliness at baseline were significantly associated with higher levels of depression over the six-year follow-up.

DISCUSSION

The most important conclusion to be drawn from this study among depressed older patients is that the long-term prognosis for this group is poor in terms of mortality and course of depression. Attrition in the patient group was almost twice as high as in the comparison group. During six years of follow-up, nearly 47% of the depressed patients were lost to follow-up, mainly due to mortality (relative risk of 2.5 versus nondepressed comparisons) and cognitive impairment. Sixteen percent had an unfavorable course type,

i.e., chronic or recurrent; 25% had a partial remission; and only 13% had a full remission. Nonetheless, almost half of those reaching full remission at six-year follow-up still had clinically relevant depression at two-year follow-up, which is an important finding and should encourage clinicians to prolong and optimize treatment in depressed older patients, even after two years.

We also demonstrated that results were biased in the direction of a more favorable prognosis if attrition was excluded as outcome, as this may lead to a selection of more healthy and motivated patients (30% would have had an unfavorable course, 46% partial remission, and 24% full remission). Furthermore, strict criteria were used to define full remission, as a result of which the proportion of patients with a full remission may be underestimated. The rationale for this decision was based on the previous finding that residual symptoms have been associated with a poor outcome,[48,49] indicating that the goal must be to keep the patient as symptom-free as possible.[48]

In a longitudinal study of 127 depressed older patients in the community, it was shown that at three years 30% had died, 35% had chronic or recurrent depression, 25% had another mental illness, and only 10% had maintained a full remission.[5] Stek et al.[11] examined the long-term prognosis of major depression in hospitalized older patients six to eight years after clinical treatment and found that 40% had died, while among the survivors 33% had no residual symptoms or relapses,[11] which approximately corresponds to our finding that among survivors 24% reached full remission. These numbers, from both community and clinical studies, are in line with our results and strongly indicate that depression in later life is a disabling chronic disorder with a poor outcome.

Depression is a complex multifactorial disease, implicating that multiple factors from different domains of functioning contribute to its onset and prognosis.[21] This study found that an unfavorable course of depression was associated with a younger age at onset of depression, a higher severity of depression, chronic pain, neuroticism, and loneliness, which is in accordance with current literature.[4,26,28,50,51] Furthermore, partial remission could not be distinguished from full remission using depression-related clinical factors, but was more likely associated with chronic diseases and loneliness. This finding could imply that these factors are important targets for interventions to prevent relapse, as partial remission is a strong predictor of relapse and chronicity.[52] Our findings do not point to single factors that may be important for the prognosis of depression, but rather point to multiple factors from different domains of functioning that are all important, with each factor having a small but significant contribution.

Recently, Brown et al.[53] found that biological age was more important than chronological age in predicting the incidence and course of depressive symptoms over long-term follow-up.[53] The authors stated that their findings support the evolving biological view of late-life depression as resulting from deleterious age-associated changes.[53,54] Our study suggests, however, that a more holistic view, allowing identification of nonbiological factors as well, is appropriate in targeting older adults at risk for an unfavorable prognosis and thus for prevention and treatment interventions.[21,50]

Our study has some limitations. First, because of a lack of power, multivariate analyses were not performed on course types, making it difficult to clarify the strongest prognostic factors of an unfavorable course type. On the other hand, we did perform multivariate analyses using mixed models with the IDS as assessed every 6 months, which allowed a more accurate assessment of prognostic factors. Second, there might be a great chance of a Type I error due to multiple statistical comparisons. However, on a theoretical basis, we included multiple factors from biopsychosocial domains of functioning that have been previously associated with a poor outcome of late-life depression in studies to date, thereby minimizing the risk of a Type I error (or chance). Also, most of the variables that remained statistically significant (p < 0.05) in the final multivariate model had a stronger association with the outcome in the preceding group-wise models at p ≤ 0.01 (except for "age of onset"). Furthermore, predictors that are associated with a poor outcome from multinomial regression analyses are more or less the same predictors that are associated with a poor outcome from mixed model analyses, which should affirm the validity of our findings. Moreover, the factors uncovered in this study are in line with previous research, because of which we think our results are solid and accurate. Third, although the strength of NESDO is that the results generalize to clinical practice, they are not generalizable to the community. Moreover, in the Netherlands, general practitioners provide primary care for depression.

Depressed patients who do not recover are subsequently referred to specialist mental healthcare. This situation may have induced some selection bias in our sample, with relatively many patients with treatment-resistant depression. Finally, by using depression diagnosis at two measurement points over six years, information was lacking on short-term relapses and recurrences in between these measurements. Since recurrence and chronicity are both unfavorable outcomes, this limitation was tackled by combining both groups. For future research, a latent class analysis of the IDS data would provide more detailed information about detailed trajectories of depression.

Despite the limitations, the study has numerous strengths. The prognosis of late-life depression was captured based on the depression diagnosis according to DSM criteria, in combination with the IDS, at separate measurement points over six years, which increases the external validity and usability for clinicians. Furthermore, we examined not only the course but also attrition among patients with late-life depression, which made it additionally clear that the long-term prognosis of late-life depression is poor.

The clinical implication of this study may be that a multidimensional approach targeting the uncovered factors is valuable in improving the prognosis of late-life depression. Depressed patients with a partial remission might benefit further from interventions targeting chronic diseases and loneliness to obtain full recovery. At the same time, the risk of a poor outcome, such as chronicity, cognitive impairment, or death, may be inevitable in depressed patients when their depression is more severe or started at a younger age or if health and psychosocial problems also exist. Careful long-term monitoring of depression among older adults may be key in optimizing maintenance treatment strategies.

APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2018.05.005.

References

1. Power C, Greene E, Lawlor BA: Depression in late life: etiology, presentation, and management. In: Chiu H, Shulman K, eds. Mental Health and Illness of the Elderly. Mental Health and Illness Worldwide. Singapore: Springer, 2016.
2. Haigh EAP, Bogucki OE, Sigmon ST, et al: Depression among older adults: a 20-year update on five common myths and misconceptions. Am J Geriatr Psychiatry 2018; 26:107–122
3. Singh-Manoux A, Dugravot A, Fournier A, et al: Trajectories of depressive symptoms before diagnosis of dementia. JAMA Psychiatry 2017; 74:712
4. Blazer DG: Depression in late life: review and commentary. J Gerontol 2003; 58:249–265
5. Denihan A, Kirby M, Bruce I, et al: Three-year prognosis of depression in the community-dwelling elderly. Br J Psychiatry 2000; 176:453–457
6. Beekman ATF, Geerlings S, Deeg D, et al: The natural history of late-life depression. Arch Gen Psychiatry 2002; 59:605–611
7. Henderson AS, Korten AE, Jacomb PA, et al: The course of depression in the elderly: a longitudinal community-based study in Australia. Psychol Med 1997; 27:119–129
8. Sharma VK, Copeland JR, Dewey ME, et al: Outcome of the depressed elderly living in the community in Liverpool: a 5-year follow-up. Psychol Med 1998; 28:1329–1337

9. Brodaty H, Luscombe G, Peisah C, et al: A 25-year longitudinal, comparison study of the outcome of depression. Psychol Med 2001; 31:1347–1359

10. Lyness JM, Caine ED, King DA, et al: Depressive disorders and symptoms in older primary care patients: one-year outcomes. Am J Geriatr Psychiatry 2002; 10:275–282

11. Stek ML, Van Exel E, Van Tilburg W, et al: The prognosis of depression in old age: outcome six to eight years after clinical treatment. Aging Ment Heal 2002; 6:282–285

12. Hybels CF, Pieper CF, Blazer DG, et al: Heterogeneity in the three-year course of major depression among older adults. Int J Geriatr Psychiatry 2016; 31:775–782

13. 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; 15:20

14. Katon WJ, Fan MY, Lin EH, et al: Depressive symptom deterioration in a large primary care-based elderly cohort. Am J Geriatr Psychiatry 2006; 14:246–254

15. Mitchell AJ, Subramaniam H: Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. Am J Psychiatry 2005; 162:1588–1601

16. Kok RM, Reynolds CF: Management of depression in older adults. JAMA 2017; 317:2114. doi:10.1001/jama.2017.5706

17. Alexopoulos GS, Kiosses DN, Klimstra S, et al: Clinical presentation of the "Depression–Executive Dysfunction Syndrome" of late Life. Am J Geriatr Psychiatry 2002; 10:98–106

18. Groeneweg-Koolhoven I, Ploeg M, Comijs HC, et al: Apathy in early and late-life depression. J Affect Disord 2017; 223:76–81

19. Yuen GS, Bhutani S, Lucas BJ, et al: Apathy in late-life depression: common, persistent, and disabling. Am J Geriatr Psychiatry 2015; 23:488–494

20. Rhebergen D, Lamers F, Spijker J, et al: Course trajectories of unipolar depressive disorders identified by latent class growth analysis. Psychol Med 2012; 42:1383–1396

21. Blazer DG, Hybels CF: Origins of depression in later life. Psychol Med 2005; 35:1241

22. Andreescu C, Lenze EJ, Dew MA, et al: Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. Br J Psychiatry 2007; 190:344–349

23. Kennedy GJ, Kelman HR, Thomas C: Persistence and remission of depressive symptoms in late life. Am J Psychiatry 1991; 148:174–178

24. Bruce ML: Depression and disability in late life: directions for future research. Am J Geriatr Psychiatry 2001; 9:102–112

25. Karp JF, Weiner D, Seligman K, et al: Body pain and treatment response in late-life depression. Am J Geriatr Psychiatry 2005; 13:188–194. doi:10.1097/00019442-200503000-00003

26. Holvast F, Burger H, de Waal MM, et al: Loneliness is associated with poor prognosis in late-life depression: longitudinal analysis of the Netherlands study of depression in older persons. J Affect Disord 2015; 185:1–7

27. Wielaard I, Comijs HC, Stek ML, et al: Childhood abuse and the two-year course of late-life depression. Am J Geriatr Psychiatry 2017; 25:633–643

28. Manning KJ, Chan G, Steffens DC: Neuroticism traits selectively impact long term illness course and cognitive decline in late-life depression. Am J Geriatr Psychiatry 2017; 25:220–229

29. Comijs H, van Marwijk H, van der Mast R, et al: The Netherlands study of depression in older persons (NESDO); a prospective cohort study. BMC Res Notes 2011; 4:524

30. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. Washington, DC: American Psychiatric Publishing, 2000

31. Rush AJ, Gullion CM, Basco MR, et al: The inventory of depressive symptomatology (IDS): psychometric properties. Psychol Med 1996; 26:477

32. Trivedi MH, Rush AJ, Ibrahim HM, et al: The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004; 34:73–82

33. Beck AT, Epstein N, Brown G, et al: An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56:893–897

34. Folstein MF, Folstein SE, McHugh PR: Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198

35. Starkstein SE, Mayberg HS, Preziosi TJ, et al: Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4:134–139

36. Levine DW, Kaplan RM, Kripke DF, et al: Factor structure and measurement invariance of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess 2003; 15:123–136

37. 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. J Clin Epidemiol 1996; 49:1407–1417

38. Chwastiak LA, Von Korff M: Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. J Clin Epidemiol 2003; 56:507–514

39. Marijnissen RM, Smits JEMP, Schoevers RA, et al: Association between metabolic syndrome and depressive symptom profiles—Sex-specific? J Affect Disord 2013; 151:1138–1142

40. Von Korff M, Miglioretti DL: A prognostic approach to defining chronic pain. Pain 2005; 117:304–313

41. Craig CL, Marshall AL, Sjöström M, et al: International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc 2003; 35:1381–1395

42. Babor TF, Kranzler HR, Lauerman RJ: Early detection of harmful alcohol consumption: comparison of clinical, laboratory, and self-report screening procedures. Addict Behav 1989; 14:139–157

43. Costa PT Jr, McCrae RR: Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. J Pers Assess 1995; 64:21–50

44. de Graaf R, Bijl RV, Ten Have M, et al: Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. J Affect Disord 2004; 82:461–467

45. de Jong-Gierveld J, Kamphuls F: The development of a rasch-type loneliness scale. Appl Psychol Meas 1985; 9:289–299

46. Stansfeld S, Marmot M: Deriving a survey measure of social support: the reliability and validity of the Close Persons Questionnaire. Soc Sci Med 1992; 35:1027–1035

47. Brugha T, Bebbington P, Tennant C, et al: The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. Psychol Med 1985; 15:189–194

48. Judd LL: Dimensional paradigm of the long-term course of unipolar major depressive disorder. Depress Anxiety 2012; 29:167–171

49. Meeks TW, Vahia IV, Lavretsky H, et al: A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. J Affect Disord 2011; 129:126–142

50. Fiske A, Wetherell JL, Gatz M: Depression in Older Adults. Annu Rev Clin Psychol 2009; 5:363–389

51. Tunvirachaisakul C, Gould RL, Coulson MC, et al: Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis. J Affect Disord 2017; 227:164–182

52. Steffens DC, McQuoid DR, Krishnan KR: Partial response as a predictor of outcome in geriatric depression. Am J Geriatr Psychiatry 2003; 11:340–348

53. Brown PJ, Wall MM, Chen C, et al: Biological age, not chronological age, is associated with late life depression. J Gerontol Series A 2017 glx162

54. Rutherford BR, Taylor WD, Brown PJ, et al: Biological aging and the future of geriatric psychiatry. J Gerontol A Biol Sci Med Sci 2016; 72:343–352