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

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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 of 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.

Abstract (Words: 234/250)

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 multi-site naturalistic prospective cohort study with six-year follow-up.

Participants: 378 clinically depressed patients according to DSM-IV-TR criteria and 132 non-depressed comparisons were included at baseline between 2007-2010.

Measurements: Depression was measured by the Inventory of Depressive Symptoms at six-month intervals and a diagnostic interview at two-year and six-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 loss 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 (RR) of mortality in depressed patients was 2.5 (95%-CI:1.26-4.81) when compared with non-depressed comparisons. An unfavorable course of depression was associated with a younger age of depression onset, higher symptom severity of depression, pain, 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 of relapse and chronicity.

Key words: Depression; Old Age; Risk Factors; Prognosis; Outcome.

Introduction (Words: 558)

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. (2002) 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 the 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 to identify distinct long-term trajectories of depressive symptoms using latent class analyses. Hybels et al. (2016) 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 proved to be useful in obtaining a better insight in 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 purpose, 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 on 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 (Words: 1284)

Study Design

The Netherlands Study of Depression in Older persons (NESDO) is a multi-site 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 health care facilities and general practitioners. Non-depressed 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 for dementia based on clinician's 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 six-months, including a questionnaire on self-reported depressive symptoms. Well-trained research assistants conducted the interviews. All interviews were audio taped and quality controlled. The research coordinator regularly evaluated interviews on the basis of their audiotapes. Question wording and probing behavior of interviewers were regularly monitored by checking a random selection of each interviewer. Written informed consent was obtained from all participants. NESDO' study protocol has 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 the Radboud university medical center Nijmegen.

Sample

At baseline, NESDO included 378 depressed patients, having 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 (DSM-IV-TR criteria),[30] and 132 non-depressed comparisons, aged ≥ 60 years.[13] Depressed patients did not differ from non-depressed 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-diagnosis of major depression, dysthymia and minor depression was assessed with the Composite Interview Diagnostic Instrument (CIDI, WHO, version 2.1) at two- and six-year of follow-up.[30] Severity of depressive symptoms was measured by a postal assessment every six months as a continuous variable with the Inventory of Depressive Symptoms (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 < 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 measurement 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 < 14 at six-year follow-up (at measurement cycles 12 and 13, thereby covering six months). Partial remission was defined as the absence of a depression diagnosis at six-year follow-up, but with an IDS score ≥ 14 at six-year follow-up (at measurement cycle 12 and 13). Absence of a depression diagnosis at two-year, but presence of a diagnosis at six-year was labeled as 'recurrent'. Presence of a depression diagnosis both at two- and six-year follow-up was labeled as 'chronic'. The last two categories (recurrent and chronic) were based on diagnosis of depression according to the CIDI only.

Prognostic factors

Demographics were assessed using standard questions and included sex, age, and educational 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) 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 Index (BAI),[33] global cognitive functioning was assessed by the Mini Mental State Examination (MMSE),[34] apathy was assessed by the Apathy Scale (AS),[35] sleep problems was assessed by the Women's Health Initiative Insomnia Rating Scale (WHIIRS),[36] use of antidepressants and frequent use of benzodiazepines were assessed by inspection of the medication. The following health and

182 *lifestyle factors* were included: chronic physical diseases were self-reported and assessed by
183 the LASA Questionnaire (LAPAQ),[37] functional limitations were assessed by the WHO-
184 Disability Assessment Scale II (WHODAS 2.0),[38] metabolic syndrome was assessed by the
185 original ATP-III criteria,[39] chronic pain was assessed by the Chronic Graded Pain Scale
186 (CPGS),[40] body-mass-index was measured by weight (kg)/squared height (m^2), physical
187 activity was assessed by the International Physical Activities Questionnaire (IPAQ) and
188 dichotomized (low versus moderate/high),[41] smoking was assessed by asking current
189 smoking behavior (y/n), and alcohol use was assessed by Alcohol Use Disorders
190 Identification (AUDIT).[42] The following *psychosocial factors* were included: neuroticism was
191 assessed by the NEO-Five Factor Inventory (NEO-FFI),[43] childhood trauma was assessed by
192 the Netherlands Mental Health Survey and Incidence Study (NEMESIS) Questionnaire,[44]
193 partner status (y/n) was asked, loneliness was assessed by the Rasch-Type Loneliness Scale
194 (RTLS),[45] social support was assessed by the Close Person Inventory and dichotomized (poor:
195 < 2 confidents versus good: ≥ 2 confidents),[46] and recent life events were assessed by the
196 Brugha Questionnaire.[47]
197
198 ***Statistical Analyses***
199 First, descriptive analyses were used to describe attrition and its determinants in the patient
200 group (eTable 1). For both the patient group and non-depressed comparison group, attrition
201 rates were calculated by dividing the proportion of respondents that were loss to follow-up
202 with the total number of respondents at baseline. Subsequently, bivariate and multivariate
203 logistic regression analyses were used to identify determinants of attrition (eTable 2).
204 Second, study sample characteristics were described according to the 'course of late-life

depression', in which the groups 'recurrent' and 'chronic' were combined to ensure equal group sizes for the purpose 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 > 0.70 was found between all the independent variables. The highest correlations observed were between BAI and neuroticism (0.52), BAI and WHODAS 2.0 (0.45). Also, the correlations between the independent variables at baseline and the dependent variable IDS at baseline, and at two-year and six-year follow-up, were retrieved. At baseline, none of the variables was correlated with IDS at > 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 reference group (Table 2). An additional analysis was performed using 'partial remission' as 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 'symptom severity of depression' (IDS) as 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 $p<.05$ 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

229 between the null model and each fitted fixed-effects model. Analyses were performed using

230 IBM SPSS 22.0.

Results (Words: 550)

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 group 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 non-depressed comparison group was refusal (9.1%). A total of seventy participants (13.7%) died during six-year follow-up, including sixty-two depressed patients and eight non-depressed comparisons. The relative risk of mortality among depressed patients was 2.47 time (95% CI: 1.26-4.81) higher when compared with non-depressed comparisons, $\chi^2(1) = 8.84$, p=.003.

Among depressed patients, attrition was the same for men and women, $\chi^2(1) = 0.78$, p=.38 (eTable 1). In bivariate analyses (eTable 2), determinants of attrition in the patient group were higher age (OR: 1.08, 95%-CI: 1.05-1.11), less education (OR: 0.93, 95%-CI: 0.87-0.98), a higher age of 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 of 378 depressed patients at baseline, 177 (46.8%) were loss to follow-up, 60 (15.9%) had a recurrent or chronic depression, 93 (24.6%) had a partial remission and only 48 (12.7%) had a full remission at six-year follow-up. Of those with a full remission at six years, 43.8% reached this after two years.

Table 1 shows the characteristics from 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 (SD: 6.5) years. Sixty (29.9%) depressed patients had an unfavorable course type (8.0% recurrent, 21.9% chronic), 93 (46.3%) had a partial remission, and 48 (23.9%) had a full remission. The symptom severity levels of depression (IDS) at six-month intervals according to the prognosis of 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 of 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 of 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 of 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 (Words: 1124)

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 loss to follow-up, mainly due to mortality (relative risk of 2.5 versus non-depressed 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 the 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 a chronic or recurrent depression, 25% had another mental illness, and only 10% had maintained a full remission.[5] Stek et al. (2002) examined the long-term prognosis of major depression in hospitalized older patients six to

eight year 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 of 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 all are important, with each factor having a small but significant contribution.

Recently, Brown et al. (2017) 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 non-biological 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 six 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 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 groupwise models at $p\leq0.01$ (except for 'age of onset'). Furthermore, predictors that were associated with a poor outcome from multinomial regression analyses, are more or less the same predictors that were 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, from which we think that 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 health care. This situation may have induced some selection bias in our sample, with relatively many patients with a 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

356 future research, a latent class analysis on the IDS data would provide more detailed
357 information about detailed trajectories of depression.

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

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

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Study concept and design: Comijs, Oude Voshaar, Van der Mast, Naarding, Stek, Beekman

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Jeuring

Critical revision of the manuscript for important intellectual content: All authors

Administrative, technical or material support: Comijs, Beekman

Study supervision: Comijs, Stek, Huisman, Beekman

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552 **Figure legends**

553 **Figure 1:** Flowchart of NESDO and long-term prognosis of late-life depression.

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555 **Figure 2.** Symptom severity levels of depression (IDS) at six-month intervals according to the
556 prognosis of depressed patients after six-year follow-up.

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560 **Table 1. Characteristics of N=201 depressed patients at baseline and according to their course type of late-life depression at follow-up.**

	Baseline	Six-year follow-up, course types		
	Total	Full remission	Partial remission	Recurrent or Chronic
Prognostic factors	**N=201**	**N=48**	**N=93**	**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, AUDIT, 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)

SD = standard deviation; IQR = interquartile range; AUDIT = Alcohol Use Disorders Identification Test.

564 **Table 2. Prognostic factors associated with long-term course types of late-life depression from bivariate analyses using multinomial logistic regression.**

	Partial remission (ref: full remission)				Recurrent or Chronic (ref: full remission)				Recurrent or Chronic (ref: partial remission)			
Prognostic factors	**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	.13	1.81	(0.81-4.03)	2.09	.15	1.04	(0.51-2.12)	0.01	.93
Age	1.03	(0.97-1.08)	0.89	.35	1.00	(0.94-1.06)	0.01	.95	0.98	(0.93-1.03)	0.88	.35
Education	1.00	(0.90-1.11)	0.00	.99	1.02	(0.92-1.14)	0.15	.70	1.02	(0.93-1.12)	0.22	.64
Depression-related clinical factors												
Previous episode depression, yes	1.46	(0.48-4.50)	0.44	.51	1.58	(0.45-5.54)	0.51	.47	1.08	(0.34-3.48)	0.02	.90
Age of onset of depression	1.00	(0.98-1.02)	0.04	.84	0.98	(0.96-1.00)	4.11	.043	0.98	(0.96-0.99)	6.59	.010
Severity depressive symptoms	1.02	(0.99-1.05)	1.36	.24	1.06	(1.02-1.10)	11.27	.001	1.04	(1.01-1.07)	8.07	.005
Comorbid anxiety diagnosis, yes	0.87	(0.42-1.81)	0.14	.71	2.08	(0.96-4.54)	3.41	.065	2.40	(1.23-4.68)	6.60	.010
Severity anxiety symptoms	1.01	(0.98-1.05)	0.46	.50	1.06	(1.02-1.10)	7.68	.006	1.04	(1.01-1.08)	6.99	.008
Global Cognitive Functioning	1.08	(0.87-1.34)	0.45	.50	0.90	(0.72-1.13)	0.83	.36	0.84	(0.69-1.02)	3.16	.076
Apathy	1.07	(1.00-1.14)	3.36	.067	1.08	(1.00-1.17)	4.24	.040	1.01	(0.95-1.08)	0.20	.66
Sleep problems	0.99	(0.92-1.06)	0.17	.68	1.01	(0.94-1.09)	0.12	.73	1.03	(0.97-1.10)	0.73	.39
Use of antidepressants, yes	0.46	(0.20-1.04)	3.45	.063	1.35	(0.51-3.58)	0.37	.55	2.93	(1.32-6.52)	6.94	.008
Use of benzodiazepines, yes	0.63	(0.31-1.31)	1.53	.22	0.93	(0.43-2.02)	0.03	.86	1.47	(0.75-2.90)	1.25	.26
Health and lifestyle factors												
Chronic diseases	1.42	(1.08-1.87)	6.15	.013	1.65	(1.23-2.21)	10.99	.001	1.16	(0.94-1.43)	1.95	.16
Functional Limitations	1.00	(0.97-1.03)	0.00	.95	1.04	(1.00-1.07)	4.34	.037	1.04	(1.01-1.07)	6.29	.012
Metabolic syndrome, yes	1.77	(0.80-3.92)	1.95	.16	1.44	(0.60-3.44)	0.68	.41	0.82	(0.41-1.64)	0.32	.57
Chronic Pain, yes	1.16	(0.58-2.33)	0.17	.68	2.29	(1.04-5.03)	4.25	.039	1.97	(0.99-3.90)	3.83	.050
Body-Mass-Index	1.08	(0.98-1.18)	2.57	.11	1.10	(1.00-1.21)	3.50	.061	1.02	(0.95-1.10)	0.23	.63
Physical activity, low	0.51	(0.22-1.19)	2.45	.12	1.21	(0.52-2.80)	0.19	.66	2.38	(1.09-5.17)	4.75	.029
Smoking, yes	1.32	(0.57-3.05)	0.43	.51	1.05	(0.42-2.66)	0.01	.92	0.80	(0.37-1.72)	0.34	.56
Alcohol use	1.05	(0.95-1.16)	0.78	.38	0.89	(0.77-1.03)	2.43	.12	0.85	(0.75-0.97)	5.90	.015
Psychological and social factors												
Neuroticism	1.04	(0.98-1.10)	1.53	.22	1.14	(1.06-1.22)	12.90	<.001	1.09	(1.03-1.16)	8.98	.003
Childhood Trauma Index	1.11	(0.81-1.52)	0.39	.53	1.26	(0.90-1.76)	1.83	.18	1.14	(0.87-1.50)	0.88	.35
Partner, no	0.67	(0.33-1.35)	1.25	.26	0.87	(0.41-1.88)	0.12	.73	1.30	(0.68-2.50)	0.64	.43
Loneliness	1.20	(1.08-1.34)	10.78	.001	1.26	(1.11-1.42)	13.58	<.001	1.05	(0.94-1.16)	0.75	.39
Social support, poor	0.94	(0.46-1.89)	0.03	.86	0.98	(0.46-2.10)	0.00	.95	1.04	(0.54-2.00)	0.02	.90
Recent life events	1.24	(0.95-1.63)	2.45	.12	1.17	(0.88-1.57)	1.13	.29	0.95	(0.74-1.20)	0.21	.65

565 OR = odds ratio; CI = confidence interval; degrees of freedom for Wald χ^2 statistic = 1.

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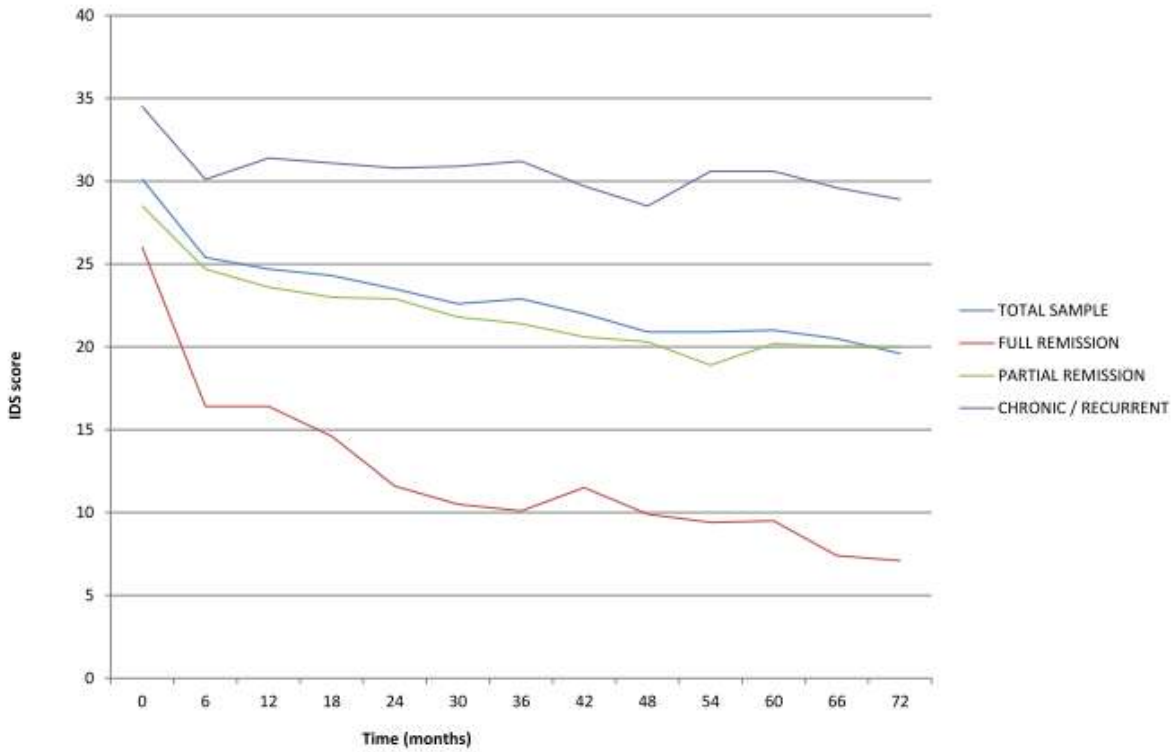
567 **Table 3. Prognostic factors associated with higher symptom levels of depression during six years from bivariate and multivariate linear mixed models analyses.**

	Bivariate models			Multivariate models, group wise			Multivariate model, final		
Prognostic factors	**β (SE)**	**p-value**	**df.**	**β (SE)**	**p-value**	**df.**	**β (SE)**	**p-value**	**df.**
Demographics									
Women	2.24 (1.60)	.16	198						
Age	-0.03 (0.12)	.79	199						
Education	0.04 (0.22)	.87	199						
a) Depression-related clinical factors				**group wise model a**					
Previous episode depression, yes	7.70 (2.52)	.003	191	-0.18 (2.19)	.93	165			
Age of onset of depression	-0.16 (0.04)	<.001	193	-0.08 (0.03)	.017	165	-0.06 (0.03)	.040	166
Severity depressive symptoms	0.55 (0.05)	<.001	198	0.40 (0.06)	<.001	167	0.32 (0.07)	<.001	168
Comorbid anxiety diagnosis, yes	3.73 (1.51)	.014	198	0.88 (1.23)	.48	165			
Severity anxiety symptoms	0.51 (0.06)	<.001	189	0.22 (0.07)	.002	168	0.11 (0.07)	.11	170
Global Cognitive Functioning	-0.57 (0.46)	.22	201						
Apathy	0.69 (0.14)	<.001	188	0.30 (0.12)	.011	166	0.15 (0.12)	.20	166
Sleep problems	0.57 (0.14)	<.001	190	-0.09 (0.13)	.48	165			
Use of antidepressants, yes	-0.52 (1.70)	.76	196						
Use of benzodiazepines, yes	-0.25 (1.56)	.87	198						
b) Health and lifestyle factors				**group wise model b**					
Chronic diseases	2.70 (0.45)	<.001	198	1.43 (0.43)	.001	187	0.68 (0.39)	.084	165
Functional Limitations	0.41 (0.05)	<.001	192	0.25 (0.06)	<.001	187	-0.05 (0.06)	.46	168
Metabolic syndrome, yes	3.92 (1.61)	.015	199	-0.68 (1.52)	.66	188			
Chronic Pain, yes	7.80 (1.39)	<.001	198	4.22 (1.32)	.002	188	2.60 (1.21)	.033	167
Body-Mass-Index	0.81 (0.17)	<.001	201	0.46 (0.17)	.009	189	0.23 (0.14)	.12	167
Physical activity, low	-1.41 (1.79)	.43	193						
Smoking, yes	0.92 (1.77)	.60	198						
Alcohol use	-0.47 (0.21)	.025	196	-0.14 (0.18)	.43	186			
c) Psychological and social factors				**group wise model c**					
Neuroticism	0.89 (0.11)	<.001	188	0.73 (0.11)	<.001	185	0.24 (0.12)	.043	167
Childhood Trauma Index	1.56 (0.64)	.015	198	0.81 (0.55)	.15	184			
Partner, no	1.15 (1.50)	.44	198						
Loneliness	1.18 (0.21)	<.001	188	0.70 (0.20)	.001	185	0.39 (0.18)	.036	166
Social support, poor	-0.19 (1.50)	.90	197						
Recent life events	0.53 (0.56)	.35	198						

568 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 contains 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 ($\chi^2(7) = 2370.073$, $p<.001$), model b ($\chi^2(6) = 607.702$, $p<.001$), model c ($\chi^2(3) = 956.429$, $p<.001$), final model ($\chi^2(10) = 2042.444$, $p<.001$).

575 Figure 2.



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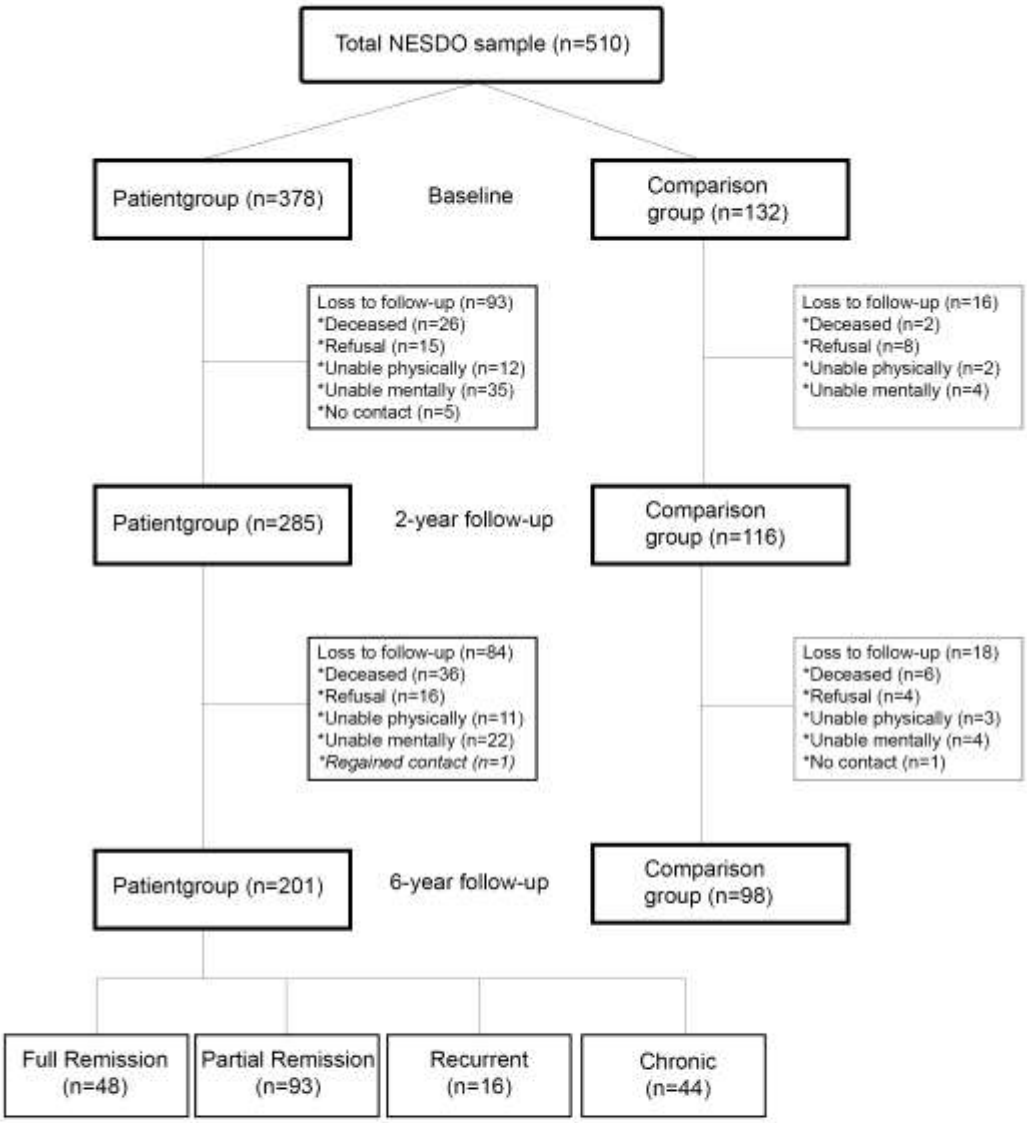

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