Associations between age and the course of major depressive disorder: a 2-year longitudinal cohort study

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Summary

Background Although there is some evidence that older people might have a poorer course of major depressive disorder (MDD) than younger or middle-aged people, and that age-related course differences might affect the optimisation of MDD treatment, large-scale studies with a broad age range, including consistent course assessments, are needed to properly address this issue. Therefore, we aimed to longitudinally examine whether older age was associated with a poorer naturalistic course trajectory of MDD than that of younger ages and to establish which prognostic—clinical, social, and health—factors could explain this potentially poorer course.

Methods For this longitudinal cohort study, we used baseline and 2-year follow-up data from the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Study of Depression in Older Persons (NESDO) cohorts. People aged between 18 and 88 years, with an MDD diagnosis at baseline, and a valid clinical assessment at 2-year follow-up were included. The primary outcome was the 2-year course of MDD, which was assessed by use of four indicators: having a depression diagnosis (MDD or dysthymia) after 2 years, having a chronic symptom course (depressive symptoms present during 80% or more of the 2-year follow-up period), time to remission, and depression severity change. We used multivariate analyses to examine associations between continuous age and these MDD course indicators. We also examined whether prognostic clinical (eg, comorbid anxiety), social (loneliness and social support), and health (body-mass index, pain, and chronic diseases) factors contributed to the differences in the course of MDD between age groups.

Findings Between 2004–2012, baseline and 2-year follow-up data were obtained for 1042 participants from the NESDA and NESDO cohorts, of whom 690 (66%) were women. Older age was significantly associated with a worse 2-year MDD course for all four indicators (MDD diagnosis: odds ratio [OR] 1·08, 95% CI 1·00–1·17; chronic symptom course: OR 1·24, 1·13–1·35; time to remission: hazard ratio [HR] 0·91, 0·87–0·96; and depression severity change: regression coefficient 1·06, p<0·0001; all per 10-year increase). The course of MDD worsened linearly with age, and people aged 70 years or older had the worst outcomes compared with those of the reference group of people aged 18–29 years (MDD diagnosis: OR 2·02, 95% CI 1·18–3·45; chronic symptom course: OR 3·19, 1·74–5·84; time to remission: HR 0·60, 0·44–0·83; and depression severity change: –12·64 [SD 10·85] in those aged 18–29 years and –5·57 [11·14] in those aged 70 years or older). These results were slightly reduced, but remained mostly significant when adjusting for prognostic clinical, social, and health factors.

Interpretation Older age was found to be a consistent and important risk factor for a poorer MDD course, which could not be explained by a range of well established risk factors. Further investigation of potential underlying mechanisms—including the effect of cognitive impairment, for example—is needed to prevent the negative consequences of a long-term MDD burden in older people.

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Introduction

Almost one in five adults is expected to have at least one episode of major depressive disorder (MDD) sometime during his or her life,[1,2] but the course of such an episode can be highly variable. According to systematic reviews[3,4] on the course of depression, older people seem more likely to have a chronic depression course than younger peers. A systematic review,[5] published in 2005, found that older populations (65 years or older) showed remission rates and response to treatment similar to those of middle-aged people, whereas relapse rates seemed higher in older age. However, this conclusion was based on a comparison of different studies that were not always similar in terms of their populations and measurement instruments. Some of the included studies had small sample sizes or insufficient adjustment for confounding factors, such as sociodemographic and clinical characteristics. Additionally, by only comparing middle-aged people with older people, differences between these ages and younger age groups and differences within age groups (eg, younger-old *vs* older-old) were not taken into account. Consequently, there is

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and reference lists from previously identified studies for relevant literature published in English before Aug 31, 2017. In this search, we used terms related to ageing ("age", "older persons") and depression ("depress*") and to course and prognosis ("course", "prognos*") in combination. Few previous studies directly compared course outcomes of major depressive disorder in different age groups; one systematic review was done in 2005, comparing course outcomes of middle-aged participants with those of older participants. This study showed similar remission rates and response to treatment for older people compared with those of middle-aged people, whereas relapse rates seemed higher in older age. However, no information was provided about younger adults, and the studies included in the review did not take a wide range of other prognostic factors into account when trying to explain age differences in the course of depression, or used small samples. Therefore, there was insufficient unequivocal evidence that older people have a poorer course of major depressive disorder than younger or middle-aged people, because this association required a large-scale study with a broad age range, including consistent course assessments.

Added value of this study

In a large sample with a wide age range (18–88 years), we found the 2-year course of major depressive disorder to be substantially poorer in older age compared with that of younger ages, a result that was consistent across various operationalisations of course outcome with multiple variables. We also showed that this poorer course could not be explained by recruitment differences, sample selection, or a wide range of clinical, social, and health factors. To our knowledge, ours is the first study to include a large sample of participants representing the entire adult lifespan, use clinical diagnoses of major depressive disorder and various course indicators, and take a wide range of other relevant prognostic factors into account.

Implications of all the available evidence

Our findings suggest a growing need for age-tailored treatment of major depressive disorder. Older people are given treatment guidelines that are almost similar to those used for younger patients, but our findings suggest that older people might need multidisciplinary and highly structured treatment, including closer monitoring of effects by use of collaborative care, because major depressive disorder in this life phase appears to be much more persistent than in other phases.

insufficient unequivocal evidence that older people truly have a poorer MDD course, because it requires a large-scale study that includes a broad age range and consistent course assessments. Older age might be a prognostic factor for MDD course[6] because of the increased likelihood for other unfavourable prognostic factors to occur, such as being widowed, having a small social network or low family support,[7–9] somatic diseases,[4,8–12] physical and functional impairment,[4,8,9] and cognitive decline,[10] which can all affect the naturalistic course. A history of depression and recurrent depressive episodes is also associated with a worse prognosis[3,10] and older people, by definition, have a higher chance of having had more episodes during their life course. On the one hand, all these factors suggest that the prognosis of MDD might be worse in old age than in younger ages. On the other, an increased depression burden during life might be associated with premature mortality, and people with an increased burden who do reach old age might have acquired effective coping skills, which might reduce differences between age groups in the course of depression.

The aim of this 2-year longitudinal cohort study was to examine whether there is indeed an association between age and the naturalistic course and prognosis of MDD and, for that purpose, we included a broad age range (18–88 years) and four different course indicators. To further understand potential differences between age groups, we also examined whether unfavourable prognostic factors that might differ between younger and older people (clinical characteristics, social and health factors) could explain the differences between age groups in the course of MDD. We hypothesised that the course of MDD would be more unfavourable for older people because of a higher prevalence of other unfavourable prognostic factors in older age.

For the **NESDA** see www.nesda.nl
For the **NESDO** see http://nesdo.onderzoek.io

Methods

Study design and participants

We combined data from two longitudinal multicentre cohort studies: the Netherlands Study of Depression and Anxiety (NESDA)[13] and the Netherlands Study of Depression in Older Persons (NESDO).[14] NESDA and NESDO used similar measurements and infrastructures, and investigated the natural course, determinants, and consequences of depression. Both studies are described in more detail elsewhere.[13,14]

For our study, we used baseline and 2-year follow-up data. At baseline, the NESDA sample comprised 2981 people aged 18–65 years with a diagnosis done in the preceding 6 months of a depressive or anxiety disorder (1701 of 2981), a remitted depressive or anxiety disorder (628 of 2981), or no history of depressive or anxiety disorders (652 of 2981). Recruitment took place in the general population (with an overall response rate of 56%), primary health care (45%), and outpatient mental health-care facilities (57%).[13] 87% (2596 of 2981) of people who enrolled in the study participated in the 2-year follow-up. Attrition in NESDA was due to participants not being able or willing to participate (328 [11%] of 2981),

not being able to be contacted (51 [2%] of 2981, with 12 [<1%] of those having moved abroad), and death of the participant (six [<1%] of 2981). The NESDO sample consisted, at baseline, of 510 participants aged 60–93 years, with a diagnosis present in the preceding 6 months of a depressive disorder (378 of 510) or no history of depressive or anxiety disorders (132 of 510). Recruitment took place in primary health care (response rate of 64%) and in both outpatient and inpatient mental health-care facilities (49%). At 2-year follow-up, 79% (401 of 510) of people who enrolled in the study still participated in NESDO. Within NESDO, attrition was due to not being able or willing to participate (76 [15%] of 510), not able to be contacted (five [1%] of 510—with one [<1%] of those having moved abroad)—and death of the participant (28 [5%] of 510). Inclusion criteria for both studies were only age-related: participants in NESDA had to be between 18 and 65 years of age. Exclusion criteria for both studies were an insufficient command of the Dutch language or insufficient capability to participate and a primary clinical diagnosis of a severe psychiatric disorder other than depressive and anxiety disorders. For NESDO, clinician-suspected dementia or having a Mini-Mental State Examination (MMSE)[15] score lower than 18 (of 30) was also considered an exclusion criterion. The presence of depressive or anxiety disorders was established by use of the DSM-IV-based Composite International Diagnostic Interview (CIDI, lifetime version)[16] and was done by trained research assistants.

Selection criteria for our study were the following: not being an inpatient, with an MDD diagnosis (and possibly comorbid dysthymia) in the preceding 6 months, and a depression severity score from the self-report Inventory of Depressive Symptomatology (IDS-SR)[17] of at least 14 (of 84) at baseline. Additionally, a valid clinical assessment at 2-year follow-up was required. Baseline face-to-face assessments were completed at participating centres between 2004 and 2007, for NESDA, and between 2007 and 2010, for NESDO. 2-year follow-up assessments took place between 2006 and 2009, for NESDA, and between 2009 and 2012, for NESDO. All participants provided written informed consent, and all ethical review boards of the participating centres provided approval.

Measures

We asked the sex, age, and years of education of participants during the baseline interview by use of standard questions. Baseline depression severity was assessed by use of the 30-item IDS-SR, with total scores ranging from 0 to 84.[17] The presence of a comorbid DSM-IV-based anxiety disorder in the preceding 6 months, whether the MDD episode was a first episode or recurrent, and the number of self-reported MDD episodes (categorised into one, two, or three or more), were established by use of the CIDI interview.[16] Anxiety severity was measured by use of the 21-item Beck Anxiety Inventory.[18] Finally, antidepressant use was defined according to the WHO Anatomical Therapeutic Chemical (ATC) classification[19] and was categorised as use of tricyclic antidepressants (ATC-code N06AA), selective serotonin reuptake inhibitors (ATC-code N06AB), or other antidepressants (ATC-codes N06AF, N06AG, N06AX).

In our analyses, we included social (loneliness, social network size, and social support) and health factors (functional impairments, pain, chronic diseases, body-mass index [BMI]), which were operationalised as previously described.[20] Loneliness was assessed by use of the 11-item Loneliness and Affiliation Scale, ranging from 0 (no loneliness) to 11 (very severe loneliness).[21] Participants were asked about their social network size by use of standard questions, depicting the number of adults with whom participants had regular and important contacts. Social support was measured by use of the Close Person Inventory,[22] in which questions about confiding and emotional support, practical support, and negative aspects of relationships were assessed for a partner, a first confidant, and a second confidant. For participants who had no partner, the partner items were coded as missing. For participants who had no first or second confidant, confidant items were coded as zero. Social support was expressed as the mean of all items across all three relationships, with items belonging to negative aspects of relationships recoded. Functional impairments were assessed by use of the self-report 36-item WHO Disability Assessment Schedule II.[23] Examples of daily activities that were included in the assessment were mobility, self-care, and participation in society. Pain was assessed by use of the Chronic Pain Grade,[24] on which participants were categorised into five grades on the basis of a combination of pain intensity and pain disability: grade 0 (no pain symptoms), grade 1 (low pain intensity, low disability), grade 2 (high intensity, low disability), grade 3 (high disability, moderately limiting), and grade 4 (high disability, severely limiting). Furthermore, the number of chronic diseases that participants had under treatment was ascertained.[25] Chronic diseases included were lung disease, heart disease, diabetes, stroke, osteoarthritis, cancer, ulcers, intestinal disease, liver disease, epilepsy, and thyroid disease. BMI was calculated with measured weight and height (kg/m^2).

Outcomes

The primary outcome of this study was the 2-year course of MDD, which was assessed by use of four course indicators that describe the development of depression over time. At baseline, depression diagnoses and depression severity (total score range 0–84) were established by use of the CIDI,[16] for diagnoses, and the IDS-SR,[17] for severity. The CIDI and IDS-SR were used again to ascertain the presence of depression diagnoses and depression severity at the 2-year follow-up. Additionally, at 2-year follow-up, the Life Chart Interview was completed to assess the presence of depressive symptoms between the two timepoints. The Life Chart

Interview has been described in detail elsewhere[26] and has been shown to be valid and reliable.[27] Briefly, in the Life Chart Interview, participants reported presence (yes or no) and severity (no severity or minimal, mild, moderate to severe, or very severe) of depressive symptoms for each month of the 2-year follow-up period. This was done by use of a calendar method in which life events were reported to better recall feelings of depression in those time periods. When symptoms were of at least mild severity, they were considered present in that month.

The CIDI, Life Chart Interview, and IDS-SR were used to create the four course indicators, capturing various ways in which depression can develop over time. First, the presence (yes or no) of 6-month depression diagnoses (MDD, dysthymia, or both) after 2 years was ascertained on the basis of CIDI data. Second, a chronic course of depressive symptoms (yes or no) was assessed with Life Chart Interview data and considered present when depressive symptoms of at least mild severity were felt for at least 80% of the time during the 2-year follow-up period. Third, time to remission was also calculated with Life Chart Interview data and displayed the time since baseline assessment to the first timepoint at which no depressive symptoms or symptoms of mild severity were reported for 3 consecutive months. Fourth, depression severity change was defined as the depression severity score at 2-year follow-up minus the baseline depression severity.

Statistical analysis

Throughout our main analyses, age was used as a continuous measure. For interpretative purposes, we computed continuous age as per 10-year increase, so that odds ratios and other effect sizes could be interpreted per 10-year increase in age rather than per 1-year increase. To provide insight into the course of depression at multiple timepoints throughout the adult lifespan, we also provided information for six age categories separately: 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and 70 years or older. All social and health variables were used as a continuous measure.

Percentages and means for baseline characteristics and 2-year course indicators were provided across age groups. Additionally, these characteristics were associated with continuous age in simple regression analyses, with age as the outcome measure. For all four 2-year depression indicators, we provided unadjusted percentages, means, and incidence rates across all age categories. Again, associations between these indicators and continuous age were also assessed with simple linear regression analyses. We examined associations between continuous age (per 10-year increase) and presence of a depression diagnosis after 2 years with logistic regression. We used three adjustment models: the first model adjusted for sex and years of education, the second model additionally adjusted for clinical covariates that showed significant associations with continuous age at baseline, and the third model additionally adjusted for prognostic covariates (social and health factors) that showed significant associations with continuous age at baseline. We then analysed the association between age and having a chronic course of depression (yes or no) in the same way. We analysed the association between age and time to remission with a Cox proportional hazards analysis. Time to remission was the dependent variable and we calculated this as the number of months between baseline and remission. If no remission was reached, we censored time to remission at 24 months. The same prognostic covariates were included. Finally, we assessed the association between age and depression severity change with multiple linear regression analysis. In addition to covariates, this analysis was also adjusted for baseline depression severity.

Because recruitment differences existed between NESDA and NESDO (eg, NESDA also recruited from the general population, whereas NESDO did not), we wanted to explore whether selection bias possibly threatened our findings. Therefore, we did our main analyses in three stratified subsamples. Stratification was done by recruitment setting (primary care *vs* specialised mental health care), by cohort (NESDA *vs* NESDO), and by antidepressant use (people using antidepressants *vs* people not using them). We did these analyses for the second model of our main analyses, with the exception that the stratified analyses for antidepressant use were not adjusted for antidepressant use. We also pooled findings for the stratified subsamples.

We also did a sensitivity analysis (for the second model only) omitting participants with an MMSE score lower than 25, to further take potential selection bias into account.

Because of the presence of missing values, especially for the prognostic covariates (from two [0·2%] of 1042 missing for BMI to 94 [9%] of 1042 missing for loneliness), we imputed missing values by use of a multiple imputation (five imputation sets), in which age and all socio-demographic, clinical, and prognostic covariates were used as predictors. Subsequently, pooled estimates were provided for all multivariable analyses. An α of 5% was used to ascertain statistical significance, and analyses were done in SPSS, version 22. To pool the stratified analyses, the rmeta package in R (version 3.4.4) was used, with a random-effects model.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Following application of our selection criteria to the NESDA and NESDO cohorts, a sample of 1042 participants (832 from NESDA, 210 from NESDO)

was included in analyses. Figure 1 displays how the sample was established and what reasons explained missing data at 2-year follow-up. Within the final sample of 1042 participants, three (<1%) participants from the NESDO cohort had missing data on the Life Chart Interview, and 36 (3%) participants had no IDS-SR data, 35 of whom were from the NESDA cohort and one from the NESDO cohort. Consequently, analyses for the indicators chronic course of depression and time to remission were based on 1039 (>99%) participants, and analyses for the indicator depression severity change were based on 1006 (97%) participants.

Baseline characteristics were assessed across the six age groups. The age range in our study was 18–88 years. In older age groups, there was a higher percentage of participants using antidepressants than in younger age groups. The numbers of previous MDD episodes and chronic diseases were also higher in the older age groups, as were the levels of loneliness, BMI, and pain. In older age groups, the number of women, years of education, percentage of participants with anxiety disorders, and social support were lower (table 1) than in younger age groups. Age was unrelated to the severity of depression or anxiety, having a first or recurrent MDD episode, functional impairments, and social network size.

Table 2 shows unadjusted means, percentages, and remission rates for the MDD course indicators across multiple age groups. Various MDD course indicators were more unfavourable in older than in younger age groups. For instance, a depression diagnosis was still present after 2 years in 36% (61 of 170) of the people aged 18–29 years, but in 51% (50 of 99) of people aged 70 years or older, which was even clearer in the chronic course outcomes (18·2% in 18–29 years *vs* 40·6% in 70 years or older). Additionally, the 2-year change in depression severity scores showed a much stronger decline in the 18–29 year group than in the 70 years or older group. For time to remission, the (unadjusted) Kaplan-Meier graph (appendix) showed a steady pattern in which time to remission was longest for participants in the oldest age categories.

Table 3 shows adjusted analyses with continuous age as a predictor for the MDD course outcomes. As can be seen in table 3, model 1, continuous age was significantly associated with all four course indicators of MDD (depressive disorder: odds ratio [OR] 1·08, 95% CI 1·00–1·17; chronic course: OR 1·24, 1·13–1·35, time to remission: hazard ratio [HR] 0·91, 0·87–0·96; and depression severity change: regression coefficient 1·06, p<0·0001). To view the age trend in more detail, we provided a graphic representation of course indicators across the six age groups in figure 2, showing that all four course indicators were least favourable for participants aged 70 years or older. The strongest age-related effects were found in the indicators presence of a chronic course of depression and mean depression severity change. The greater likelihood of older people to still have a depression diagnosis after 2 years compared with that of younger age groups was mainly driven by the increased likelihood of older people to have a dysthymia diagnosis after 2 years. People aged 70 years or older showed the worst outcomes compared with those of the youngest age group (18–29 years, the reference group) in the presence of a depressive disorder (OR 2·02, 95% CI 1·18–3·45), chronic symptom course (OR 3·19, 1·74–5·84), and time to remission (HR 0·60, 0·44–0·83). Additionally, mean depression severity change was –12·64 (SD 10·85) in those aged 18–29 years, and only –5·57 (11·14) in those aged 70 years or older (adjusted means). For most indicators, the course of depression seemed to worsen linearly with age. Only in presence of any depression diagnosis were there differences that seemed to be smaller between the older age groups than those between younger age groups.

To check whether associations between age and course indicators could be better explained in a non-linear manner, we did post-hoc analyses for model 1, including a quadratic continuous age term while adjusting for the linear continuous age term. We only found one significant quadratic association, between age and presence of

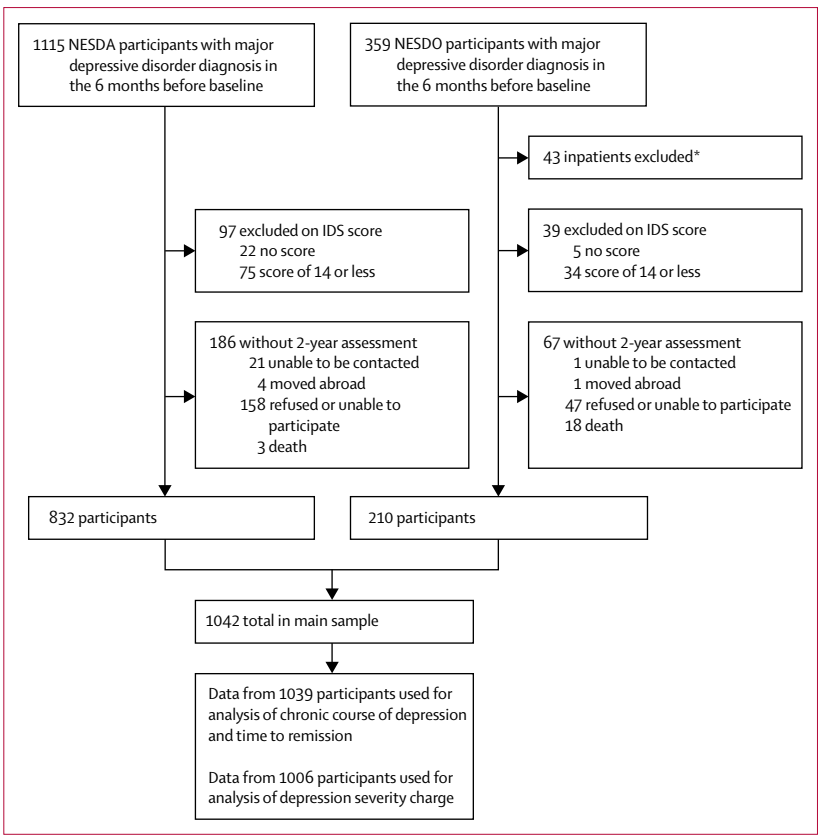

Figure 1: **Flowchart of the selection of participants and reasons for attrition between baseline and 2-year follow-up**
NESDA=Netherlands Study of Depression and Anxiety. NESDO=Netherlands Study of Depression in Older Persons. IDS=Inventory of Depressive Symptomatology. *NESDA had no inpatients; to have comparable samples, inpatients from NESDO were excluded.

See Online for appendix

	18–29 years; n=170	30–39 years; n=183	40–49 years; n=229	50–59 years; n=193	60–69 years; n=168	≥70 years; n=99	Age continuous; B (p value)
Demographic characteristics							
Age	24·11 (3·31)	34·43 (2·92)	44·47 (2·80)	54·12 (2·82)	63·61 (2·81)	77·11 (5·15)	..
Sex, women	130 (76%)	130 (71%)	141 (62%)	122 (63%)	101 (60%)	66 (67%)	−2·29 (0·031494)
Years of education	11·87 (2·75)	12·09 (3·46)	11·12 (3·18)	11·52 (3·32)	11·19 (3·39)	10·02 (3·43)	−0·68 (<0·0001)
Clinical characteristics							
Had an ongoing first episode at baseline	90 (53%)	87 (48%)	102 (45%)	86 (45%)	80 (48%)	47 (47%)	1·09 (0·28)
Number of episodes	..	..	..	..	..	..	2·15 (<0·0001)
One	90 (54%)	87 (49%)	102 (47%)	86 (46%)	45 (28%)	26 (28%)	..
Two	14 (8%)	18 (10%)	20 (9%)	23 (12%)	32 (20%)	23 (25%)	..
Three or more	64 (38%)	73 (41%)	95 (44%)	77 (41%)	83 (52%)	43 (47%)	..
Depression severity	31·74 (9·93)	33·32 (10·57)	35·02 (11·43)	34·67 (10·93)	33·22 (10·87)	32·29 (11·09)	0·02 (0·65)
Had simultaneous anxiety and depression diagnoses	109 (64%)	115 (63%)	149 (65%)	132 (68%)	87 (52%)	26 (26%)	−5·55 (<0·0001)
Anxiety severity	16·82 (9·41)	18·16 (11·15)	19·14 (10·76)	18·76 (10·93)	18·10 (10·57)	19·52 (11·70)	0·07 (0·12)
Antidepressant use	56 (33%)	77 (43%)	117 (51%)	98 (51%)	91 (55%)	72 (73%)	7·03 (<0·0001)
Social factors							
Loneliness	5·51 (3·47)	6·14 (3·41)	6·92 (3·33)	6·47 (3·71)	6·86 (3·39)	6·82 (3·28)	0·45 (0·002735)
Social network size	2·70 (0·94)	2·42 (0·85)	2·40 (0·98)	2·24 (0·99)	2·44 (1·09)	2·57 (1·21)	−0·63 (0·21)
Social support	26·49 (13·38)	27·68 (12·82)	24·14 (14·23)	24·17 (13·78)	21·54 (12·99)	24·49 (14·16)	−0·11 (0·002293)
Health factors							
Functional impairments	26·43 (10·86)	28·88 (11·59)	29·90 (11·72)	28·49 (12·58)	27·93 (11·11)	25·70 (12·19)	−0·01 (0·76)
Pain	1·66 (0·95)	1·98 (1·20)	2·16 (1·22)	2·09 (1·10)	2·07 (1·16)	2·06 (1·35)	1·30 (0·002647)
Number of chronic diseases	0·32 (0·55)	0·51 (0·79)	0·72 (0·95)	1·18 (1·12)	1·57 (1·26)	1·73 (1·23)	6·48 (<0·0001)
Body-mass index	23·93 (5·02)	25·93 (5·65)	26·29 (5·70)	27·39 (5·11)	26·80 (4·64)	25·94 (4·44)	0·40 (<0·0001)

Data are mean (SD) or n (%). B=regression coefficient. Data are unadjusted and non-imputed; n values of some variables can be lower than those of the respective age group.

Table 1: **Baseline characteristics across six age categories and linear associations with continuous age**

	18–29 years; n=170	30–39 years; n=183	40–49 years; n=229	50–59 years; n=193	60–69 years; n=168	≥70 years; n=99	Age continuous; B (p value)
Had a persistent depression diagnosis	61 (36%)	84 (46%)	114 (50%)	98 (51%)	84 (50%)	50 (51%)	2·30 (0·022479)
Major depressive disorder	59 (35%)	77 (42%)	97 (42%)	90 (47%)	76 (45%)	45 (45%)	1·91 (0·060765)
Dysthymia	20 (12%)	41 (22%)	53 (23%)	55 (28%)	43 (26%)	28 (28%)	3·86 (0·001232)
Had a chronic symptom course	31 (18%)	36 (20%)	58 (25%)	61 (32%)	56 (33%)	39 (41%)	5·59 (<0·0001)
Time to remission	19·31	17·50	12·50	9·02	8·64	6·26	..
Depression severity change	−11·80 (11·06)	−10·63 (12·43)	−10·99 (12·01)	−8·58 (9·73)	−8·37 (10·81)	−5·53 (12·81)	0·21 (<0·0001)

Data are mean (SD) or n (%), unless otherwise noted. Data are unadjusted and non-imputed; n values of some variables can be lower than those of the respective age group. Time to remission is presented as incidence per 100 person-months.

Table 2: **2-year depression course indicators across six age categories and linear associations with continuous age**

dysthymia (data not shown). Therefore, associations between age and 2-year course indicators of MDD seemed to be linear.

To rule out selection bias as a possible explanatory factor for this age trend, we did analyses among stratified subsamples. Associations between age and the four 2-year MDD indicators were stratified for recruitment setting, cohort, and antidepressant use (appendix). For the majority of associations in the subsamples, the magnitude of the age–MDD course association is similar or even larger than that of the original findings. For two course indicators (having a chronic course and time to remission), the estimates were slightly lower in the NESDO subsample than in the NESDA subsample, which could be due to either the smaller sample size or the smaller age range (60–88 years) of this analysis. However, for the other two course indicators (presence of depressive disorder and change in depression severity), effect sizes were slightly larger in the NESDO subsample than in the NESDA subsample. Pooled findings across the stratified subsamples also showed that age–MDD course findings remained present. An additional sensitivity analysis done only in participants with an MMSE score higher than 25 (1035 [99%] of 1042) showed results similar to our initial

findings of a more unfavourable course with older age (data not shown).

Because age was associated with some clinical and other prognostic indicators (table 1), we examined whether these indicators explained the unfavourable effect of age on MDD course. Table 3 shows that, after adjusting for the number of MDD episodes, comorbid anxiety, and antidepressant use covariates (model 2), older age remained significantly associated with increased odds of still having a depression diagnosis (MDD and dysthymia) and chronic symptom course, a reduced likelihood of reaching remission, and a reduced decrease in depression severity.

Additional adjustments for loneliness, social support, pain, number of chronic diseases, and BMI (table 3, model 3) only reduced age associations slightly. For three of four indicators (having a chronic course, time to remission, and depression severity change), a significant association between continuous age and depression was still present. For the presence of any depression diagnosis (but also for MDD and dysthymia separately), associations with age lost significance. This loss was mostly caused by the adjustment for loneliness, as it was the only significant prognostic factor in the model. Looking at effect sizes rather than significance, and after adjusting for clinical characteristics with model 2, the strength of associations hinted more strongly than significance in the model 1 results towards a more unfavourable course in older people. After additionally including social and health factors with model 3, associations with most indicators only reduced slightly, as coefficients changed between 2% and 5% for three of four indicators (data not shown). The more unfavourable findings towards older age only decreased to a somewhat larger extent when adding social and health factors for depression severity change (the regression coefficient decreased by 26%).

	Model 1	Model 2	Model 3
Presence of any depression diagnosis (n=1042)	1·08 (1·00–1·17, 0·0406)	1·11 (1·02–1·20, 0·0160)	1·05 (0·98–1·18, 0·34)
Presence of major depressive disorder	1·07 (0·99–1·15, 0·0891)	1·08 (1·00–1·17, 0·0613)	1·02 (0·96–1·15, 0·68)
Presence of dysthymia	1·15 (1·05–1·26, 0·0019)	1·18 (1·06–1·30, 0·0008)	1·16 (1·05–1·32, 0·0079)
Chronic symptom course (n=1039)	1·24 (1·13–1·35, <0·0001)	1·25 (1·10–1·37, <0·0001)	1·18 (1·04–1·31, 0·0023)
Time to remission (n=1039)	0·91 (0·87–0·96, <0·0001)	0·91 (0·87–0·96, <0·0001)	0·94 (0·88–0·99, 0·0150)
Depression severity change (n=1006)	1·06 (0·21, <0·0001)	1·20 (0·22, <0·0001)	0·78 (0·24, 0·0012)

Data are odds ratio (95% CI, p value) for presence of any depression diagnosis, major depressive disorder, or dysthymia and chronic symptom course; hazard ratio (95% CI, p value) for time to remission; and regression coefficient (SE, p value) for depression severity change. Model 1 is adjusted for sex and years of education. Model 2 is additionally adjusted for the number of major depressive disorder episodes, anxiety diagnosis, and antidepressant use. Model 3 is additionally adjusted for social factors (loneliness and social support) and health factors (pain, chronic diseases, and body-mass index). Depression severity change analysis was additionally adjusted for baseline depression severity.

Table 3: **Pooled estimates for linear associations between continuous age (per 10-year increase) and the 2-year course of depression**

Discussion

This large-scale study among people aged 18–88 years showed that, compared with younger peers, the naturalistic 2-year course of MDD mostly worsens linearly with age. In the oldest age group, this worsening was reflected in a two to three times higher likelihood of still having a depression diagnosis after 2 years, in a more chronic symptom course, in a smaller likelihood of reaching remission, and in less improvement in depression severity, compared with the indicators of younger age groups. In a previous meta-analysis, Mitchell and colleagues[5] found that middle-aged and older people showed rather similar remission rates. Our findings showed that, when taking more course indicators into account, the situation is less optimistic than previously suggested. However, findings might be hard to compare because this is the first study to examine age differences in the course of MDD within a naturalistic design, with uniform assessments across the entire adult age span.

The more unfavourable course of MDD towards old age was only explained to a small extent by clinical, social, and health factors that are common in old age and that are thought to worsen the course of the disease.[3,4,7–12] First, having a first MDD episode and depression severity at baseline were unrelated to age and could not have caused an imbalance between age groups at the starting point. The other explanatory factors that were included in our analyses, when added simultaneously to the statistical model, were not associated with the 2-year MDD course indicators, with the exception of loneliness. Additionally, apart from depression severity change, the effect sizes of all course indicators were only slightly reduced when adjusting for clinical, social, and health factors. The larger decrease for depression severity can be explained by the larger item overlap between the IDS-SR and social and health factors included in our analyses (eg, loneliness and somatic symptoms).

In a previous study,[20] we showed that some risk factors were more strongly associated with MDD when they occurred in an age phase in which they were least common and expected—eg, the number of chronic diseases, which is assumed to be highest in older age, was most strongly associated with MDD in people aged 18–39 years. These risk factors concerned aspects of poor health, such as BMI, pain, and number of chronic diseases. The combination of the results of that study with our current findings that these risk factors only slightly explained the unfavourable course of MDD in older age suggests that the importance of co-existing physical health problems in late-life depression might be somewhat overestimated.

Our findings might be explained by differences in the use of psychotherapeutic treatment or the suboptimal antidepressant treatment of MDD. We did not examine psychotherapeutic treatment but, compared with younger

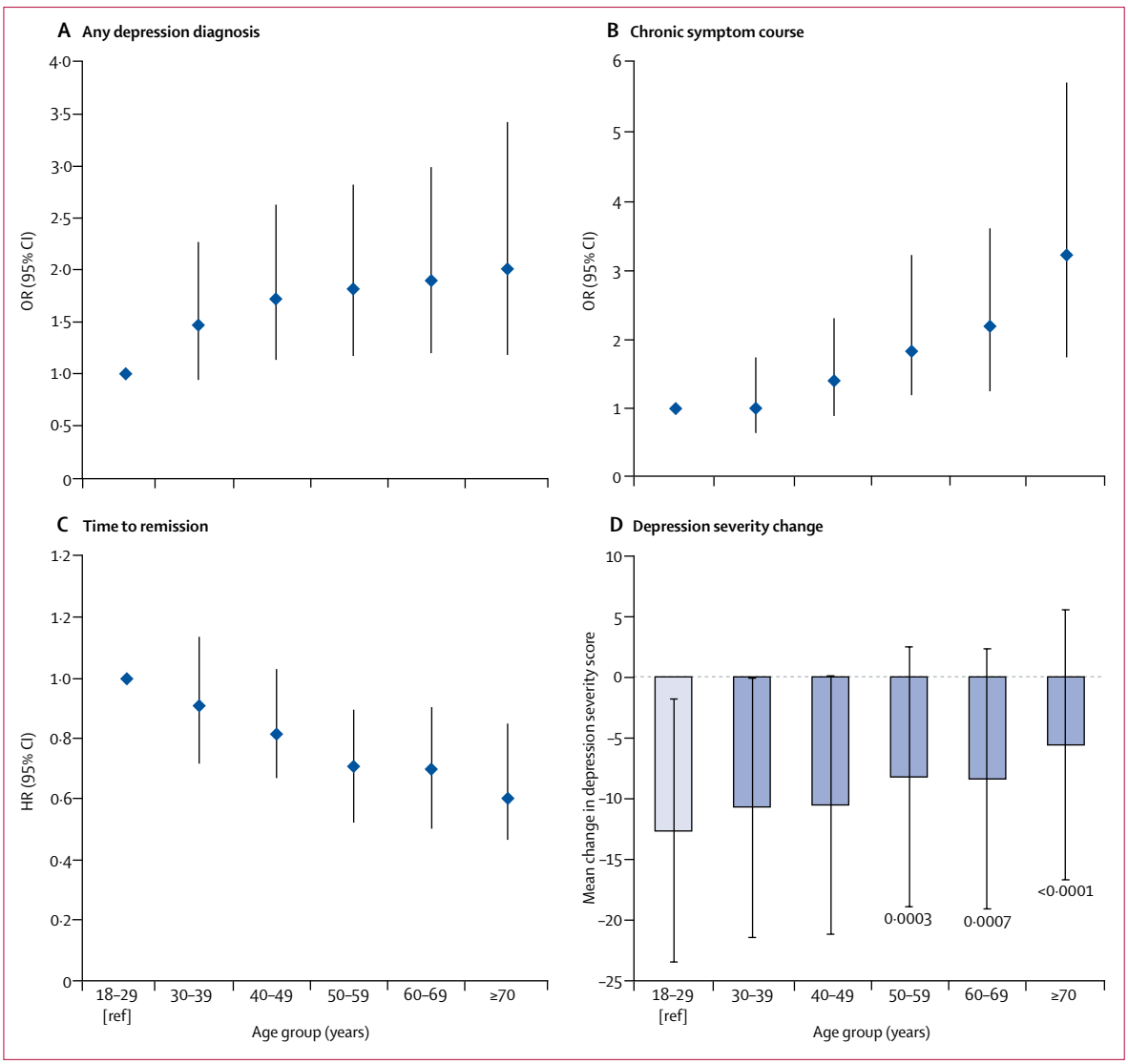

Figure 2: **Associations between age and 2-year depression outcomes**
(A) Odds ratio (OR) and 95% CI for the association between age groups and participants still having a depressive disorder after 2 years. (B) OR and 95% CI for the association between age groups and participants having a chronic symptom course over 2 years. (C) Hazard ratio (HR) and 95% CI for the association between age groups and time to remission within the 2-year follow-up period. (D) Mean change in depression severity score during the 2-year follow-up period, adjusted for baseline depression severity; error bars represent the SD. All analyses were adjusted for sex, education, number of major depressive disorder episodes, anxiety diagnosis, and antidepressant use. [ref]=reference age group.

adults, this type of treatment is less often provided in older age.[28] In our study, older age groups were more likely to use antidepressants than younger age groups. It has been suggested that the effectiveness of antidepressants in older ages can be impaired because of medical comorbidity, frailty, and drug–drug interactions.[29] We cannot comment about the effectiveness of antidepressant treatment in this study. However, adjustment for antidepressant use at baseline did not substantially change our findings, and stratified analyses for participants who did and did not use antidepressants revealed consistent age–MDD course associations for both subsamples. These results suggest that our findings are not only due to potential differences in treatment response. A known factor involved in MDD in older adults is reduced cognitive functioning,[10,30] which was not assessed in NESDA and, therefore, could not be included in our analyses. It has been shown that cognitive decline hampers recovery from MDD and reduces treatment effectiveness.[31] Although suspected dementia and a low score on the MMSE were exclusion criteria for the oldest participants, and a sensitivity analysis that excluded NESDO participants with an MMSE score below 25 showed no differences, we cannot rule out that the presence of early phase dementia

in the oldest age group might have contributed to our findings. It is paramount to assess the role of cognitive impairment in subsequent studies attempting to unravel age differences in the course of MDD. Furthermore, although we included a range of explanatory health factors, specific aspects of health not considered in our study—such as physical fitness and cardiovascular or neurobiological functioning—might further explain age differences in the course of MDD. In NESDO, more participants died between baseline and follow-up than in NESDA. Our findings, therefore, might be slightly underestimated, assuming that mortality would be associated with poorer mental health. In general, some differences between NESDA and NESDO existed, mainly in the way that participants were recruited. However, several analyses of subsamples showed that our findings were robust across these different samples. Subsample analyses with NESDO data showed non-significant associations for three of four indicators, but this result might be related to the smaller sample size and more narrow age range (60–88 years) of NESDO, compared with NESDA (18–65 years), making it harder to establish an age trend. Looking at effect sizes, the magnitude of the association between age and having any depression diagnosis was even larger in NESDO than in NESDA. Overall, it seems unlikely that these cohort differences were responsible for the age differences found in this study. The strengths of this study include the large sample size and wide age range, providing us with the opportunity to not only directly compare age groups but also study the effects of age across almost the entire adult age span. We used clinical DSM-IV-based diagnoses to establish MDD and used both clinical diagnoses and self-report information to determine 2-year course indicators.

For clinical practice, our findings suggest that there might be a growing need for age-tailored treatment of MDD. Currently, older people are treated with almost similar treatment guidelines as those used in younger ages, but our findings suggest that older people might require more maintenance treatment.[32] Multidisciplinary and highly structured treatment, including closer monitoring of effects by collaborative care, might also be especially well suited to improve outcomes for late-life depression in the primary care setting.[33]

In conclusion, in our study, the 2-year natural course of MDD worsened linearly with increasing age. We could not explain the effect of age by including a range of well established clinical, social, and health factors. Although this conclusion raises the need to examine other explanatory factors, with cognitive impairment among the most important ones, it also shows that it is appropriate to implement optimal treatment or devise specific treatment regimens for depression in later life.

Contributors

RS formulated the research question, did the statistical analyses, wrote the manuscript, and incorporated feedback from co-authors. FL and RMK provided feedback in drafts of the manuscript, and critically interpreted the results. ATFB, BWJHP, and HCC reviewed and provided feedback for the research question, provided feedback in all drafts of the manuscript, and critically interpreted the results. BWJHP is the principal investigator of NESDA. HCC is the principal investigator of NESDO. All authors edited and approved the final manuscript.

Declaration of interests

BP has received research funding from Janssen Research and Boehringer Ingelheim, not related to this study. All other authors declare no competing interests.

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