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Depression, Depression Treatments, and Risk of Incident Dementia: A Prospective Cohort Study of 354,313 Participants

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ABSTRACT

BACKGROUND: The purpose of this study was to investigate the associations between courses of depression, the application of depression treatment, and the risk of incident dementia.

METHODS: In this prospective cohort study, 354,313 participants ages 50–70 years were recruited from the UK Biobank between 2006 and 2010 and were followed until 2020, with a total of 4,212,929 person-years. We initially studied the effect of depression on dementia incidence across 4 subgroups characterized by courses of depressive symptoms. Then, 46,820 participants with a diagnosis of depression were further categorized into treated and untreated groups. We compared the risk of dementia among different depression treatment groups in all participants who were depressed as well as 4 courses of depressive symptoms by performing survival analyses.

RESULTS: Depression was associated with a 51% higher risk of dementia, among which the increasing, chronically high, and chronically low courses were associated with increased dementia risk, while no association was found in the decreasing course. Compared to those who were depressed but untreated, receiving depression treatments corresponded to a hazard ratio of 0.7 (95% CI, 0.62–0.77). Among the 3 detrimental courses, treatments for increasing and chronically low symptoms of depression were associated with a 32% and 28% lower risk of dementia, respectively, while the reduction effect for chronically high symptoms was insignificant.

CONCLUSIONS: The negative association between depression treatment and incident dementia was significant in the increasing and chronically low courses, highlighting the necessity of timely interventional strategies before depression progresses to a chronically severe state.

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Dementia is a major and severe public health concern that exacerbates cognitive impairment, increases the mortality rate, and poses substantial global financial burdens (1). To date, no treatment for dementia has been able to slow its progression; thus, its prevention via modifiable risk factors is critical (2). Growing evidence implies that depression is one such modifiable risk factor, contributing to 4% of population attributable fraction (indicator calculating the number of dementia cases that probably resulted from depression among all risk factors) of dementia (1). Different effective treatments, primarily pharmacotherapies and psychotherapies, have been developed to treat depression (3) and may indirectly reduce the incidence of subsequent dementia (1,4). However, the associations between psychotherapy and subsequent dementia remain inadequately addressed (3). In addition, previous studies of pharmacotherapy yielded inconsistent results on whether pharmacotherapy for depression reduces the risk of subsequent dementia, with some positive (5,6), some negative (7), and others neutral (8,9) (Table S1). Further studies are required to clarify this discrepancy.

More importantly, older individuals appear to experience different patterns of depression symptoms over time (10,11). Conventional approaches that assess depression at a single time point neglect the remitting and relapsing nature of depression and therefore might not be suitable for studying long-term health outcomes. A dynamic categorization of depression might provide further insight into the complex correlation of depression and dementia. Previous research has revealed that the risk of incident dementia reportedly differs with different courses of depressive symptoms, with increasing course (i.e., mild initial symptoms that steadily increase) being related to a higher risk of dementia (12,13). However, to our knowledge, there have been no published studies on the effectiveness of depression treatments on different courses of depressive symptoms.

Therefore, we aimed to investigate associations between the courses of depressive symptoms, depression treatments, and the risk of incident dementia in a large population-based cohort. First, we studied the effect of depression on the incidence of dementia. Thereafter, we compared the risk of

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dementia among all treated and untreated patients with depression, as well as in 4 subgroups characterized by different courses of depressive symptoms. We hypothesized that the risk of dementia, which is elevated by depression in older individuals, would be lowered by depression treatments. In addition, intraindividual variability of depression courses might confer different risk of dementia as well as heterogeneity in the effectiveness of depression treatment in relation to dementia prevention.

METHODS AND MATERIALS

Participants

The UK Biobank (UKB) (https://www.ukbiobank.ac.uk/) is a nationwide, health-oriented, population-based prospective cohort study that recruited more than 500,000 participants. Detailed information about the UKB is provided in Population of the UK Biobank Cohort in Supplemental Methods.

For this study, we evaluated depressive symptom courses from January 1, 2000, to December 31, 2010 (the last date of baseline recruitment). Time 0 was defined as January 1, 2006. Participants were followed from recruitment until the date of incident dementia diagnosis or the date of end point (December 31, 2020), whichever came first. We further classified participants with depression at baseline into treated and untreated groups. The treated group was defined as receiving treatment from January 1, 2000, until 2 years before the end of follow-up. Timeline of this study is visualized in Figure S1.

The study population was restricted to individuals who were at least 50 years of age when recruited (157,142 excluded). We excluded 496 participants with dementia diagnosed before recruitment or depression onset and 11,208 participants who developed incident depression during follow-up to ensure that the courses of depression occurred before dementia onset. We further compared the baseline characteristics between the treatment-resistant depression (TRD) group [defined by at least 2 switches between antidepressants, each prescribed for at least 6 weeks (14)] and the non-TRD group. Nonresponse after the second medication switch was confirmed for subjects considered treatment resistant, and 6457 participants with TRD were excluded from the main analysis due to potential heterogeneity (Table S2). Among the depressed individuals identified, we further excluded 12,151 participants who received initial treatment within 2 years before the end of follow-up (end point for participants without dementia and the initial diagnosis date of participants with dementia) (15), intending to avoid insufficient treatment exposure period as well as causal reverse (12,16). The flowchart of the cohort and the study design is shown in Figure 1, while the evidence that supported the exclusion criteria is elaborated in Inclusion and Exclusion Criteria in Supplemental Methods. These analyses were conducted under UKB application number 19542.

Exposures

Depression was diagnosed by ICD-10 codes F31.0-F31.9 (depressive episode), F32.0-F32.9 (recurrent depressive disorder), Read Codes (Read Codes Clinical Terms versions 2 and 3, developed by National Health Services, used in the diagnosis of primary care in the United Kingdom) (17), and the UKB data showcases (field ID 20124, 20125) before December 31, 2010; and these were further categorized into remission, mild, moderate, or severe according to the ICD-10 codes, Read Codes, and rating determined by the UKB (Table S3). The rating of severity of depression in the UKB was based on structured and validated diagnostic criteria that applied a preestablished criterion to individuals' answers to the Structured Clinical Interview for DSM-IV Axis I Disorders and Patient Health Questionnaire (18,19). Categorization of participants was subsequently validated against other demographic and clinical information available from the UKB, and lifetime prevalence rates were consistent with other population-based estimates across both sexes (18). Linked hospital admission records (ICD-10 codes) and primary care diagnosis records (Read Codes) were also used to identify a primary or secondary diagnosis of depression and its severity.

The total length of depression course was 11 years (2000–2010) and was divided into 5 time points (2000–2002,

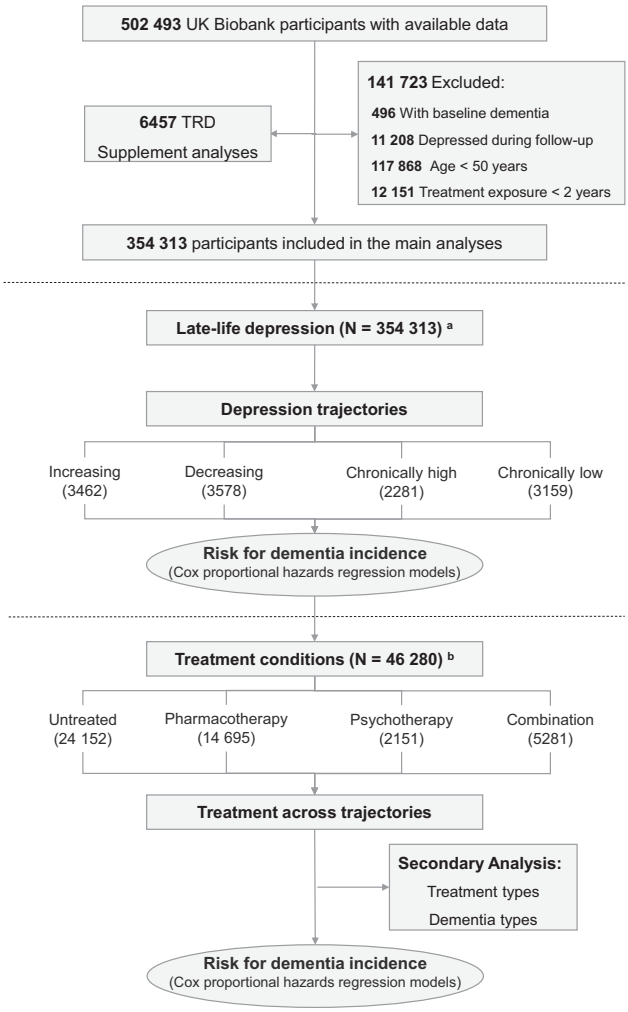

Figure 1. Eligible criteria and study profile. [a]N = number of total participants (including nondepressed and depressed participants). [b]N = number of depressed participants. TRD, treatment-resistant depression.

2003–2004, 2005–2006, 2007–2008, 2009–2010). The depression courses were defined by the records of at least 2 depression diagnoses during the 5 time points. Based on the severity, clinical diagnosis codes from hospital inpatients, primary care diagnosis, and results assessed by the UKB, we defined 4 distinct courses of depressive symptoms, including 1) new onset or deterioration of depression symptoms (increasing course); 2) remission or degradation of depression symptoms (decreasing course); 3) chronically severe depressive symptoms (chronically high course); and 4) the maintenance of mild or moderate depressive symptoms (chronically low course). The specific definitions of the 4 courses are provided in Defining the Four Depression Courses in Supplemental Methods as well as depicted schematically in Figure S2.

Treatment information included records of antidepressant use or psychotherapy attendance. Drug use information was categorized according to the British National Formulary codes 0403010 (tricyclic and related antidepressant drugs), 0403020 (monoamine oxidase inhibitors), 0403030 (selective serotonin reuptake inhibitors), 0403040 (other antidepressant drugs), Read Codes, and the UKB data showcases, which is detailed in Table S4. Psychotherapy attendance is categorized by Read Codes and results collected by the UKB, including attending cognitive behavioral therapy, group therapy, interpersonal therapy, mindfulness-based cognitive therapy, psychodynamics, family therapy, and others (Table S4). Participants with depression who never used antidepressants or received psychotherapy since January 1, 2000, were classified as the untreated group.

Outcomes

ICD-10 codes (20), including F00.0-9 (dementia in Alzheimer's disease [AD]), F01.0-9 (vascular dementia [VD]), F02.0-8 (dementia in other diseases classified elsewhere), F03 (unspecific dementia), and G30.0-9 (AD), were used to identify participants with dementia if one or more of these codes were recorded as a primary or secondary diagnosis in the health records or recorded as the underlying or contributory cause of death in the death registers. A subsample of the population was also retrieved from primary care data using Read Codes (version 2 or 3) (21). Detailed measurement of dementia is provided in Measurement of Incident Dementia in Supplemental Methods.

Data Analysis

Statistical analysis was conducted from April 1, 2021, to July 26, 2022. Baseline characteristics of participants are presented as mean (standard deviation) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Cox proportional hazards regression was used to investigate the associations of depression, depression courses, and depression treatments with incident dementia.

We fitted 3 models to account for potential confounding, with model 1 unadjusted and model 2 (the priority model) adjusted for age, sex, socioeconomic status, and qualification levels. For model 3, we reviewed 119 articles (Table S5) to develop a directed acyclic graph to characterize covariates that might be confounders (Figure S3) (22,23). These variables, including smoking, alcohol assumption, obesity, social interaction, and *APOE* $\varepsilon 4$ carrier status, were additionally adjusted in model 3. The data on covariates were obtained at baseline recruitment. Details of covariates are described in Table S6.

Proportional hazards of the associations between depression, depression treatments, and dementia risk were tested using scaled Schoenfeld's residuals without indication for a violation of the consumption (Figures S4, S5) (24).

Sensitivity analyses were further conducted to ensure the robustness of the findings. First, participants were stratified by age, sex, qualification, and socioeconomic status. Second, we combined the TRD population with the total depression population and investigated the effectiveness of treatment in the combined population. We also investigated the effects of depression treatment among TRD participants by performing survival analyses in samples restricted to the TRD population and untreated population. Third, the UKB recruited relatively healthy participants. By comparing the overall health rating (assessed by UKB, field ID 2178) between the general UKB population with that of primary care population, we found that overall UKB participants were healthier than participants from primary care (χ^2 test for disease status: $p < .001$). Thus, to mitigate potential selection and information bias (25), we performed additional analyses in which the population only consisted of 151,676 individuals in primary care. This approach allowed us to mimic real-world scenarios linking depression, depression treatment, and dementia.

We performed a secondary analysis to investigate whether hazard ratio (HR) differs in relation to specific types of outcomes or exposures. We initially investigated the heterogeneity between depression and dementia subtypes by categorizing dementia into AD (F00.0-9, G00.0-9), VD (F01.0-9), and other dementia (unspecific dementia [F03] and dementia in other diseases classified elsewhere [F02.0-8]). To capture potential discrepancy between antidepressant types, we disaggregated the pharmacotherapy group by prescriptions of selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) as well as by a more general classification of overall anticholinergics prescription (antidepressants with anticholinergic cognitive burden score) or nonanticholinergics prescription (26). For psychotherapy, we conducted a secondary analysis by restricting the psychotherapy group to those who received individual psychotherapy (psychotherapies that excluded group therapy and family therapy). Details of the study design are presented in Figure 1.

All p values were adjusted using the false discovery rate correction in subgroup analyses. The significance threshold is a two-sided $p < .05$ after adjustment. Analyses were performed using the survival package in R, version 4.1.2 (https://cran.r-project.org/).

RESULTS

Our analytic sample comprised 354,313 participants with an average age of 60.1 years (SD = 5.4), of whom 189,440 (53.5%) were women. Among the 46,280 general depressed population, depression was diagnosed 94,689 times before December 31, 2010. During the median follow-up period of 11.9 years (interquartile range: 11.2–12.6), 4493 participants

were diagnosed with dementia, including 2074 AD, 1052 VD, and 1367 other dementia. Demographic and clinical characteristics of the participants are summarized in Table 1.

Increasing, Chronically Low, and Chronically High Courses Are Associated With a Higher Risk of Dementia

A total of 46,280 participants were diagnosed with late-life depression at baseline, of whom 725 developed dementia during the follow-up period. In all 3 models, the depression group had an increased risk of developing dementia (HR, 1.51; 95% CI, 1.38–1.63; $p < .001$) (Figure 2A; Table S7), indicating that compared with healthy individuals, depressed subjects were 51% more likely to develop incident dementia. This association remained statistically significant and robust in sensitivity analyses by using primary care population (Table S8).

Among the 46,280 participants with depression, 3462 (27.7%) had an increasing course of symptoms, 3578 (28.7%) had a decreasing course, 2281 (18.3%) had chronically high depression, and 3159 (25.3%) had chronically low depression. For participants included in the trajectories, there was an average of 2.4 depression diagnostic follow-ups, with up to 78 times at most and 2 times at least per participant. Compared with the nondepressed group, the increasing course (HR, 2.95; 95% CI, 2.43–3.58; $p < .001$), chronically low course (HR, 1.98; 95% CI, 1.54–2.55; $p < .001$), and chronically high course (HR, 1.79; 95% CI, 1.32–2.42; $p < .001$) groups were significantly associated with a higher risk of dementia, while no association was observed for the decreasing course group (HR, 0.84; 95% CI, 0.56–1.24; $p = .37$) (Figure 2B; Table S9).

Depression Treatments Are Associated With a Lower Incidence of Dementia

Among the 46,280 participants who experienced late-life depression at baseline, 22,128 received treatment, including 32% ($n = 14,695$) who underwent pharmacotherapy alone, 5% ($n = 2151$) who underwent psychotherapy alone, and 11% ($n = 5281$) who underwent both forms of therapy. The median treatment exposure period was 9.5 years for antidepressants and 5.0 years for psychotherapy. Relative to the untreated group, the treated group had a low risk of dementia (HR, 0.69; 95% CI, 0.62–0.77; $p < .001$) (Figure 3A; Table S10). After being stratified according to treatment, the results were in line with those of primary outcomes (pharmacotherapy: HR, 0.77; 95% CI, 0.65–0.91; $p = .002$; psychotherapy: HR, 0.74; 95% CI, 0.58–0.94; $p = .01$; and combination therapy: HR, 0.62; 95% CI, 0.53–0.73; $p < .001$) (Figure 3B; Table S11).

These associations were robust in primary care participants, with an approximately 26% lower risk of dementia among

Table 1. Demographic and Clinical Characteristics According to Depression Conditions

Characteristic[a]	Nondepression, $n = 308,033$	Depression, $n = 46,280$	Increasing, $n = 3462$	Decreasing, $n = 3578$	Chronically High, $n = 2281$	Chronically Low, $n = 3159$
Follow-up Time, Years, Median	11.9	11.6	11.4	12.3	10.9	11.1
Age, Years, Mean (SD)	60.2 (5.4)	59.5 (5.3)	59.4 (5.5)	58.9 (5.1)	59.5 (5.4)	59.3 (5.4)
Sex, *n* (%)						
Female	160,308 (52.0%)	29,132 (62.9%)	2099 (60.6%)	2385 (66.7%)	12815 (6.2%)	1978 (62.6%)
Male	147,725 (48.0%)	17,148 (37.1%)	1363 (39.4%)	1193 (33.3%)	10004 (3.8%)	1181 (37.4%)
Ethnicity[b], *n* (%)						
Others	13,403 (4.4%)	1684 (3.6%)	167 (4.8%)	54 (1.5%)	118 (5.2%)	126 (4.0%)
White	292,958 (95.1%)	44,375 (95.8%)	3280 (94.7%)	3508 (98.0%)	2160 (94.7%)	3026 (95.8%)
Socioeconomic Status, Median (IQR)[c]	−2.4 (−3.8, 0.1)	−1.8 (−3.4, 1.0)	−1.5 (−3.3, 1.5)	−2.3 (−3.7, 0.7)	−1.4 (−3.2, 1.7)	−1.6 (−3.3, 1.3)
Qualification Levels[d], *n* (%)						
Higher	140,428 (45.6%)	21,420 (46.3%)	1436 (41.5%)	2059 (57.5%)	1134 (49.7%)	1514 (47.9%)
Lower	161,121 (52.3%)	24,270 (52.4%)	1975 (57.0%)	1476 (41.3%)	1136 (49.8%)	1628 (51.5%)
No. of Dementia Cases	3768 (1.2%)	725 (1.6%)	111 (3.2%)	26 (0.7%)	42 (1.8%)	63 (1.9%)
Untreated Depression, *n* (%)						
Untreated[e]	NA[g]	24,152 (52.2%)	1852 (53.5%)	309 (8.6%)	965 (42.3%)	1358 (43.0%)
Dementia cases[f]	NA[g]	486 (2.0%)	77 (4.2%)	1 (0.3%)	26 (2.7%)	36 (2.7%)
Treated Depression, *n* (%)						
Treated[e]	NA[g]	22,128 (47.8%)	1610 (46.5%)	3269 (91.4%)	1316 (57.7%)	1801 (57.0%)
Dementia cases[f]	NA[g]	239 (1.1%)	34 (2.1%)	25 (0.8%)	16 (1.2%)	27 (1.5%)

NA, not applicable.

[a]Percentages may not sum to 100 because of rounding or missingness of sociodemographic information.

[b]The ethnicity groups "Others" and "White" are based on data collected by the UK Biobank.

[c]Socioeconomic status was measured by Townsend deprivation index, which combines information on social class, employment, car availability, and housing.

[d]Higher qualifications was defined as college/university degree or other professional qualification, and lower qualifications was defined as without college/university/professional qualifications.

[e]Participants in different treatment conditions in depression conditions.

[f]Incident dementia cases in participants with different treatment conditions and depression conditions.

[g]The untreated group and treated group were only classified in participants with late-life depression.

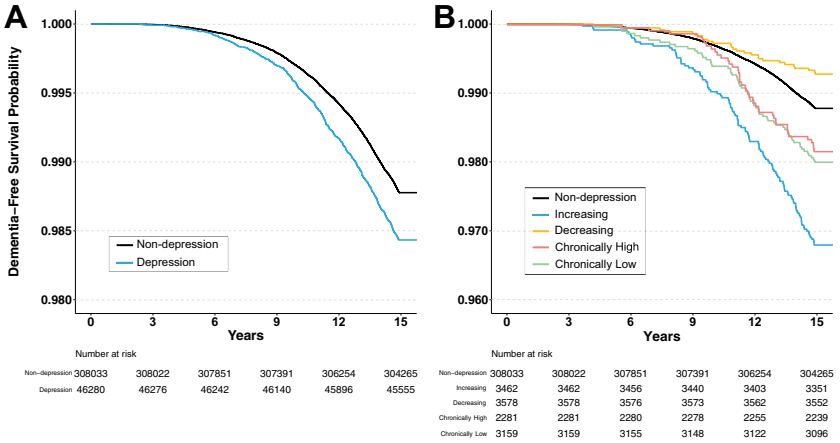

Figure 2. Association between depression, depressive symptom course, and dementia-free survival. Risk of incident dementia according to depression **(A)** and its different courses **(B)** during 11 years of follow-up in the UK Biobank. **(A)** The blue line represents the number of cases of incident dementia in depressed patients, and the black line represents the nondepressed population (reference group). **(B)** The blue line (increasing course), yellow line (decreasing course), red line (chronically high course), green line (chronically low course), and black line (nondepressed population, reference group) represent risk of dementia in different courses.

patients who received treatment (HR, 0.86; 95% CI, 0.74–0.99; $p = .04$) (Table S12). However, the protective correlation between psychotherapy and the risk of dementia was attenuated in male participants, participants without a college degree, and those younger than 60 years. Only combination therapy seemed to work in preventing the onset of dementia among depressed participants with better socioeconomic status (HR, 0.61; 95% CI, 0.48–0.77; $p < .001$) and those older than 60 years (HR, 0.67; 95% CI, 0.56–0.79; $p < .001$). No other heterogeneity was observed. Additional details are presented in Tables S13 to S20. No substantial changes were seen in the association between dementia incidents and receiving treatments after including the TRD population (HR, 0.82; 95% CI, 0.71–0.94; $p = .0003$) (Table S21). However, when restricting the population to those with TRD and those untreated, those with TRD were noticeably associated with a higher risk of dementia (HR, 1.34; 95% CI, 1.11–1.61; $p = .0002$) (Figure S6; Table S22).

After grouping by dementia types, we found that all 3 types of treatment failed to prevent the onset of AD (pharmacotherapy: $p = .45$; psychotherapy: $p = .55$; and combination therapy: $p = .26$) (Table S23). Prescribing antidepressants or receiving combination therapy remarkably decreased the risk when restricting the outcome to VD (pharmacotherapy: HR, 0.62; 95% CI, 0.45–0.86; $p = .005$ and combination therapy: HR, 0.64; 95% CI, 0.47–0.86; $p = .004$) (Table S24), while the results of receiving psychotherapy remained insignificant (psychotherapy: $p = .06$) (Table S24). For other dementia, the protective effect was significant only in those receiving combination therapy (HR, 0.52; 95% CI, 0.37–0.73; $p < .001$) (Table S25).

When considering specific drug types, the TCA group was not distinctively linked to dementia ($p = .17$) (Table S26). Efficacy of SSRIs was observed in model 1 (HR, 0.73; 95% CI, 0.60–0.88; $p < .001$) but diminished after adjustment of covariates ($p = .30$) (Table S26). Treatment with anticholinergic antidepressants appeared not to be linked to the risk of dementia, but the protective effect also diminished ($p = .37$) (Table S27). The nonanticholinergics that addressed late-life depression remained efficacious in decreasing the risk of incident dementia (HR, 0.64; 95% CI, 0.45–0.90; $p = .009$) (Table S27). After restricting the psychotherapy group to those who received individual therapy, the negative association was aligned with the result of total psychotherapy (HR, 0.77; 95% CI, 0.60–0.98; $p = .03$) (Table S28).

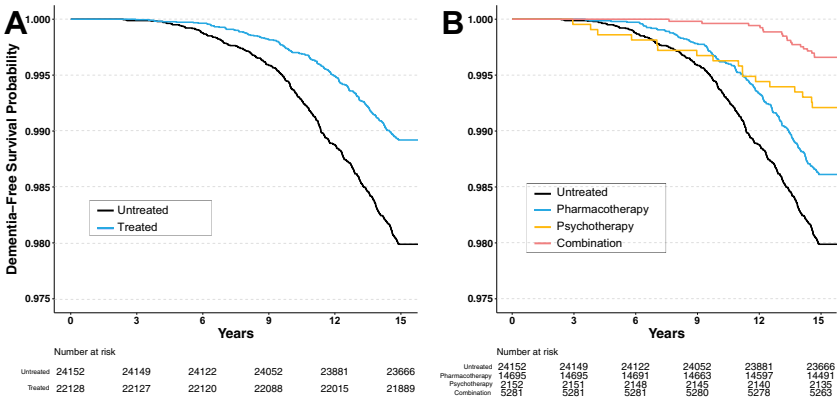

Figure 3. Exposure to depression treatments and dementia-free survival probabilities. A total of 46,280 participants with depression were involved, including 24,152 untreated (reference group) and 22,128 who received treatments, among whom 14,695 were treated with antidepressants, 2151 were treated with psychotherapy, and 5281 were treated with both forms of therapies. **(A)** Cumulative probability of dementia risk in relation to untreated (black line) and treated (blue line) (treated by pharmacotherapy, psychotherapy, or combination therapy) conditions. **(B)** Survival data for incident dementia in relation to untreated conditions (black line), independent pharmacotherapy (blue line), independent psychotherapy (yellow line), and combination therapy (red line).

Depression Treatment Is Associated With a Lower Risk of Dementia in Increasing and Chronically Low Courses

To further investigate the effects of depression treatments in reducing the risk of dementia across different courses of depression, we conducted subgroup analyses according to the different depression courses for participants with 2 reports of depression. The proportions of treatment conditions across the different courses are presented in Table 1.

Relative to the untreated group, the treated group was associated with a 32% lower risk of incident dementia in the increasing course (HR, 0.68; 95% CI, 0.52–0.89; p = .005) (Figure 4; Table S27). A 28% lower risk was also observed in the chronically low (HR, 0.72; 95% CI, 0.53–0.98; p = .04) (Figure 4; Table S27) course group, but not in the decreasing course group (HR, 1.28; 95% CI, 0.82–1.99; p = .28) (Figure 4; Table S27). In the chronically low course group, the treated group had a slightly lower risk of dementia, but the risk was insignificant after false discovery rate adjustment (p = .07) (Figure 4; Table S27). By further grouping participants into those who received antidepressants or psychotherapy, only the increasing course yielded robust significant results in both types of treatments (pharmacotherapy: HR, 0.64; 95% CI, 0.47–0.86; p = .04 and psychotherapy: HR, 0.65, 95% CI, 0.47–0.90; p = .04) (Table S30). In the 2 chronic courses, no trend of correlation was observed between receiving pharmacotherapy and the risk of dementia. Psychotherapy was correlated with a lower risk of dementia, but the effect diminished after further adjustment of covariates (Table S30). The results of individual psychotherapy were consistent with those in main analysis (Table S31).

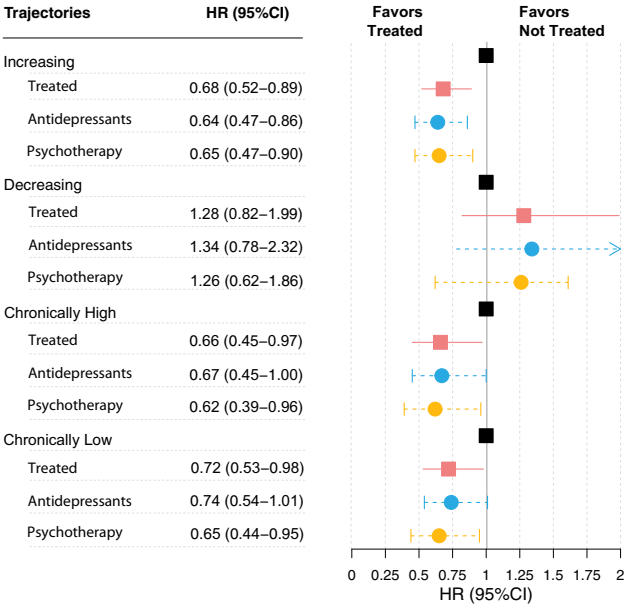

Figure 4. Exposure to depression treatments and dementia-free survival probabilities across 4 depression courses. The red squares, blue circles, and yellow circles represent the hazard ratio (HR) of dementia of total treatment group, the antidepressants group (including independent pharmacotherapy and combination therapy), and the psychotherapy group (including independent psychotherapy and combination therapy), respectively, in the 4 depression courses where the untreated group (black square) is used as reference. The red, blue, and yellow horizontal lines indicate the corresponding 95% confidence intervals (CIs) around the HRs. HRs were calculated using Cox proportional hazards regression analysis after adjustments for age at baseline, sex, ethnicity, socioeconomic status, and qualification level.

DISCUSSION

In this study, we investigated the relationship between depression and the risk of dementia, as well as how depression treatment affects the risk of dementia. For patients with depression, increasing and chronically high or low courses of symptom severity were associated with a significantly higher risk of developing dementia than not having depression. In addition, our results showed that participants with depression who were untreated were 30% more likely to develop dementia than participants who received either corresponding antidepressants or psychotherapy. The protective effect was most significantly observed in the increasing course.

Our study indicated that patients who were prescribed antidepressants had a lower risk of dementia than patients with depression who received no depression treatment. Consistent with our study, several observational and experimental studies suggest that pharmacological interventions may not only ameliorate depressive symptoms but also decrease the risk of dementia (27,28). Notably, randomized, placebo-controlled trials suggested that treatment with an SSRI may improve cognitive function and daily living in patients with mild cognitive impairment and those with AD (29–31). Besides SSRIs, a previous randomized controlled trial suggested that donepezil treatment in patients with mild cognitive impairment slowed their conversion to AD only when these subjects were comorbid with depression (32). Some demographic variables, including younger age, lower vascular risk score, and higher baseline Mini-Mental State Examination scores, predicted better cognitive improvement in depressed older adults treated with citalopram (33).

As with antidepressants, psychotherapy for depression is associated with a lower risk of dementia. Furthermore, psychotherapy remained associated with a lower risk of dementia in patients with increasing courses. Specific psychotherapies, such as supportive therapy and problem-solving therapy, have been developed to remedy the behavioral deficits of depressed older adults with cognitive impairments associated with poor response to antidepressants (34). Moreover, because most psychological interventions follow certain principles, including increase of social interaction, stimulation of memory, and stabilization of a patient's sense of identity, it is not altogether surprising that psychotherapy may improve cognitive function and delay the onset of dementia (35–37).

Other effective treatment included computerized cognitive remediation treatment, which induces a clinically meaningful improvement of both cognitive and affective symptoms in depressed older patients who failed to remit using conventional antidepressants (38).

According to our study, the depression-dementia relationship depends on the patterns of depression symptoms, and only patients with a decreasing course of depressive symptoms were not at a higher risk of dementia. As a decreasing

course of symptom severity may indicate a good prognosis, it is not surprising that the differences between the treated group, the untreated group with a decreasing course, and the nondepression group were insignificant. Thereafter, we investigated whether the treatment-dementia relationship is similarly heterogeneous. We discovered that although an increasing course of symptoms elevates the incidence of dementia most rapidly, receiving depression treatments could negate the rising risk, while treatments did not lower the risk in patients with a chronically high level, even if the coefficient value of the chronically high course was less than that in the increasing course. The difference between the increasing and chronically high courses emphasized that timely diagnosis and management of depression is vital not only to control the depression but also to lower the patient's risk of dementia (39). To our knowledge, there are few studies in which the influence of depression treatments on the risk of dementia was estimated for patients with different courses of depressive symptoms. Among 2 prior studies about the association between the progression of depression and incidence of dementia, the effect of treatments could not be investigated in one because of the small sample size and the absence of information on nonpharmacological interventions (13). In the other study, the assessment involved either inclusion of antidepressants as a covariate or not (12).

The main strength of our study is in the identification of the effects of treatments across patients with different courses of depressive symptoms. Different depressive symptom profiles may be used not only for the differential prediction of the risk of dementia but also for determination of the effect of depression treatments on the development of dementia. Previous studies might have suffered from confounding by indications of the severity of depression, as it is likely that individuals who are treated are more severely depressed than those who do not receive depression treatment. In our study, the associations were derived for different depression courses to balance the severity of depression, which may have helped us to avoid those confounders. Other strengths of our study include its population-based setting and long follow-up period.

This study also had several limitations. First, as the UKB cohort comprised participants ages 40 to 69 years, it is unclear whether the conclusions of this study are generalizable to older patients. Second, research has so far proved inconclusive on whether depression is a prodromal phase or an independent risk factor for dementia (40,41). The onset of depression might be reverse causation of dementia progression, especially for those in more chronic and severe courses, and accordingly might increase their likelihood of being prescribed an antidepressant. Thus, the relationship between depression and dementia should still be interpreted with caution. Third, because the ICD-10 diagnoses used in this study were binary outcomes without specific information on criteria and measures, there might be individual differences in diagnosis of depression severity. Moreover, by relying on diagnosis codes, our approach may lead to missing undiagnosed depression. It is also possible that clinicians are not diligent enough to update depression coding in practice, which leads to misjudging the depression courses. Fourth, because no consensus definition existed for TRD, we defined TRD according to the most common definition. However, there still might be limitations with this approach. Fifth, as more than 50% of the participants attended depression assessments only twice, the assumptions made in courses might not be accurate enough. Finally, we could not exclude any residual confounding factors. Although we adjusted for a large number of variables by using a directed acyclic graph, there might have been unmeasured factors that influenced the treatment effectiveness and risk of dementia. For example, poor adherence to antidepressant medication and psychotherapy is common in late-life depression. By failing to exclude subjects with early discontinuation and nonadherence, it is possible that the findings could be a conservative estimate of the relationship between depression treatment and reduced dementia risk. The directions of confounding factors were mixed.

In conclusion, these findings suggest that depression therapy reduces the risk of dementia, especially among patients with increasing depression course. These findings highlight the importance of timely treatment of older individuals diagnosed with depression.

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J-TY conceptualized the study and revised the manuscript. LY, Y-TD, Y-ZL, and S-YH analyzed and interpreted the data. LY, YL, Y-NO, S-DC, X-YH, Y-RZ, and WC prepared all the figures and tables. LY, Y-TD, YL, Y-NO, B-SW, KK, WF, J-FF, WC, JS, ADS, and J-TY drafted the manuscript. All authors contributed to the writing and revisions of the paper and approved the final version.

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