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DOI:

[10.1016/j.jad.2020.01.021](https://doi.org/10.1016/j.jad.2020.01.021)

Document Version

Peer reviewed version

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Citation for published version (APA):

Cai, W., Mueller, C., Shetty, H., Perera, G., & Stewart, R. (2020). Predictors of mortality in people with late-life depression: a retrospective cohort study. *Journal of Affective Disorders*, 266, 695-701.
<https://doi.org/10.1016/j.jad.2020.01.021>

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Predictors of mortality in people with late-life depression: A retrospective cohort study

Abstract:

Objectives: Late-life depression (LLD) is associated with an increased mortality risk in the general older population. It remains however unclear which signs or symptoms are predictive of mortality in those suffering from LLD.

Setting and Participants: Patients aged over 65 years with depressive disorder diagnosed in Southeast London between January 2008 and December 2017.

Methods: We assembled patients aged over 65 years old with late-life depression from the Maudsley Biomedical Research Centre Case Register linked to mortality data. Using depression diagnosis as index date, we followed patients until death or censoring point. Sociodemographic data, scores of Health of the Nation Outcome Scales (HoNOS 65+) including a physical illness scale, profiles of depressive symptoms, antidepressant and antipsychotic medication were extracted and modeled in multivariable survival analyses to determine predictors of mortality.

Results: Of 4,243 patients with LLD (mean age 77.0 years; 61.2% female), 2,327 (54.8%) died over a median follow-up time of 3.5 years. In multivariable Cox regression models, an increased risk of all-cause mortality was associated with older age, memory problems, physical illness/disability, ADL problems, apathy, reduced appetite and mirtazapine prescription; conversely, female gender, non-white ethnicity, guilt feelings, tearfulness, impaired concentration, disturbed sleep and delusions prescription were associated with lower mortality risk.

Conclusions: Besides demographic factors and prescriptions, different depressive symptoms were significantly associated with the prognosis of LLD. Elderly patients presenting with depressive symptoms predicting higher mortality risk should be examined and followed more closely.

Keywords: Late-life depression; all-cause mortality; depression; depressive symptoms; retrospective; cohort study

Introduction

Depressive disorder is a common psychiatric disorder in adults aged 65 years or older with the prevalence of 25.1% (95% CI: 20.6-29.6) (Forlani et al., 2014). Late-life depression (LLD) is associated with a higher burden of medical illnesses and comorbid psychiatric disorders (Gallegos-Carrillo et al., 2009). It is also associated with adverse outcomes including a higher risk of dementia (Diniz et al., 2013) and cognitive impairment (Yen et al., 2011). One USA study revealed that total health care costs were 47% to 51% higher for older people with depression compared to those without depression after adjustment for chronic medical illness (Katon et al., 2003).

Recent studies have reported increased all-cause mortality in community-dwelling older adults with LLD, which was robust after adjust for cognitive decline, lifestyle, health behavior and comorbidities (Almeida et al., 2010; Kohler et al., 2013; Sun et al., 2011). More important than suicide as a direct but relatively rare outcome, older adults with depression are less likely to accept preventive health care or follow medication prescription, increasing mortality from other more common causes (Murphy et al., 1988; Schulz et al., 2002). Although previous studies investigated factors that predict mortality in people with LLD including age, gender, ethnicity, depression severity, functional or physical problems, antidepressant use and comorbidities, the results are inconsistent and there was little examination of the association between specific depressive symptoms and mortality.

As a result, we conducted a retrospective cohort study to investigate predictors of all-cause mortality in a naturalistic secondary care cohort of patients with LLD. We hypothesized that the aforementioned factors known from the literature and some specific depressive symptoms would be associated with a higher mortality risk.

Methods

Study setting and data source

A retrospective cohort study was conducted using data from the South London and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre (BRC) Case Register. SLaM serves a geographic catchment of four South London boroughs with a population over 1.3 million residents. The data for the study were extracted using the Clinical Record Interactive Search (CRIS) application, which renders anonymized information from SLaM's electronic health record accessible for research projects within a robust and patient-led governance framework (Perera et al., 2016; Stewart et al., 2009). CRIS data have been linked to a number of other informative data sources, including data on all hospitalisations regardless of specialty or location in England (national Hospital Episode Statistics; HES) and mortality records (Office for National Statistics). The SLaM BRC Case Register contains data on more than 400,000 cases with a range of mental disorders and has supported a range of studies. CRIS data have been extensively supplemented through natural language processing applications using Generalised Architecture for Text Engineering software, applying information extraction techniques to derive structured information from the text fields held in the mental health record (Perera et al., 2016). The database has full approval for secondary analysis from Oxford Research Ethics Committee (Oxford Research Ethics Committee C, reference 18/SC/0372).

Sample

We identified all patients aged 65 years or older who had received a diagnosis of depressive disorder diagnosis according to ICD-10 code of F32 and F33 from SLaM services between 1st January 2008 and 31st December 2017. The date of the first recorded depression diagnosis after the age of 65 served as the index date for follow-up and covariate definition. Patients were excluded if a diagnosis of dementia (ICD-10 code F00 to F03) was recorded in their health records before or up to three months after index date.

Outcomes

Patient records were linked with Office for National Statistics (ONS) for mortality data. Patients were followed until death or a censoring point on 31st December 2017.

Predictors

We extracted independent variables from CRIS closest to the index date described above. Demographic information included age at index date, gender, ethnic group, marital status and

neighbourhood-level socioeconomic status measured by the index of multiple deprivation (IMD). Ethnicity was grouped into White, Black, Asian and other. Marital status was dichotomized into cohabiting (civil partnership, married, cohabiting) and non-cohabiting (single, divorced, civil partnership dissolved, widowed, separated) status. The IMD is a standard measure derived for Lower Super Output Area administrative units (approximating 1500 residents) by applying 2011 Census data across several domains including income, employment, health, education, barriers to housing and services, living environment and crime (Noble M, 2007).

Items measuring cognitive impairment, depression severity, physical illness and activities of daily living (ADL) problems were included from the routinely administered Health of the Nation Outcome Scales (HoNOS 65+ (Burns et al., 1999)) which is a clinician rated instrument comprising 12 simple scales measuring behaviour, wellbeing, symptoms and functioning for those in the 65 years + age group. The scale is completed electronically at every significant clinical encounter and we ascertained the recording closest to the index date. HoNOS65+ subscales are scored between 0 (no problem) to 4 (moderate-severe problem). For this analysis, respective scores were classified into “no or minor problem” (score 0-1), “mild problem” (score 2) and “moderate to severe problem” (score 3-4).

Using the aforementioned natural language processing platform and algorithms derived for a range of mental disorder symptoms (Jackson et al., 2017), we extracted depressive symptoms from text fields of the electronic mental health record (primarily case notes and correspondence) within a period from 6 months before to 6 months after the index date. The algorithms specifically exclude negation and irrelevant text strings and precision and recall are assessed against a manual gold standard (Downs et al., 2019; Jackson et al., 2017; Perera et al., 2016). Presence of any symptom was ascertained as follows: guilt feelings, helplessness, hopelessness; anhedonia, poor motivation, apathy, tearfulness; agitation, reduced appetite, impaired concentration, disturbed sleep; hallucinations, delusions; suicidal ideation.

Recorded psychotropic medication was also ascertained in a 12-month window around index date using natural language processing algorithms identifying known medications from the British National Formulary recorded as being taken by the patient in text fields. For this analysis we ascertained the receipt of any antipsychotic drug, and antidepressant agents grouped into the following classes: mirtazapine, serotonin-norepinephrine reuptake inhibitors (SNRIs, i.e. venlafaxine and duloxetine), selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Co-morbidity was captured through the physical illness and disability scale of the aforementioned HoNOS65+ instrument.

Statistical analysis

Stata software (version 13) was used in all statistical analyses with a significance level of 5%. Cox proportional hazards regression models were applied for potential risk factors affecting time to all-cause mortality. Model I was adjusted for age and gender, Model II for age, gender, ethnic group, cohabiting status, IMD score, depression severity, physical illness/disability, ADL problems and memory problems (the envisaged major predictors of mortality in this population), and Model III for all covariates to determine independent associations. ‘We assessed the proportional-hazard assumptions on the basis of Schoenfeld residuals and included variables as time-varying if they were violated.’ As 19.5% of the study sample had missing data on at least one of the other covariates, we imputed missing values using chained equations to maximize statistical power. We created 20 imputed datasets through replacing missing values through simulated values assembled from potential covariates and outcome values (DB, 2004; Oudshoorn CGM, 1999).

We conducted the following sensitivity analyses: We compared those taking only mirtazapine, SNRI or TCA to those only prescribed an SSRI in relation to mortality. Moreover, we excluded patients with a history of depression before the age of 65 years on the source record or a diagnosis of recurrent depression (ICD-10 code F33) to generate a sub cohort of patients with new-onset depression, for which we repeated the main analyses.

Results

We identified 5,175 patients age 65 years or older with a diagnosis of late-life depression. After we excluded 932 (18.0%) patients with a previous or concurrent diagnosis of dementia, the final sample for analysis consisted of 4,243 patients. (Supplementary Table 1).

Characteristics of the cohort

As presented in Table 1, mean (SD) age at depression diagnosis was 77.0 (7.9) years and 61.2 % of the sample were female; 2,327 (54.8%) patients died in the study period, and the median follow-up time until death or censoring was 3.5 years (interquartile range 1.5 to 6.4 years).

Predictors of all-cause mortality

Table 2 presents hazard ratios for potential predictors of all-cause mortality in our cohort with LLD. In Model I (adjusted for age and gender), older age at depression diagnosis, cognitive impairment severity, depression severity, physical illness/disability, ADL impairment, recorded apathy and mirtazapine use were associated with a higher risk of mortality, while female gender, black and other ethnicity, guilt feelings, hopelessness, poor motivation, tearfulness, impaired concentration, disturbed sleep, delusions, SNRI and TCA use were associated with reduced mortality. In model III, fully adjusted for all included variables, increased age, cognitive impairment, physical illness/disability, ADL problems, apathy, lack of appetite and mirtazapine were significant predictors of mortality, while female gender, ethnic minority groups, guilt feelings, tearfulness, impaired concentration, disturbed sleep and delusions were associated with a lower mortality risk.

Sensitivity analyses

First, we conducted head-to-head comparisons of antidepressant medications. We compared those only prescribed mirtazapine (n=1,322), SNRI (n=259) or TCA (n=250) to those only prescribed an SSRI (n=1,148). In the age & gender adjusted model, Mirtazapine prescription yielded a higher mortality risk and SNRI or TCA prescription a lower mortality risk compared to SSRI. In Model 3, adjusted for all demographics, HoNOS65+ scales, depressive symptoms and antipsychotic prescribing, Mirtazapine continued to yield a significantly increased mortality hazard, increased by 51% compared to SSRI prescription. The protective effect of SNRI compared to SSRI was attenuated to a non-significant trend.

Second, we repeated the main analyses excluding 1,328 (31.3%) patients with a previous history of depression. Of 3,095 patients with new-onset depression, 1,784 (57.5%) died in the follow-up period. Predictors of mortality in this sub cohort are presented in Supplementary Table 1 and in

terms of significance only differed from the main cohort in the depression severity scale, whereby more severe depression predicted a higher mortality risk.

Discussion

Our cohort had a large sample of more than 4000 patients over 65 years old with a secondary care clinical diagnosis of depression, nearly 55% of whom died over around 3.5 years follow-up, compared with around 65.2% of depressed adults who died over 19-year follow up in a longitudinal study (Gilman et al., 2017). All-cause mortality was independently predicted by older age, memory problems, physical illness/disability, ADL problems, apathy, lack of appetite and prescription of mirtazapine, while female gender, non-white ethnicity, guilt feelings, tearfulness, impaired concentration, disturbed sleep and delusions predicted lower risk of death. Interestingly, we found no evidence that depression severity, or antipsychotic prescription were independently associated with mortality.

Increased age was identified as an independent risk factor for mortality, which was in line with previous literature (Jorgensen et al., 2016; Kemper et al., 2011; Melkas et al., 2010; Naess et al., 2010; Ried et al., 2011; Williams et al., 2004). Also consistent with existing literature (Gjonca et al., 2005; Mesle, 2004), female gender was significantly associated with longer survival. In line with other studies of older patients drawn from this data source (Mueller et al., 2018b; Sharma et al., 2018), we found that patients from non-white ethnic groups had longer survival, which might be explained by population movement effects (people moving out of the country and no longer being captured by the death register) or larger social support networks (Nicklett and Taylor, 2014).

Patients with mental disorders are known to have greater physical health morbidity and mortality compared to people without these disorders, and previously proposed underlying explanations have included adverse lifestyles, less adequate physical healthcare and side effects of medication (Leucht and Fountoulakis, 2006). Consistent with previous cohort studies of LLD (Lenze et al., 2001; Murphy et al., 1988), physical illness or disability was significantly associated with an increased risk of death. ADL impairment has been reported to be associated with comorbid conditions such as cerebrovascular and cardiovascular disease, diabetes and cancer which themselves predict higher mortality in elders (Stineman et al., 2012). In line with studies on unselected older community samples (Manini et al., 2006; Nakazawa et al., 2012), ADL problems in our clinical sample significantly predicted mortality. Cognitive impairment severity on the HoNOS65+ was associated with an increased risk of death patients with LLD, which also is in line with previous researches (Georgakis et al., 2016; Lavretsky et al., 2010; Mehta et al., 2003).

Previous studies have found that depression severity predicts all-cause mortality (Castro-Costa et al., 2019; Jeong et al., 2013; Saglimbene et al., 2017). In our study, since individuals were under

secondary care for depression, the severity of the functional impairment related to depressive disorder lacked predictive ability with regard to mortality. Whereas, in our sub-cohort with new-onset depression, indicating that the HoNOS65+ subscale for ‘problems with depressive symptoms’ works better for those with new onset depression instead of recurrent depression.

In terms of antidepressant prescription, we found that mirtazapine was significantly associated with higher mortality, which was consistent with a cohort study of large sample size (92,542 participants (Khan et al., 2013)). The two most common side effects of mirtazapine are daytime sedation and weight gain, both of which may result in functional impairment and, potentially, higher mortality as a consequence. Alternatively, mirtazapine has been proven to be safer and well tolerated in patients with ischemic heart disease (Rivelli and Jiang, 2007), so that patients with cardiovascular comorbidities may be more likely to receive mirtazapine, with higher mortality arising as a consequence of confounding by indication. In our study, while SSRI prescription was not associated with either raised or lowered mortality, SNRI prescription was associated with a lower risk of death. SNRIs are an effective alternative to SSRIs for LLD patients when SSRIs are ineffective or contraindicated; however, the most commonly prescribed SNRI venlafaxine is associated with hypertension and arrhythmia (Isbister, 2009; Johnson et al., 2006), so it is likely to be avoided in patients with higher levels of (in particular, cardiovascular) comorbidity and frailty, which might partly explain this finding.

Considering different types of depressive symptoms, apathy and reduced appetite significantly predicted higher mortality. Nijsten et al. (Nijsten et al., 2017) found that apathy was associated with mortality over a 4-month period in elders of nursing home units even when adjusted for depression, and reduced appetite caused by depression has potentially obvious consequences on nutritional status and frailty that might result in morbidity and mortality (Ahmed and Haboubi, 2010). We found that guilt feelings were associated with lower mortality. As this is frequently associated with a negative life event (Girz et al., 2017), presence of guilt might make an underlying organic cause for depressive symptoms less likely, leading to a longer survival. Interestingly, tearfulness also predicted lower mortality. Impaired concentration can be a consequence of disturbed sleep (Manjavong et al., 2016). However, evidence has revealed that disturbances of sleep such as insomnia complaints and extremes of sleep duration contribute to all-cause mortality (Dew et al., 2003). Elderly depressed patients reporting symptoms of disturbed sleep, impaired concentration and tearfulness suggest a degree of higher insight into their difficulties and might trigger greater clinical input. Our finding that delusions were associated with lower mortality is somewhat surprising as late-life psychosis has been reported to predict higher mortality (Gale et al., 2012;

Meesters et al., 2016). Generally speaking, since delusions are severe symptoms of depression, most patients with delusions can receive better care than those without delusions, which might be an explanation.

Strengths of the study include the large sample size and comprehensive ascertainment of mortality as an outcome (since the only reason for missed ascertainment would be an unrecorded death outside the UK). Some limitations should be noted when interpreting the findings.

First, the sample for this study was drawn from a specialist mental health care sample, so that depressive syndromes are likely to be more severe than those ascertained in screened community samples.

Second, cause of death was not the focus of the study, and cause-specific mortality should be examined in future studies.

Third, the symptoms ascertained as covariates were derived from those recorded in text, rather than those that might be ascertained through a screening instrument. Natural language processing algorithms are largely designed to yield a high precision (positive predictive value), which can adversely impact recall (sensitivity), so it should be borne in mind that non-recording does not necessarily reflect the absence of a symptom.

Fourth, we only assessed the impact of single depressive symptoms on mortality. As these symptoms rarely occur in isolation future studies could usefully apply cluster analysis to explore how different combinations of symptoms affect the risk of mortality.

Fifth, comorbidity was ascertained through the HoNOS65+ physical illness and disability subscale. Although the HoNOS65+ physical illness subscale is relatively brief without details on the specific long-term conditions defining its score. It has however been shown to have useful predictive validity of adverse outcomes in other studies on this data source (Mueller et al., 2018a; Mueller et al., 2017).

Sixth, we assessed the use of antidepressants only in a window ranging from six months before to six months after depression diagnosis. This could introduce a bias in our results as median duration of antidepressant prescription of antidepressants on people of the age of 65 years in the UK is about one year (Coupland et al., 2011), but is likely to be longer in a secondary care population.

Further, as we did not make statistical corrections for the effects of multiple comparisons, some of our findings, in particular those with p-values in the 0.02–0.05 range, could have arisen by the effects of chance. However, the most common approaches to adjustments for multiple comparisons are considered conservative methods in survival analysis (Colak et al., 2017) and meaningful results have been derived by previous analyses without adjustment in this data source (Sharma et al., 2018).

Finally, as previously mentioned, causal inferences cannot be conclusive in an observational study of this nature, and medications as exposures should be viewed with particular caution because of the possibility of confounding by indication, despite the multiple adjustments incorporated in the analysis design.

Conclusions / Relevance:

In a large cohort with LLD, all-cause mortality was predicted by older age, memory problems, physical illness/disability, ADL problems, apathy, lack of appetite and prescription of mirtazapine. Meanwhile, mortality risk was lower in those with female gender, non-white ethnicity, guilt feelings, tearfulness, impaired concentration, disturbed sleep and delusions. No evidence was found that depression severity, SNRI/SSRI/TCA prescription and other depressive symptoms (helplessness, hopelessness, anhedonia, poor motivation, agitation, and hallucinations) had significant associations with mortality. In clinical practice, elderly patients presenting with depressive symptoms predicting higher mortality risk should be examined and followed more closely.

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Predictors of mortality in people with late-life depression: A retrospective cohort study

Tables

Table 1: Sample characteristics

Risk factors	Whole cohort (n=4,423)
Sociodemographic status ^a	
Mean age (SD)	77.0 (7.9)
Female gender, %	61.2%
Ethnicity, %	
White	82.3%
Black	9.9%
Asian	5.0%
Other	2.8%
Cohabiting status, %	33.3%
Mean IMD score (SD)	26.5 (11.9)
HoNOS Scales ^a	
<i>Cognitive problem</i>	
No or minor problem	80.5%
Mild problem	15.1%
Moderate-severe problem	4.4%
<i>Depression severity</i>	
No or minor problem	27.9%
Mild problem	36.6%
Moderate-severe problem	35.5%
<i>Activity of daily living problem</i>	
No or minor problem	48.5%
Mild problem	25.3%
Moderate-severe problem	26.2%
Depressive symptoms profiles, % ^b	
<i>Negative cognitions</i>	
Guilt feelings	25.9%
Helplessness	13.6%
Hopelessness	30.6%
<i>Affective symptoms</i>	
Anhedonia	15.6%
Apathy	6.5%
Poor motivation	39.8%
Tearfulness	45.2%
<i>Somatic symptoms</i>	
Agitation	33.4%
Lack of appetite	54.8%
Impaired concentration	35.2%
Disturbed sleep	56.3%
<i>Psychotic symptoms</i>	

Delusions	16.7%
Hallucinations	10.3%
<i>Suicidal ideation</i>	20.7%
Medication prescription, % ^b	
<i>Antidepressants</i>	
Mirtazapine	41.2%
SNRI	13.2%
SSRI	50.7%
TCA	11.9%
<i>Antipsychotics</i>	21.8%
Comorbidity history, % ^a	
<i>HoNOS65+ Physical illness or disability</i>	
No or minor problem	29.0%
Mild problem	24.1%
Moderate-severe problem	46.9%

^a At the time or closest to depression diagnosis.

^b Six months before and after the time of depression diagnosis.

SD = standard deviation; IMD = index of multiple deprivations; HoNOS65+ = Health of the Nation Outcome Scale for those age 65 years or older

Table 2: Predictors of all-cause mortality (Hazard ratios, 95% CIs)

Risk factors	Model I	P	Model II	P	Model III	P
Sociodemographic status ^a						
Mean age (SD)	1.07 (1.06-1.08)	<0.001	1.05 (1.04-1.05)	<0.001	1.04 (1.03-1.05)	<0.001
Female gender	0.56 (0.50-0.63)	<0.001	0.59 (0.52-0.67)	<0.001	0.62 (0.54-0.70)	<0.001
<i>Ethnicity</i>						
White	1		1		1	
Black	0.77 (0.66-0.90)	0.001	0.73 (0.62-0.85)	<0.001	0.71 (0.60-0.84)	<0.001
Asian	0.81 (0.66-1.00)	0.051	0.76 (0.61-0.94)	0.014	0.75 (0.60-0.93)	0.008
Other	0.70 (0.53-0.93)	0.014	0.71 (0.54-0.95)	0.019	0.70 (0.52-0.94)	0.016
Cohabiting status	0.99 (0.91-1.09)	0.905	0.99 (0.90-1.09)	0.828	0.99 (0.89-1.09)	0.784
Mean IMD score (SD) / 10	1.02 (0.98-1.06)	0.266	1.01 (0.97-1.04)	0.708	1.01 (0.97-1.04)	0.786
HoNOS65+ Scales ^a						
<i>Memory problems</i>						
No or minor problem	1		1		1	
Mild problem	1.42 (1.26-1.60)	<0.001	1.21 (1.07-1.37)	0.003	1.18 (1.04-1.33)	0.011
Moderate-severe problem	1.91 (1.55-2.35)	<0.001	1.40 (1.13-1.73)	0.002	1.34 (1.08-1.65)	0.007
<i>Depression severity</i>						
No or minor problem	1		1		1	
Mild problem	1.44 (1.26-1.65)	<0.001	1.11 (0.96-1.27)	0.151	1.14 (0.99-1.31)	0.074
Moderate-severe problem	1.58 (1.34-1.86)	<0.001	1.11 (0.94-1.32)	0.219	1.19 (0.99-1.43)	0.057
<i>Activity of daily living problems</i>						
No or minor problem	1		1		1	
Mild problem	2.15 (1.88-2.45)	<0.001	1.51 (1.30-1.74)	<0.001	1.51 (1.30-1.75)	<0.001
Moderate-severe problem	3.89 (3.32-4.55)	<0.001	2.10 (1.75-2.52)	<0.001	2.02 (1.68-2.43)	<0.001
Depressive symptoms profiles ^b						
<i>Negative cognitions</i>						
Guilt feelings	0.56 (0.48-0.65)	<0.001	0.67 (0.57-0.79)	<0.001	0.79 (0.66-0.95)	<0.001
Helplessness	1.06 (0.94-1.20)	<0.001	1.01 (0.89-1.14)	0.878	1.06 (0.92-1.22)	0.442
Hopelessness	0.86 (0.75-0.98)	0.023	0.84 (0.73-0.97)	0.017	0.95 (0.82-1.11)	0.537
<i>Affective symptoms</i>						
Anhedonia	0.98 (0.87-1.10)	0.715	1.03 (0.91-1.17)	0.596	1.05 (0.92-1.20)	0.468
Apathy	1.23 (1.04-1.46)	0.013	1.32 (1.11-1.57)	0.001	1.33 (1.11-1.59)	0.002
Poor motivation	0.74 (0.66-0.84)	<0.001	0.80 (0.70-0.92)	0.001	0.90 (0.78-1.03)	0.137
Tearfulness	0.80 (0.71-0.91)	<0.001	0.80 (0.70-0.91)	0.001	0.86 (0.75-0.98)	0.020
<i>Somatic symptoms</i>						
Agitation	0.79 (0.69-0.89)	<0.001	0.85 (0.74-0.96)	0.012	0.99 (0.86-1.15)	0.925
Lack of appetite	1.05 (0.97-1.14)	0.223	1.06 (0.97-1.16)	0.202	1.14 (1.04-1.26)	0.008
Impaired concentration	0.61 (0.54-0.70)	<0.001	0.70 (0.61-0.80)	<0.001	0.80 (0.69-0.93)	0.003
Disturbed sleep	0.65 (0.58-0.74)	<0.001	0.70 (0.62-0.79)	<0.001	0.72 (0.63-0.82)	<0.001
<i>Psychotic symptoms</i>						
Delusions	0.60 (0.50-0.72)	<0.001	0.71 (0.59-0.85)	<0.001	0.81 (0.66-0.99)	0.037
Hallucinations	1.08 (0.94-1.23)	0.279	1.05 (0.91-1.20)	0.528	1.13 (0.97-1.31)	0.109
Suicidal ideation	0.77 (0.66-0.89)	0.001	0.81 (0.70-0.95)	0.011	0.99 (0.84-1.16)	0.866
Medication prescription ^b						
<i>Antidepressants</i>						

Mirtazapine	1.45 (1.28-1.63)	<0.001	1.38 (1.22-1.56)	<0.001	1.51 (1.32-1.72)	<0.001
SNRI	0.60 (0.49-0.73)	<0.001	0.71 (0.57-0.89)	0.002	0.81 (0.65-1.02)	0.071
SSRI	0.99 (0.91-1.07)	0.735	0.93 (0.86-1.02)	0.110	0.98 (0.90-1.07=	0.684
TCA	0.69 (0.56-0.84)	<0.001	0.74 (0.60-0.91)	0.004	0.83 (0.68-1.03)	0.090
<i>Antipsychotics</i>	0.74 (0.64-0.87)	<0.001	0.86 (0.73-1.02)	0.076	1.01 (0.85-1.21=	0.887
Comorbidity ^a						
<i>HoNOS65+ Physical illness or disability Scale</i>						
No or minor problem	1		1		1	
Mild problem	2.61 (2.21-3.08)	<0.001	2.21 (1.84-2.64)	<0.001	2.07 (1.74-2.45)	<0.001
Moderate-severe problem	5.90 (4.87-7.16)	<0.001	3.90	<0.001	2.43 (2.76-4.26)	<0.001

^a At the time or closest to depression diagnosis.

^b Six months before and after the time of depression diagnosis.

Model I - adjusted for age, gender.

Model II - adjusted for age, gender, race, cohabiting status, IMD score, depression severity, physical illness and disability, ADL problems and memory problems.

Model III - adjusted for all the variables.

SD = standard deviation; IMD = index of multiple deprivations; HoNOS65+ = Health of the Nation Outcome Scale for those age 65 years or older

Table 3: Head-to-head comparison of antidepressant medication (Hazard ratios, 95% CIs)

Risk factors	Model I	<i>P</i>	Model II	<i>P</i>	Model III	<i>P</i>
Mirtazapine vs. SSRI	1.44 (1.24-1.66)	<0.001	1.40 (1.21-1.63)	<0.001	1.51 (1.30-1.76)	<0.001
SNRI vs. SSRI	0.58 (0.43-0.79)	<0.001	0.70 (0.50-0.97)	0.032	0.73 (0.52-1.02)	0.062
TCA vs. SSRI	0.74 (0.55-0.99)	0.045	0.81 (0.60-1.10)	0.181	0.89 (0.66-1.22)	0.475

Model I - adjusted for age, gender.

Model II - adjusted for age, gender, race, cohabiting status, IMD score, depression severity, physical illness and disability, ADL problems and memory problems.

Model III - adjusted for the above plus depressive symptoms and antipsychotic prescription.

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Supplementary Tables

Supplementary Table 1: Comparison of patients with late-life depression with and without a co-morbid dementia diagnosis

Risk factors	LLD without dementia (n=4,423)	LLD with dementia (n=932)	p
Sociodemographic status ^a			
Mean age (SD)	77.0 (7.9)	81.0 (7.5)	<0.001
Female gender, %	61.2%	64.8%	0.038
Ethnicity, %			0.003
White	82.3%	77.1%	
Black	9.9%	13.1%	
Asian	5.0%	6.2%	
Other	2.8%	3.6%	
Cohabiting status, %	33.3%	28.9%	0.012
Mean IMD score (SD)	26.5 (11.9)	28.0 (11.3)	<0.001
HoNOS Scales, % ^a			
<i>Cognitive problem</i>			<0.001
No or minor problem	80.5%	22.8%	
Mild problem	15.1%	40.2%	
Moderate-severe problem	4.4%	37.0%	
<i>Depression severity</i>			<0.001
No or minor problem	27.9%	37.4%	
Mild problem	36.6%	36.2%	
Moderate-severe problem	35.5%	26.4%	
<i>Activity of daily living problem</i>			<0.001
No or minor problem	48.5%	30.9%	
Mild problem	25.3%	30.6%	
Moderate-severe problem	26.2%	38.5%	
Depressive symptoms profiles, % ^b			
<i>Negative cognitions</i>			
Guilt feelings	25.9%	16.2%	<0.001
Helplessness	13.6%	8.8%	<0.001
Hopelessness	30.6%	22.0%	<0.001
<i>Affective symptoms</i>			
Anhedonia	15.6%	11.2%	0.001
Apathy	6.5%	12.7%	<0.001
Poor motivation	39.8%	36.8%	0.094
Tearfulness	45.2%	49.8%	0.011
<i>Somatic symptoms</i>			
Agitation	33.4%	46.6%	<0.001
Lack of appetite	54.8%	50.0%	0.008
Impaired concentration	35.2%	31.7%	0.040
Disturbed sleep	56.3%	48.7%	<0.001
<i>Psychotic symptoms</i>			
Delusions	16.7%	21.0%	0.001
Hallucinations	10.3%	17.1%	<0.001

<i>Suicidal ideation</i>	20.7%	15.0%	<0.001
Medication prescription, % ^b			
<i>Antidepressants</i>			
Mirtazapine	41.2%	40.5%	0.656
SNRI	13.2%	10.0%	0.007
SSRI	50.7%	55.8%	0.005
TCA	11.9%	8.6%	0.004
<i>Antipsychotics</i>	21.8%	23.1%	0.398
Comorbidity history, % ^a			
<i>HoNOS65+ Physical illness or disability</i>			0.003
No or minor problem	29.0%	29.3%	
Mild problem	24.1%	29.2%	
Moderate-severe problem	46.9%	41.5%	

^a At the time or closest to depression diagnosis.

^b Six months before and after the time of depression diagnosis.

SD = standard deviation; IMD = index of multiple deprivations; HoNOS65+ = Health of the Nation Outcome Scale for those age 65 years or older

p-values were calculated using t-test or chi² test

Supplementary Table 2: Predictors of all-cause mortality in 3,095 patients with new onset depression (Hazard ratios, 95% CIs)

Risk factors	Model I	P	Model II	P	Model III	P
Sociodemographic status ^a						
Age (1-year increase)	1.06 (1.05-1.07)	<0.001	1.05 (1.04-1.05)	<0.001	1.04 (1.03-1.05)	<0.001
Female gender	0.58 (0.50-0.66)	<0.001	0.61 (0.53-0.70)	<0.001	0.64 (0.56-0.75)	<0.001
<i>Ethnicity</i>						
White	1		1		1	
Black	0.72 (0.60-0.85)	<0.001	0.71 (0.59-0.84)	<0.001	0.69 (0.58-0.82)	<0.001
Asian	0.67 (0.53-0.86)	0.002	0.64 (0.49-0.82)	0.001	0.63 (0.49-0.80)	<0.001
Other	0.56 (0.40-0.77)	<0.001	0.60 (0.43-0.83)	0.002	0.59 (0.42-0.82)	0.002
Cohabiting status	0.99 (0.89-1.10)	0.893	0.98 (0.88-1.10)	0.777	0.98 (0.87-1.09)	0.684
IMD score / 10 (1-point increase)	1.01 (0.97-1.05)	0.556	1.01 (0.96-1.05)	1.05	1.00 (0.96-1.05)	0.878
HoNOS65+ Scales ^a						
<i>Memory problems</i>						
No or minor problem	1		1		1	
Mild problem	1.41 (1.24-1.60)	<0.001	1.23 (1.08-1.41)	0.001	1.21 (1.06-1.39)	0.006
Moderate-severe problem	1.79 (1.42-2.25)	<0.001	1.36 (1.09-1.71)	0.007	1.32 (1.05-1.64)	0.016
<i>Depression severity</i>						
No or minor problem	1				1	
Mild problem	1.49 (1.29-1.73)	<0.001	1.16 (1.00-1.35)	0.049	1.21 (1.04-1.42)	0.015
Moderate-severe problem	1.59 (1.32-1.91)	<0.001	1.16 (0.96-1.41)	0.134	1.28 (1.04-1.59)	0.021
<i>Activity of daily living problems</i>						
No or minor problem	1				1	
Mild problem	2.03 (1.74-2.35)	<0.001	1.44 (1.23-1.69)	<0.001	1.43 (1.21-1.68)	<0.001
Moderate-severe problem	3.62 (3.05-4.30)	<0.001	1.99 (1.63-2.44)	<0.001	1.89 (1.54-2.32)	<0.001
Depressive symptoms profiles ^b						
<i>Negative cognitions</i>						
Guilt feelings	0.53 (0.44-0.64)	<0.001	0.63 (0.52-0.77)	<0.001	0.75 (0.61-0.93)	0.008
Helplessness	1.05 (0.91-1.20)	0.509	0.97 (0.84-1.12)	0.685	1.03 (0.88-1.20)	0.750
Hopelessness	0.86 (0.75-1.00)	0.051	0.85 (0.73-0.99)	0.039	0.96 (0.81-1.14)	0.669
<i>Affective symptoms</i>						
Anhedonia	0.98 (0.86-1.12)	0.769	1.05 (0.91-1.21)	0.492	1.09 (0.94-1.27)	0.251
Apathy	1.25 (1.04-1.51)	0.017	1.34 (1.11-1.63)	0.003	1.32 (1.08-1.62)	0.008
Poor motivation	0.77 (0.67-0.89)	<0.001	0.83 (0.72-0.96)	0.014	0.94 (0.80-1.10)	0.421
Tearfulness	0.76 (0.66-0.87)	<0.001	0.76 (0.66-0.87)	<0.001	0.80 (0.69-0.93)	0.003
<i>Somatic symptoms</i>						
Agitation	0.75 (0.65-0.87)	<0.001	0.82 (0.70-0.95)	0.009	0.95 (0.81-1.12)	0.557
Lack of appetite	1.05 (0.96-1.15)	0.305	1.08 (0.98-1.20)	0.121	1.19 (1.06-1.32)	0.002
Impaired concentration	0.63 (0.54-0.73)	<0.001	0.72 (0.61-0.84)	<0.001	0.82 (0.69-0.96)	0.014
Disturbed sleep	0.61 (0.54-0.70)	<0.001	0.67 (0.58-0.77)	<0.001	0.68 (0.59-0.80)	<0.001
<i>Psychotic symptoms</i>						
Delusions	0.60 (0.49-0.74)	<0.001	0.72 (0.58-0.88)	0.002	0.83 (0.66-1.04)	0.110
Hallucinations	1.05 (0.90-1.23)	0.501	1.05 (0.90-1.23)	0.517	1.17 (0.99-1.38)	0.062
Suicidal ideation	0.79 (0.66-0.94)	0.008	0.83 (0.70-0.99)	0.042	1.01 (0.83-1.22)	0.958
Medication prescription ^b						
<i>Antidepressants</i>						
Mirtazapine	1.40 (1.23-1.60)	<0.001	1.31 (1.14-1.51)	<0.001	1.40 (1.21-1.63)	<0.001

SNRI	0.56 (0.43-0.74)	<0.001	0.67 (0.50-0.90)	0.007	0.76 (0.56-1.02)	0.068
SSRI	0.92 (0.84-1.02)	0.100	0.87 (0.79-0.95)	0.004	0.92 (0.83-1.02)	0.111
TCA	0.75 (0.60-0.94)	0.011	0.79 (0.63-1.00)	0.050	0.91 (0.72-1.15)	0.439
<i>Antipsychotics</i>	0.71 (0.59-0.87)	0.001	0.85 (0.70-1.04)	0.112	1.00 (0.80-1.25)	0.987
Comorbidity a						
<i>HoNOS65+ Physical illness or disability scale</i>						
No or minor problem	1		1		1	
Mild problem	2.66 (2.19-3.24)	<0.001	2.30 (1.86-2.84)	<0.001	2.11 (1.70-2.61)	<0.001
Moderate-severe problem	5.92 (4.74-7.40)	<0.001	3.98 (3.07-5.18)	<0.001	3.46 (2.65-4.52)	<0.001

^a At the time of depression diagnosis.

^b Six months before and after the time of depression diagnosis.

Model I - adjusted for age, gender.

Model II - adjusted for age, gender, race, cohabiting status, IMD score, depression severity, physical illness and disability, ADL problems and memory problems.

Model III - adjusted for all the variables.

IMD = index of multiple deprivations; HoNOS65+ = Health of the Nation Outcome Scale for those age 65 years or older; bold = p<0.05