Published in final edited form as:

Depress Anxiety. 2018 July ; 35(7): 658–667. doi:10.1002/da.22772.

Predictors of Recurrence in Remitted Late-Life Depression

Yi Deng, MD^a, Douglas R. McQuoid, MPH^b, Guy G. Potter, PhD^b, David C. Steffens, MD, MHSc^c, Kimberly Albert, PhD^a, Meghan Riddle, MD^a, John L. Beyer, MD^b, and Warren D. Taylor, MD, MHSc^{a,d}

^aThe Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, 37212, USA

^bDepartment of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, 27710, USA

^cDepartment of Psychiatry, University of Connecticut Health Center, Farmington, CT, 06030, USA

^dGeriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, 37212, USA

Abstract

Background—Late-life depression (LLD) is associated with a fragile antidepressant response and high recurrence risk. This study examined what measures predict recurrence in remitted LLD.

Methods—Individuals age 60 years or older with a DSM-IV diagnosis of major depressive disorder were enrolled in the Neurocognitive Outcomes of Depression in the Elderly study. Participants received manualized antidepressant treatment and were followed longitudinally for an average of five years. Study analyses included participants who remitted. Measures included demographic and clinical measures, medical comorbidity, disability, life stress, social support, and neuropsychological testing. A subset completed structural MRI.

Results—Of 241 remitted elders, over approximately four years 137 (56.8%) experienced recurrence and 104 (43.2%) maintained remission. In the final model, greater recurrence risk was associated with female sex (hazard ratio [HR]=1.536; CI=1.027–2.297), younger age of onset (HR=0.990; CI=0.981–0.999), higher perceived stress (HR=1.121; CI=1.022–1.229), disability (HR=1.060; CI=1.005–1.119), and less support with activities (HR=0.885; CI=0.812–0.963). Recurrence risk was also associated with higher MADRS scores prior to censoring (HR=1.081; CI=1.033–1.131) and baseline symptoms of suicidal thoughts by MADRS (HR=1.175; CI=1.002–1.377) and sadness by CESD (HR=1.302; CI=1.080–1.569). Sex, age of onset, and suicidal thoughts were no longer associated with recurrence in a model incorporating report of multiple prior episodes (HR=2.107; CI=1.252–3.548). Neither neuropsychological test performance nor MRI measures of aging pathology were associated with recurrence.

Correspondence: Warren D. Taylor, MD, MHSc, Vanderbilt University Medical Center, 1601 23rd Avenue South, Nashville, TN 37212, USA, warren.d.taylor@vanderbilt.edu, Telephone: (615) 322-1073, Fax: (615) 875-0686.

Conflict of Interest: The authors deny any conflicts of interest and have no disclosures to report.

Conclusions—Over half of depressed elders who remitted experienced recurrence, most within two years. Multiple clinical and environmental measures predict recurrence risk. Work is needed to develop instruments that stratify risk.

INTRODUCTION

Late-life depression (LLD) is associated with significant negative outcomes including disability and greater all-cause mortality (Taylor 2014). Antidepressant medications may be helpful but are less effective in older populations (Taylor & Doraiswamy 2004; Tedeschi et al. 2011) and LLD is associated with a high risk of recurrence. Community studies examining LLD report that 19–34% recover, 27%–32% remain chronically ill, and approximately 40% experience a fluctuating course (Beekman et al. 2002). However, key clinical, environmental, and neurobiological factors that influence recurrence are poorly understood.

Although few studies of recurrence focus on LLD, existing research largely examined clinical factors. Recurrence is most consistently associated with residual symptoms (Judd et al. 1998; Nierenberg et al. 2010) and number of prior depressive episodes, while depression severity and age of initial depression onset are inconsistently reported (Alexopoulos et al. 1989; Hinrichsen & Hernandez 1993; Stoudemire 1997; Alexopoulos et al. 2000). Demographic differences are not related to recurrence, other than female sex that is associated with recurrence in midlife (Mueller et al. 1999; Solomon et al. 2004; Gueorguieva et al. 2017) but not necessarily later life (Hinrichsen & Hernandez 1993; Alexopoulos et al. 2000; Solomon et al. 2004). Comorbid psychiatric symptoms including sleep and anxiety symptoms predict recurrence (Reynolds et al. 2006; Andreescu et al. 2007), but not medical comorbidity or disability (Alexopoulos et al. 1989; Hinrichsen & Hernandez 1993; Alexopoulos et al. 2000; Reynolds et al. 2006). Environmental influences are anecdotally related to recurrence, but published data are mixed. Positive social supports including marriage may reduce recurrence risk but this is not consistently supported (Hinrichsen & Hernandez 1993; Mueller et al. 1999; Solomon et al. 2004; Burcusa & Iacono 2007; Patten et al. 2010; Kuehner & Huffziger 2013; van Loo et al. 2015). Similarly, negative stressful life events including lower socioeconomic status are not consistently associated with recurrence (Alexopoulos et al. 1989; Hinrichsen & Hernandez 1993; Solomon et al. 2004; Burcusa & Iacono 2007; Patten et al. 2010; van Loo et al. 2015).

Few studies used neurocognitive or neuroimaging assessments to examine recurrence. Although poor cognitive performance is common in LLD and associated with poor antidepressant response (Sheline et al. 2012), the effects on recurrence are unclear. While some did not associate recurrence with cognitive impairment (Butters et al. 2004), others identify executive dysfunction but not memory impairment as a risk factor (Alexopoulos et al. 2000). Using neuroimaging, hippocampal atrophy in the elderly is associated with greater and persistent depression severity (Taylor et al. 2014; Buddeke et al. 2016). Greater change in white matter hyperintensity (WMH) volumes, a marker of vascular risk, is also associated with poorer longer term depression outcomes (Taylor et al. 2003).

These data do not provide a clear picture of the factors most predictive of depression recurrence in remitted LLD. Existent reports often focus on specific clinical features and do not provide a holistic picture. The purpose of this study was to examine a wide range of clinical, environmental, medical, cognitive and imaging measures in the longitudinal Neurocognitive Outcomes of Depression in the Elderly (NCODE) cohort in order to determine what factors best predict recurrence in LLD. We hypothesized that, in conjunction with other measures, residual depressive symptoms, female sex, and stress exposure would predict recurrence.

METHODS

Participants

NCODE methods have previously been described (Steffens et al. 2004). The NCODE study enrolled participants from 1995 to 2006 at Duke University Medical Center. Eligible subjects were 60 years or older with a DSM-IV diagnosis of major depressive disorder and a Center for Epidemiologic Studies - Depression (CES-D) score >15 . Exclusion criteria included 1) another major psychiatric illness, although comorbid anxiety was allowed; 2) current or past alcohol or drug dependence; 3) primary neurologic illness, including dementia; 4) Mini-Mental State Examination (MMSE) score <25 ; 5) physical disability precluding cognitive testing; and 6) for magnetic resonance imaging (MRI), any specific MRI contraindications. This study included a treatment as detailed below and only subjects who achieved remission during their study participation were included in analyses.

The study was approved by the Duke University Institutional Review Board. All participants provided written informed consent.

Clinical Assessments and Treatment

A trained interviewer administering the Duke Depression Evaluation Schedule (DDES) (Landerman et al. 1989) assessed for depression using the NIMH Diagnostic Interview Schedule. The DDES also assessed for comorbid generalized anxiety disorder (GAD) per DSM-IV criteria. A study geriatric psychiatrist confirmed diagnoses based on clinical interview and other instruments, including the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg 1979).

The NCODE study operated in a naturalistic milieu where subjects were treated according to the Duke Somatic Treatment Algorithm for Geriatric Depression (Steffens et al. 2002) (Supplemental Methods). For participants who achieve remission, the protocol recommends continued treatment for at least 1 to 2 years, if not indefinitely. Participants were seen at least every 3 months, medication use documented, and MADRS administered. Psychotropic medication use was categorized into drug classes, including antidepressants, anxiolytics, sedative/hypnotics, and antipsychotics, including lithium. When available, antidepressant dose at censoring was calculated using fluoxetine dose equivalents (Supplemental Methods) (Hayasaka et al. 2015).

Demographic, Environmental, and Medical Assessments

The DDES interview acquired demographic information, age of initial depression onset and number of prior depressive episodes. Using our prior approach (Burke et al. 2011; Riddle et al. 2017), we dichotomized the sample into early onset depression (EOD, onset before age 50 years) and late onset depression (LOD, onset at age 50 years or later). Guided by past recommendations (Nierenberg et al. 2003), we examined number of prior episodes as a continuous measure and by dichotomizing the sample by those who reported more than three prior episodes.

Assessments are detailed in the Supplemental Methods. Medical illness was quantified using the Cumulative Illness Rating Scale (CIRS) (Miller et al. 1992) and disability by self-report of instrumental activities of daily living (IADL) (Steffens et al. 1999). Measurements of life stress assessed perceived stress severity (on a 10-point scale), the occurrence and valence of stressful events common in later life (negative, positive, or neutral) (Hays et al. 1997), and participant ability to meet their financial needs. The Duke Social Support Index assessed social network size, frequency of interactions, social assistance with instrumental activities (instrumental social support), and subjective social support (Landerman et al. 1989).

Neuropsychological Assessment

The neuropsychological test battery was previously described (Steffens et al. 2004; Potter et al. 2015). Per our previous strategy (Potter et al. 2015; Riddle et al. 2017), we created z-scores for each neuropsychological measure derived from performance across all participants so we could combine different neuropsychological tasks for a measure of overall cognitive domain performance. We created cognitive domain scores by averaging z-scores across tests, grouped into rational cognitive domain constructs of episodic memory, executive function, working memory, and verbal fluency (Supplemental Methods). For these analyses, we examined z-transformed cognitive domain scores calculated from the entire NCODE sample (including depressed and never-depressed participants) and also examined domain z-scores calculated only from the sample included in this study (depressed participants who remitted).

Neuroimaging

Neuroimaging was initiated after the original study had started, so imaging data are not available for all participants. Subjects were imaged with a 1.5T whole-body MRI system (Signa, GE Medical Systems) using the standard head (volumetric) radiofrequency coil. MRI was obtained at baseline or within the first two weeks; acquisition parameters and volumetric analyses have been previously described (Steffens et al. 2000; Payne et al. 2002) (Supplemental Methods).

Statistical Analyses

Statistical analyses were conducted using SAS 9.4 (Cary, NC). Initial univariate analyses tested for differences between individuals who did and did not experience recurrence. Remission was defined as a MADRS score of 7 or less and recurrence as a subsequent MADRS score of 15 or greater.

Survival analyses examined time to recurrence or censoring. This approach used Cox proportional hazards models (PROC PHREG in SAS) with *a priori* defined core covariates of age and sex, selected due to our focus on an older population and because depression is more common in women. Additional covariates were added as scientifically indicated, such as education for models assessing cognition and intracranial volume when assessing MRI variables. Using these covariates, most initial models examined single predictor variables. For analyses of individual items derived from the baseline depression scales, we first tested for group differences in individual item scores then incorporated items exhibiting a statistically significant group difference into a proportional hazard model predicting time to recurrence. Backward stepwise regression was then conducted to identify individual items predictive of recurrence.

A similar approach was used for the final analyses. Variables exhibiting a statistically significant relationship with time to recurrence in previous analyses at an $\alpha=0.05$ were included in a final proportional hazards model. A final parsimonious model was developed using backwards regression, after which we calculated hazard ratios and 95% confidence intervals. As we intended to consider both total scores on depression scales and individual depression scale items, we planned for two competing models examining these different approaches. Our final results utilized the model with the best statistical fit per Akaike Information Criteria (AIC) and Schwarz Bayesian Information Criteria (SBC).

RESULTS

Of 412 total depressed elders, 171 (41.5%) did not achieve remission during study participation so were not included in analyses. Of the 241 elders who remitted, 137 (33.3.1% of the total sample, or 56.8% of the remitted sample) experienced recurrence of depression during subsequent study participation, while 104 did not (25.2% of the total sample, or 43.2% of the remitted sample). This remitted population was followed in the NCODE study for a mean 3.75 years ($SD=3.79y$).

Recurrent and nonrecurrent groups did not significantly differ in demographic characteristics (Table 1), but differed in time followed after remission but before censoring (Figure 1). Approximately 75% of those who experienced recurrence did so within two years of remission. In an initial model examining age, sex, race, education, and baseline depression severity by MADRS, no variable was significantly associated with recurrence. However, in a parsimonious model of *a priori* defined demographics, female sex (Wald $X^2 = 4.72$, $p=0.0299$) but not age (Wald $X^2 = 0.39$, $p=0.5303$) was associated with recurrence.

Clinical Factors

We first focused on clinical factors related to depression (Table 1). In univariate analyses, time to remission did not significantly differ between recurrent and non-recurrent groups. In contrast to the clinician-rated MADRS, the recurrent group exhibited higher baseline scores on the patient-rated CES-D; in models controlling for age and sex, total CES-D score was associated with recurrence risk (Wald $X^2 = 19.51$, $p < 0.0001$). Individuals with recurrent depression also exhibited significantly higher MADRS scores in the evaluation prior to recurrence or censoring, although the mean difference between groups was only two points.

In models controlling for age and sex, pre-censoring MADRS scores were associated with recurrence risk (Wald $X^2=16.34$, $p < 0.0001$).

We next examined individual baseline CES-D and MADRS items. In univariate analyses, subjects exhibited higher scores on many CES-D items, but only MADRS items of reported sadness and suicidal thoughts (Supplemental Results, Tables 1 and 2). When incorporated into a model and after backwards regression, time to recurrence was associated only with CES-D item 18 (felt sad; Wald $X^2=13.30$, $p=0.0003$) and MADRS item 10 (suicidal thoughts; Wald $X^2=6.42$, $p = 0.0113$).

The recurrent group also exhibited an earlier age at first depressive episode (Table 1). When controlling for age and sex, an earlier age of initial depression onset was associated with recurrence risk (Wald $X^2=5.80$, $p=0.0160$). When dichotomizing the sample into early-onset (EOD; $N = 148$) and late-onset depression (LOD; $N = 109$), the EOD group was more likely to experience recurrence (LOD: 47.7%, $N=52$; EOD: 66.9%, $N=99$; Wald $X^2 = 6.45$, $p = 0.0111$). Finally, comorbid GAD rates did not differ between recurrence groups and GAD did not predict recurrence risk (Wald $X^2 = 0.28$, $p = 0.5983$).

Psychotropic Medication Use

We examined psychotropic medication use both at study entry and at time of censoring. After controlling for age and sex, psychotropic medication use (antidepressants, anxiolytics, sedative/hypnotics, or antipsychotics) at enrollment was not associated with recurrence risk (Supplemental Results Table 3). Similarly, psychotropic medication use at censoring was not associated with recurrence risk, aside from anxiolytic use that was associated with increased recurrence risk (recurrent: 32.9% ($N=45$); nonrecurrent: 19.2% ($N=20$); Wald $X^2=5.28$, $p=0.216$). The majority of study participants were taking an antidepressant medication at censoring (recurrent: 89.1%, $N=122$; nonrecurrent: 83.7%, $N=87$; $X^2 = 1.50$, 1df, $p = 0.2213$). Although not available for all participants, at censoring the recurrent group was taking a higher mean fluoxetine-equivalent antidepressant dose than the nonrecurrent group (recurrent, $N=122$: 42.7mg (29.5mg); nonrecurrent, $N=75$: 33.6mg (20.6mg); Satterthwaite $t = 2.53$, 191.86 df, $p=0.0122$).

Medical and Environmental Factors

Medical—Greater IADL disability but not greater medical morbidity as measured by the CIRS was associated with recurrence risk (Table 2).

Stress—Aside from positively-valenced stressful events, all stress measures were associated with recurrence (Table 2). In adjusted models, the total number of stressful life events score was associated with recurrence, a finding primarily driven by negative stressful events. Similarly, higher perceived stress was associated with recurrence.

We next explored financial stress. We observed a discrepancy where there was no group difference in having enough money to meet their needs ($X^2 = 0.09$, 1df, $p = 0.7653$), but there was a difference in having difficulty making payments ($X^2 = 5.42$, 1df, $p = 0.0199$). In models, only difficulty with payments was associated with time to recurrence (Table 2).

Social Support—In adjusted models, lower levels of instrumental social support and less subjective social support was associated with risk of recurrence, but not social network size or social interactions (Table 2). We did not observe a relationship between current marital status and recurrence.

Neuropsychological Test Performance

The mean z-transformed cognitive test domain scores calculated from the entire NCODE sample were generally lower for recurrent than the non-recurrent group. However, in adjusted models, no domain score was significantly associated with recurrence risk (Table 3). Similarly, baseline MMSE score was not associated with recurrence risk. In secondary analyses, we recalculated z-scores based on only participants included in this analysis. Again, we did not find an association between domain scores and recurrence risk (data not shown).

Neuroimaging Predictors

We examined the effects of baseline neuroimaging markers of brain aging on risk of recurrence in individuals with MRI data. There were no demographic differences between those with and without neuroimaging data. After adjusting for covariates, we did not associate recurrence risk with total cerebral volume, total gray matter, ventricular volume, hippocampus volume, or WMH volume (Table 3).

Composite Models Predicting Time to Recurrence

We incorporated the variables identified in the above analyses into composite models and conducted backwards regression to create final parsimonious models. We examined two competing models examining time to recurrence, with the plan to use the model with the best statistical fit in the final results. The first model examined independent variables of age, sex, age of onset, anxiolytic use (at censor), negative stressors, average stress, ability to meet payments, IADL function, instrumental social support, subjective social support, MADRS score (at assessment prior to censor), and baseline CES-D score. The second model included the same variables but replaced baseline CES-D score with baseline CES-D item 18 (feeling sad) and baseline MADRS item 10 (suicidal thoughts). Given missing data, we reserved analyses including number of prior depressive episodes for a secondary model.

After backwards regression, the model with individual scale items exhibited the better statistical fit (AIC=1107.8, SBC=1132.9). In this final parsimonious model examining 214 participants (121 recurrent, 93 nonrecurrent), depression recurrence was associated with female sex, younger age of onset, higher perceived stress, greater IADL deficits, lower instrumental social support, and higher scores on the pre-censoring MADRS, baseline MADRS item 10, and baseline CESD item 18 (Table 4).

Finally, we added the dichotomized number of prior depressive episodes variable to the parsimonious model, reducing the sample size to 182 participants (Table 4). Having more than 3 prior episodes significantly predicted recurrence risk, while female sex, younger age of onset, and baseline MADRS item 10 no longer predicted recurrence.

DISCUSSION

Over a mean duration of approximately four years and despite most continuing antidepressant treatment, 56.8% of older adults with remitted depression experienced recurrence while 43.2% remained in remission. Approximately 75% of those experiencing recurrence did so within two years of remission. This replicates prior clinical and population studies (Alexopoulos et al. 1989; Alexopoulos et al. 2000; Beekman et al. 2002; Reynolds et al. 2006) despite differences in interventions and duration. Our primary finding is that several variables predicted risk of recurrence, including younger age of initial onset, female sex, greater perceived stress, greater disability, and less social support with activities. Specific symptoms during acute depression also predicted recurrence, including thoughts of death measured by MADRS and greater frequency of sadness measured by CESD. Recurrence risk was also related to greater residual symptom severity, measured at the evaluation prior to censoring. However, psychotropic medication use, neuropsychological test performance and structural measures of brain aging were unrelated to recurrence.

Effects of Demographic Variables and Clinical Measures

Demographic factors associated with recurrence differ from past studies. We found that women were approximately 50% more likely than men to experience recurrence. This was not observed in a prior study of LLD (Hinrichsen & Hernandez 1993), and conclusions are mixed in mid-life depression (Mueller et al. 1999; Kuehner & Huffziger 2013). An earlier age of initial depressive episode is also a risk factor for recurrence, although past studies have not always observed this relationship (Stoudemire 1997; Burcusa & Iacono 2007; Patten et al. 2010). Importantly, in a secondary model with a slightly reduced sample, neither age of onset nor sex was associated with recurrence after including a dichotomous variable of reporting more than three prior depressive episodes. Thus, earlier age of onset and female sex may be characteristics of a highly recurrent depression phenotype.

Past studies inconsistently report relationships between environmental stressors and recurrence. In our final parsimonious model, perceived stress severity but not quantitative measures of stressful events predicted recurrence. This suggests that stressful events themselves may be less relevant to recurrence than one's subjective response. Higher levels of social support could potentially mitigate the effect of stress, however recurrence risk was reduced only by higher levels of instrumental social support, or social assistance with activities. This social support measure may be particularly associated with greater disability. This is an important consideration as we excluded individuals with severe physical disabilities that interfered with cognitive testing. The combination of greater disability and less assistance with activities may be a particularly problematic combination.

Effects of Depressive Symptomatology

Our association of recurrence with greater residual depressive symptoms measured during the pre-censoring assessment is concordant with past reports that residual symptoms increase risk of recurrence. However, the mean group difference of 2 points in pre-censoring MADRS score may be challenging to distinguish and interpret clinically. Thus, symptom severity monitoring alone may not clearly inform who needs clinical intervention.

Two specific depressive symptoms also predicted recurrence. One item, measured by self-report on the CESD, is the frequency of sad feelings, a finding not observed for the comparable physician-assessed MADRS item. This discrepancy may be related to the structure of the MADRS item that incorporates sadness intensity and does not purely focus on frequency. It could also be related to differences in reporting bias between physician- and self-report measures, as subject responses may be influenced by the relationship with their physicians. This symptom may reflect a persistently decreased ability to self-regulate mood. The discrepancy between CESD and MADRS items raises concerns for type 1 errors, however this concern is mitigated by our focus on the final statistical models. The second symptom was the presence of thoughts of death measured by MADRS. This is particularly important as not all subjects develop thoughts of death or suicidality, while suicidality is associated with distinct neurobiological findings (Desmyter et al. 2011; Taylor et al. 2015). However, this item was no longer associated with recurrence after adjusting for reporting more than three prior episodes, supporting that suicidality may be more common in highly recurrent depression.

Important Negative Findings

There are several important negative findings. Although continuation treatment reduces risk of relapse or recurrence (Reynolds et al. 2006; Gueorguieva et al. 2017), our study did not associate cessation of antidepressant medications with recurrence. However, over 90% of study subjects were taking antidepressants at censoring, so this analysis may have been underpowered to detect an effect in the small number of participants who stopped antidepressant medications. In contrast, anxiolytic use was associated with increased recurrence risk in initial models, but not the final parsimonious model. Anxiolytic use may be a marker of residual anxiety as more severe anxiety symptoms in LLD are associated with recurrence (Andreescu et al. 2007). Unfortunately, we did not have a measure of anxiety severity, only a dichotomous diagnosis of GAD at entry.

Measures of neuropsychological performance and brain aging were also unrelated to recurrence risk. This is consistent with prior work in LLD examining the relationship between recurrence risk and executive dysfunction (Butters et al. 2004), but not reports in non-geriatric adult depression associating memory impairment with recurrence risk (Maeshima et al. 2016). This difference may be related to timing of the neuropsychological testing: our testing occurred during an active depressive episode, while others measured performance at remission (Maeshima et al. 2016). As cognitive performance can improve with antidepressant treatment (Barch et al. 2012), our findings may differ had the battery been administered at remission. Similarly, we did not observe a relationship between imaging measures of brain aging and recurrence. However only a subsample of participants had MRI data, decreasing our power to identify relationships with recurrence risk. Moreover, our past work has reported that cross-sectional assessments may be less related to long-term outcomes than longitudinal measures of change (Taylor et al. 2003; Taylor et al. 2014). These negative imaging and neuropsychological findings are concordant with our observation that earlier age of depression onset is associated with greater recurrence risk, as individuals with an earlier ages of onset often have less severe age-related brain changes (Herrmann et al. 2008). Perhaps other factors contributing to early onset depression such as

sex, genetics, and early adversity may be more relevant for recurrence than brain aging and cognitive decline.

Strengths and Limitations

To our knowledge, this is the largest study of recurrence in a clinical LLD sample. It has several strengths, including the duration of follow-up and assessments across a range of environmental, social, and biological domains, even if it did not assess potentially important variables such as duration of the current depressive episode. Most participants continued on antidepressant treatment throughout the study, thus providing data related to recurrence risk with continued treatment. However, our findings are not generalizable to individuals who stop antidepressant medications. In contrast, the heterogeneity of medications used may also be considered a limitation compared to more structured and rigid clinical trial designs. Due to heterogeneity in treatment and changes in treatment over time, we could not measure effects of specific medications and had no formal assessments of medication adherence.

Another limitation is that assessments were conducted prior to remission, when subjects were symptomatic. This may have biased some responses and also negatively affected our analyses examining cognitive function as neuropsychological test performance may improve with remission. Also, neuroimaging measures were limited to volumetric assessments related to aging and did not include neuroimaging measures of cortical thickness, white matter microstructure, or functional connectivity. These limitations are related to relying on lower resolution 1.5T MRI data, but also magnified by the relatively smaller sample size of individuals with MRI data. These factors may have decreased our ability to identify effects of MRI measures on recurrence risk.

Implications and Future Directions

In conclusion, specific demographics, environmental factors, and depressive symptoms predict recurrence in late life. These data provide a starting point for clinicians and patients in a shared decision-making process about ongoing treatment and recurrence risks after remission and suggests possible targets for interventions aimed at maintaining remission. This work will inform future research aimed at developing a personalized risk stratification algorithms that may be applied clinically. Further directions also include exploring how differences in cognition and brain function that persist with remission may be related to recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This research was supported by National Institute of Mental Health grants R01 MH102246, R01 MH054846, and K24 MH110598

References

- Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, Sirey JA, Hull J. Executive dysfunction and long-term outcomes of geriatric depression. *Archives of General Psychiatry*. 2000; 57:285–290. [PubMed: 10711915]
- Alexopoulos GS, Young RC, Abrams RC, Meyers B, Shamoian CA. Chronicity and relapse in geriatric depression. *Biological Psychiatry*. 1989; 26:551–564. [PubMed: 2675989]
- Andreescu C, Lenze EJ, Dew MA, Begley AE, Mulsant BH, Dombrovski AY, Pollock BG, Stack J, Miller MD, Reynolds CF. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *British Journal of Psychiatry*. 2007; 190:344–349. [PubMed: 17401042]
- Barch DM, D'Angelo G, Pieper C, Wilkins CH, Welsh-Bohmer K, Taylor W, Garcia KS, Gersing K, Doraiswamy PM, Sheline YI. Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. *American Journal of Geriatric Psychiatry*. 2012; 20:682–690. [PubMed: 22430020]
- Beekman AT, Geerlings SW, Deeg DJ, Smit JH, Schoevers RS, de Beurs E, Braam AW, Penninx BW, van Tilburg W. The natural history of late-life depression: a 6-year prospective study in the community. *Archives of General Psychiatry*. 2002; 59:605–611. [PubMed: 12090813]
- Buddeke J, Kooistra M, Zuithoff NP, Gerritsen L, Biessels GJ, van der Graaf Y, Geerlings MI, Group SS. Hippocampal volume and the course of depressive symptoms over eight years of follow-up. *Acta Psychiatrica Scandinavica*. 2016
- Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clinical Psychology Review*. 2007; 27:959–985. [PubMed: 17448579]
- Burke J, McQuoid DR, Payne ME, Steffens DC, Krishnan RR, Taylor WD. Amygdala volume in late-life depression: relationship with age of onset. *American Journal of Geriatric Psychiatry*. 2011; 19:771–776. [PubMed: 21873832]
- Butters MA, Bhalla RK, Mulsant BH, Mazumdar S, Houck PR, Begley AE, Dew MA, Pollock BG, Nebes RD, Becker JT, Reynolds CF 3rd. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *American Journal of Geriatric Psychiatry*. 2004; 12:387–394. [PubMed: 15249276]
- Desmyter S, van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2011; 35:796–808. [PubMed: 21216267]
- Gueorguieva R, Chekroud AM, Krystal JH. Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis. *Lancet Psychiatry*. 2017; 4:230–237. [PubMed: 28189575]
- Hayasaka Y, Purgato M, Magni LR, Ogawa Y, Takeshima N, Cipriani A, Barbui C, Leucht S, Furukawa TA. Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *Journal of Affective Disorders*. 2015; 180:179–184. [PubMed: 25911132]
- Hays JC, Krishnan KR, George LK, Pieper CF, Flint EP, Blazer DG. Psychosocial and physical correlates of chronic depression. *Psychiatry Research*. 1997; 72:149–159. [PubMed: 9406904]
- Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008; 79:619–624.
- Hinrichsen GA, Hernandez NA. Factors associated with recovery from and relapse into major depressive disorder in the elderly. *American Journal of Psychiatry*. 1993; 150:1820–1825. [PubMed: 8238636]
- Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Paulus MP, Kunovac JL, Leon AC, Mueller TI, Rice JA, Keller MB. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *Journal of Affective Disorders*. 1998; 50:97–108. [PubMed: 9858069]
- Kuehner C, Huffziger S. Factors predicting the long-term illness course in a cohort of depressed inpatients. *European Archives of Psychiatry and Clinical Neuroscience*. 2013; 263:413–423. [PubMed: 23108435]

- Landerman R, George LK, Campbell RT, Blazer DG. Alternative models of the stress buffering hypothesis. *American Journal of Community Psychology*. 1989; 17:626–642.
- Maeshima H, Baba H, Satomura E, Shimano T, Inoue M, Ishijima S, Suzuki T, Arai H. Residual memory impairment in remitted depression may be a predictive factor for recurrence. *Journal of Clinical Psychiatry*. 2016; 77:247–251. [PubMed: 26930522]
- Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant B, Reynolds CF 3rd. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Research*. 1992; 41:237–248. [PubMed: 1594710]
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
- Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry*. 1999; 156:1000–1006. [PubMed: 10401442]
- Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychological Medicine*. 2010; 40:41–50. [PubMed: 19460188]
- Nierenberg AA, Petersen TJ, Alpert JE. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *Journal of Clinical Psychiatry*. 2003; 64(Suppl 15):13–17.
- Patten SB, Wang JL, Williams JV, Lavorato DH, Khaled SM, Bulloch AG. Predictors of the longitudinal course of major depression in a Canadian population sample. *Canadian Journal of Psychiatry*. 2010; 55:669–676. [PubMed: 20964946]
- Payne ME, Fetzter DL, MacFall JR, Provenza JM, Byrum CE, Krishnan KRR. Development of a semi-automated method for quantification of MRI gray and white matter lesions in geriatric subjects. *Psychiatry Research Neuroimaging*. 2002; 115:63–77.
- Potter GG, McQuoid DR, Steffens DC. Appetite loss and neurocognitive deficits in late-life depression. *International Journal of Geriatric Psychiatry*. 2015; 30:647–654. [PubMed: 25315155]
- Reynolds CF 3rd, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, Schlermitzauer MA, Whyte EM, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ. Maintenance treatment of major depression in old age. *The New England Journal of Medicine*. 2006; 354:1130–1138. [PubMed: 16540613]
- Riddle M, Potter GG, McQuoid DR, Steffens DC, Beyer JL, Taylor WD. Longitudinal cognitive outcomes of clinical phenotypes of late-life depression. *American Journal of Geriatric Psychiatry*. 2017; 25:1123–1134. [PubMed: 28479153]
- Sheline YI, Disabato BM, Hranilovich J, Morris C, D'Angelo G, Pieper C, Toffanin T, Taylor WD, MacFall JR, Wilkins C, Barch DM, Welsh-Bohmer KA, Steffens DC, Krishnan RR, Doraiswamy PM. Treatment course with antidepressant therapy in late-life depression. *American Journal of Psychiatry*. 2012; 169:1185–1193. [PubMed: 23534057]
- Solomon DA, Leon AC, Endicott J, Mueller TI, Coryell W, Shea MT, Keller MB. Psychosocial impairment and recurrence of major depression. *Comprehensive Psychiatry*. 2004; 45:423–430. [PubMed: 15526252]
- Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, MacFall JR, Krishnan KRR. Hippocampal volume in geriatric depression. *Biological Psychiatry*. 2000; 48:301–309. [PubMed: 10960161]
- Steffens DC, Hays JC, Krishnan KRR. Disability in geriatric depression. *American Journal of Geriatric Psychiatry*. 1999; 7:34–40. [PubMed: 9919318]
- Steffens DC, McQuoid DR, Krishnan KRR. The Duke Somatic Treatment Algorithm for Geriatric Depression (STAGED) approach. *Psychopharmacology Bulletin*. 2002; 36:58–68. [PubMed: 12397841]
- Steffens DC, Welsh-Bohmer KA, Burke JR, Plassman BL, Beyer JL, Gersing KR, Potter GG. Methodology and preliminary results from the neurocognitive outcomes of depression in the elderly study. *Journal of Geriatric Psychiatry and Neurology*. 2004; 17:202–211. [PubMed: 15533991]

- Stoudemire A. Recurrence and relapse in geriatric depression: a review of risk factors and prophylactic treatment strategies. *J Neuropsychiatry Clin Neurosci*. 1997; 9:208–221. [PubMed: 9144100]
- Taylor WD. Clinical practice. Depression in the elderly. *The New England Journal of Medicine*. 2014; 371:1228–1236. [PubMed: 25251617]
- Taylor WD, Boyd B, McQuoid DR, Kudra K, Saleh A, MacFall JR. Widespread white matter but focal gray matter alterations in depressed individuals with thoughts of death. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2015; 62:22–28. [PubMed: 25963377]
- Taylor WD, Doraiswamy PM. A systematic review of antidepressant placebo-controlled trials for geriatric depression: limitations of current data and directions for the future. *Neuropsychopharmacology*. 2004; 29:2285–2299. [PubMed: 15340391]
- Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampus Atrophy and the Longitudinal Course of Late-life Depression. *American Journal of Geriatric Psychiatry*. 2014; 22:1504–1512. [PubMed: 24378256]
- Taylor WD, Steffens DC, MacFall JR, McQuoid DR, Payne ME, Provenzale JM, Krishnan KRR. White matter hyperintensity progression and late-life depression outcomes. *Archives of General Psychiatry*. 2003; 60:1090–1096. [PubMed: 14609884]
- Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC, Papakostas GI. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*. 2011; 72:1660–1668. [PubMed: 22244025]
- van Loo HM, Aggen SH, Gardner CO, Kendler KS. Multiple risk factors predict recurrence of major depressive disorder in women. *Journal of Affective Disorders*. 2015; 180:52–61. [PubMed: 25881281]

Figure 1. Time to censoring for recurrent and non-recurrent groups

Survival curve displays time to censor (recurrence or withdrawal from the study) over 5 years. X-axis displays days, Y-axis displays survival percentage. Mean time to censoring differed between recurrence groups (red: recurrent (N=127): 423.4 days (SD = 1162.3 days); blue: nonrecurrent (N=114): 1162.3 days (SD = 1034.4 days); Satterthwaite $t = 9.96$, 180.2 df, $p < 0.0001$).

Table 1

Group differences in demographic and clinical factors

Demographic Variables	Recurrent N=137	Non-Recurrent N=104	Test statistic	p value
Age	67.7 (6.8)	68.6 (6.6)	t = 1.04, 239 df	0.3012
Sex (% Women)	67.2% (92)	55.8% (58)	X ² = 3.26, 1df	0.0710
Race (% Caucasia)	80.3% (110)	82.7% (86)	X ² = 0.22, 1df	0.6358
Education	14.2 (2.6)	14.3 (2.6)	t = 0.23, 262 df	0.8186
Time to Relapse / Censoring	593.1 (751.0)	1699.9 (1717.4)	t = 6.60, 141.83 df	< 0.0001
Clinical Variables				
MADRS, baseline	24.8 (5.7)	23.5 (4.7)	t = 1.93, 237.5 df	0.0546
MADRS, prior to censoring	6.2 (3.8)	4.2 (3.6)	t = 4.13, 239 df	< 0.0001
CESD, baseline	N=131 31.4 (10.3)	N=102 25.5 (12.1)	t = 4.06, 231 df	< 0.0001
Comorbid GAD	39.9% (54)	39.4% (37)	X ² = 0.37, 1 df	0.5426
Time to Remission (days)	328.0 (407.7)	256.4 (342.2)	t = 1.44, 239 df	0.1496
Age of Onset	39.6 (20.53)	47.4 (21.1)	t = 2.86, 239 df	0.0050
Prior Depressive Episodes (number)	N=111 5.1 (6.2)	N=84 4.5 (6.9)	t=0.67, 193 df	0.5058
More than 3 prior depressive episodes	N=111 59.5% (66)	N=84 31.0% (26)	X ² = 15.59, 1 df	< 0.0001

All analyses examine 241 participants, except for CESD analyses that examine 233 participants and prior episode analyses that examine 195 participants due to missing data. Analyses of categorical variables used chi-square tests. Analyses of continuous variables used pooled, two-tailed t-tests, except for analyses of time to relapse / censoring and baseline MADRS that used the Satterthwaite t-test due to unequal variances. CESD = Center for Epidemiological Studies – Depression Scale; df = degrees of freedom; GAD = Generalized Anxiety Disorder; MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2

Medical and environmental factor effects on recurrence risk

Medical Measures	Recurrent N=135	Non-recurrent N=102	Wald X ²	p value
CIRS	4.7 (3.0)	4.6 (3.2)	1.45	0.2279
IADL Deficits	2.6(3.5)	1.9 (2.9)	8.91	0.0028
Environmental Stress Measures				
Total Stress	2.8 (1.8)	2.4 (1.8)	6.82	0.0090
Positive Stress	0.5 (0.7)	0.5 (0.7)	0.12	0.7250
Negative Stress	1.9 (1.6)	1.4 (1.4)	14.22	0.0002
Perceived Stress Severity	N=134 6.8 (2.0)	N=101 6.1 (2.0)	13.72	0.0002
Sufficient Money (Yes responses)	N=133 91.0% (121)	N=101 92.1% (93)	0.17	0.6796
Difficulty with Payments (Yes responses)	N=134 38.1% (51)	N=101 23.8% (24)	8.51	0.0035
Social Support Measures				
Social Network Size	1.9 (2.2)	1.8 (1.9)	0.18	0.6757
Social Interaction Scale	5.9 (2.5)	6.3 (2.6)	3.56	0.0592
Instrumental Social Support	8.7 (2.1)	9.2 (1.8)	12.96	0.0003
Subjective Social Support	23.2 (3.9)	24.3 (3.0)	15.31	< 0.0001
Marital Status (% Married)	54.8% (74)	61.8% (63)	0.48	0.4873

All analyses examine 241 participants, except for analyses examining perceived stress and financial problems due to missing data. Results are presented for models controlling for age and sex. CIRS = Cumulative Illness Rating Scale severity index; IADL = Instrumental Activities of Daily Living.

Table 3

Neuropsychological and neuroimaging factor effects on recurrence

Neuropsychological Assessments	Recurrent	Non-recurrent	Wald X ²	p value
MMSE	N=135 28.1 (2.0)	N=102 28.2 (2.4)	1.60	0.2061
Episodic Memory	N=113 −0.026 (0.798)	N = 77 0.006 (0.686)	1.89	0.1697
Executive Function	N=110 −0.090 (0.943)	N = 76 −0.055 (0.850)	1.86	0.1726
Verbal Fluency	N=112 −0.047 (0.851)	N=77 −0.103 (0.874)	0.01	0.9558
Working Memory	N=104 −0.062 (0.829)	N=74 −0.002 (0.758)	0.52	0.4688
Neuroimaging Measures				
White Matter Hyperintensity Volume	N=59 6.21 (8.93)	N=57 5.83 (8.96)	0.09	0.7613
Hippocampus, left	N=47 2.98 (0.54)	N=33 2.94 (0.37)	0.75	0.3867
Hippocampus, right	N=47 3.01 (0.47)	N=33 3.11 (0.34)	1.54	0.2151
Lateral Ventricles	N=59 36.28 (21.33)	N=57 39.59 (26.21)	0.50	0.4795
Total Cerebral Gray Matter Volume	N=59 591.0 (87.5)	N=57 573.2 (82.6)	3.76	0.0525
Total Cerebral Volume	N=59 1148.2 (132.9)	N=57 1163.1 (139.9)	0.15	0.6965

Neuropsychological test models examine z-transformed cognitive domain scores, controlling for age, sex, and education. Neuroimaging measures are presented in milliliters and models control for age, sex, and total cerebral volume, except for models focusing solely on total cerebral volume that control only for age and sex. Sample size included for each model due to missing data. MMSE = Mini-mental state exam.

Table 4

Final parsimonious models predicting recurrence of depression

Variable	Primary Model (N=214)			Secondary Model (N=182)		
	Hazard Ratio	Wald X ²	p value	Hazard Ratio	Wald X ²	p value
Age	1.032 (0.999 – 1.067)	3.54	0.0599	1.030 (0.994–1.068)	2.66	0.1026
Sex	1.536 (1.027 – 2.297)	4.38	0.0365	1.457 (0.941 – 2.257)	2.84	0.0919
Age of Onset	0.990 (0.981 – 0.999)	4.66	0.0310	1.000 (0.988 – 1.013)	0.01	0.9742
CESD Item 18, baseline (felt sad)	1.302 (1.080 – 1.569)	7.66	0.0056	1.357 (1.108 – 1.663)	8.69	0.0032
MADRS Item 10, baseline (suicidal thoughts)	1.175 (1.002 – 1.377)	3.96	0.0466	1.131 (0.952 – 1.344)	1.97	0.1610
MADRS total, pre-censoring score	1.081 (1.033 – 1.131)	11.42	0.0007	1.081 (1.030 – 1.134)	9.86	0.0017
Perceived stress severity	1.121 (1.022 – 1.229)	5.84	0.0157	1.125 (1.109 – 1.243)	5.42	0.0199
IADL	1.060 (1.005 – 1.119)	4.56	0.0327	1.061 (1.003 – 1.123)	4.24	0.0394
Instrumental Social Support	0.885 (0.812 – 0.963)	7.98	0.0047	0.846 (0.766 – 0.934)	10.94	0.0009
More than 3 prior depressive episodes	-	-	-	2.107 (1.252 – 3.548)	7.87	0.0050

Data presented as Hazard Ratio (95% Confidence Interval). CESD = Center for Epidemiological Studies – Depression Scale; IADL = Instrumental Activities of Daily Living; MADRS = Montgomery-Asberg Depression Rating Scale.