ORIGINAL RESEARCH

Psychosocial Risk Factors for Cognitive Decline in Late-Life Depression: Findings from the MTLD-III Study

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ABSTRACT

Background

Cognitive impairment and depression frequently co-occur in late life. There remains a need to better characterize psychosocial risk factors of cognitive decline in older adults with depression. We hypothesized that certain psychosocial factors would be associated with higher risk of cognitive decline in individuals with late-life depression.

Methods

130 individuals aged ≥ 65 years who had achieved remission from a major depressive episode were randomized to donepezil or placebo and then closely followed for two years. Using Cox proportional hazard models, we examined the association between baseline median household income, education level, race, marital status, and social support and cognitive decline over the follow-up.

Results

Lower interpersonal support (OR = 0.86 [0.74-0.99], $p = .04$) and lower baseline global neuropsychological score (OR = 0.56 [0.36-0.87], $p = .001$) predicted shorter time to conversion to MCI or dementia in univariate models. These exposures did not remain significant in multivariate analyses. Neither socioeconomic status nor other psychosocial factors independently predicted cognitive diagnostic conversion ($p > .05$).

Conclusions

We did not find reliable associations between cognitive outcome and any of the psychosocial factors examined. Future large-scale, epidemiological studies, ideally using well-validated subjective measures, should better characterize psychosocial risk factors for cognitive decline in late-life depression.

Key words: psychosocial risk factors, late-life depression, cognition, dementia, mild cognitive impairment, medical illness burden

INTRODUCTION

Cognitive impairment is common in late-life depression.[1-3] Likewise, depression is an important co-morbidity and risk factor for both mild cognitive impairment (MCI) and dementia.[4-8] Some authors have even described depression, mild cognitive impairment (MCI), and dementia as being on a clinical continuum.[9,10]

In a previous study, our group found that 30% of older adults demonstrated cognitive impairment when assessed during a major depressive episode.[11] Nearly all patients with cognitive dysfunction while depressed (94%) exhibited sustained cognitive impairment when re-assessed one year following depression remission, compared to only 23% of individuals with normal cognitive function while depressed.[11] Other studies have also demonstrated the persistence of cognitive impairment in late-life depression.[12,13] Similarly, a history of recurrent depressive episodes in middle or late-life has been associated with worse cognitive outcome in older adults,[1] with those having a combination of MCI and depression being at greater risk of developing future dementia.[4] In spite of knowledge that pre-morbid cognitive reserve, Apolipoprotein E4 (ApoE4) status, and cardiovascular factors can affect cognition,[9] there remains a dearth of adequate biological interventions[14] for cognitive decline in older adults with depression. Given this reality, there is a pressing need to better understand psychosocial risk factors which may be modifiable in this population.

Psychosocial risk factors for cognitive decline have been examined in several studies, some of which have investigated older adults with depression. In a large population-based longitudinal analysis, attending religious services regularly was associated with less cognitive decline among depressed women.[15] Although cognitive reserve is a protective factor for Alzheimer's dementia,[16] education level does not appear to be associated with one-year cognitive outcome in depressed older adults.[17]

Complementing data from depressed samples, studies in non-depressed patients have identified additional protective psychosocial factors against cognitive decline. These include: being employed,[18] being married,[18] performing mentally stimulating activities,[16] being socially engaged,[16] and the absence of subjective feelings of loneliness.[19] Although large community-based surveys have been performed, the data are almost all cross-sectional and the sizes for the observed associations are relatively small, possibly due to the use of insensitive measures of cognitive function (e.g., the Mini-Mental State (MMSE) and Modified MMSE (3MS) [20]).[15,18,19] Whether or not social engagement/isolation or demographic variables such as age, sex, race, and marital status predict cognitive decline in older depressed individuals has yet to be examined, using longitudinal studies incorporating detailed neuropsychological testing for MCI or dementia.

Additionally, several lines of research suggest that higher socioeconomic status (SES) may protect against a wide variety of health outcomes,[21] including both cognitive decline and depression. Recent cross-sectional surveys of community-dwelling older adults found that lower median household income[18] and lower median neighborhood income[22] were independent predictors of worse cognitive function. Other studies in older adults have also demonstrated that lower median neighborhood income is associated with increased rates of depression[23] and poor antidepressant treatment response.[24,25] Even though depression and cognitive impairment frequently co-occur and low SES is associated with both depression and cognitive impairment, the existing studies examining SES and cognitive function are cross-sectional and have involved only the use of the MMSE and 3MS.[18,22] Since patients with late-life depression are at particularly high risk for cognitive impairment,[1] a longitudinal study using detailed neuropsychological assessment could, potentially, adequately assess whether SES and other social variables predict cognitive decline in euthymic older adults with major depressive disorder.

In this report, we examined whether SES and other potential social risk factors, such as race, education level, marital status, sex, and social support, are important in predicting cognitive decline over two years in older adults with non-psychotic, non-bipolar major depressive disorder.

METHODS

This is an exploratory analysis of data from a trial entitled "Maintenance Treatment in Late-life Depression-III" (MTLD-III, clinicaltrial.gov identifier: NCT00177671). We have previously reported the methods used, CONSORT diagram, and primary outcome results.[14]

Patient Study Group and Recruitment Procedures

In the MTLD-III study, patients were recruited between April 2004 and September 2009 from primary care practices, mental health clinics, other federally-sponsored research projects, and advertisements. Two hundred-ninety-nine non-demented participants aged 65 years and older experiencing non-psychotic, non-bipolar major depressive episodes were screened and recruited, of whom 220 qualified for and provided written consented to participate. Of the 158 non-demented individuals who then responded to open-label antidepressant treatment and were either cognitively normal or had MCI, 130 agreed to randomization to a two-year maintenance phase in which participants received either double-blind donepezil or placebo, in addition to maintenance anti-depressant pharmacotherapy. Of these, 104 reached the study's endpoint, either by completing detailed two-year neuropsychological follow-up or by converting to MCI/dementia during the trial, with 26 individuals (20%) dropping out prematurely. More information about study recruitment and full eligibility criteria are described elsewhere.[14]

For the purpose of this report, we analyzed the data of all 130 depressed individuals who achieved remission/response to open-label antidepressant therapy and were then randomized to double-blind donepezil or placebo treatment.

Assessments

Baseline global neuropsychological function score was calculated by 1) transforming the raw scores for 17 well-established neuropsychological tests into Z-scores using the baseline mean and standard deviations of a non-depressed, cognitively normal control group (n = 36) equated to the depressed participants for age and years of education; and 2) taking the average Z-score over all 17 tests. The tests have been used and described previously.[3,14] We performed neuropsychological assessment after participants had responded to acute treatment and were euthymic, in order to: a) avoid any state effects of depression on cognitive function, and b) maximize generalizability of our results to individuals with a history of, as opposed to individuals in a current episode of, MDD.

We estimated median household income by using 2000 census data (http://factfinder2.census.gov) and then converting participants' addresses into their associated latitude/longitude (http://geocoder.us[26]) and census tract number. The additional step of converting addresses to latitude/longitude was performed to maintain patient confidentiality and was achieved by means of an honest broker authorized to access MTLD-III data, but who was not involved in performing this secondary analysis. To obtain the most accurate estimate of neighborhood household income, data from participants'

census tract city block groups were used whenever available. Because study recruitment was performed between 2004 and 2009, we used 2000 census data, which had complete information for all participants' census tracts and more complete information on block groups than other census data (e.g., 2005-2010 census data).[27]

Our approach to estimating SES with census tracts has been widely used, including one of our studies.[24] Median neighborhood household income was used both as a continuous variable and as an ordinal variable based on tertiles of household income. Lowest tertile was used since federal definitions of poverty required knowing the number of people living in each household and may not accurately characterize SES in older adults[28] who are largely retired with lower incomes than other groups. This method has also been used in other studies of depressed older adults.[24,25] Based on 2000 census data from Allegheny County, PA, in which 81.5% (106/130) of participants lived, the lowest tertile had a median household income of $0–$24,999, while the other tertiles had incomes of $25,000–$49,999 and >$50,000, respectively.[27]

We measured social support using both participants' total and subscale scores on the Interpersonal Support Evaluation List Short Form (ISEL-SF), a well-validated scale of subjectively perceived social support[29,30] which uses 16 of the 40 items from the original version.[31] The ISEL-SF is made up of four subscales of perceived support: Appraisal –that others are available to talk about personally important matters; Belonging – that others are available for social interaction; Self-Esteem – that one is favourably comparable to one's peers; and Tangible Assets – that money and/or other material aid is available.[30] Each subscale contains four items scored on a scale of 0–3, making a maximum of 12 points, with higher scores indicating higher levels of perceived support.[30] Individual subscale scores and total scores have both been used extensively as covariates in psychosocial research.[29] We have also previously reported that pre-treatment ISEL scores significantly influence trajectory of major depression's clinical response to antidepressant treatment combining medication and psychotherapy.[32]

We also assessed other factors, including psychosocial factors, potentially associated with cognitive function: current age, race (black or white), years of education, marital status (married or not currently married), sex, lifetime duration of depression, medical co-morbidity as measured by the Cumulative Illness Ratings Scale-geriatrics (CIRS-G)[33] (a 13 item scale ranging from 0 to 52 with higher scores indicating worse medical illness severity), and treatment allocation (donepezil or placebo). The MMSE[34] and Executive Interview (EXIT),[35] both well-established cognitive tests, were also performed as baseline measures to characterize the sample. In addition, baseline acute depression symptoms were assessed primarily using Hamilton Depression Rating Scale-17 (HDRS).[36] This is a 17-item scale rating depression symptoms where total score can range from 0 to 52, with 0 indicating no depression symptoms and higher scores indicating worse severity.

Outcomes

Our main dichotomous outcome was cognitive decline, defined as whether patients with normal cognitive function or MCI converted to MCI or dementia, respectively, during the course of two-year follow-up. Cognitive status (normal, MCI, dementia) was adjudicated by the University of Pittsburgh Alzheimer's Disease Research Center (ADRC) using neuropsychological data, clinical history, MRI data, and Performance Assessment of Self-Care Skills (PASS) data, in accordance with National Alzheimer Coordinating Center criteria.[37] In the 26 patients who did not complete two-year follow-up, cognitive status was known until the time of drop-out.

Our secondary continuous outcome measure was change in global neuropsychological score during two-year follow-up. This was calculated as described above, at baseline and the two-year follow-up time points, using the difference between scores at baseline and at two-year follow-up.

Although continuous outcome variables (e.g., global cognitive function score) are usually more sensitive clinical outcome measures, depressed participants in this study, who converted to dementia during the course of the study, often did not undergo neuropsychological assessment at the end of two-years since, for ethical reasons, they were required to be withdrawn prior to the study's end to receive treatment for dementia, including open-label cholinesterase inhibitor pharmacotherapy.[14] As a result, we chose to use conversion to MCI or dementia as our primary outcome measure.

Data Analysis

Descriptive statistics were generated to characterize the whole study population and participants divided according to our primary outcome measure of MCI/dementia "converters" and "non-converters". Univariate Cox proportional hazard models were used to examine predictors of time to conversion to MCI/dementia. Variables that were significant $p < .05$ in univariate models were included in a multivariate Cox proportional hazard model. Cases were censored at the date of conversion, loss to follow-up or last assessment. Since ideally there should be at least 10 conversion events for each variable in the model,[38] we constrained multivariate modeling by testing only the three variables that were significant on univariate Cox-regression. The proportional hazards assumption had been checked.

Spearman's correlational analyses were performed to assess associations between our secondary outcome measure (change in global neuropsychological score) with SES, psychosocial, and other variables. A two-tailed alpha of 0.05 was used to determine statistical significance. All analyses were performed using SPSS 20.0 statistical software (IBM, Chicago, IL) or SAS 9.3 (SAS Institute Inc. Cary, NC).

RESULTS

Participants' descriptive characteristics at baseline are described in Table 1. With respect to clinical characteristics, the 130 participants assessed at baseline were not significantly different from the 104 participants who either completed two-year follow-up or whose cognitive status converted to dementia.[14] Twenty-six patients converted: 1 cognitively normal participant and 12 MCI participants converted to dementia, while 13 cognitively normal participants converting to MCI. Follow-up was 121.9 person-years in patients without baseline cognitive dysfunction and 229.2 person-years for the entire group. The incidence of conversion to MCI and dementia was 10.7%/person-year and 5.7%/person-year, respectively, with an 11.2%/person-year conversion to dementia if there was baseline MCI.

TABLE 1.
Baseline demographics and clinical characteristics (n = 130)

	Mean (±SD) or %(n)	*Median*
Demographics and Psychosocial Factors		
Age (yrs)	73.5 (±6.2)	73.0
%Male	23.1% (n=30)	-
%White	90.0% (n=117)	-
%Currently Married	44.6% (n=58)	-
Education (yrs)	13.6 (±2.5)	13.0
Cumulative Illness Rating Scale - Geriatrics (CIRS-G)	10.6 (±3.2)	11.0
Interpersonal Support Evaluation List (ISEL - Total)	37.4 (±7.1)	39.0
Median Household Income	$45,985 (±$19,890)	$42,498
% Median Household Income ≤$24,999	13.1% (n=17)	-
% Median Household Income $25,000–$49,999	32.3% (n=42)	-
% Median Household Income ≥$50,000	54.6% (n=71)	-
Other Important Baseline Clinical Variables		
Baseline Hamilton Rating Scale for Depression	18.7 (±3.3)	18.0
Duration of Past Depression (mos)	176.8 (±459.7)	40.0
Baseline Global Neuropsychological Score	-0.47 (±0.82)	-0.42
Baseline Mild Cognitive Impairment (MCI)	43.8% (57)	-
Mini-Mental State Exam (MMSE)	28.4 (1.4)	29.0
Executive Interview (EXIT)	15.5 (±86.8)	8.0
% Randomized to Donepezil	51.5% (67)	-

SD = Standard Deviation

Univariate Cox regression revealed positive associations between time-to-conversion to MCI/dementia and three variables - higher CIRS-G (HR = 1.13 [1.01-1.26] ($\chi(1)^2 = 4.91$, $p = .03$)), lower ISEL-belonging (HR = 0.86 [0.74-0.99] ($\chi(1)^2 = 4.05$, $p = .04$)), and lower baseline global neuropsychological score (HR = 0.56 [0.36-0.87] ($\chi(1)^2 = 6.66$, $p = .001$)). Higher age approached significance ($p < .09$), while sex, race, marital status, education, median household income, depression duration, HRSD, and donepezil treatment did not ($p > .10$) (Table 2). Similarly, in an exploratory analysis ISEL-belonging was associated with time-to-conversion after controlling for the standard confounders of age, sex, and education (HR = 0.85 [0.73-0.99], $p = .045$), which was not the case for marital status and median household income.

The multivariate Cox proportional hazards model including CIRS-G, ISEL-belonging, and baseline global neuropsychological score demonstrated that higher CIRS-G remained a significant predictor of time to MCI/dementia conversion (HR = 1.13 [1.01-1.27] ($\chi(1)^2 = 4.23$, $p = .04$)), while lower ISEL-belonging and lower baseline global neuropsychological score did not ($p = .12$ and .11, respectively). CIRS-G, ISEL-belonging, and baseline global neuropsychological score were not collinear. For every point indicating higher medical burden score, participants were 13% more likely to convert to MCI or dementia status.

Ninety-one of the 104 participants who completed the MTLD-III study underwent detailed neuropsychological assessment at two-year follow-up. Univariate correlational analyses with change in global neuropsychological score (n = 91) found that none of the potential predictor variables considered in Table 2 approached statistical significance. Similarly, exploratory multiple linear regression did not yield associations between any of the psychosocial factors and change in global neuropsychological score after controlling for age, sex, and education.

In exploratory analyses, higher EXIT scores (HR = 1.13/point on EXIT [1.03-1.24], $p = .012$), which indicate worse performance, as well as lower baseline memory (HR = 2.38/unit lower z-score [1.54, 4.34], $p < .001$) and visuospatial domain scores (HR = 2.17/unit z-score [1.22, 3.84], $p = .008$) predicted higher risk of conversion to MCI/dementia. Only lower baseline memory (HR = 2.23/unit z-score [1.43, 3.57], $p < .001$) and visuospatial domain scores (HR = 1.96/unit z-score [1.08, 3.57], $p < .028$) remained significant in multivariate Cox regression after controlling for ISEL belonging and CIRS-G. There was no significant association between individual language, executive or processing speed domain scores and conversion to MCI/dementia ($p > .05$).

DISCUSSION

Our exploratory analysis of the MTLD-III data did not detect an independent effect of SES or any other psychosocial factor on cognitive outcome in late-life depression. Indeed, the only factor that independently predicted time to conversion to MCI or dementia was medical illness burden (CIRS-G). However, education, baseline neuropsychological score, and depressive severity/duration, all previously linked with cognitive decline,[1,16] were not identified as independent risk factors in our secondary analysis. This may have been due in large part to the low absolute number of cognitive events (conversions) that occurred in MTLD-3 (n = 26). For example, even though low baseline neuropsychological score

TABLE 2.
Univariate and Multivariate Cox proportional hazard models with time to MCI/dementia conversion as dependent variable (n = 130)

	Did not Convert to MCI or Dementia during follow-up N=104	*Converted to MCI or Dementia during follow-up N=26*	*Univariate test for time to conversion Hazard Ratio (HR) [95% CI] (chi-square, p-value)*	*Multivariate test for time to conversion Hazard Ratio [95% CI] (chi-square, p-value)*
Age (yrs)	73.04 (5.95)	75.31 (6.73)	1.05 [0.99-1.11] ($\chi(1)^2$=2.85,p=.09)	-
%Male	20.19 (n=21)	34.62 (n=9)	0.55 [0.24-1.23] ($\chi(1)^2$=2.11,p=.15)	
%White	90.38 (n=94)	88.46 (n=23)	0.66 [0.20-2.19] ($\chi(1)^2$=0.47,p=.49)	
%Currently Married	45.63 (n=47)	44.00 (n=11)	1.01 [0.46-2.23] ($\chi(1)^2$=0.001,p=.98)	
Education (yrs)	13.42 (2.44)	14.27 (2.71)	1.09 [0.94-1.26] ($\chi(1)^2$=1.31,p=.25)	-
Cumulative Illness Rating Scale - Geriatric	10.33 (3.37) N=103	11.81 (2.32)	1.13 [1.01-1.26] ($\chi(1)^2$=4.91,p=.03)	1.13 [1.01-1.27] ($\chi(1)^2$=4.23,p=.04)
Median Income	$45,481 ($20,060)	$48,000 ($19,444)	1.09 [0.89-1.32] (hazard per $10,000) ($\chi(1)^2$=0.67,p=.41)	-
Interpersonal Support Evaluation List (ISEL - Total)				
Total	37.73 (6.86)	36.31 (7.85)	0.96 [0.92-1.02] ($\chi(1)^2$=1.96, p=.16)	
Self-esteem	8.26 (2.26)	7.65 (2.94)	0.90 [0.77-1.06] ($\chi(1)^2$=1.91, p=.17)	
Belonging	9.89 (2.26)	9.12 (2.23)	0.86 [0.74-0.99] ($\chi(1)^2$=4.05,p=.04)	0.88 [0.74-1.03 ($\chi(1)^2$=2.46,p=.12)
Appraisal	9.91 (2.28)	9.88 (2.23)	0.96 [0.82-1.12] ($\chi(1)^2$=0.24,=0.62)	
Tangible	9.66 (2.44)	9.65 (2.53)	0.97 [0.82-1.15] ($\chi(1)^2$=0.12,p=.73)	
Hamilton Depression Rating Scale-17	18.85 (3.39)	18.08 (3.08)	0.98 [0.87-1.11] ($\chi(1)^2$=0.10,p=.76)	-
Duration of Past Depression (mos)	189.83 (499.84)	125.38 (243.59)	0.99 [0.98-1.02] (hazard per year) ($\chi(1)^2$=0.02,p=.88)	-
Baseline global neuropsychological score	-0.41 (0.86)	-0.70 (0.64)	0.56 [0.36-0.87] ($\chi(1)^2$=6.66,p=.001)	0.69 [0.43-1.09] ($\chi(1)^2$=2.53,p=.11)
%Randomized to Donepezil Treatment	55.77 (n=58)	34.62 (n=9)	0.60 [0.27-1.36] ($\chi(1)^2$=1.50,p=.22)	-

HR = Hazard Ratio; MCI = Mild Cognitive Impairment; ISEL = Interpersonal Support Evaluation List

had a significant univariate association with conversion to MCI/dementia ($p < .001$), only low baseline memory and visuospatial domain scores remained significant in exploratory multivariate analyses. Nonetheless, we were still adequately powered to detect a univariate HR of 0.86 ($p = .04$) on the ISEL belonging measure. Given the relatively small effect sizes observed between potential predictors and cognitive function in previous studies,[1,15,16,19,22] although a public health effect cannot be excluded, it appears likely that most psychosocial factors are unimportant at a clinical level.

Of note, though, a higher subjective belonging on the ISEL-SF was the psychosocial factor closest to independently predicting conversion to MCI/dementia (HR = 0.88, $p = .12$), whereas this was not the case for SES, race, and marital status. Unlike the other objective psychosocial measures we used, the ISEL-SF is a well-validated subjective measure of social support.[30,31] In a recent study examining social belonging/isolation, objective social isolation, defined as "never being married/not currently being married, living alone, or not receiving [formal] social support," was not associated with developing incident dementia in the three following years.[19] Those who did not perceive themselves as socially isolated ("feeling lonely or very lonely"), though, had a 1.64 times lower rate of incident dementia.[19] Similarly, social engagement is a well-established protective factor in Alzheimer's disease.[16] Even though feeling isolated may simply be an early sign of dementia[39] or a feature of depression,[40] it is also possible that subjective belonging score on the ISEL-SF may be a more clinically useful measure of social engagement/isolation than formal "objective" measures, such as marital status. Furthermore, simply being of a particular race or having a certain median household income may not adequately capture the true subjective effect of racial and financial disadvantage on health outcomes (e.g., occupational prestige may be more important than actual income[21]).

We did, however, find that increased medical co-morbidity (CIRS-G) independently predicted conversion to MCI/dementia. It is possible that cardiovascular burden may have explained the increased the risk of conversion. In Alzheimer's disease, cardiovascular disease is a well-established risk factor[9,16] and white matter lesions associated with cardiovascular disease are causally implicated in cognitive decline.[41] In patients with mood disorders, though, it remains unclear whether white matter lesions and cardiovascular factors are as important.[42] Other mechanisms of cognitive decline are also possible; medical illness is often associated with inflammation, pain, polypharmacy, and other factors which may adversely affect cognition.[43]

Limitations

It is important to note the limitations of this study. The data analyzed were not from a community-based sample, but from a single-site, double-blind, placebo-controlled randomized trial. Patients in RCTs often have less medical and psychiatric co-morbidities, less concomitant medication use, and higher SES compared to the general population,[44] although participants in the MTLD-III study had substantial medical co-morbidity and patients were excluded only if they were acutely unstable or terminally ill. Although psychosocial factors do not likely have a large clinical impact on individual patients, they may have more subtle public health and policy implications. Similarly, our multivariate Cox-regression analyses were limited by the presence of only 26 events of MCI/dementia conversion. It is also possible that predictors for conversion to MCI and conversion to dementia may not be the same, and so stratification by MCI/dementia could have been an option had there been more outcome events, although combining MCI and dementia outcomes was necessary to maximize statistical power. Especially given statistical power limitations, we chose our method of selecting variables for multivariate regression based on significance on bivariate analysis, although other variable selection methods are available.[45] Although correlations between psychosocial risk factors and cognitive sub-domains (e.g., visiospatial functioning) could potentially exist, we chose to assess global cognition as our secondary outcome to avoid alpha-inflation.

In addition, this was an exploratory analysis. Although the data were from an RCT, the MTLD-III study was not specifically designed to compare the effects of psychosocial risk factors on cognitive outcome. In light of our results, it appears that, in order to detect the effect of psychosocial factors, one may need nuanced, often subjective/informal, well-validated, continuous measures. Along similar lines, neighbourhood income data have their limitations as a measure of a person's financial support. Lastly, since individuals who converted to dementia during the course of the study often did not undergo neuropsychological assessment at the end of two-years because of ethical and scientific considerations, there was potential bias, making it was more difficult to accurately and sensitively detect correlations with our continuous cognitive outcome variable.

CONCLUSION

Our study did not detect an independent association between socioeconomic status or any other social factor and cognitive outcome in late-life depression. The only observed risk factor for cognitive decline was higher medical burden. Meanwhile, other important biologic factors, such as baseline neuropsychological functioning and donepezil use, were not found to independently affect participants' cognitive trajectory.

Future epidemiologic studies in late-life depression will be necessary to further examine the relationship between psychosocial factors and cognitive outcome. This will ideally involve large community-based samples, longitudinal assessments of cognitive function, controlling for important biologic factors (e.g., medical illness burden), and the use of well-validated and continuous measures to quantify the effects of potential psychosocial factors (e.g., instead of "do you have any social supports"). Using such methods will maximize the

likelihood of accurately identifying psychosocial risk factors for cognitive decline in late-life depression.

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CONFLICT OF INTEREST DISCLOSURES

Charles F. Reynolds III reports receiving pharmaceutical supplies for his NIH-sponsored work from Forest Laboratories, Pfizer/Eisai, Bristol-Myers Squibb, Wyeth, and Eli Lilly.

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