Depressive Symptoms Precede Memory Decline, but Not Vice Versa, in Non-Demented Older Adults

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OBJECTIVES: To determine whether depressive symptoms typically precede or follow memory declines.

DESIGN: An autoregressive latent trajectory model was used to examine the direction of the relationship between depressive symptoms and memory decline observed over 12 years.


PARTICIPANTS: Older adults initially without dementia (N = 2,425).

MEASUREMENTS: Memory composite scores were computed from three subscores of the Selective Reminding Test. Depressive symptoms were assessed using a 10-item version of the Center for Epidemiologic Studies Depression Scale. Analyses controlled for age, sex, recruitment wave, education, black race, and Hispanic ethnicity measured at baseline and chronic disease burden measured at each study visit.

RESULTS: Initial depressive symptoms predicted worse memory scores at the second study visit (B weight = −0.03; P = .003) and accelerated memory decline over the entire study period (B weight = −0.02; P = .03). Memory scores did not predict subsequent depressive symptoms.

CONCLUSION: These findings suggest that depressive symptoms precede memory decline, but not vice versa, in late life. This pattern of results is in line with hypotheses that depression is a prodrome of dementia or a causal contributor to memory decline. Clinicians should be aware that depressive symptoms may represent an early indicator not only of dementia, as reported previously, but also of memory decline more generally. J Am Geriatr Soc 2013.

Key words: depression; episodic memory; statistical modeling

Recent meta-analyses have demonstrated that depression is a major risk factor for mild cognitive impairment (MCI) and dementia.1,2 Depressive symptoms also increased dementia risk in the Washington/Hamilton Heights Inwood Columbia Aging Project (WHICAP),3 but because depressive symptoms did not predict greater risk of MCI in cognitively normal older adults, it was concluded that depression accompanies, but does not precede, cognitive impairment, but this study was not explicitly designed to test for leading and lagging relationships between depressive symptoms and cognitive impairment that would clearly demonstrate which occurs first. The present study sought to elucidate the temporal ordering of depressive symptoms and memory decline in WHICAP.

The question of whether depressive symptoms precede the development of memory impairment is of theoretical and practical importance. Several hypotheses have been proposed. Depression may reflect a psychological reaction to the perception of memory decline.4 Memory dysfunction may be a risk factor for late-onset psychiatric illness.5 Depression may be a prodrome of dementia.6 Depression may be a causal contributor to memory decline.7 Depression may lower the threshold for clinical detection of dementia without directly influencing brain pathology.8 Some evoke a reciprocal relationship.9 Each hypothesis provides specific predictions regarding the directionality of the relationship between depressive symptoms and memory decline. These predictions can be tested only in a longitudinal framework, allowing for estimation of both potential outcomes simultaneously.

The current study used the autoregressive latent trajectory (ALT) framework to test the direction of the relationship between depressive symptoms and memory decline in older adults. ALT is a structural equation model that combines two well-developed approaches: multivariate latent growth curve modeling and autoregressive cross-lagged panel analysis.10 ALT tests whether the initial level of one
outcome influences the subsequent trajectory of another outcome while simultaneously testing for lagged relationships at individual occasions. The current study examined whether depressive symptoms precede memory impairment or vice versa over the course of 12 years in a sample of 2,425 older adults initially without dementia.

METHODS

Participants and Procedures

The 2,425 older adults were participants in WHICAP, a prospective, community-based longitudinal study of aging and dementia in a racially and ethnically diverse sample. Study procedures have been previously described.\textsuperscript{11,12} Participants within the geographic area of northern Manhattan were identified from Medicare records and recruited in two waves: 1992 (N = 478) and 1999 (N = 1,947). Ongoing follow-up at 18- to 24-month intervals includes a battery of cognitive, functional, and health measures administered in the participant’s preferred language (English or Spanish). This study complies with the ethical rules for human experimentation stated in the Declaration of Helsinki, including approval of the local institutional review board and informed consent. Race and ethnicity are determined through self-report using the format of the 2000 U.S. Census. Baseline characteristics of the sample are shown in Table 1.

Because the depression instrument used in these analyses was not included in the original WHICAP battery, the first visit was defined as the first at which each participant was administered this instrument. The current sample included only participants who did not meet Diagnostic and Statistical Manual of Mental Disorders, Third Edition, criteria for dementia at this first visit, according to consensus conference. Four visits (follow-up of 12 years) were used in the current analyses to maximize covariance coverage.

Outcomes

Episodic memory was assessed using the Selective Reminding Test (SRT),\textsuperscript{13} which was chosen because of its sensitivity to longitudinal change and dementia conversion in this population. Participants are given six trials to learn 12 words. After each trial, participants are reminded only of words they failed to recall. Total learning is the number of words recalled after six learning trials. Delayed recall is the number of words recalled after a 15-minute delay. Delayed recognition is the number of words recognized immediately after delayed recall. Total learning, delayed recall, and delayed recognition scores at each occasion were standardized to a z-score metric using the sample’s means and standard deviations (SDs) at the initial occasion. Memory composite scores were computed by averaging the three z-scores at each occasion. Higher scores indicate better memory.

Depressive symptoms were assessed using a 10-item version of the Center for Epidemiologic Studies Depression Scale (CES-D).\textsuperscript{14} Participants self-report responses to 10 dichotomous items. Total scores range from 0 to 10, with higher scores indicating worse depression.

Statistical Analysis

Descriptive statistics were computed using SPSS version 19 (IBM Corp., Armonk, NY). Growth curve and ALT analyses were conducted in Mplus version 7 (Muthén & Muthén, Los Angeles, CA) using maximum likelihood estimation. Time was parameterized as years from study entry, accommodating differing intervals between visits. The average number of years between visits was 2.6 ± 0.9. Missing data were managed using full information maximum likelihood (FIML), which accumulates and maximizes case-wise likelihood functions computed using all available data for each participant. FIML produces less-biased estimates than alternative methods.\textsuperscript{15} FIML does not assume that data are missing completely at random and can therefore accommodate missingness related to previous scores. This feature of FIML is desirable because participants lost to follow-up are often those who scored lower at earlier occasions.

First, unconditional latent growth curve models (LGCs) were estimated separately for the two outcomes (episodic memory and depressive symptoms) to characterize their trajectories. Models allowing only linear change were statistically compared with models allowing linear and quadratic change using the chi-square ($\chi^2$) test.

Next, best-fitting univariate LGCs were combined into the ALT model shown in Figure 1. In the latent part of the model, initial levels (intercepts), rates of change (linear slopes), and changes in rates of change (quadratic slopes) were estimated as latent variables using information from all four occasions. To determine whether initial levels of depressive symptoms and memory impairment were uniquely associated with subsequent changes in either
Autoregressive Latent Trajectory Model

Best-fitting univariate models were combined, and all covariates were added, as shown in Figure 1. All reported associations were independent of all other associations in the model, including covariate effects.

Associations Between the Latent Variables

Initial level of depressive symptoms was not associated with subsequent changes in depressive symptoms ($P = .22$). Initial level of depressive symptoms was not associated with initial memory score (covariance = $0.06; P = .35$). Rates of change in depressive symptoms and memory were not correlated (covariance = $0.01; P = .52$).

Higher initial memory scores were associated with slower subsequent memory decline ($B = 0.07; P = .01$). Independent of this relationship, higher initial level of depressive symptoms was associated with accelerated memory decline ($B = -0.02; beta = -0.26; P = .03$). Specifically, each additional depressive symptom was associated with 0.02 more points of annual decline on the age 77, male sex, recruitment in 1992, and 10 years of education. Finally, a time-varying covariate reflecting overall illness burden was allowed to correlate with depressive symptoms and memory scores at each occasion. One point each was assigned for the presence of heart disease, hypertension, stroke, diabetes mellitus, pulmonary disease, thyroid disease, liver disease, renal insufficiency, peptic ulcer disease, peripheral vascular disease, cancer, Parkinson’s disease, Essential tremor, multiple sclerosis, and arthritis. Points were summed to reflect illness burden at each occasion as previously described. All reported associations from the ALT model are independent of all covariates.

RESULTS

Unconditional Univariate Models

Characterizing the Trajectories

Trajectories of change for each outcome were characterized using unconditional univariate growth models. Fit was better in models allowing for curvilinear change in memory ($Δχ^2(4) = -64.03, P < .001$) and depressive symptoms ($Δχ^2(4) = -35.55, P < .001$) than in models allowing for only linear change. Therefore, models estimating both linear and quadratic slopes were retained.

Descriptions of the Trajectories in the Best-Fitting Univariate Models

In these unconditional univariate models, memory scores declined by 0.13 points per year ($P < .001$). This rate of change decelerated by 0.01 points per year ($P < .001$). Participants with higher initial memory scores exhibited slower subsequent decline (covariance = $0.04, P = .003$). Scores on the CES-D improved by 0.12 points per year ($P < .001$). This rate of change decelerated by 0.02 points per year ($P < .001$). Initial level of depressive symptoms was not related to subsequent changes (covariance = $-0.21, P = .08$).

The ALT model also controlled for covariates. Associations between age, sex, recruitment year, education, black race, and Hispanic ethnicity, measured at baseline, and the latent variables for each outcome were estimated. These time-invariant covariates were centered to facilitate parameter interpretation. Specifically, values of 0 correspond to domain over the entire study period, rates of change in each symptom type were regressed on initial levels of each symptom type. All other relationships between latent variables were estimated as correlations.

In the autoregressive cross-lagged part of the model, within-domain autoregressive paths, cross-lagged regression paths, and occasion-specific correlations across domains were estimated. Type 1 error was controlled by applying a Bonferroni correction to these parameter estimates ($0.05/16 = 0.003125$). Cross-lagged paths tested whether depressive symptoms at one study visit predicted depressive symptoms at the next visit and vice versa.

The ALT model also controlled for covariates. Associations between age, sex, recruitment year, education, black race, and Hispanic ethnicity, measured at baseline, and the latent variables for each outcome were estimated. These time-invariant covariates were centered to facilitate parameter interpretation. Specifically, values of 0 correspond to
memory composite scores, independent of initial memory score and all covariates. Initial memory score was not associated with subsequent changes in depressive symptoms ($B = -0.06; \beta = -0.15; P = .08$). This pattern of results was unchanged after exclusion of individuals with MCI at baseline.  

**Autoregressive and Cross-Lagged Paths**

No within-domain autoregressive paths were significant. Cross-lagged paths are shown in Figure 1. Memory scores did not predict depressive symptoms at the next visit. Greater depressive symptoms at the first visit significantly predicted worse memory scores at the second visit ($P = .003$) after Bonferroni correction. No other cross-lagged paths were significant. This pattern of results was unchanged after excluding individuals with MCI at baseline.

**Covariate Effects**

Effects of the time-invariant covariates are shown in Table 2. Greater illness burden was associated with more depressive symptoms at each occasion (all $P < .001$). Illness burden was not associated with memory scores at any occasion.

**DISCUSSION**

Depressive symptoms preceded memory decline in this sample of 2,425 older adults initially without dementia followed up to 12 years. Specifically, higher scores on the depression measure at the first study visit predicted lower scores on a memory composite at the next study visit. Furthermore, higher initial level of depression predicted faster rate of memory decline measured over the entire study period. This is the first study to directly examine the temporal ordering of depressive symptoms and memory impairment in older adults using the ALT framework. These results have implications for memory prognosis and theories regarding how depressive symptoms relate to memory decline in late life.

These findings add to those of a recent study that used survival analyses to reveal an association between depressive symptoms and greater dementia risk in this sample. That study did not find an association between baseline depressive symptoms and conversion from a normal cognitive state to MCI. In contrast, the present study found that depressive symptoms predicted steeper cognitive decline even in individuals who were cognitive normal at baseline. It is likely that these discrepancies relate to the earlier study’s focus on conversion rather than the rate of cognitive decline and the dichotomization of the CES-D de-emphasizing subsyndromal depressive symptoms.

Results are in line with two prominent hypotheses regarding the nature of the relationship between depressive symptoms and memory impairment in late life. Specifically, depression may be a prodrome of dementia or a causal contributor to memory decline. The current finding that memory scores did not predict subsequent changes on a depression instrument do not support hypotheses that depression reflects a psychological reaction to the perception of memory decline or that memory dysfunction is a risk factor for late-onset depression, although neither participants’ perceptions of memory impairment nor formal psychiatric diagnoses were analyzed in this study. In addition, the results of this large-scale study do not imply that such relationships do not exist for individual cases.

The finding that depressive symptoms predicted worse subsequent memory decline was independent of age, sex, education, race, ethnicity, recruitment year, and illness burden, including vascular disease. It has been suggested that vascular health may mediate the link between depression and dementia risk, but epidemiological data do not strongly support such a link. Furthermore, a previous report from our group showed that vascular risk factors and stroke did not explain the prospective relationship between depressive symptoms and Alzheimer’s disease (AD).

If depression represents a prodrome of dementia, one might predict an association between depressive symptoms and dementia neuropathology. Worse AD pathology (e.g., plaques and tangles) has been reported in individuals with AD with a history of major depression, although recent studies have found more subcortical Lewy bodies, hippocampal neuronal loss, and white matter lesions, but not AD pathology, in the brains of older adults with depression without dementia.

If depression is a causal contributor to dementia, one might expect depressive symptoms to predict subsequent changes in brain integrity. For example, depression may cause hippocampal damage through a glucocorticoid cascade. A recent longitudinal study of 334 older adults with mild cognitive impairment (MCI) found that depressive symptoms predicted accelerated cortical thinning in the prefrontal cortex, where glucocorticoid receptors are highly expressed, but it is also possible that a separate pathology (e.g., hippocampal sclerosis) causes depressive symptoms and memory loss in older adults.

The present results complement and clarify those from a recent study that used ALT to show reciprocal relationships between depressive symptoms and disability in community-dwelling adults in Taiwan. That study concluded that disability is a stronger predictor of depressive symptoms than vice versa. Together, these studies support depression as a negative prognostic indicator for cognition and disability, although the lack of a relationship between

| Table 2. Effects of the Time-Invariant Covariates Measured at Baseline |
|---------------------------|---------------------------|---------------------------|---------------------------|
| **Covariate**              | **Depressive Symptoms**    | **Memory**                |                          |
|                           | **Initial Level**          | **Rate of Change**        | **Initial Level**         | **Rate of Change**         |
| Age                       | 0.008                     | -0.002                    | -0.037                   | -0.007                    |
| Female sex                | 0.530                     | 0.021                     | 0.254                    | 0.024                     |
| Black                     | -0.498                    | -0.022                    | -0.308                   | -0.029                    |
| Hispanic                  | 0.262                     | -0.071                    | -0.300                   | 0.048                     |
| Education, years          | -0.015                    | -0.001                    | 0.049                    | 0.003                     |
| Recruitment year          | 0.177                     | -0.115                    | -0.109                   | -0.109                    |


P < .05, * < .001.
memory and subsequent depressive symptoms in the present study suggests that it is unlikely that memory decline mediates the previously described link between disability and changes in depressive symptoms. Rather, physical changes that limit the performance of activities of daily living are more likely to lead to depressive symptoms than is memory decline. A future study that includes measures of depression, memory, and disability is needed to test this hypothesis directly.

Strengths of this study include its large sample size, long follow-up period, and statistical framework. Limitations include the brief measure of depressive symptoms and the use of a single memory measure. Although the association between initial memory performance and rate of change in depressive symptoms was not significant in this study of 2,425 older adults followed over 12 years ($P = .08$), it is possible that this association could be significant in a larger study. In addition, depressive symptoms are less common in this and other community-based samples than in clinic-based samples. Future studies should determine whether these findings differ in clinic-based samples and investigate whether temporal relationships between depressive symptoms and cognitive status differ for different cognitive domains.

CONCLUSION

Depressive symptoms preceded memory decline, but not vice versa, in this sample of older adults initially without dementia followed for 12 years. Clinicians should be aware that depressive symptoms may represent an early indicator not only of dementia, as reported previously, but also of memory decline more generally. This pattern of results is in line with hypotheses that depression is a prodrome of dementia or a causal contributor to memory decline.

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REFERENCES

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