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Depressed Mood in Informal Caregivers of Individuals With Mild Cognitive Impairment

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This study estimates the prevalence of depressed mood in caregivers of individuals with mild cognitive impairment (MCI) and assesses whether demographics, stressors, intrapsychic strain, and gain are associated with depressed mood. A secondary analysis of baseline data from the Alzheimer's Disease Cooperative Study MCI trial was conducted using a cross-sectional, correlational design. Descriptive statistics to estimate the prevalence of caregiver depressed mood and univariate and blockwise logistic regression analyses were used. The prevalence of depressed mood in 769 caregivers was 24.6% (95% confidence interval, 21.5-27.7). The odds of being depressed were significantly higher in younger, nonspousal caregivers with less education, who cared for MCI patients with lower activities of daily living functioning, and who perceived greater relational deprivation, higher levels of self-loss, and personal gain. Controlling for relevant variables, relational deprivation and caregiver education continued to be significantly associated with depressed mood. Relational deprivation may be important for future interventions.

Keywords: caregiving; depression; mild cognitive impairment; stress

Alzheimer's disease is a major public health problem with costly consequences for patients, their families, and society that will become increasingly problematic as our population continues to age.[1–4] With advances in earlier diagnoses, clinicians and researchers have identified a population of older adults with mild cognitive impairment (MCI). Furthermore, community- and population-based studies indicate that MCI progresses to Alzheimer's disease (AD) at a very high rate, from 13 to 48% over 12–60 months.[5–7] This finding will result not only in individuals losing productivity earlier than expected, but their families and friends will need to assist them with deficits for a longer period of time. The related burden and stressors on caregivers will accompany the progression of memory loss,[8,9] thus increasing the public health concerns even more.

The prevalence of depressed mood in AD informal caregivers has been identified in many studies,[10–13] yet little is known about the prevalence of depressed mood in caregivers of individuals with MCI. Likewise, although several demographic variables have been associated with caregiver depressed mood in AD context, little is known about informal caregivers of MCI individuals. MCI generally is defined by selective memory loss that is normatively rare among matched peers with intact activities of daily living and by no

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Y.Y. Lu planned the secondary data analysis study and prepared the manuscript. M.G. Austrom consulted on the study and helped with manuscript preparation. S.M. Perkins consulted on the methods of data analysis and helped with manuscript preparation. T. Bakas helped with manuscript preparation. M.R. Farlow consulted on the study, served as local site Principal Investigator for data collection, and helped with manuscript preparation. F. He helped with data analysis. S. Jin and A. Gamst supervised the data analysis process.

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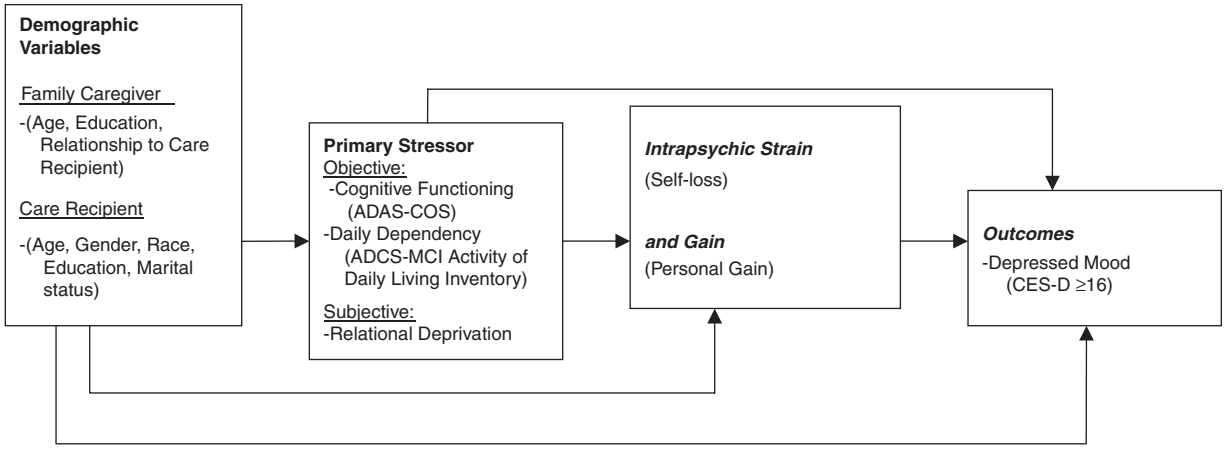

Figure 1. Conceptual domains from the Stress Process Model of Pearlin et al (1990).

ADAS-COS = Alzheimer Disease Assessment Scale–Cognitive Functions Subscales; ADCS-MCI = Alzheimer's Disease Cooperative Study–Mild Cognitive Impairment; CES-D = Center for Epidemiological Studies–Depression.

dementia.[9,14–16] MCI is associated with significant morbidity and economic loss as well as distress to individuals, families, and society.[8,17–20]

Depressed mood often results from the demands of the caregiving situation and is the most common index of emotional well-being in AD caregiver research.[21–24] It is widely recognized that caregiving stressors (eg, care recipient's cognitive functional status and daily dependency and caregiver's feelings of relational deprivation) significantly increase the risk for AD caregivers' depressed mood.[22] However, there is limited research on the relationship between caregiving stressors and depressed mood in caregivers of MCI individuals. Because earlier interventions may be beneficial to AD caregivers who experience problems with depressed mood, it is very important to identify the MCI caregivers' characteristics and caregiving stressors that are related to their depressed mood. Therefore, the main purposes of this study are to (1) estimate the prevalence of depressed mood in a sample of informal caregivers of MCI individuals, and (2) assess whether selected demographic variables, primary stressors (care recipient's cognitive functioning and daily dependency, caregiver's relational deprivation), and intrapsychic strain and gain (self-loss and personal gain) are associated with depressed mood in informal caregivers of MCI individuals. Ultimately, the results of this research may help determine priority areas for developing early intervention strategies for these individuals. Using the Stress Process Model (SPM) by Pearlin et al,[25] we hypothesize that certain demographic variables, as well as the primary stressors and intrapsychic strain and gain factors listed above will be associated with depressed mood in informal caregivers of MCI individuals.

Conceptual Model

The SPM[25] consists of demographic variables for caregivers and care recipients, primary stressors, and caregiver's intrapsychic strain and gain and predicts how these variables are associated with caregiver depressed mood (Figure 1). Primary stressors in this context are the care recipient's level of cognitive functioning and the range and difficulty of daily dependency. It is assumed that caregivers' depressed mood can change over time and is associated with increasing dependence by the individual with MCI and with changes in the caregivers' expectations. Another primary stressor in this context is relational deprivation, which refers to the ability of caregivers to sustain satisfying relationships with their impaired relatives. The SPM proposes that primary stressors contribute to intrapsychic strain and gain (self-loss, personal gain). The model depicts self-loss and personal gain as mediating the relationships between stressors and stressed mood as well. The SPM[25] was selected to guide this study because it has been widely used in the AD caregiver literature,[26,27] yet it has not been tested in caregivers of MCI individuals.

Depressed Mood

Depressed mood is the major outcome of AD caregivers' emotional well-being, but little is known about this factor in MCI individuals. Several studies have found that the prevalence rates of risk for depression (using the conventional threshold of 16 on the Center for Epidemiological Studies–Depression [CES-D] scale) among community-dwelling caregivers of persons with AD to be significantly higher than that of community-dwelling older adults (40% to 70% vs 8% to 16%).[10,12,13,28] Experiencing high depressed mood is harmful to caregivers' emotional well-being and can affect their continued ability to provide care for their loved one and to address their own health needs.[29] Identifying the prevalence of depressed mood among caregivers of MCI individuals is prerequisite to providing appropriate early interventions.

Primary Stressors

The cognitive decline and functional impairment of the person with AD that can affect caregivers' depressed mood have been frequently reported in caregiving studies.[12,24,30] Memory deficits are the most prominent feature of MCI in older adults, particularly visual and verbal memory, which are more pronounced than in age-matched and education-matched controls.[31] Cognitive functioning is a multidimensional concept and refers to the disruption levels of memory, language function, motor activity execution, object recognition, abstract thinking, information processing, spatial orientation, and judgment. Several studies found that MCI individuals had more severe overall neuropsychiatric and depressed mood symptoms than normal aging groups.[32,33] AD care recipients' cognitive functioning has been shown to be an important predictor of their caregivers' depressed mood,[26,30] but in informal caregivers of MCI individuals, this relationship has not been studied.

Daily dependency is defined as the care recipients' degree of dependency for basic activities of daily living (ADL). MCI individuals experience more difficulty in recalling persons' names, some visual information,[34] and remembering to perform some instrumental activities of daily living (IADL; eg, financial management and shopping) than the general older population.[35,36] Therefore, caregivers of MCI individuals need to take on more responsibilities, including financial management, household chores, social arrangements, and future planning. Such responsibilities require time, learning new skills, and knowledge, and the changes in established role patterns can be stressful and disruptive for family members.[37] In summary, given the importance of the relationships among caregiver depressed mood, cognitive functioning, and daily dependency in AD, examining these variables in MCI is essential.

Relational deprivation is defined as the negative restructuring of the relationship between caregiver and care recipient, which can develop from the caregiver's feelings of being deprived of a relationship with a significant companion or the loss of an affectionate exchange as cognitive impairment progresses.[25] Caregivers may feel increasingly separated from their loved one as MCI progresses. Many empirical studies found that these factors contribute to stress and depressed mood in AD caregivers.[26,38,39] It is unclear whether relational deprivation contributes to depressed mood in caregivers of MCI individuals. Our qualitative study found that spouse caregivers of MCI individuals experience increasing tension in the marital relationship and a sense of loss as the memory of the individual with MCI declines, suggesting a need to examine this variable further.[40]

Intrapsychic Strain and Gain

Self-loss and personal gain have been identified as 2 important responses of caregivers in the literature. Research has demonstrated that the more caregivers experienced a sense of loss of self, the more they reported feelings of depressed mood.[38] Self-loss is considered an intrapsychic strain and refers to a loss of identity or self-concept in this context, characterized by the loss of significant others, not easily replaced, who have been important sources of validation and confirmation of one's self-referenced knowledge.[38] As the disease progresses, MCI individuals require frequent reminders to perform daily activities. AD studies have shown that caregiver social activities are often reduced during the caregiving process,[12,41] leading to a loss of self. Examination of this variable in MCI is needed.

Personal gain is defined as a positive affective feeling of increased self-esteem or sense of meaning that results from caregiving.[25] Previous studies have recognized that being an AD caregiver can produce positive or productive outcomes.[38,42] AD caregivers who perceive positive aspects of caring are more likely to report better health status and experience less burden and depressed mood.[42,43] Studies have found that individual characteristics (eg, race, ethnicity, gender,

and education) may be related to perceived rewards from caregiving, suggesting that the "gain" perspective may be a particularly meaningful area for research and intervention.[42,43] Therefore, it is important to identify the relationship between personal gain and depressed mood in caregivers of MCI individuals. Unfortunately, caregivers' gender, race, and marital status were not collected at the time of the original study; therefore, these variables were not available for analysis here.

Demographic Variables

AD caregivers' gender, age, and relationship to the persons with AD have been significantly associated with their health outcomes, including depressed mood.[26,38,39] Clinical observations suggest that, when an individual develops MCI, family members, particularly the spouse caregiver, face uncertainty in dealing with the symptoms, diagnosis, treatment, relationship with other family members, as well as future plans. Therefore, these sociodemographic variables were included in the model as potential variables associated with depressed mood.

In summary, it appears that study of depressed mood in caregivers of MCI individuals has been limited and more knowledge is needed in this area. Although previous studies have documented variables associated with depressed mood in AD caregivers, this secondary data analysis will provide much needed information on depressed mood in caregivers of MCI individuals. The primary aims of this study are to estimate the prevalence of depressed mood in a sample of caregivers of MCI individuals and to identify variables associated with depressed mood in the sample using the SPM.[25]

Methods

Study Design

A cross-sectional correlational design and secondary analyses were used. The data were drawn from a baseline evaluation of a double-blind, placebo-controlled, parallel-group multicenter study administered by the Alzheimer's Disease Cooperative Study (ADCS).[44]

Participants

A total of 769 subjects were enrolled from 69 ADCS sites across the United States and Canada. Caregivers were responsible for bringing the patient to the clinical investigator's office, were at least 18 years old, were engaged in caregiving, and provided detailed observations concerning quality-of-life issues, behavior, and emotional status of both the MCI individual and themselves during the month previous to the interview.[44] The general inclusion/exclusion criteria for the care recipients were amnestic MCI of a degenerative nature (insidious onset and gradual progression).[45] The appendix lists complete criteria.

Procedure

Approval was obtained from the Institutional Review Board of Indiana University–Purdue University Indianapolis and the Research Committee of the ADCS at the University of California at San Diego. The caregivers and their MCI relatives completed the in-clinic screening evaluation and were interviewed at baseline and at 7 follow-up visits during the 3-year study. For this study, a secondary analysis was conducted on baseline data and obtained from the ADCS MCI trial without any personal identifiers.

Measures

Depressed mood was measured by the CES-D 20-item scale of depressed mood.[46] Range of scores is 0–60, with a higher score indicating greater depressed mood. A score of 16 or higher indicates risk for clinical depression.[47,48] Cronbach's α was .75 in this sample.

Cognitive functioning was measured by the 13-item Alzheimer Disease Assessment Scale–Cognitive Functions Subscales (ADAS-COS),[47] which evaluates memory, attention, reasoning, language, orientation, and praxis. A higher score indicates more impairment (range, 0–70). Cronbach's α was .97 in this sample.

Daily dependency was measured by the 23-item ADCS–Activities of Daily Living (ADCS-ADL) scale, [49] which consists of 18 items from traditional basic ADL scales and 5 items from IADL scales. Higher scores indicate better ADL functioning (range, 0–53). In a structured interview format, caregivers are asked to assess the MCI individual's attempts to accomplish each item during the previous 4 weeks and the level of performance. Cronbach's α was .91.

Relational deprivation was measured by the 6-item Relational Deprivation Scale, which uses a Likert-type response scale from 1 (*not at all*) to 4 (*completely*).[25]

Table 1. Descriptive Statistics of Family Caregiver and PWMCI Demographic Data

Variable		Caregiver N = 769		PWMCI N = 769	
Age	Mean (SD)	65.5 (12.4)		72.9 (7.3)	
	Min–Max	18–94		55–91	
Education	Mean (SD)	14.6 (2.8)		14.6 (3.1)	
	Min–Max	3–20		2–20	
		n	%	*n*	%
Caregiver relationship with PWMCI	Spouse			Data not available	
	Husband	205	28.2		
	Wife	355	46.7		
	Nonspouse				
	Adult children	109	13.5		
	Relative	27	2.7		
	Friend and other	73	8.9		
Gender	Male	Data not available		417	53.3
	Female			352	46.7
Race	White	Data not available		708	93.0
	Non-white				
	Native American			3	0.4
	Asian			7	0.4
	Black			18	2.7
	Hispanic			30	3.5
	Other			3	0.0

PWMCI = person with mild cognitive impairment.

Higher scores indicate a greater feeling of relational deprivation. Cronbach's α was .88.

Self-loss was measured by the 2-item Self-loss Scale, which uses a Likert response scale from 1 (*not at all*) to 4 (*completely*).[25] Higher scores indicate a greater feeling of self-loss. Cronbach's α was .81.

Personal gain was measured by the Personal Gain Scale,[25] a 4-item measure using a Likert response scale from 1(*not at all*) to 4 (*very much*). Higher scores indicate a greater feeling of personal gain (range, 4–16). Cronbach's α was .89.

Demographic Variables

See Table 1 shows both caregiver and care recipient demographic statistics, including caregiver age, education, and relationship to the care recipients as well as MCI individuals' age, education, gender, and race. Caregivers' gender, race, and marital status were not collected in the original study and, therefore, were not available for analysis here.

Statistical Analyses

Analyses were conducted using the statistical package R.[50] The sample consisted of 769 informal caregivers; because of missing data, the smallest sample size in any model was 746. The sample size was sufficient to produce relatively stable estimates for β weights in a multivariable model containing up to 18 predictors, using the 10 observations per-predictor rule of thumb in the response group with the lowest sample size[51] and the fact that the risk for clinical depressed mood was approximately 25% in this sample.

Descriptive statistics, frequency distributions, histograms, correlational statistics, and testing for internal reliability of the instruments were conducted for preliminary analysis. The prevalence of depressed mood in caregivers was estimated with a 95% confidence interval (95% CI). Univariate and multivariate logistic regressions were used to examine the respective associations between depressed mood and selected demographic variables, primary stressors, and intrapsychic

Table 2. Descriptive Data for Major Variables

Variable	N (%)	Actual Score Min–Max	Mean	SD	Median	Possible Scale Range
Prevalence of depressed mood (CES-D ≥ 16)	187 (24.6% [95% CI, 21.5-27.7])					
CES-D	759	0–57	13.53	5.03	13	0–60
Primary stressors						
wMCI cognitive status (ADAS-COG)	766	3.7–35	17.72	6.07	17	0–70
IwMCI daily dependency (ADCS-ADL)	765	18–53	46.06	4.73	47	0–53
Caregiver relational deprivation	762	6–23	8.75	3.14	8	6–24
Secondary stressors						
Perceived self-loss	764	2–8	2.43	0.94	2	2–8
Perceived personal gain	764	4–16	8.57	2.94	8	4–16

SD = standard deviation; CES-D = Center for Epidemiological Studies–Depression; CI = confidence interval; IwMCI = individual with mild cognitive impairment; ADAS-COG = Alzheimer Disease Assessment Scale-Cognitive Functions Subscales; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living.

strain and gain. For caregivers who were at risk for clinical depression, a coding of a "nondepressed mood" as 0 and a "depressed mood" as 1 was used. Hence, unless otherwise indicated, an odds ratio greater than 1.0 indicates that higher values of an independent variable are associated with higher odds of clinically depressed mood. Significance was assessed using the Wald test with its associated *z* score and *P* value.[52]

First, zero-order associations between risk for clinical depressed mood and each caregiver and care recipient variable were examined in univariate logistic regression models to identify those variables with very weak or no associations with risk for clinical depressed mood. Because the care recipients were predominantly Caucasian, we did not fit a model with care-recipient race. All variables with *P* values for associations of .20 or less were selected to enter into the block stepwise method (described below) with the exception of caregiver education, because of its relatively high correlation to care recipients' education (Spearman's $\rho = .4$). Therefore, 6 demographic variables (caregiver's age and education; care recipient's age, gender, and education; and caregiver relationship with MCI individuals) were used in the block stepwise models.

For the multivariate logistic regression models, we used a block stepwise analysis strategy that entered variables by blocks that were consistent with the 3 conceptual domains specified in the SPM (Figure 1). Depressed mood was regressed onto 3 blocks of variables entered in steps: Step 1, demographic variables; Step 2, primary stressors; and Step 3, secondary intrapsychic strain and personal gain. As each block was entered, only variables significant at the .05 level or less were carried on to the next step. Finally, for Step 4, all variables no longer significant at the .05 level were removed. Only main effects were considered as is consistent with Pearlin's model.

The data were collected at 69 ADCS sites, and the site could have been associated with risk for depressed mood. We fit models with and without considering the site as a random effect and found that the estimates and *P* values were substantively similar. Therefore, we report the results from the model without the random effect for the site.

Results

The descriptive data for the prevalence of depressed mood and of primary and secondary stressors are shown in Table 2. For the primary stressors, the mean for the overall ADAS-COG score was 17.72, indicating slightly impaired functioning for the sample, on average. The mean ADL scale intensity score was 46.06, indicating good function on activities of daily living. The mean Relational Deprivation scale score was 8.75, indicating a deterioration in the caregiver's relationship

Table 3. Coefficients, SE, *z* Scores, *P* Values, and ORs With 95% CI for the 11 Univariate Logistic Regression Models

Variable	B	SE	z Statistic	*P* Value	OR = exp(B)	CI for OR
Caregiver age[a]	–.01	.01	–2.13	.033	0.99	0.97-0.99
Caregiver education[b]	–.06	.03	–2.08	.038	0.94	0.88-0.99
IwMCI age	–.01	.01	0.84	.399	1.01	0.99-1.03
IwMCI gender	–.03	.17	–0.19	.853	0.97	0.70-1.35
IwMCI education	–.05	.03	–1.75	.080	0.95	0.90-1.01
Caregiver relationship with IwMCI (spouse vs nonspouse)	–.45	.18	–2.49	.013	0.64	0.45-0.91
IwMCI cognitive functioning	.01	.01	0.53	.595	1.01	0.98-1.04
IwMCI daily dependency	–.05	.02	–2.84	.005	0.95	0.92-0.98
Caregiver relational deprivation	.11	.03	4.41	< .001	1.12	1.06-1.18
Perceived self-loss	.36	.08	4.33	< .001	1.43	1.22-1.68
Perceived personal gain	.07	.03	2.56	.011	1.08	1.02-1.14

SE = standard error; OR = odds ratio; CI = confidence interval; IwMCI = individual with mild cognitive impairment.
a. For each 10-year increase in years of age of the caregiver, the odds ratio increased by 1.15 (95% CI, 1.01-1.31).
b. For each 3-year decrease in years of education of the caregiver, the odds ratio increased by 1.21 (95% CI, 1.01-1.45).

with the person with MCI. For the *secondary stressors*, the mean Self-loss scale score was 2.43, indicating some feelings of self-loss and the mean Personal Gain Scale score was 8.57, reflecting some personal gains in the relationship as well.

Prevalence of Depressed Mood

As shown in Table 2, depressed mood was relatively high among this sample of MCI informal caregivers (mean = 13.53). The prevalence of depressed mood was 24.6% (95% CI, 21.5-27.7). Differences in the prevalence of depressed mood in MCI caregivers based on demographic variables, primary stressors, intrapsychic strain (caregivers' sense of self-loss), and personal gain are shown in Table 3. In this sample, 3 demographic factors (caregiver age, education, and being a nonspouse family caregiver), 2 primary stressors (care recipient dependency level and relational deprivation), intrapsychic strain, and personal gain were significantly associated with depressed mood in the univariate models. The odds of being at risk for clinical depressed mood were significantly higher in younger, nonspouse caregivers with less education. In addition, the odds of being at risk for depressed mood were significantly higher for caregivers of MCI individuals with poor ADL functioning, as well as in caregivers who perceived greater relational deprivation, higher levels of self-loss, and more personal gain.

Theory-Based Predictors of Depressed Mood in Caregivers of People With MCI

The results of the block stepwise procedure derived from the SPM are shown in Table 4. In the first step, only caregiver education was related to depressed mood, with more education associated with lower depressed mood. In the second step, which added primary stressors to the model, only 1 primary stressor, greater relational deprivation, was significantly related to depressed mood. In the third step, which added intrapsychic strain and gain, again only caregiver relational deprivation was significantly related to depressed mood. Finally, in the fourth step, after removing all variables not significant at the .05 level, both caregiver education and relational deprivation were significantly related to caregiver depressed mood.

Discussion

This study provided information regarding the prevalence of depressed mood and also assessed relationships among selected demographic variables, primary stressors, and intrapsychic strain and gain in caregivers of persons with MCI using the SPM.[25] Approximately a quarter of caregivers of MCI individuals were at risk for depression at baseline. The prevalence of depressed mood in these caregivers was higher than that reported by community-dwelling older adults as

Table 4. Results of Block Stepwise Logistic Regression Analysis Predicting Caregiver (CG) Depressed Mood

Independent Variable	B	SE	Z Statistic	*P* Value
Step 1 (n = 756)				
Background CG characteristics				
CG age	–.01	.01	–0.99	.323
CG education	–.07	.03	–2.26	.024
CG marital relationship with CR	–.37	.22	–1.18	.086
Step 2 (n = 746)				
CG education	–.06	.03	–1.80	.072
Primary stressors				
IwMCI cognitive functioning	–.01	.02	–0.60	.547
IwMCI daily dependence	–.02	.02	–0.93	.354
CG relational deprivation	.11	.03	3.83	< .001
Step 3 (n = 748)				
CG education	–.05	.03	–1.46	.144
CG relational deprivation	.07	.04	2.02	.043
Intrapsychic strain and gain				
Perceived self-loss	.19	.11	1.72	.085
Perceived personal gain	.04	.03	1.29	.197
Step 4 (n = 751)				
CG education	–.06	.03	–1.97	.049
CG relational deprivation	.11	.03	4.41	< .001

SE = standard error; CR = care receiver; IwMCI = individual with mild cognitive impairment.

measured by the CES-D (9% to 16%),[28,53] but it was lower than that of AD caregivers (28% to 55%) as reported by others.[12]

The factors related to depressed mood in MCI caregivers were similar to those for AD caregivers, specifically, caregivers' age, education, and marital status. We found that younger, nonspouse MCI caregivers with less education were at greater risk for depressed mood. Although data on caregiver gender were not available in this study, our findings were similar to other studies of sociodemographic variables affecting caregiver depressed mood such as caregivers' age and relationship to the care recipient.[41,54] According to the National Alliance for Caregiving,[55] nonspouse caregivers such as adult children may have to change their life goals or lifestyle, living arrangements, and role responsibilities while caring for a relative with cognitive impairment. They often have competing responsibilities, must share limited resources, and experience stressors at both the personal and family levels. Personal responsibilities and stressors include working full-time, raising a family, dealing with their own illnesses and illnesses of other family members, missing work, as well as other losses (eg, loss of a job). Financial concerns also weigh heavily on caregivers who live on a fixed income and have to bear the cost of illness-related expenses such as a live-in caregiver.

The prevalence of depressed mood did not differ by the care recipient's level of cognitive impairment or daily dependency in this study. This finding was probably because the care recipient's cognitive functioning was better than that of persons in mild or later stages of AD. Higher level functions such as complex household competencies, occupational demands, and social functioning may have been affected by their cognitive impairment,[34] but an inclusion criterion for care recipients in this study was that their ADL abilities be intact. We measured ADLs because ADL abilities are gradually influenced by the progression of memory problems.

An important issue when assessing daily dependency in MCI individuals is the use of informant-based rather than performance-based evaluations. Performance-based evaluations assess function directly by asking patients to perform an activity, which is then observed and evaluated in a formal way. However, both care recipients' levels of cognitive functioning and daily dependency in this study were baseline informant-based measures that may have changed over time with the progression of cognitive impairment. Estimates of the conversion rates of MCI to AD range from 10% to 15% per year,[5,56] and the median conversion time from diagnosis of MCI to AD is 4.4 years.[56] Therefore, it is important to follow stressors over time to determine whether the stressors predict depressed mood in

caregivers of MCI individuals as cognitive impairment progresses. MCI individuals are still able to understand and follow verbal communication; thus, it is imperative that performance-based measures are used whenever possible. Self- and informant-reported ratings should be used in follow-up visits to monitor functional changes and the effectiveness of early interventions. MCI individuals in this study had high Mini-Mental State Examination scores (24–30) and ADL function. Cognitive functioning and daily dependency were not associated with caregiver depressed mood at baseline but this would be expected to change as the care recipients' functional ability deteriorates over time.

Depressed mood was associated with greater relational deprivation in caregivers, consistent with previous studies,[26,38,39] and remained significant after controlling for other variables in the analysis. The quality of the relationship between informal caregivers and MCI individuals might be related to the progression of MCI and the caregiving situation.[17,40,57,58] Several causes of conflicted relationships in various conditions have been reported. For example, MCI individuals' lack of awareness of functional deficits related to possible engagement in unsafe tasks (driving) or placing themselves at risk may cause stress to their caregivers.[58,59] In addition, caregivers might inaccurately judge their relatives' cognitive and functional abilities,[60] and the differences in perspectives could impair communication and create challenges in daily living resulting in increased tension in the relationship. Feelings of relational deprivation may contribute to the development of caregivers' emotional distress and decreased quality of life. In our ongoing qualitative study, some caregivers criticized the care recipient for having unrealistic expectations and judgments of their own abilities.[40] In this study, relational deprivation was related to depressed mood in caregivers, even at this stage of MCI. Therefore, this may be an important area in which to test interventions in MCI individuals and their caregivers.

Unlike previous studies, the relationship between self-loss and depressed mood predicted by the SPM was not supported at baseline in this study.[25,38] This finding may have been because of the relatively low feelings of self-loss in the baseline data and because caring for an MCI relative who retains a capability for ADL performance and for verbal and nonverbal communication is relatively less stressful. However, because those abilities change over time, it is essential to study changes in self-loss over time, because caregiver depressed mood appears to be strongly related to caregivers' perception of self-loss, as reported in previous studies of bereavement issues among caregivers.[61]

Of interest, those caregivers who reported a high level of personal gain also experienced increased risk for depressed mood in this study, although this relationship was no longer significant when controlling for education and relational deprivation. Data from our ongoing qualitative study suggest that positive aspects of caregiving do not counteract a difficult and stressful caregiving experience, particularly for spouses of MCI individuals who have limited resources or support from healthcare providers.[40] Similarly, positive and meaningful themes have been identified along with burdensome and painful descriptions of caregiving for AD individuals.[62] Thus, continued research in this area is necessary.

A particular strength of this study was the use of the SPM[25] to choose key stress variables associated with depressed mood in MCI caregivers. Nonetheless, this study also has several limitations. First, the data were cross-sectional, unlike the original methodology testing the SPM,[25] which included 8 waves of data. Without longitudinal data, it is impossible to identify effects of subjective and objective stressors on depressed mood. We hope that these findings prompt further and more detailed inquiry into the longer term effects of caregiving for MCI individuals. Almost all our subjects were Caucasian; thus the results cannot be generalized to different racial and ethnic groups. Finally, important caregiver demographics (gender, race) were not recorded in the original data set, so it was not possible to include them in these analyses and to determine whether the results apply equally to female and male caregivers. Unfortunately, the absence of information on caregiver gender makes it impossible to determine the impact of gender on depressed mood in this sample. Thus, effects of gender in MCI caregivers remains an important issue to be researched further.

This study provides a new perspective on studying depressed mood in MCI caregivers, and findings suggest that depressed mood remains an important index of health outcomes for this group. Our ongoing qualitative study suggests that the IADLs of MCI individuals are considerably affected by declining memory, but there remains a strong desire to preserve integrity or wholeness of self and the ability to perform usual tasks.[40] Many researchers have

suggested that future work is needed to develop skill-based interventions for MCI individuals and their caregivers.[9] Many intervention studies have been focused on outcomes for AD patients and their caregivers,[22,24,63] yet few researchers have focused specifically on MCI individuals and their spouses. The current study found that caregivers who were younger, had less education, were nonspouses, and reported greater relational deprivation and higher levels of self-loss and personal gain were at greater risk for depressed mood. Controlling for demographic variables, other primary stressors, and intrapsychic strain and gain, the key variable of relational deprivation continued to be a significant predictor of depressed mood, indicating that interventions related to quality of relationships between caregivers and their MCI relatives may be a priority area for future intervention research. Further research is needed to test early interventions and the possibility of reducing levels of depressed mood in caregivers as MCI progresses. If begun early enough, interventions to improve caregivers' coping skills could possibly prevent depressed mood before they become overwhelmed with their relatives' behavioral problems or entangled in caregiving crises. Similarly, helping MCI individuals develop coping strategies to live with their cognitive impairment can assist them to live independently as long as their function permits.

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Appendix
Inclusion and Exclusion Criteria for Care Recipients With Mild Cognitive Impairment (MCI)

The inclusion criteria for individuals with MCI were:

1. Memory complaints and memory difficulties that were verified by a family caregiver.
2. Abnormal memory function documented by scoring below education-adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) of the Wechsler Memory Scale–Revised (the maximum score is 25):
   - ≤ 8 to 16 or more years of education
   - ≤ 4 for 8–15 years of education
   - ≤ 2 for 0–7 years of education
3. Mini-Mental State Examination score ≥ 24 and 30 (inclusive). Exceptions might be made for subjects with < 8 years of education at the discretion of the project director.
4. Clinical Dementia Rating = 0.5. Memory Box score must be at least at 0.5.
5. General cognition and functional performance sufficiently preserved such that a diagnosis of AD could not be made by the site physician at the time of the screening visit.
6. No significant cerebrovascular disease.
7. Age between 55 and 90 years.
8. Permitted medications stable for at least 1 month before screening. In particular:
   - Subject may take stable doses of antidepressants lacking significant anticholinergic side effects
   - Estrogen replacement therapy is permissible
   - Ginkgo biloba is permissible but discouraged
9. Hamilton Depression rating scale score ≤ 12 on the 17-item scale.
10. Informant is available who has frequent contact with the subject (eg, an average of 10 hours per week or more), agrees to monitor administration of study drug, observes for adverse events, and accompanies the subject to all clinic visits for the duration of the protocol.
11. Computed tomography or magnetic resonance imaging scans within 12 months before screening without evidence of infection, infarction, or other focal lesions and without clinical symptoms suggestive of intervening neurological disease.
12. Adequate visual and auditory acuity to allow neuropsychological testing.

13. Good general health with no additional diseases expected to interfere with the study.
14. Normal vitamin B_{12}, rapid plasma reagin, and thyroid function tests or without any clinically significant abnormalities that would be expected to interfere with the study.
15. Electrocardiogram without clinically significant abnormalities that would be expected to interfere with the study.
16. Subject is not pregnant, lactating, or of childbearing potential (ie, women must be 2 years postmenopausal or surgically sterile).
17. Agreement not to take other vitamin supplements (including vitamin E) or multivitamins other than those provided by the study.

Exclusion criteria for individuals with MCI were:

1. Any significant neurologic disease other than suspected incipient Alzheimer's disease, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.
2. Major depression or another major psychiatric disorder as described in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), within the past 2 years.
3. Psychotic features, agitation, or behavioral problems within the past 3 months that could lead to difficulty complying with the protocol.
4. History of alcohol or substance abuse or dependence within the past 2 years (*DSM-IV* criteria).
5. History of schizophrenia (*DSM-IV* criteria).
6. Any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol including:
   - History of systemic cancer within the past 5 years (nonmetastatic skin cancers are acceptable)
   - History of myocardial infarction in the past year or unstable or severe cardiovascular disease including angina or congestive heart failure with symptoms at rest
   - Clinically significant obstructive pulmonary disease or asthma
   - Clinically significant and unstable gastrointestinal disorder such as ulcer disease or a history of active or occult gastrointestinal bleeding within 2 years
   - Clinically significant laboratory test abnormalities on the battery of screening tests (hematology, prothrombin time, chemistry, urinalysis, electrocardiogram)
   - Insulin-requiring diabetes or uncontrolled diabetes mellitus
   - Uncontrolled hypertension (systolic blood pressure > 170 or diastolic blood pressure > 100)
   - History of clinically significant liver disease, coagulopathy, or vitamin K deficiency within the past 2 years
7. Medications:
   - Use of centrally active β-blockers, narcotics, methyldopa, and clonidine within 4 weeks before screening
   - Use of anti-Parkinson medications (eg, Sinemet®, amantadine, bromocriptine, pergolide, and selegiline) within 2 months before screening
   - Use of neuroleptics or narcotic analgesics within 4 weeks before screening
   - Use of long-acting benzodiazepines or barbiturates within 4 weeks before screen
   - Use of short-acting anxiolytics or sedative hypnotics more frequently than 2 times per week within 4 weeks before screening (note: sedative agents should not be used within 72 hours of screening)
   - Initiation or change in dose of an antidepressant lacking significant cholinergic side effects within the 4 weeks before screening (use of stable doses of antidepressants for at least 4 weeks before screening is acceptable)
   - Use of systemic corticosteroids within 3 months before screening
   - Medications with significant cholinergic or anticholinergic side effects (eg, pyridostigmine, tricyclic antidepressants, meclizine, and oxybutynin) within 4 weeks before screening
   - Use of anticonvulsants (eg, phenytoin, phenbarbital, carbamazepine) within 2 months before screening
   - Use of warfarin (Coumadin®) within 4 weeks before screening
8. Vitamin supplements:
   - Use of vitamin supplements other than the standard multivitamin included as part of the treatment intervention used in this protocol within 2 weeks before screening
9. Any prior use of any Food and Drug Administration–approved medications for the treatment of Alzheimer's disease (eg, tacrine, donepezil, or other newly approved medications).
10. Use of any investigational drugs within 30 days or 5 half-lives, whichever is longer, before screening.
11. Subjects who, in the investigator's opinion, will not comply with study procedures. Resource: MCI Protocol which is based on ADC-008/Alzheimer's Disease Cooperative Study.

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