Published in final edited form as:

Alzheimer Dis Assoc Disord. 2014 ; 28(3): 253–260. doi:10.1097/WAD.000000000000020.

Social Relationships and Risk of Incident Mild Cognitive Impairment in U.S. Alzheimer's Disease Centers

Willa D. Brenowitz, MPH^{*,†}, Walter A. Kukull, PhD^{*,†}, Shirley A. A. Beresford, PhD^{*,‡}, Sarah E. Monsell, MS[†], and Emily C. Williams, PhD, MPH^{§,||}

^{*}Department of Epidemiology, University of Washington, Seattle, Washington

[†]National Alzheimer's Coordinating Center, University of Washington, Seattle, Washington

[‡]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

[§]Department of Health Services, University of Washington, Seattle, Washington

^{||}Denver-Seattle Center of Innovation for Veteran-Centered and Value-Driven Care, Veterans Affairs (VA) Puget Sound Health Care System, Seattle, WA

Abstract

Social relationships are hypothesized to prevent or slow cognitive decline. We sought to evaluate associations between social relationships and mild cognitive impairment (MCI). Participants from the National Alzheimer's Coordinating Center database who were cognitively normal, aged 55 and older at baseline, and had at least two in-person visits (n=5,335) were included. Multivariable Cox proportional hazard models evaluated the association between four social relationships at baseline (marital status, living situation, having children, and having siblings) and risk of developing MCI (based on clinician diagnosis following established criteria). Primary models were adjusted for baseline demographics. Participants were followed, on average, for 3.2 years; 15.2% were diagnosed with MCI. Compared to married participants, risk of MCI was significantly lower for widowed participants (hazard ratio [HR]: 0.87; 95% confidence interval [CI]: 0.76, 0.99) but not for divorced/separated or never married participants. Compared to living with a spouse/partner, risk of MCI was significantly higher for living with others (HR: 1.35; 95% CI: 1.03, 1.77) but not for living alone. Risk of MCI was not associated with having children or having siblings. These results did not consistently identify social relationships as a strong risk factor for, or independent clinical predictor of, MCI.

Keywords

social relationships; marital status; living situation; mild cognitive impairment; dementia

Corresponding Author: Willa Brenowitz, MPH; University of Washington; National Alzheimer's Coordinating Center; 4311 11th Ave NE #300; Seattle WA 98105; Phone: (206) 616-5647; Fax: (206) 616-5927; wbrenow@u.washington.edu.

Conflicts of Interest

Walter Kukull is a member of the Editorial Advisory Board for *Alzheimer Disease & Associated Disorders*. The remaining authors declare no conflicts of interest.

INTRODUCTION

Approximately 14% of older adults in the U.S. have dementia;¹ ranging from 1.9% of adults age 65–69 to 47.5% of adults aged 90 and older.² Unless strategies to prevent or delay the onset of dementia are identified, the prevalence and the associated costs of dementia could nearly triple by 2050.^{3,4}

One strategy proposed to help older adults maintain cognitive function has been to improve aspects of an individual's social relationships.^{5,6} It is hypothesized that having social relationships may positively influence health behaviors and psychological processes^{7,8} and provide mental stimulation, which may enhance cognitive reserve or the ability of the brain to function despite neuropathology.^{9,10} Several previous studies provide evidence that important social relationships, such as being married and living with someone, are associated with lower risk of developing dementia^{11–13} and with slower rates of cognitive decline^{14–17} independent of the perceived quality of the relationship.

However, other studies have failed to find consistent longitudinal associations between social relationships and cognitive impairment.^{18–22} There is a concern that positive associations have been observed previously because early cognitive decline may lead to social isolation (reverse causation).²³ Therefore, it may be important to use sensitive measures of cognition at study baseline in order to exclude participants with subtle cognitive impairments.

It may also be useful to follow participants for clinical outcomes that mark early disease states such as mild cognitive impairment (MCI), an intermediate clinical diagnosis of early cognitive impairment thought to lie along a general continuum to dementia.²⁴ This approach may help identify older adults at higher risk of cognitive decline in earlier stages of the disease pathogenesis, and it may inform the development of preventive strategies. Furthermore, if social relationship status is independently associated with risk of MCI, social relationship status could easily be assessed by clinicians. To our knowledge no prior study has extensively evaluated the role of a variety of important social relationships with risk of MCI.

The primary objective of this study was to evaluate the associations between important social relationships and risk of incident MCI in cognitively normal older adults who were evaluated by one of the National Institute on Aging's (NIA) Alzheimer's Disease Centers (ADCs). We hypothesized that participants who reported having social relationships would have a lower risk of MCI compared to those who did not. We also assessed whether associations between social relationships and risk of MCI would differ according to sex, as there may be gender-specific effects of social relationships on health status²⁵ and cognitive decline.¹³ Finally, because genetic predisposition to dementia may modify the effect of social relationships on risk of MCI,¹⁴ we also investigated the interaction between social relationships and having the major genetic risk factor for late-onset Alzheimer's disease (the APOE ϵ 4 allele).²⁶

METHODS

Data Source

Data were obtained from the National Alzheimer's Coordinating Center (NACC). NACC maintains the Uniform Data Set (UDS),^{27,28} which includes standardized clinical data from participants who were evaluated by one of 34 past and present ADCs throughout the U.S. Each ADC recruits and enrolls participants according to its own protocols; participants are generally volunteers who want to take part in a research study or were referred to the ADC due to concerns about their health, cognition, or behavior.

Methods and rationale for the UDS have been previously published.²⁸ Briefly, data were collected by clinicians or trained interviewers through in-person office visits at each ADC. Research participants were asked to attend with a friend or family member who could provide information on their cognitive and functional abilities.²⁹ All participants received an initial clinical evaluation and up to seven annual follow-up evaluations.^{27,28} Informed consent was obtained from all participants at the individual ADCs. Centers had IRB approval to gather data, and data received from NACC were de-identified. This research was approved by the University of Washington IRB.

Study Sample

The analytic sample consisted of UDS participants who had data entered into the NACC database between September 2005 and September 2012. Participants were eligible for this analysis if they were aged 55 years and older at the initial visit and had "normal" cognition. Normal cognition was defined based on clinician assessment and scoring within the normal range on both the Clinical Dementia Rating³⁰ (CDR; sum of boxes=0) and Mini-Mental State Examination³¹ (MMSE; score 24–30). Only participants with complete (no missing or unknown) information on all measures were included.

Measures

Primary Exposures: Social Relationships—Data from baseline interview assessments on marital status, living situation, and biological family members were used to derive four primary measures of social relationships. Marital status was defined as a four-category indicator variable: married or living as married (reference), widowed, divorced/separated, or never married. Living situation was defined as living with spouse/partner (reference), living with others (i.e., living with relatives or living in a group), or living alone. Having children was defined as having at least one biological child, living or deceased (reference), or none; having siblings was defined similarly.

Primary Outcome: Mild Cognitive Impairment—Diagnoses of MCI were made at all ADCs by either a single clinician or consensus group of clinicians, after a review of all evaluation information available. The diagnosis was established according to published criteria,³² such that participants were determined to have MCI if they did not meet criteria for dementia diagnosis but had complaints about their cognition, their cognition was not normal for their age, and they had recent cognitive decline but essentially normal functional activities.³²

Covariates—Demographic factors were assessed via baseline structured interviews. These included age at initial intake, level of education achieved (categorized as high school or less (0–12 years); some college (13–15 years); graduated college (16 years); or graduate school (16+ years) in this analysis), and sex (male, female). Both race and Hispanic ethnicity were recorded. For this analysis race and ethnicity were combined into the following categories: Caucasian-Non-Hispanic, African American-Non-Hispanic, Hispanic (any race), and Other-Non-Hispanic.

Cigarette-smoking status was dichotomized into current vs. previous/never smoker for this analysis, based on history of cigarette smoking (assessed by the question: “Has the subject smoked more than 100 cigarettes in her/his life?”) and current smoking status (assessed by the question: “Has the subject smoked in the last 30 days?”). Problematic alcohol use was assessed by asking for the clinician’s best judgment about whether over a 12-month period the subject had experienced significant impairment in work, driving, legal or social areas due to alcohol use. Responses were recorded as absent, recent/active, remote/inactive, or unknown. We derived a measure of current problematic drinking based on a response of “recent/active” to this question.

Clinicians also assessed a series of other physical and mental health conditions, for example, cardiovascular diseases, diabetes, hypertension, and depression. With the exception of depression, participant history for each condition was recorded as absent, recent/active, remote/inactive, or unknown. Depression was recorded as active within the past two years (yes, no, unknown) and as episodes prior to two years (yes, no, unknown). For this analysis, the number of physical health conditions documented at baseline as recent/active or remote/inactive was categorized as none, one, two, three, or four or more conditions). History of depression (yes, no) was defined as any current or prior history of the condition.

Based on each ADC’s protocol and participant preference, APOE genotyping was conducted for a select sample of participants, and genotype information was linked to the UDS; APOE $\epsilon 4$ allele status, a primary genetic risk factor for late-onset AD, was defined as having at least one $\epsilon 4$ allele or none.

Statistical Analyses

Our analyses assessed time to first clinical MCI diagnosis (any subtype) as reported in the UDS. All participants at baseline were considered cognitively normal but capable of developing MCI. The onset of MCI was estimated as the midpoint between the last cognitively normal evaluation and the first-ever evaluation with a diagnosis of MCI or dementia if there were no previous diagnosis of MCI (participants were assumed to have passed through a MCI stage). Participants who did not develop MCI were censored at their last clinical evaluation.

Participant characteristics were described for the entire analytic sample and compared across clinical outcome (did not develop MCI vs. developed MCI). Comparisons across two measures of social relationships (marital status and living situation) were also conducted. Comparisons were not made across other measures of social relationships due to the small

numbers of those that did not have children or siblings. Categorical measures were compared with χ^2 tests.

To describe unadjusted differences in risk of developing MCI according to social relationships. Incidence of MCI per 1000 person-years was assessed by social relationship status. Kaplan-Meier graphs were used to visualize unadjusted differences in probability of developing MCI with time according to social relationship measures. Survival functions were compared across social relationship status for each exposure using log-rank tests.

Subsequently, multivariable Cox proportional hazard models were fit to evaluate the associations between baseline social relationships and risk of developing MCI. Cox models were assessed separately for each exposure measure, years since initial visit were used as the time scale, and the Efron method³³ was used to handle events that occurred at the same time. Models included adjustment for clustering by ADC to account for potential correlation of evaluations within Centers. Primary models were adjusted for age at baseline, sex, education, and race/ethnicity. Age at baseline was modeled continuously using a linear spline, a piecewise linear function, that allowed the slope to vary among age categories (55–64, 65–74, 75–84, and 85+). Baseline hazards were allowed to vary according to race/ethnicity in order to account for non-proportionality. Secondary models were also adjusted for baseline smoking status and problematic alcohol use, as well as the number of physical health conditions and depression at baseline. A sequential modeling approach was taken for adjustment of covariates because health behaviors and health conditions included in secondary models are potential confounders (they may be associated with risk of cognitive impairment⁶ and social relationship status), but they are also potential mediators because health behaviors and health conditions may be influenced by social relationships.^{7,8} Since depression could be a preclinical symptom of dementia,³⁴ we also separately assessed the association of depression at baseline and MCI to determine whether it was likely independent of the relationship between social relationships and risk of MCI.

Next, because the association between social relationships and risk of MCI may vary based on sex¹³ or APOE $\epsilon 4$ allele status,¹⁴ we repeated main analyses but included a multiplicative interaction term for each potential effect modifier (i.e., sex $\times$ social relationship and APOE $\epsilon 4$ allele $\times$ social relationship). In models where there was no significant interaction between APOE $\epsilon 4$ allele status and social relationships, APOE $\epsilon 4$ allele status was included as a covariate, since APOE $\epsilon 4$ is strongly associated with dementia risk²⁶ and may act as a potential confounder if the distribution of APOE $\epsilon 4$ allele status differed by social relationships due to study selection factors, for example. Proportional hazards assumptions were assessed and satisfied analytically (by testing Schoenfeld residuals and including covariates as time dependent) and graphically (Schoenfeld residuals vs. time plots and log-log plots). Statistical analyses were performed using STATA 12.0. All tests were two-tailed with α -levels set to 0.05. The term “significant” was used to indicate statistical significance.

RESULTS

The final analytic sample comprised 5,335 participants, among whom there were 812 cases of incident MCI during follow-up (Figure 1). On average, participants were followed for 3.2

years after the initial visit (SD=1.8). The vast majority (91.7%) of participants came to the ADC as a volunteer to participate in a research study.

Compared to participants who did not develop MCI during follow-up, participants who developed MCI tended to be older and had worse cognition at baseline. A higher proportion were men, were non-Hispanic Caucasians, had lower levels of achieved education, had more health conditions, and had at least one APOE $\epsilon 4$ allele (Table 1). A majority of participants were married (58.2%), lived with their spouse/partner (57.0%), had at least one child (83.6%), and had at least one sibling (88.3%). Relatively few participants were never married (5.5%) or living with someone other than their spouse or partner (6.8%).

There were substantial differences in demographic characteristics and health histories according to marital status and living situation (see Tables, Supplementary Digital Content 1 and 2, which describe baseline characteristics by marital status and living situation, respectively). In general, married participants were more often Caucasian men, were non-smokers, and tended to have fewer health conditions than widowed, divorced/separated, or never-married participants. Widowed participants also tended to be older and less educated than married, divorced/separated, and never-married participants. Participants who lived with others (not their spouse) or alone were more often women, older, non-Caucasian, less educated, and had more health conditions than participants who lived with their spouse/partner. Participants who lived with others were more often younger, non-Caucasian, less educated, a smoker, and depressed, and were more likely to have at least one APOE $\epsilon 4$ allele than participants who lived alone.

The overall incidence of MCI was 47.3 per 1,000 person-years; however, rates were higher among participants who, at baseline, were widowed, living with others or living alone, or had no siblings (Table 2). Kaplan-Meier survival curves showing the estimated probability of not developing MCI (Figure 2) were lower for widowed participants compared to other marital statuses and for participants living alone or with others compared to participants living with a spouse/partner. Overall, survival functions were significantly different among marital statuses and living situations but not for having children or having siblings (Figure 2).

Adjusted hazard ratios and 95% confidence intervals are presented in Table 3 for primary and secondary models. In primary analytic models, risk of any MCI was significantly lower for those widowed at baseline (vs. married); however, there was no significant difference in risk of MCI for participants who were divorced/separated or never married at baseline compared to married participants. Meanwhile, risk of MCI was significantly higher for those living with others (vs. living with spouse/partner) but not for those living alone (vs. living with spouse/partner). There was no evidence to support an association between risk of MCI and having children or having siblings in multivariable models. Results were similar after additional adjustment for health behaviors and health conditions (Table 3). There was a significant association between depression and risk of MCI after adjustment for age, sex, education, race/ethnicity, smoking status, problematic alcohol use, and number of health conditions (HR: 1.36; 95% CI: 1.12, 1.66; $P=0.002$); however, results did not differ

substantially based on inclusion or exclusion of adjustment for depression in secondary models, so models including depression are presented (Table 3).

There were no significant interactions between any measure of social relationships and sex or APOE $\epsilon 4$ allele. After additional adjustment for APOE $\epsilon 4$ allele among 4,168 participants with known APOE genotype, risk of MCI was significantly reduced for participants living alone vs. living with spouse/partner (HR: 0.88; 95% CI: 0.78, 1.00; $P=0.05$); however, no other results were significantly changed.

With concern that results could be driven by participants with rapid disease onset, we conducted a sensitivity analysis excluding 102 participants who were diagnosed with dementia after a visit with normal cognition (i.e., there was no observed MCI diagnosis); results were somewhat attenuated, such that the difference in risk of MCI between widowed and married participants was no longer significant, but otherwise similar (data not shown).

To explore the influence of age on our results we conducted additional sensitivity analyses. First we ran models with age as the only covariate, which resulted in similar estimates as primary adjusted models (data not shown). Next we re-ran primary analyses stratifying according to baseline age (< 75 and ≥ 75 years). Among participants <75 years, there were no significant associations between social relationships and risk of MCI (Supplementary Digital Content 3). However, among participants ≥ 75 years, those who were widowed and those who were living alone had a significantly lower risk of MCI compared to those married and living with a spouse, respectively (Supplementary Digital Content 3).

DISCUSSION

We investigated the individual associations between risk of MCI and four types of important social relationships (being married, living with others, having children and having siblings) in older adults using a large multi-center clinical research dataset. Contrary to our hypothesis that having social relationships would be associated with lower risk of MCI, we found inconsistent relationships between social relationships and MCI after iterative adjustment for demographics alone as well as demographics, substance use, and comorbidities.

Several prior studies did not find evidence for a longitudinal association between having social relationships and cognitive functioning, independent of potential confounders.^{18–21,35} Our study extends these findings to risk of MCI, a pre-dementia based clinical diagnosis. However, our results were unexpected as many studies have found associations between social relationships and cognitive outcomes.^{12,14–16,36} Discrepancy between prior studies and our results may be due to several important differences. Our study improved upon many prior studies by using strict entry criteria to try to eliminate participants with subtle cognitive deficits that may have influenced their social relationships before study enrollment. Positive findings in some prior studies may have been due to reverse causation; individuals with good cognition may retain social relationships over time compared to participants with poor or declining cognition.²³ When potential reverse causation is better accounted for, results are less consistent.^{14–16,35}

On the other hand, this was a sample of clinical research volunteers, and an individual's social relationship status may have influenced enrollment. For instance, participants may be more likely to participate if they had more social relationships, possibly because of pressure from family or friends. Little variation in social relationships may have reduced our power to detect an association. In addition, frequency of contact and quality of relationships were not assessed in the UDS. Measures that integrate information on quality and quantity of social relationships tend to be stronger predictors of mortality than basic relationships³⁷ and may have more power to detect associations.

In this analysis, despite increased rates of MCI for widowed participants and those living alone or with others, after iterative adjustment for potential confounders, widowed participants had a reduced risk of MCI compared to married participants, while participants living with others had an increased risk of MCI compared to those living with a spouse/partner. Risk of MCI did not differ between divorced/separated or never married participants and married participants or between those living alone and those living with a spouse. Additionally, there was no evidence for an association between risk of MCI and having children or siblings. Finally, we did not find evidence that sex and APOE $\epsilon 4$ allele status modified the effect of social relationships on risk of MCI; however, among participants with the same APOE $\epsilon 4$ allele status, participants living alone had a reduced risk of MCI compared to those living with their spouse. Our sensitivity analyses suggest that adjustment for age alone drove our primary results, and that associations may differ by age. Our findings with marital status, in particular, may have been primarily due to associations among older aged participants.

Together our results suggest that social relationships, in general, are not consistently associated with MCI. Participants who were unmarried at baseline or were living alone may have been under-diagnosed compared to married participants, perhaps due to lack of a knowledgeable witness. Widowed participants, in particular, may have a reduced risk of MCI, in this sample, due to the competing risk of death³⁸ and/or enrollment of individuals that had found ways to stay healthy and active after bereavement. These factors may have greater effect among older ages, which could help explain why reduced risk of MCI for widowed participants (and those living alone) was limited to older participants. Furthermore, although we restricted our sample to those without cognitive impairment (CDR-SB=0) onset of sub-clinical cognitive problems or poor physical health prior to enrollment could have influenced individuals to live with others, which may explain our finding that living with others but not living alone was associated with increased risk of MCI compared to living with a spouse/partner. While the present study had limited data regarding death of participants, future research in samples with standardized ascertainment of death and/or data on health and living status prior to study enrollment should be conducted to further explore these possibilities.

There are several important limitations to this study. Our results could have been biased if there were differential drop-out or follow-up of participants (non-differential drop-out is assumed by the model). For example, participants with social relationships may be more likely than those without to keep returning to visits. Meanwhile, socially isolated participants may be more likely to drop out, especially when they develop cognitive

problems, perhaps due to lack of assistance. Consequently, risk of MCI could be estimated in our study as falsely high among participants with social relationships, which could cancel out additional risk associated with social isolation, if any. Lack of data on participant drop-out and death limits our ability to assess this potential bias. Short follow-up period and censoring in the data may have limited the power of our study to detect differences. We attempted to maximize power by assessing risk of any MCI; however, clinical presentation of MCI is heterogeneous, and recent research on incident MCI suggests that risk factors may differ depending on MCI subtype.³⁶ We used baseline measures of social relationships, however these may have changed over follow-up. In addition, children and siblings were counted whether they were alive or deceased and regardless of quality or frequency of contact. Finally, our results may not be generalizable to the U.S. population, as participants may have been motivated to participate in research due to high education level or to family history of dementia or other risk factors.

Nevertheless, this study has important strengths as well. This study was a large multi-center prospective study of the associations between multiple social relationships and risk of MCI. Participants underwent in-depth neuropsychological testing and clinical evaluation at each visit, and diagnosis of MCI was based on established criteria. Identification of persons potentially at risk of MCI may point to potential targets for prevention. Other strengths included allowing for potential differences between sub-categories of participants who were not currently married or living with their spouse in our definitions of marital status and living situation. Finally, we included robust and iterative adjustment for potential confounders.

In conclusion, we did not find consistent evidence to support the hypothesis that having social relationships is associated with reduced risk of MCI after adjustment for important confounders. More research may be needed to elucidate the relationships between risk of MCI and social relationships prior to deciding that enhancing social relationships should not be a focus of interventions to prevent dementia or to identify at-risk patients. The role of children and siblings on the development of MCI could be studied further, as well as the relationships between marital status and living situation. Studies should recruit from diverse populations that have variability in social relationships. Protocols should be used for regular follow-up at defined periods, and efforts should be made to obtain some information for those who fail to attend follow-up evaluations. Further efforts to use more sensitive analytic tools should be attempted. Longitudinal methods of continuous measures that can detect early changes in cognition may be more sensitive than time-to-event analysis to detect an association, while still focusing on early-stage cognitive impairment. Yet our results suggest that demographic information may be a stronger and more clinically relevant predictor of risk for MCI. Further research is needed determine whether other potentially important modifiable risk factors for dementia are also associated with risk of MCI. Identifying other potentially modifiable factors could help find alternative strategies to prevent MCI and progression to dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding:

This study was funded by the National Institute on Aging (U01 AG016976). ECW is supported by a Career Development Award from VA Health Services Research & Development (CDA 12-276) and is an investigator with the Implementation Research Institute (IRI) at the George Warren Brown School of Social Work at Washington University in St. Louis. IRI is supported through an award from the National Institute of Mental Health (R25 MH080916-01A2) and the Department of Veterans Affairs, Health Services Research & Development Service, Quality Enhancement Research Initiative (QUERI). Preliminary versions of this work were included in the thesis submitted in partial fulfillment of the requirements for the degree of Master of Public Health from the Department of Health Services, University of Washington (WDB).

We are grateful to the patients, clinicians, and other staff at the ADCs who made this research possible. We would also like to thank NACC staff for help with NACC data, including Elizabeth Robichaud for helpful feedback; and acknowledge the NIA for providing support to the ADCs and NACC.

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Figure 1. Study sample flow chart. Abbreviations: MCI=Mild Cognitive Impairment, NACC=National Alzheimer's Coordinating Center, UDS=Uniform Data Set.

Figure 2.

Kaplan-Meier survival estimates for risk of any mild cognitive impairment (MCI) by baseline marital status (A) and baseline living situation (B), as well as by whether the participant had living or deceased children (C) and siblings (D) at baseline ($n=5,335$) Note: Graphs show only 60–100% survival.

Table 1

Participant Characteristics at Baseline

Characteristic	No MCI (n=4,523)	Any MCI (n=812)	All Participants (n=5,335)	P*
N(%)				
Age (yrs)				<0.001
55–64	815 (18.0)	55 (6.8)	870 (16.3)	
65–74	1,916 (42.4)	220 (27.1)	2,136 (40.0)	
75–84	1,381 (30.5)	334 (41.1)	1,715 (32.2)	
85+	411 (9.1)	203 (25.0)	614 (11.5)	
Female	3,072 (67.9)	508 (62.6)	3,580 (67.1)	0.003
Race/Ethnicity				0.07
Caucasian	3,494 (77.3)	660 (81.2)	4,154 (77.9)	
Black	653 (14.4)	93 (11.5)	746 (14.0)	
Hispanic	191 (4.2)	28 (3.5)	219 (4.1)	
Other Non-Hispanic	185 (4.1)	31 (3.8)	216 (4.1)	
Education				0.003
High school or less	852 (18.8)	176 (21.7)	1,028 (19.3)	
Some College	927 (20.5)	183 (22.5)	1,110 (20.8)	
College graduate	1,042 (23.0)	203 (25.0)	1,245 (23.3)	
Graduate school	1,702 (37.6)	250 (30.8)	1,952 (36.6)	
Reason for coming to ADC				0.04
Participate in research	4,164 (92.1)	726 (89.4)	4,890 (91.7)	
Clinical evaluation	314 (6.9)	77 (9.5)	391 (7.3)	
Other/unknown	45 (1.0)	9 (1.1)	54 (1.0)	
Current Smoking	181 (4.0)	27 (3.3)	208 (3.9)	0.36
Current Alcohol Problem	21 (<1)	3 (<1)	24 (<1)	0.71
Health conditions[†]				0.03
0	623 (14.0)	94 (11.6)	726 (13.6)	
1	1,149 (25.4)	198 (24.4)	1,347 (25.3)	
2	1,191 (26.3)	203 (25.0)	1,394 (26.1)	
3	875 (19.4)	164 (20.2)	1,039 (19.5)	
4 or more	676 (15.0)	153 (18.8)	829 (15.5)	
Depression	988 (21.8)	180 (22.2)	1,168 (21.9)	0.84
Any APOE ε4 allele[‡]	959 (27.2)	210 (32.8)	1,169 (28.1)	0.004
Social Relationships				
Marital Status				<0.001
Married	2,666 (58.9)	440 (54.2)	3,106 (58.2)	
Widowed	1,011 (22.4)	252 (31.0)	1,263 (23.7)	
Divorced/Separated	590 (13.0)	81 (10.0)	671 (12.6)	
Never Married	256 (5.7)	39 (4.8)	295 (5.5)	
Living Situation				0.001

Characteristic	No MCI (n=4,523)	Any MCI (n=812)	All Participants (n=5,335)	<i>P</i> [*]
Living with spouse	2,625 (58.0)	418 (51.5)	3,043 (57.0)	
Living with others	292 (6.5)	73 (9.0)	365 (6.8)	
Living alone	1,606 (35.5)	321 (39.5)	1,927 (36.1)	
Children				0.24
Yes	3,768 (83.3)	690 (85.0)	4,458 (83.6)	
Siblings				0.31
Yes	4,000 (88.4)	708 (87.2)	4,708 (88.3)	

* Calculated using Pearson chi-square test (categorical measures)

[†] Health conditions included: history or presence of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, B12 deficiency, thyroid disease, incontinence, or neurologic condition.

[‡] APOE genotype missing for 1,167 participants (21.9%).

Table 2

Social Relationships at Baseline and MCI Events Among Participants.

Characteristic	Persons at risk	Person-years of follow up	MCI events	Incidence rate per 1,000 person-years (95%CI)
Marital Status				
Married	3,106	10, 151	440	43.3 (39.5, 47.6)
Widowed	1,263	4,062	252	62.0 (54.8, 70.2)
Divorced/Separated	671	2,083	81	38.9 (31.3, 48.4)
Never Married	295	880	39	44.3 (32.4, 60.7)
Living Situation				
Living with spouse	3,043	9,950	418	42.0 (38.2, 46.2)
Living with others	365	1,081	73	67.5 (53.7, 84.9)
Living alone	1,927	6,145	321	52.2 (53.7, 84.9)
Children				
Yes	4,458	14,409	690	47.9 (44.4, 51.6)
No	877	2,768	122	44.1 (36.9, 52.6)
Siblings				
Yes	4,708	15,173	708	46.7 (43.3, 50.2)
No	627	2,003	104	51.9 (42.8, 62.9)

MCI, Mild cognitive impairment

Table 3

Adjusted Association Between Risk of MCI and Social Relationships.

Social Relationship	Primary Model*			Secondary Model†		
	Hazard ratio	95% CI	P‡	Hazard ratio	95% CI	P‡
Marital Status						
Married	1.00	---		1.00	---	
Widowed	0.87	(0.76, 0.99)	0.04	0.85	(0.74, 0.98)	0.02
Divorced/Separated	0.95	(0.76, 1.20)	0.69	0.91	(0.72, 1.16)	0.45
Never Married	1.06	(0.74, 1.51)	0.76	1.05	(0.74, 1.48)	0.79
Living Situation						
Living with spouse	1.00	---		1.00	---	
Living with others	1.35	(1.03, 1.77)	0.03	1.32	(1.00, 1.72)	0.05
Living alone	0.93	(0.81, 1.08)	0.36	0.91	(0.78, 1.06)	0.22
Children						
Yes	1.00	---		1.00	---	
No	1.03	(0.83, 1.29)	0.78	1.03	(0.83, 1.29)	0.78
Siblings						
Yes	1.00	---		1.00	---	
No	1.09	(0.89, 1.35)	0.41	1.09	(0.89, 1.34)	0.41

MCI = Mild Cognitive Impairment

* Model adjusted for age at baseline, sex, education, and race/Hispanic ethnicity

† Model adjusted for age at baseline, sex, education, and race/Hispanic ethnicity, smoking status, alcohol problem, number of health conditions, and depression.

‡ P-values calculated with Wald test