MIDLIFE MARITAL STATUS AND SUBSEQUENT
COGNITIVE DECLINE OVER 20 YEARS:
DISCOVERY FROM THE ATHEROSCLEROSIS RISK IN
COMMUNITIES (ARIC) STUDY

by

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Abstract

Background — Recent studies have shown that marriage is associated with a protective effect against cognitive decline among older adults. However, evidence from large prospective cohorts is lacking. Even less is known about the association between marital status during midlife and domain-specific cognitive decline in later life.

Objective — To investigate the effect of midlife marital status on subsequent domain specific cognitive decline over 20 years among community dwelling older adults.

Methods — Prospective cohort study of a biracial population of 14148 participants in the Atherosclerosis Risk in Communities (ARIC) study. Participants were followed from 1990-1992 through 2011-2013 and underwent three cognitive assessments at visit 2 (1990-1992), visit 4 (2004-2006) and visit 5 (2011-2013). Factor scores of cognitive functions were developed from neurocognitive tests during three visits and harmonized into three cognitive domains including executive, memory and language as well as general cognitive performance. Marital status was collected at visit 2 and categorized into four groups: married, divorced or separated, widowed, and never married. Multiple imputation using chained equations (MICE) was applied to address the challenge of informative attrition. Multivariable mixed effect linear models were applied after imputation with a spline term at year six to represent non-linear cognitive decline and a random slope to allow individual variations in cognitive decline after year six. Models were adjusted for age, sex, race, education, hypertension, diabetes, alcohol consumption, smoking status, and BMI measured at baseline.

Results — The median age of 14148 participants was 56.8 years; 24.2% of participants were black and 55.6% were female. Median follow-up time was 20.78 years. For the first six years,

there was no statistically significant cognitive decline difference comparing groups without partners at baseline to the married group. After year six, models suggested that being widowed at baseline was associated with greater cognitive decline compared to the married group across all cognitive domains. In the general cognitive domain, the difference in annual cognitive decline comparing the widowed group to the married group was -0.019 standard deviation (SD) units [95%CI (-0.023, -0.015)] ($p < 0.001$). Similarly, the corresponding difference in cognitive decline in the memory domain was -0.017 [95%CI (-0.023, -0.012), $p < 0.001$] unit, and for language was -0.028 [95%CI (-0.032, -0.024) , $p < 0.001$]. For participants who were divorced or separated, annual cognitive decline only presented statistically significant difference in language domain with -0.006 [95%CI (-0.010, -0.003) , $p = 0.001$] unit greater decline but not in other cognitive domains compared to the married group. There was no difference in the rate of cognitive decline between the married and never-married group.

Conclusion — Widowhood by midlife might increase the risk of cognitive decline across all cognitive domains, while being divorced or separated in midlife might be associated with greater annual cognitive decline in language domain. Being never married may not to be associated with greater cognitive decline.

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1. Introduction

Dementia has increasingly become a public health challenge as the world population is aging. The number of people living with dementia worldwide in 2010 is estimated to be 35.6 million and is expected to rise to 115.4 million in 2050 (Prince et al., 2013). In the US, a recent community cohort study documented the prevalence of dementia among 69 to 88 years old community dwelled older adults to be 9% and mild cognitive impairment (MCI) to be 21% (Knopman et al., 2016). Research shows that 32% of older adults with MCI will develop Alzheimer's disease within 5 years (Ward et al., 2013), thus it is important to understand the contributing factors to cognitive impairment.

Social networks and social engagement have been recognized as important protective factors against cognitive decline. A growing body of literature documents that poor social networks and lower level of social engagement are associated with increased risk of dementia or cognitive impairment in older adults (Bassuk et al., 1999; Fratiglioni et al., 2004 ; Saczynski et al., 2006; Wang et al., 2002; Yoshitake et al., 1995).

Chief among social networks, a marital relationship affects health and cognitive function of older people and has increasingly drawn the attention of researchers. Emerging evidence suggest marital status could be an independent correlate of cognitive decline. Compared to married people, living without a partner -- either being divorced, separated

or unmarried -- has been shown in studies to increase the risk of cognitive impairment or dementia (Fratiglioni et al., 2000; Xu et al., 2017; Sundström et al., 2016 ; Gelder et al., 2006; Hakansson et al., 2009; Fan et al., 2015; Feng et al., 2014). However, there are inconsistencies in associations across studies. One prospective cohort study, for example, reported an elevated risk of dementia among never married individuals but not in divorced or widowed groups. (Helmer et al., 1999). Another cohort with 1609 participants in Sweden reported an increased risk among the widowed but not in the divorced or married population (Sundström et al., 2014). Evidence from prospective cohort studies with large sample size and long follow-up time remains lacking. Even less is known about whether living without a partner may increase the risk of cognitive decline in general cognition or specific cognitive domains such as memory, language or executive function. Nevertheless, understanding domain-specific cognitive trajectory change is essential to untangle mechanism of mild cognitive impairment and to develop intervention strategies to prevent cognitive impairment.

In this paper, we aim to investigate the association between midlife marital status and subsequent 20-year cognitive decline in different cognitive domains after controlling for other variables using a prospective cohort study with 14148 community dwelling older adults in US. Untangling the role of marital status on domain-specific cognitive change could improve our understanding about the risk and protective factors of cognitive impairment and enhance our knowledge in the effect of social network on cognitive decline.

2 . Methodology

2.1 Study Design and Participants:

The ARIC study is a prospective cohort study of atherosclerotic disease and the association between middle age vascular factors and later life cognitive decline in community dwelling middle-aged adults. Participants were recruited by probability sampling from four U.S. communities: Forsyth County, NC, Jackson, MS; Northwestern suburbs of Minneapolis, MN and Washington County, MD. In all, 15792 participants aged 45 to 64 years were recruited in 1987-1989 and followed up for more than 20 years for cognitive performance at three visits (visit 2 in 1990-1992; visit 4 in 1996-1998, and visit 5 in 2011-2013). The ARIC study protocol was approved by institutional review boards at each study center and informed consent was obtained from participants.

For our present analysis, time origin was set at visit 2, the first visit where cognitive data were collected. Calendar year was used as time scale. Of 15792 participants in ARIC, we excluded 1644 participants who were missing cognitive outcome across three visits. 14148 participants were included in final analyses.

2.2 Exposure, outcome and covariates

2.2.1 Exposure:

Marital status was measured at visit 2 and visit 4 via self-report. Response options included five categories: married, divorced, separated, widowed and never married. We combined divorced and separated people together and grouped marital status into four categories. In our analysis, marital status at visit 2 was used as primary exposure while marital status at visit 4 was taken into consideration in sensitivity analysis.

2.2.2 Outcome:

Cognitive tests were administrated at visit 2, visit 4, and visit 5 in a quiet room by trained investigators using standardized procedures. The performance of examiners was recorded and reviewed for quality control. During visit 2 and visit 4, cognitive tests included Digital Symbol Substitution Test (DSST), Word Fluency Test (WFT) and Delayed Word Recall Test (DWRT). During the neurocognitive study at visit 5, a more detailed neurocognitive battery was applied. The tests incorporated three tests measured at previous visits and also the Boston Naming Test (BNT), Logical Memory Test (LMT), Animal Naming Test (ANT), Incidental Learning Test (ILT) and trail making test (TMT).

DSST from the Wechsler Adult Intelligence Scale Revised (Kaufman, 1983), is a test measuring the information processing speed and new learning ability. Participants are asked to translate numbers into symbols based on a sample key. The final score equals the total number of symbols correctly translated from numbers within 90 seconds, ranging from 0 to 93.

WFT, developed by Benton et al., measures both language and executive functions (Benton et al., 1989). Participants are instructed to generate meaningful words beginning with letter A, F and S as many as possible. Sixty seconds are given to each letter and the total score equals the sum of acceptable words generated for the three letters.

DWRT is a test for verbal learning and short memory (Knopman et al., 1989). Participants are given ten nouns that they will learn in each sentence and asked to recall the words within sixty seconds after five-minute delay. The total number of words successfully recalled are counted as the final score.

BNT is a measurement for language ability to verbally name the pictures of common objects in daily life and can be used to detect anomia (Kaplan et al., 1983). Participants are administered to name each object within 20 seconds with a total of 60 items. The score is the number correctly named and ranges from 0 to 60.

ANT is a test measuring the semantic fluency and participants are guided to spontaneously generate words from a specific category (Benton et al., 1989), which is animal in this specific test. The total words generated within 60 seconds comprise final scores.

LMT is a test measuring immediate and delayed memories based on Wechsler Memory Scale- Revised (WMS-R) (Wechsler et al., 1987). Two stories with 25 pieces of information for each are presented to the participants by the investigators. The participants are instructed to recall the information immediately and after 30-minute delay. The pieces of information correctly recalled during immediate free recall compose scores for LMT I while the pieces of information identified during delayed free recall are counted as scores for LMT II.

ILT is a test where participants are required to memorize the symbols and the matching patterns in previously administered DSST as many as possible within 60 seconds. Then participants are given 60 seconds to fill in the symbols based on the cues of numbers. The results are composed of two parts: symbol scores and pair scores. Symbol score equals the total number of symbols correctly recalled while pair score equals the pairs correctly identified. Both scores range from 0 to 10.

TMT measures the executive functions and processing speed and is composed of two parts (Reitan et al., 1958). In TMT-A, participants are required to connect the numbers from 1 to 25, which are randomly spread in a sheet, in a consequential order as quickly as possible. In TMT-B, switching task is added and participants are asked to draw consecutive lines alternating from numbers 1 to 13 to letters A to L. When an error is made, the investigators ask the participants to correct it before they move to the next dot. The total scores of the test are the time (in seconds) it takes to finish the task with a maximal limitation of 240 seconds allotted.

For our research purpose, we used factor scores, developed by Gross and colleagues to represent general cognitive performance and specific cognitive domains including memory, language and executive functions (Gross et al., 2015). Factor scores of different cognitive domains were derived from neurocognitive tests during three visits. Memory was represented by WRT, LMT and ILT. TMT-A, TMT-B and DSST were used to represent executive function while WFT, BNT and ANT were used to represent language ability. Compared to Z scores used by other researchers to study cognitive function, factor scores have several advantages. First, factor scores derived from latent variable methods maximize the utilization of cognitive tests information since the missing cognitive tests during visit 2 and visit 4 are not missing due to a person's cognitive status (Gross et al., 2015). Moreover, factor scores take weights into consideration for each cognitive test, yielding more accurate estimates of cognitive performance.

2.2.3 Covariates:

Demographic information including age, race (black and non-black), sex, and education (less than high school, high school and more than high school) were collected at visit 1.

Health or lifestyle information including hypertension (yes or no), BMI (weight (kg)/height (m)²), diabetes (yes or no), drinking history (yes or no), and smoking status (yes or no) were measured at visit 2. Hypertension was defined as systolic pressure more than 140mmHg, diastolic pressure more than 90 mmHg or any use of antihypertensive medication in the previous 2 weeks. Diabetes was defined as fasting glucose level more than 126 mg/dl, a non-fasting glucose level more than 200 mg/dl or a self-reported history of diabetes. Serum glucose level was assessed by the hexokinase method. Drinking history and smoking status were assessed through self-reported questionnaires including three categories of never, former and current drinker or smoker. We further dichotomized drinking history and smoking status into current drinker/ smoker or non-current drinker/smoker.

2.3 Statistical Analysis:

We used multivariable linear mixed effect models to model cognitive trajectory over 20 years and to estimate the association between marital status and cognitive decline. We treated time as a continuous variable and added a spline term at year six to account for the non-linear relationship between cognitive decline and time. We explored individual cognitive trajectory change using spaghetti plots and investigated group cognitive scores change using lowess smoothers. To allow the individual baseline cognitive performance variations and account for individual cognitive slope heterogeneity, we introduced random intercepts and random slopes in the model. We compared models with different random slopes and chose a model with one random slope for the second-time period after year six based on exploratory data analysis and best AIC selection. We assumed that the correlation patterns between random intercept and random slope are exchangeable based on best AIC selection. We included marital status, time and the interaction between marital status and time into the model. Primary coefficients of

interests were interactions between categorical marital status and two time spline terms. Final models were also adjusted for potential confounders including age, sex, race, education level, diabetes, hypertension status, cigarette smoking, alcohol consumption status and BMI. To produce interpretable intercept, we centered continuous variables including BMI and baseline age at their median.

2.4 Missing Data Imputation:

To handle missing data and account for attrition over 20 years, which may be differential by level of cognitive status, we used multiple imputation using chained equations (MICE) assuming that data were missing at random (MAR) (Rawlings et al., 2016). MICE is a flexible method allowing different types of variables and is compatible with mixed effect modelling (White et al. 2011). MICE is also more efficient than other imputation methods such as Inverse Probability Weighting (IPW) since it maximizes the utilization of information. Moreover, MICE is especially useful when auxiliary information is available, which applies to our case (Rawlings, 2016). To optimize our imputation results, we used auxiliary information of cognitive function measurements including Telephone Interview for Cognitive Function (TICS-m), a test offered to all participants who didn't attend visit 5 and a random sample of participants at visit 5 (Knopmman et al., 2010), suspect dementia status, which was obtained by proxy or ICD-code on hospital discharge record and Clinical Dementia Rating (CDR) scale, which was completed by informants who are familiar with individual's cognitive status (Manual 19, 2015). In the imputation model, we included all of the auxiliary information described above as well as mini-mental state examinations at visit 5, baseline cognitive scores, demographic information including age, sex, education, race and health information including hypertension, diabetes, cigarette smoking, alcohol consumption and BMI. We imputed 25 datasets for all of the 14148 participants. To check the imputed results, we did diagnostic plot comparing

observed and imputed cognitive scores. We also did available case analysis and compared the results with analysis after imputation. All of the statistical analysis and imputation were performed with Stata 14 (Stata Corp, College station ,TX)

2.5 Sensitivity Analysis:

To address the challenge of time-varying effect of marital status, we excluded those individuals whose marital status changed from visit 2 to visit 4 and compared the cognitive decline difference among those whose marital status remained constant using the same model. To explore the effect of the widowhood transition, we compared cognitive decline among those who remained widowed, who transitioned from being married to widowed or from widowhood to remarriage with those who remained married from visit 2 to visit 4. We also stratified the results by sex to explore whether sex is an effect measure moderator between marital status and cognitive decline. To account for the differential baseline age distributions among four groups and explore whether the association between marital status and cognitive decline differs by baseline age, we also stratified the results by age quartiles.

3. Results

3.1 Population Characteristics:

Table 1 showed demographic information, baseline health characteristics and cognitive performance of the study population by marital status. Of the total of 14148 participants, the median age was 56.8 years. About 75.8% were non-black, 55.6% were female, 22.3% of the participants were current smokers, while 56.6% of the participants were current drinkers. 14.9% of the participants were diagnosed with diabetes and 35.6% of the study population were diagnosed hypertension.

Compared to the other marital status categories, the married group was mostly non-black (81.4%), had more than a high school education (81.6%), was less likely to currently smoke (20.0%), and was unlikely to have diabetes (13.8%). Widowed participants on average were older (median age of 61.0), more likely to be female (87.4%), had diabetes (22.7%) or hypertension (48.2%) and less likely to be a current drinker (40.3%). Divorced/separated and never married groups presented similar characteristics in demographic and health characteristics. In terms of baseline cognitive functions, the married group exhibited better cognitive performance in four domains than other groups while the widowed group had the lowest scores across all cognitive domains.

There were 2783 participants missing at visit 4 and 7784 participants missing at visit 5. Among those 6364 subjects who attended visit 5, the median follow-up time was 20.78 years. Among 7784 participants who did not attend visit 5, 4069 participants (52.27%) had died. Those who died were more likely to be older (median age of 60.8), male (54.8%), current smokers (33.2%), had diabetes (25.4%), hypertension (48.4%), and presented lower baseline cognitive scores compared to those who are alive. Those who were alive and missed visit 5 were more likely to have education less than high school (26.9%), had diabetes (19.9%) or hypertension (42.5%) and presented lower cognitive scores compared to attendants (Table 2).

3.2 Longitudinal Analysis:

Table 3 presented estimates of annual cognitive decline among four groups, in addition to differences in cognitive decline comparing other groups to the married group across three cognitive domains and general cognitive performance.

The absolute cognitive change estimates comparing four cognitive domains suggested that annual cognitive decline in language was the lowest (some groups even showed improvement in the first six years) compared to other cognitive domains regardless of marital status. We added spline term at year six and estimated two different cognitive decline slopes over 20 years due to non-linearity in cognitive decline trajectory. Our results showed that cognitive function decline after six years following baseline was much greater than that in the first six years.

For each cognitive domain, we also estimated the annual cognitive decline difference comparing other marital categories to the married group. Negative values in Table 3 indicated faster annual cognitive decline compared to the married group. Results showed that for the first six years, the difference in cognitive decline was not consistently different from 0. The direction could be either positive or negative, with the majority showing non-significant differences, which implicated that midlife marital status may have a smaller association on cognition during midlife. Estimation of annual cognitive decline after year six showed that the widowed group had significantly worse cognitive performance than the married group across all of the four cognitive domains. The annual decline in general cognitive performance in widowed group was -0.019 [95%CI (-0.023, -0.015)] unit worse than that in the married group ($p<0.001$). Similarly, the cognitive decline difference in memory domain was -0.017 [95%CI (-0.023, -0.012)] SD units ($p<0.001$) and in language domain was -0.028 [95%CI (-0.032, -0.024)] unit ($p<0.001$). In the executive domain, the difference was -0.003 [95%CI (-0.005, -0.000)] ($p=0.023$).

For the divorced/separated group, however, the annual cognitive decline did not differ from the married group except for language, where divorced/separated group showed worse cognitive performance with a difference of -0.006 [95%CI (-0.010, -0.003)] ($p=0.001$). There were no differences between the never married group and the married group in any cognitive domain.

Our available case analysis with 13987 participants yielded similar results. The magnitude of cognitive decline was slightly smaller compared to imputed results while the results were qualitatively same and the conclusion remained consistent. The annual cognitive decline difference from 6 to 23 years comparing widowed to married groups was -0.017 [95%CI (-0.021, -0.012)] SD units in general cognitive domain, -0.0024 [95%CI (-0.0047, -0.00012)] SD units in executive domain -0.015 [95%CI (-0.022, -0.0084)] unit in memory domain and -0.026 [95%CI (-0.031, -0.021)] unit in language domain with p value less than 0.05. For the divorced or married group, the annual cognitive decline difference comparing to married group was -0.0066 [95%CI (-0.010, -0.0028)] ($p<0.001$), while the difference in other domains was non-significant (Table 4).

3.3 Sensitivity Analysis:

To minimize the influence of the marital status transition, we excluded those whose marital status changed from visit 2 to visit 4 or was missing at two visits, incorporating 10125 participants into our final analysis. Among those 10125 people whose marital status was consistent from visit 2 to visit 4, there were 8395 participants remaining married, 962 remaining divorced at both visits, 691 remaining widowed and 187 participants who were never married at both visits (Table 5). The analysis produced similar results of statistically significant cognitive decline difference comparing the widowed to married group across most cognitive domains. However, the difference in

executive domain was attenuated, showing a non-statistically significant difference of -0.0022 [95%CI (-0.0047,0.00031)] SD unit ($p=0.086$). The difference in cognitive decline comparing divorced/separated to widowed was also attenuated to -0.004 [95%CI (-0.0090,0.00038)] SD unit (p value= 0.072) (Table 6).

In a sensitivity analysis exploring the role of widowhood transition, there were 468 participants changing from being married to widowed and 50 participants transiting from widowhood to remarriage. Cognitive decline after year six was consistently steeper among those who remained widowed from visit 2 to visit 4. The general cognitive decline difference comparing those who remained widowed with those who remained married was -0.019 [95%CI (-0.024, -0.014)] while the cognitive decline difference in memory was -0.018 [95%CI (-0.025, -0.0097)] and in language domain was -0.029 [95%CI (-0.035, -0.024)] and all of the relevant $p<0.001$ (Table 7). Those participants who transited from being married to widowed, however, only presented significant cognitive decline difference in language domain of -0.0087 [95%CI (-0.015, -0.0022, $p = 0.008$)], while those who transited from widowhood to remarriage showed no statistically significant cognitive decline difference, together suggesting that consistently remaining widowed in midlife was deleterious for cognitive function in later life.

To investigate whether sex modifies the relationship between marital status and cognitive decline, we stratified the results by sex and observed similar patterns in both females and males (Table 8). The statistical test for interaction is not significant, suggesting that sex may not modify the relationship between marital status and cognitive decline. We also stratified the sample by baseline age quartile to minimize the confounding effect of older baseline age in widowed group, and to explore whether age is a moderator between marital status and cognitive decline. The results in each of the

four age strata were consistent with the primary findings, showing statistically significant differences in cognitive decline in the widowed group, which suggested that other factors other than older baseline age for widowed group could explain the greater cognitive decline for the widowed. Moreover, the relationship between marital status and cognitive decline may not differ by baseline age categories.

4. Discussion

The present study suggests that midlife widowhood is associated with increased risk of cognitive decline compared to those who are married during midlife. These findings also suggest that those who were widowed during both study visits six years apart had the steepest cognitive decline compared to those who transitioned from marriage to widowhood or from widowhood to remarriage. Potential contributing factors could be bereavement-related stress and depressive symptoms (Hughes et al., 2009), which lead to poorer health outcomes and cognitive decline.

Our study also uniquely presents domain-specific cognitive trajectories. Those who are divorced or separated showed significantly greater cognitive decline in language but not in executive or memory, which may be explained by less language stimuli due to not being with an intimate partner. However, separation or divorce may improve self-care and increase engagement in activities of daily living (ADL) or instrumental activities of daily living (IADL), which could neutralize the potential deleterious effect of divorce or separation on executive and memory function. As a result, the divorced or separated group presented non-significant difference in executive and memory domains from the married group in our study. Different from previous studies, however, our study does not

support a positive association between remaining single and greater cognitive decline. A potential contributing factor could be the heterogeneity among those who are never married: Reasons for being never married could vary and never married population in our study may differ from those in other studies. Further research is needed to investigate mechanisms for being never married and these pathways' potential impact on health and cognition.

Taken together, our study could have some encouraging public health implications. Our research suggests that dementia or cognitive impairment prevention programs could target at those individuals who are at high risk of cognitive decline such as those who remained widowed at midlife. Our study also shows that widowhood transition such as remarriage could balance out the risk of cognitive decline, implicating the potential benefits of remarriage for the widowed. Moreover, our research presents domain-specific cognitive decline effect, suggesting that future cognitive training program could adopt domain-specific cognitive training models.

Our study has several advantages. Most importantly, unlike previous research in which general cognitive performance was measured, multi-test cognitive batteries were administrated to investigate domain-specific cognitive decline, which could improve our understanding of mechanisms of cognitive impairment. Moreover, our research used a prospective cohort with a follow-up duration of 21 years, which enables us to estimate cognitive decline over a long-time period and capture the whole picture of cognitive trajectory change from midlife to later life. Finally, the external validity for our study is high since our study population include 14148 participants with diverse ethnic backgrounds from four community-based sites, which makes the study results and

conclusions generalizable. The large sample size in our study also guarantees efficiency and the ability to estimate impact of each marital status category on cognitive decline.

There are limitations regarding our study. First, there were only three time points of cognitive measurements across 21 years with a long gap between year 6 and year 21, which limits our ability to estimate a smooth, continuous and complete cognitive trajectory over 20 years. There is also sizable attrition at visit 5. However, we accounted for missing data at each visit using MICE, which strengthens our inferences to a certain extent. Another concern is that marital status could be time-varying across the 20 years and our exposure of marital status is time fixed at visit 2. To address this concern, we conducted sensitivity analyses excluding those whose marital status changed. Results remained similar. Another drawback is that our study did not take into consideration of duration or quality of marriage due to the limited information. However, there could be great heterogeneity among the married population since all marriages are not the same. Also, we did not investigate the mechanisms of increased risk of widowhood on cognitive decline due to limited information in datasets. It remains unknown whether widowhood influences cognition through bereavement related stress or depression, or other mediators. Lastly, our study shows cognitive scores differences are statistically significant but may not be clinically significant or relevant.

5. Conclusion

In conclusion, marital status plays an important role in the cognitive function and general health of older adults. Our prospective cohort study suggests that midlife widowhood could increase the risk of cognitive decline over 20 years while divorce or separation from partners could have greater cognitive decline in language domain. Future studies

ought to take the duration and quality of marriage into consideration and explore the mechanisms of increased risk of midlife widowhood on later life cognitive decline. Also, more research is needed to take into consideration other indicators for social network or social support and their effect on cognitive decline

Appendix

Table 1. ARIC participants demographic information, health characteristics and baseline cognitive functions by marital status at visit 2

Characteristics*	Categories	Total§	Married	Divorced/ Separated	Widowed	Never Married
Sample size		n=14148	n=11193	n=1601	n=1057	n=284
Age, median (IQR)		56.8 (52.0, 61.9)	56.8 (52.0, 61.8)	54.7 (50.9, 59.8)	61.0 (56.7, 64.8)	55.0 (50.9, 61.0)
Race	Black	3427 (24.2%)	2078 (18.6%)	758 (47.3%)	482 (45.6%)	105 (37.0%)
Education	Less than high school	3019 (21.4%)	2062 (18.4%)	463 (29.0%)	412 (39.0%)	77 (27.1%)
	High school, GED‡ or vocational school	5885 (41.7%)	4776 (42.7%)	608 (38.0%)	395 (37.4%)	102 (35.9%)
	College, graduate or professional school	5224 (37.0%)	4339 (38.8%)	527 (33.0%)	249 (23.6%)	105 (37.0%)
Sex	Male	6282 (44.4%)	5510 (49.2%)	530 (33.1%)	133 (12.6%)	104 (36.6%)
Smoking status	Current smoker	3158 (22.3%)	2240 (20.0%)	547 (34.2%)	288 (27.2%)	82 (28.9%)
Alcohol consumption	Current drinker	7997 (56.6%)	6560 (58.6%)	858 (53.6%)	426 (40.3%)	148 (52.1%)
Diabetes	Yes	2094 (14.9%)	1533 (13.8%)	266 (16.7%)	240 (22.7%)	54 (19.1%)
Hypertension	Yes	5027 (35.6%)	3792 (34.0%)	619 (38.7%)	507 (48.2%)	104 (36.6%)
BMI† in kg/m2, median (IQR)		27.1 (24.3, 30.7)	27.1 (24.3, 30.5)	27.3 (24.0, 31.5)	28.0 (24.2, 32.3)	27.0 (23.8, 31.4)
Cognitive function¶ mean (SD)	General cognitive function	0.00 (0.87)	0.08 (0.83)	-0.23 (0.93)	-0.41 (0.90)	-0.05 (0.94)
	Executive function	0.03 (0.52)	0.07 (0.51)	-0.11 (0.54)	-0.21 (0.51)	-0.01 (0.56)
	Memory	0.00 (0.46)	0.02 (0.45)	-0.03 (0.47)	-0.09 (0.46)	0.00 (0.45)

Language	0.00 (0.67)	0.04 (0.66)	-0.10 (0.69)	-0.21 (0.68)	-0.03 (0.70)
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Note:

Abbreviations: † BMI, Body Mass Index; ‡ GED, General Equivalency Diploma

* Sample size for each category: BMI, n=14148 (20 missing values); Hypertension, n= 14104 (44 missing values); Education, n= 14128 (20 missing values); Alcohol consumption, n= 14140 (8 missing values); Smoking status, n=14141 (7 missing values); Diabetes, n=14085 (63 missing values)

¶ Cognitive scores are measured at visit 2

§ 12 individuals are missing marital status at visit 2

Table 2. ARIC participants demographic information, health characteristics and baseline cognitive functions by vital status at visit 5

Characteristics*	Categories	Attended visit 5	Alive and didn't attend visit 5	Died by visit 5
N		6364	3715	4069
Age, median (IQR)		54.8 (50.8, 58.8)	57.8 (52.8, 61.8)	60.8 (55.8, 64.8)
Race	Black	1439 (22.6%)	843 (22.7%)	1145 (28.1%)
Education	Less than high school	928 (14.6%)	857 (23.1%)	1234 (30.4%)
	High school, GED‡ or vocational school	2662 (41.9%)	1623 (43.8%)	1600 (39.4%)
	College, graduate or professional school	2764 (43.5%)	1229 (33.1%)	1231 (30.3%)
Sex	Male	2619 (41.2%)	1435 (38.6%)	2228 (54.8%)
Smoking status	Current smoker	1030 (16.2%)	778 (20.9%)	1350 (33.2%)
Alcohol consumption	Current drinker	3869 (60.9%)	2006 (54.0%)	2122 (52.2%)

Diabetes	Yes	556 (8.8%)	511 (13.8%)	1027 (25.4%)
Hypertension	Yes	1732 (27.3%)	1334 (36.0%)	1961 (48.4%)
BMI† in kg/m2, median (IQR)		26.8 (24.1, 30.1)	27.2 (24.4, 30.9)	27.4 (24.4, 31.3)
Cognitive function¶	General cognitive function mean (SD)	0.22 (0.82)	-0.01 (0.82)	-0.33 (0.86)
	Executive function mean (SD)	0.15 (0.52)	0.02 (0.49)	-0.16 (0.49)
	Memory mean (SD)	0.08 (0.45)	0.01 (0.45)	-0.12 (0.45)
	Language mean (SD)	0.10 (0.65)	-0.02 (0.66)	-0.12 (0.68)

Note: Abbreviations: † BMI, Body Mass Index; ‡ GED, General Equivalency Diploma

* Sample size for each category: BMI, n=14148 (20 missing values); Hypertension, n= 14104 (44 missing values) ; Education, n= 14128 (20 missing values); Alcohol consumption, n= 14140 (8 missing values) ;Smoking status, n=14141 (7 missing values); Diabetes, n=14085 (63 missing values)

¶ Cognitive scores are measured at visit 2

Table 3_a Absolute annual cognitive decline and cognitive decline difference estimates by marital status for general cognitive domain ¶

cognitive performance*		general		
Marital status	Time (years)	Estimated rate of change (95% CI)	Difference in change compared to the married group (95% CI)	P-value
Married	0-6	-0.017(-0.019,-0.016)	reference	NA
	6-21	-0.051(-0.052, -0.050)	reference	NA
Divorced/ Separated	0-6	-0.013(-0.018,-.0071)	0.005(-0.002,0.012)	0.121
	6-21	-0.052(-0.055,-.0486)	-0.001(-0.003,0.002)	0.685
Widowed	0-6	-0.008(-0.015,-.0010)	0.010(0.001,0.019)	0.011
	6-21	-0.070(-0.074,-0.066)	-0.019(-0.023,-0.015)	0.000
Never Married	0-6	-0.025(-0.038,-0.012)	-0.007(-0.023,0.009)	0.261
	6-21	-0.050(-0.057,-0.043)	0.001(-0.006,0.007)	0.802

Table 3_b Absolute annual cognitive decline and cognitive decline difference estimates by marital status across three cognitive domains ¶

	cognitive performance*	executive	memory	language						
Marital status	Time (years)	Estimated rate of change (95% CI)	Difference in change compared to the married group (95% CI)	P- value	Estimated rate of change (95% CI)	Difference in change compared to the married group (95% CI)	P- value	Estimated rate of change (95% CI)	Difference in change compared to the married group (95% CI)	P- value
Married	0-6	-0.017(-0.018,-0.015)	reference	NA	0.0210 (0.019,0.023)	reference	NA	0.0027(0.0006,0.0047)	reference	NA
	6-21	-0.026(-0.026,-0.025)	reference	NA	-0.1323(-0.13,-0.13)	reference	NA	-0.0115(-0.012,-0.010)	reference	NA
Divorced/ Separated	0-6	-0.013(-0.017,-0.009)	0.003(-0.001,0.008)	0.133	0.022(0.015 ,0.029)	0.001(-0.009,0.011)	0.845	0.005(-0.001,0.011)	0.003(-0.006,0.011)	0.525
	6-21	-0.025(-0.026,-0.023)	0.001(-0.001,0.003)	0.195	-0.131(-0.136,-0.126)	0.002(-0.002,0.005)	0.570	-0.018 (-0.021,-0.014)	-0.006(-0.010,- 0.003)	0.001
Widowed	0-6	-0.013(-0.019,-0.008)	0.003(-0.002,0.009)	0.236	0.017(0.009 ,0.026)	-0.003(-0.015,0.009)	0.413	0.010(0.003 ,0.017)	0.008(-0.002,0.018)	0.059
	6-21	-0.028(-0.031,-0.026)	-0.003(-0.005,-0.000)	0.023	-0.149(-0.156,-0.142)	-0.017(-0.023,-0.012)	0.000	-0.040(-0.045,-0.035)	-0.028(-0.032,- 0.024)	0.000
Never Married	0-6	-0.018(-0.028,-0.009)	-0.001(- 0.011,0.008)	0.770	0.006(-0.010,0.022)	-0.015(-0.037,0.007)	0.072	-0.003(-0.016,0.011)	-0.004(-0.022,0.013)	0.433
	6-21	-0.024(-0.028,-0.020)	0.002(-0.002,0.006)	0.418	-0.123(-0.135,-0.111)	0.007(-0.002,0.017)	0.148	-0.017(-0.026,-0.008)	-0.006(-0.013,0.001)	0.264

Note:

¶ Model are adjusted for age, race, sex, education, hypertension, diabetes, smoking status, drinking history, BMI

* Model was applied in 25 imputed datasets with a sample size of 14148 participants

Table 4. Cognitive decline difference estimates by marital status among available cases ¶

	cognitive performance	general			executive		memory		language				
Marital status #	Time (years)	Difference in change compared to the married group (95% CI)		P-value	Difference in change compared to the married group (95% CI)		P-value	Difference in change compared to the married group (95% CI)		P- value	Difference in change compared to the married group (95% CI)		P-value
Divorced/ Separated	0-6	0.0045	(-0.0015,0.011)	0.141	0.0034	(-0.0011,0.0078)	0.137	0.0011	(-0.0064,0.0085)	0.780	0.0026	(-0.0036,0.0088)	0.411
	6-21	-0.00058	(-0.0037,0.0026)	0.716	0.0011	(-0.00062,0.0028)	0.210	0.0014	(-0.0038,0.0066)	0.601	-0.0066***	(-0.010,-0.0028)	0.001
Widowed	0-6	0.0085*	(0.0012,0.016)	0.022	0.0028	(-0.0025,0.0082)	0.304	-0.0034	(-0.012,0.0055)	0.454	0.0068	(-0.00071,0.014)	0.076
	6-21	-0.017***	(-0.021,-0.012)	0.000	-0.0024*	(-0.0047,-0.00012)	0.039	-0.015***	(-0.022,-0.0084)	0.000	-0.026***	(-0.031,-0.021)	0.000
Never Married	0-6	-0.0087	(-0.022,0.0044)	0.192	-0.0016	(-0.011,0.0081)	0.752	-0.016	(-0.032,0.00049)	0.057	-0.0061	(-0.020,0.0074)	0.374
	6-21	0.0036	(-0.0038,0.011)	0.340	0.0018	(-0.0022,0.0058)	0.385	0.012	(-0.00074,0.024)	0.065	-0.0024	(-0.011,0.0066)	0.597

Note: * p< 0.05

¶ sample size is 13987 and 7784 participants missing at visit 5 only contributed their information at visit 2 and/or visit 4

reference is the married group

* P value is less than 0.05

Table 5. Summary of marital status transition from visit 2 to visit 4 ¶

marital status at visit 4 marital status at visit2	Married	Divorced/separated	Widowed	Never Married
Married	8,395	206	468	30
Divorced/separated	133	962	73	28
Widowed	50	13	691	2
Never Married	16	6	5	187

Note ¶ sample size is 11265 , 12 participants missed marital status information at visit 2 while 2871 participants missed marital status information at visit 4

Table 6. Cognitive decline difference estimates by marital status among participants of consistent marital status ¶

	cognitive performanc e	general		executive		memory		language	
Marital statuas#	Time (years)	Difference in change compared to the married group (95% CI)	P- value	Difference in change compared to the married group (95% CI)	P- value	Difference in change compared to the married group (95% CI)	P- value	Difference in change compared to the married group (95% CI)	P- value
Divorced/ Separated	0-6	0.00097 (-0.0061,0.0081)	0.788	0.00094(-0.0043,0.0062)	0.726	-0.0037 (-0.013,0.0055)	0.429	0.0012 (-0.0063,0.0086)	0.759
	6-21	0.0013 (-0.0026,0.0052)	0.518	0.0015 (-0.00055,0.0036)	0.148	0.0035 (-0.0030,0.0100)	0.294	-0.0043 (-0.0090,0.00038)	0.072
Widowed	0-6	0.0068 (-0.00085,0.015)	0.081	0.0013 (-0.0045,0.0070)	0.664	-0.0056 (-0.015,0.0043)	0.268	0.0042 (-0.0038,0.012)	0.301
	6-21	-0.019*** (-0.024,-0.015)	0.000	-0.0022(-0.0047,0.00031)	0.086	-0.018*** (-0.025,-0.0098)	0.000	-0.029*** (-0.035,-0.024)	0.000
Never Married	0-6	-0.014* (-0.029,-0.00032)	0.045	-0.0031(-0.014,0.0074)	0.563	-0.016 (-0.034,0.0019)	0.080	-0.015 (-0.029,0.000029)	0.050
	6-21	0.0038 (-0.0045,0.012)	0.372	0.0016 (-0.0028,0.0060)	0.480	0.013 (-0.00067,0.027)	0.062	-0.00035 (-0.010,0.0097)	0.945

Note: ¶ total sample size is 10105, 2883 participants missed their marital status information and 1160 participants had changed marital status

reference group are those who remained married from visit 2 to visit 4 with a sample size of 8395

* P value is less than 0.05

Table 7. Cognitive decline difference estimates by widowhood transition status ¶

Cognitive performance #	Time (years)	general			executive			memory			language		
Marital status #	Time (years)	Difference in change compared to remaining married group (95% CI)			P-value	Difference in change compared to remaining married group (95% CI)			P-value	Difference in change compared to remaining married group (95% CI)			P-value
Remained widowed†	0-6	0.0068	(-0.00081,0.014)		0.080	0.0013	(-0.0044,0.0070)		0.662	-0.005	(-0.015,0.0043)		0.268
	6-21	-0.019***	(-0.024,-0.014)		0.000	-0.0022	(-0.0047,0.00032)		0.087	-0.018***	(-0.025,-0.0097)		0.000
Transited from marriage to widowhood ‡	0-6	-0.0052	(-0.011,0.00026)		0.062	-0.00079	(-0.0037,0.0021)		0.592	-0.0078	(-0.017,0.0011)		0.087
	6-21	0.0060	(-0.0031,0.015)		0.195	0.0017	(-0.0050,0.0085)		0.612	0.0034	(-0.0083,0.015)		0.566
Transited from widowhood to remarriage \$	0-6	0.022	(-0.0036,0.047)		0.093	0.01	(-0.0032,0.035)		0.102	-0.019	(-0.052,0.014)		0.265
	6-21	-0.013	(-0.027,0.0018)		0.086	-0.0030	(-0.011,0.0048)		0.454	-0.013	(-0.037,0.011)		0.274

Note: ¶ total sample size is 9604

† 691 participants remained widowed

‡ 468 participants transited from marriage to widowhood

\$ 50 participants transited from widowhood to remarriage

reference group are those who remained married from visit 2 to visit 4 with a sample size of 8395

* P value is less than 0.05

Table 8 General cognitive performance difference estimates stratified by sex

		Female ‡	Male †		
Marital status¶	Time (years)	Difference in general cognitive performance change compared to the married group (95% CI)	P-value	Difference in general cognitive performance change compared to the married group (95% CI)	P-value
Divorced/ Separated	0-6	0.000(-0.007,0.008)	0.961	0.010(-0.000,0.020)	0.056
	6-21	0.004* (0.000,0.008	0.034	-0.003(-0.009,0.002)	0.261
Widowed	0-6	0.005 (-0.004,0.013)	0.271	0.019 (-0.000,0.037)	0.051
	6-21	-0.013*** (-0.018,-0.009)	0.000	-0.016*(-0.029,-0.003)	0.015
Never Married	0-6	-0.017* (-0.034,-0.000)	0.047	0.006 (-0.014,0.027)	0.535
	6-21	0.006 (-0.003,0.016)	0.203	-0.004(-0.016,0.008)	0.526

Note: ¶ Reference group is being married

† ‡ Sample size is 7866 for female and 6282 for male

* P value is less than 0.05

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