THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2023, Vol. 78, No. 7, 1204–1211
https://doi.org/10.1093/gerona/glad085
Advance Access publication March 19, 2023

OXFORD

Research Article

Cognition and Mortality Risk Among Midlife and Older Americans

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Received: November 9, 2022; Editorial Decision Date: March 10, 2023

Decision Editor: Lewis A. Lipsitz , MD, FGSA

Abstract

Background: Cognitive impairment is associated with increased mortality rates in late life, but it is unclear whether worse cognition predicts working-age mortality.

Methods: The data come from a U.S. national survey (N = 3 973 aged 32–84 at cognitive testing in 2004–06, mean age 56.6, 56.3% female; N = 3 055 retested in 2013–18 at ages 42–94, mean age 64.6, 56.6% female; mortality follow-up through 2019). We use Cox hazard models to investigate whether cognition is associated with mortality below age 65, how the magnitude of this risk compares with the risk in later life, and whether the association persists after adjusting for potential confounders.

Results: Worse cognition is associated with mortality, but the demographic-adjusted hazard ratio (HR) diminishes with age from 2.0 per standard deviation (*SD*; 95% confidence interval [CI], 1.7–2.4) at age 55–1.4 (95% CI, 1.3–1.6) at age 85. In the fully adjusted model, the corresponding HRs are 1.4 (95% CI, 1.2–1.7) and 1.3 (95% CI, 1.1–1.4), respectively. The absolute differences in mortality by level of cognition, however, are larger at older ages because mortality is rare at younger ages. The fully adjusted model implies a 2.7 percentage point differential in the estimated percentage dying between ages 55 and 65 for those with low cognition (1 *SD* below the overall mean, 5.7%) versus high cognition (1 *SD* above the mean, 3.0%). The corresponding differential between ages 75 and 85 is 8.4 percentage points (24.6% vs 16.2%, respectively).

Conclusions: Cognitive function may be a valuable early warning sign of premature mortality, even at working ages, when dementia is rare.

Keywords: Cognitive function, Death, Working ages, United States

There is ample evidence that cognitive impairment and dementia are associated with increased mortality rates in late life (1–4). Despite the fact that dementia is underdiagnosed (5) and underreported as a cause of death (6,7), Alzheimer's disease (AD)—the most common cause of dementia—was the seventh leading cause of death in the United States in 2020 (8). Although recognizing that the prevalence of cognitive impairment or dementia at working ages is low, the degree to which poorer levels of cognition contribute to mortality risk below age 65 remains mostly unknown. Based on 2019 mortality rates, only 16% of the U.S. population died before age 65 (9), but those early deaths have a disproportionate effect on overall life expectancy. Increased mortality among working-age Americans was the main driver of the 3-year consecutive decline in U.S. life expectancy from 2015 to 2017 (10,11). Higher mortality at younger ages is also a major contributor to the U.S. disadvantage in life expectancy relative to other high-income countries (12). Identifying factors that represent warning signals of premature death could be a first step toward postponing those deaths and increasing overall life expectancy.

There are several reasons why midlife cognition could contribute to premature mortality. First, cognitive function is strongly associated with educational attainment and other markers of socioeconomic status (SES) (13,14), which are well-established predictors of mortality (15). Second, middle-aged adults with lower levels of cognition may also have poorer health habits, which also increases mortality

risk (15). Finally, lower cognitive function in midlife may be associated with physical health conditions such as cardiovascular disease or diabetes (16) that increase mortality rates. These variables could be confounders (ie, directly affect both cognition and mortality), in which case we should control for them to avoid interpreting a spurious relationship as causal. However, they could also represent mediators (ie, intervening factors that are influenced by cognition, and, in turn, affect mortality).

Most studies that examine the role of cognition in mortality have been restricted to older adults, typically 60 years and older, and many of these have focused primarily on cognitive impairment or dementia, rather than the full range of cognitive function (1–4). We are aware of only 2 studies that included individuals younger than age 60; those studies are based on regional samples and produced mixed results (17,18). A study of London-based civil servants aged 47–69 found that better short-term verbal memory and reasoning (fluid intelligence) were associated with lower mortality over the subsequent 7–9 years, but the relationships for vocabulary (ie, crystallized intelligence) and verbal fluency were not significant (17). The other study, based on adults aged 30–64 in Baltimore, found that a higher score on the executive function (EF)/visuospatial domain was associated with lower mortality over the following 9–14 years, but reported no significant relationship for global cognition, verbal memory/fluency, or attention/working memory (18). However, neither study evaluated whether the association between cognition and mortality varied by age. Thus, the role of the full range of cognition in predicting mortality and the extent to which that relationship may differ by age remains unclear.

In this paper, we first test whether cognition is associated with mortality in midlife (below age 65), and how the magnitude of this risk compares to the risk in later life. Second, we evaluate the degree to which the association between cognition and mortality is accounted for by other factors that are likely to be associated with both cognition and mortality, in particular, educational attainment and other measures of SES, health behaviors, and physical health. Our data include U.S. adults as young as their mid-30s, an age when there is typically little evidence of cognitive decline and mortality is low.

Method

Data

The Midlife in the United States (MIDUS) study targeted noninstitutionalized, English-speaking adults aged 25–74 in the contiguous United States (19). Details of the sampling strategy and response rates are provided in Supplementary Text 1. At Wave 1, the original cohort included 7 108 participants who completed a phone interview (fielded January 1995–September 1996), 6 325 of whom also completed a mail-in self-administered questionnaire (SAQ).

At Wave 2, 4 963 participants from the original cohort (75% of the survivors) completed a follow-up interview (fielded January 2004–August 2005) and 4 041 completed the SAQ. MIDUS also recruited a new cohort of African Americans in Milwaukee (aged 35–83), 592 (71% response rate) of whom completed an in-person interview (fielded April–October 2005), and 416 completed the SAQ. A cognitive assessment was administered for the first time in Wave 2. All those who completed the initial Wave 2 phone interview were also eligible for the cognitive testing (fielded February 2004–June 2006 in a separate phone interview).

At Wave 3, both the original and Milwaukee cohorts were recontacted for another follow-up phone interview, SAQ, and cognitive assessment. Among the original sample, 3 294 (55% of survivors) completed the main phone interview (fielded May 2013–April 2014) and 2 ,924 completed the SAQ. Among the Milwaukee sample, 389 (79% of survivors) were reinterviewed (June 2016–January 2017) and 327 completed the SAQ. Cognitive reassessments were administered during July 2013–January 2018.

We restricted our analysis to those who completed both the SAQ and cognitive assessments at Wave 2 (N = 3 973 respondents aged 32–84 at cognitive testing) and/or Wave 3 (N = 3 055 respondents aged 42–94 at cognitive testing), yielding a total of 7 028 observations. See Supplementary Table 1 for more details about the number of participants by wave of interview and study component.

Measures

Mortality

Vital status was ascertained through searches of the National Death Index, survey fieldwork, and longitudinal sample maintenance (20). To ensure the completeness of mortality follow-up, we analyzed deaths through December 31, 2019 (see Supplementary Text 2 for details). Among the analysis sample, there were 834 deaths; the youngest death occurred at age 42 and the oldest at age 97.

Given the total number of deaths in our analysis sample, we had limited statistical power to model cause-specific mortality. Nonetheless, we estimated auxiliary models for broad groups of causes (see Supplementary Text 2 for detailed ICD-10 codes): (a) cardiovascular disease (272 deaths); (b) cancers (222 deaths); (c) AD, dementia, and other nervous system diseases, the most common of which was Parkinson's (93 deaths); (d) respiratory diseases (93 deaths), and (e) a residual category of all other causes (140 deaths). The cause of death was unknown for 14 decedents, who were excluded from the cause-specific analyses.

Cognition

The Brief Test of Adult Cognition by Telephone (BTACT) was administered separately from the main phone interview. Prior confirmatory factor analyses (21) indicated that the 7 cognitive tasks represented 2 factors: episodic memory (EM), which comprised immediate and delayed recall of 15 words based on the Rey Auditory Verbal Learning Test (22,23), and EF, which included backward digit span (24), category verbal fluency (25,26), Stop and Go Switch Task (27), number series (28,29), and the 30 Seconds and Counting Task, a measure of processing speed (27). We standardized the scores for each cognitive task based on the pooled distribution across both waves. EM was computed as the average of the standardized scores for immediate and delayed word recall (Cronbach's α = 0.89), whereas EF was calculated as the average of standardized scores from the other 5 tasks (Cronbach's α = 0.71). The composite score was based on the average of the standardized scores from all 7 tasks (Cronbach's α = 0.77). The final scores were restandardized based on the pooled distribution. For the regression models, we reverse coded the scores so that higher values indicate worse cognition. Convergent and discriminant validity have been demonstrated among a subsample of individuals who were administered both the BTACT and an in-person comprehensive cognitive battery (21).

Demographic characteristics

We controlled for age, sex, and race/ethnicity in all models. Age was measured at the time of the cognitive testing. Race and ethnicity were based on self-identification and coded into the following categories: non-Hispanic White, non-Hispanic Black or African

American, non-Hispanic other race (including American Indian or Alaska Native, Asian, Native Hawaiian, or Pacific Islander), and Hispanic.

Other potential confounders

We adjusted for 3 groups of potential confounders, as outlined in the introduction: (1) SES, (2) health behaviors, and (3) physical health. With the exception of educational attainment, which was measured at baseline, these variables were time-varying covariates, measured at Wave 2 and updated at Wave 3.

The SES measures included educational attainment, current/previous occupation, income, and net wealth. Health behaviors comprised smoking history, alcohol abuse, drug abuse, and physical activity. Measures of physical health included 2 risk factors that are likely to be associated with vascular health and cognition (obesity, hypertension), 5 serious chronic conditions that are among the leading causes of death in the United States (heart trouble, stroke, cancer, diabetes, lung problems), and 2 measures of physical limitations (difficulty walking more than 1 mile and climbing several flights of stairs).

In sensitivity analyses, we also explored the results after adjusting for depression and social contact. Depression was measured by the Composite International Diagnostic Interview Short Form (CIDI-SF) subscale for major depression. For social contact, we used a variant of the Berkman–Syme Social Network Index (30). See Supplementary Text 3 for details about the measurement of potential confounders. Table 1 shows descriptive statistics by survey wave for all the covariates included in the analysis.

Analytic Strategy

We used standard practices of multiple imputations to handle missing data (31,32); see Supplementary Text 4 for details. We began by examining box plots of cognitive function by 10-year age groups. Then, we fitted Cox hazard models to test the association between cognition and mortality, using age as the time metric to estimate age-specific mortality. A robust variance estimator was used to correct for family-level clustering. Many previous studies used duration of study as the time metric with a control for age (linear) at baseline (2–4,17). Given that age is a time-varying covariate and the best predictor of mortality (33), we prefer to use age as the "clock," which allows the baseline hazard to follow any functional form over age and accounts for the aging of the respondent over the course of follow-up.

In addition to age, all models controlled for sex and race/ethnicity. In preliminary models, we confirmed that a linear specification for cognitive function yielded better model fit than nonlinear specifications (see Supplementary Text 5 and Supplementary Table 2). We tested the proportionality assumption across the predictors and found evidence that the hazard ratio (HR) varied significantly by age for the following covariates: non-Hispanic Black (relative to non-Hispanic White), occupation, diabetes, difficulty walking 1 mile, and cognition. Thus, the final models included interactions between age and those covariates.

To test whether cognition is associated with midlife mortality, we began with an initial model that restricted the follow-up to mortality before age 65. Then, using the full sample, we included an interaction between cognition and age because (as noted above) tests for nonproportional hazards indicated that the association between cognition and mortality varied by age. We also separately tested the association with mortality for the EM and EF subscores.

In subsequent models, we tested the degree to which the association between cognitive function and mortality was independent of selected groups of covariates. Potential confounders were added sequentially: SES (Model 2); health behaviors (Model 3); health risk factors and serious chronic conditions (Model 4); and physical limitations (Model 5).

Sensitivity analyses

In an auxiliary Model 6, we added depression and social integration. It is unclear whether depression and social contact represent confounders or mediators. A recent report by the Lancet Commission (34) listed depression and infrequent social contact among the key risk factors for dementia, although they acknowledged that the relationship is likely to be bidirectional. Negative affect and low quantity (structural) and quality (functional aspects) of social relationships have been also shown to predict mortality (15,35). Because all the covariates were measured at the same time, we cannot determine the temporal ordering. We added depression and social contact in a final auxiliary model to demonstrate how the coefficient for cognition changes after controlling for these potential confounders/mediators.

There can be a long lag between the measurement of cognition and the timing of death (or censorship): The lag was less than 5 years for 13% of the sample, but more than 10 years for 18% of observations (mean lag = 7.8 years, min = 0.1 years, max = 13.9 years). To explore the robustness of the results to the length of the lag, we re-estimated Models 1 and 5 limiting the follow-up to 5 years after cognition testing. To further evaluate whether the association between cognition and mortality diminishes with a longer lag, we split the mortality follow-up for each respondent into periods of less than 2, 2–4, 5–9, and 10 or more years after cognitive testing. Then, we included an interaction between cognition and the categorical measure for lag length to explicitly test whether the effect of cognition differed by lag length.

Results

The level of cognition declines with age, from a median of 0.65 for ages 35–44 to a median score of −1.18 for ages 85–94 (Figure 1). Although there is a clear inverse gradient in cognition by age group, there is also notable overlap in the distribution of cognition scores across the age groups: Some of the youngest respondents exhibit worse cognition than respondents who are decades older.

All-Cause Mortality

Models adjusted only for demographic characteristics

When follow-up is restricted to mortality before age 65, we find that the age-specific mortality rate doubles per standard deviation (*SD*) of worse cognition (HR = 2.0, 95% confidence interval [CI], 1.6–2.4) after adjustment for sex and race/ethnicity (data not shown). When the analysis is expanded to include mortality at all ages, lower cognitive function is strongly associated with mortality rates, but the significant interaction with age indicates that the HR diminishes with age (Supplementary Table 3, Model 1). Figure 2 shows that the demographic-adjusted HR associated with 1 *SD* of worse cognition declines from 2.0 (95% CI, 1.7–2.4) for mortality at ages 55–1.4 (95% CI, 1.3–1.6) at age 85.

Although the HR associated with lower cognition is higher at younger ages, the absolute differences in mortality rates may be smaller because mortality is very low at younger ages. To demonstrate this difference between relative (ie, HRs) and absolute

Table 1. Descriptive Statistics for Covariates by Survey Wave

	Wave 2	Wave 3
Age at cognitive testing (32–94), mean (*SD*)	56.6 (12.3)	64.6 (11.0)
Female, %	56.3	56.6
Race/ethnicity		
Non-Hispanic White, %	85.2	82.6
Non-Hispanic Black, %	9.8	12.9
Non-Hispanic Other race, %	2.4	1.9
Hispanic, %	2.6	2.6
Education (1–12), mean (*SD*)	7.2 (2.6)	7.3 (2.5)
Current/previous occupation		
Never employed, %	0.3	0.3
Manual, %	19.0	16.2
Service/sales/clerical, %	36.8	36.8
Management/business/financial, %	20.6	20.9
Professional, %	23.3	25.8
Income (0–2 382),* mean (*SD*)	70.3 (73.5)	72.6 (81.7)
Net wealth (–406 to 2 417),* mean (*SD*)	413.9 (680.0)	494.6 (760.8)
Smoking history		
Never smoked, %	50.8	54.0
Former smoker, %	34.3	36.0
Current smoker, %	14.9	10.0
Any alcohol abuse, %	4.2	4.9
Any drug abuse, %	5.3	5.3
Index of moderate/vigorous physical activity (0–5), mean (*SD*)	2.1 (1.3)	2.2 (1.4)
Body mass index		
<18.5, %	1.0	1.5
18.5–24.9, %	30.3	28.8
25–29.9, %	38.8	36.8
30–34.9, %	18.2	19.2
35+, %	11.7	13.7
High blood pressure in the past 12 months, %	32.1	41.1
Ever had heart trouble, %	18.4	22.5
Ever had stroke, %	3.2	4.8
Ever had cancer, %	13.7	19.9
Diabetes in the past 12 months, %	10.7	16.2
Lung problems in past 12 months, %	13.5	14.7
Difficulty walking 1 mile		
None, %	58.4	48.4
A little, %	16.9	19.3
Some, %	9.5	10.5
A lot, %	15.1	21.8
Difficulty climbing stairs		
None, %	57.6	49.7
A little, %	21.3	24.4
Some, %	9.1	10.2
A lot, %	12.0	15.7
CIDI-SF major depression subscale (0–7), mean (*SD*)	0.6 (1.7)	0.6 (1.7)
Social network index (0–4), mean (*SD*)	2.5 (1.1)	2.3 (1.1)
Cognitive function, reverse coded (–3.3 to 5.2), mean (*SD*)†	–0.1 (1.0)	0.1 (1.0)
Number of respondents	3 973	3 055

Notes: CIDI-SF = Composite International Diagnostic Interview Short Form; *SD* = standard deviation.

*Expressed in thousands of 2019 dollars.

†Standardized (based on the pooled distribution of observations from both waves) and reverse coded (so higher values indicate worse function).

differences in mortality, we translate the estimated mortality rates based on Model 1 into the percentage expected to die within selected age intervals for 3 levels of cognition: low (1 *SD* below the overall mean), medium (overall mean), and high (1 *SD* above the mean; Figure 3). Our estimates imply that 9.6% of those with low cognition are expected to die between ages 55 and 65 versus 2.8% of those with high cognition, a difference of 6.8 percentage points. The estimated percentages of dying between ages 65 and 75 and between ages 75 and 85 are much higher. For example, we estimate that 32.5% of those with low cognition die between ages 75 and 85 versus 16.1% of those with high cognition, which represents a differential of 16.4 percentage points. Thus, although the relative risk of dying associated with worse cognition is smaller at older ages, the absolute differences in the estimated probability of dying between those with low versus high cognition are much larger at older ages.

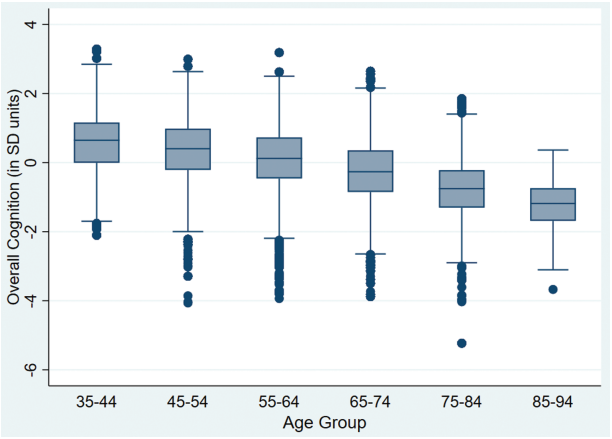

Figure 1. Box plot of cognitive function by age group. The box is defined by the 25th(P_{25}), 50th, and 75th (P_{75}) percentiles, representing the interquartile range ($IQR = P_{75} - P_{25}$). The whiskers indicate the upper ($P_{75} + 1.5 \times IQR$) and lower adjacent values ($P_{25} - 1.5 \times IQR$). The solid circles denote outliers (ie, above/below the upper/lower adjacent values). The ages at the time of cognitive testing ranged from 32 to 94, but we did not graph the values for those aged 32–34 because of small sample size (n = 17 respondents). The oldest age group should also be interpreted with caution because it comprises only 136 respondents, only 39 of whom were aged 90–94. *SD* = standard deviation.

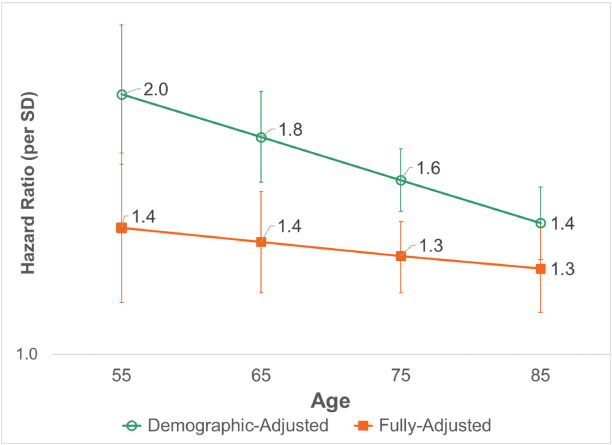

Figure 2. Hazard ratios (HRs) for worse cognitive function by age. Cognitive function is reverse coded (ie, higher values indicate worse cognition). The HRs indicate the relative increase in mortality rates associated with 1 *SD* worse cognitive function and are plotted on the log scale. The demographic-adjusted HRs are based on Model 1, whereas the fully adjusted HRs are based on Model 5 (Supplementary Table 3). The error bars represent the 95% confidence intervals. We do not show the HRs for mortality below age 55 (because only 4% of decedents died below that age). *SD* = standard deviation.

Women exhibit lower mortality rates than men (Supplementary Table 3), which is consistent with sex differences in mortality at the national level. Compared with non-Hispanic Whites, mortality rates are significantly higher for non-Hispanics of other (not White or Black) races even after controlling for cognitive function. The HR for non-Hispanic Blacks is in the same direction, but it is not significant, in part because cognitive function accounts for a large share of the Black–White differential in mortality. In a model that does not control for cognition (data not shown), the mortality rate is highest for non-Hispanic Blacks (HR = 2.85, 95% CI, 1.87–4.35, relative

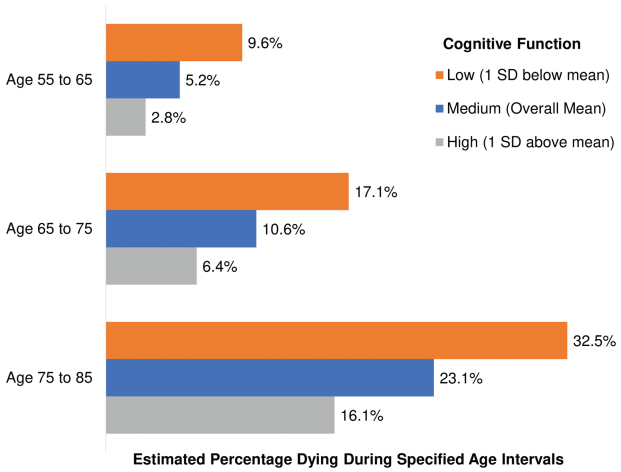

Figure 3. Estimated percentage dying during age intervals 55–65, 65–75, and 75–85 for selected levels of cognition, demographic-adjusted. Estimates are based on Model 1 (Supplementary Table 3) where cognition is set to the specified value and all other covariates (ie, sex and race/ethnicity) are fixed at the sample mean. *SD* = standard deviation.

to non-Hispanic Whites) followed by non-Hispanics of other races (HR = 1.85, 95% CI, 1.27–2.70).

Models adjusted for potential confounders

Adjusting for SES substantially weakens the association between cognition and mortality: For age 55, the HR is reduced from 2.0 (95% CI, 1.7–2.4) in Model 1 to 1.7 (95% CI, 1.4–2.1) in Model 2 (Supplementary Table 3). As expected, those with better educational attainment, higher occupational status (eg, those working in professional occupations exhibit the lowest mortality whereas manual workers and those who have never been employed have the highest mortality), and greater wealth are associated with lower mortality, although household income is not significant after adjusting for the other covariates.

Additional controls for health behaviors further attenuate the association only slightly (Model 3, HR = 1.65, 95% CI, 1.3–2.0 at age 55). The association between cognition and mortality is weakened somewhat further after adjusting for health risk factors and chronic conditions (Model 4, HR = 1.5, 95% CI, 1.2–1.8 at age 55). Finally, adjustment for physical function has little effect on the association between cognition and mortality (Model 5, HR = 1.4, 95% CI, 1.2–1.7 at age 55).

The association between cognition and mortality remains significant even after adjusting for all the potential confounders included in our analysis. The fully adjusted HR is 1.4 (95% CI, 1.2–1.7) for mortality at age 55 and 1.3 (95% CI, 1.1–1.4) by age 85 (Figure 2). When translated into the estimated percentage dying within specified age intervals (Figure 4), there are still notable mortality differentials by cognition, although they are much smaller than in the models adjusted only for demographic characteristics. Based on the fully adjusted models, the estimated percentage expected to die between ages 55 and 65 for those with low (5.7%) versus high (3.0%) cognition differs by 2.7 percentage points. Between ages 75 and 85, the corresponding differential is 8.4 percentage points (24.6% vs 16.2%, respectively).

Sensitivity analyses

When tested separately, the effect size for the 2 cognitive subscores is similar (Supplementary Table 4), but slightly weaker than for overall

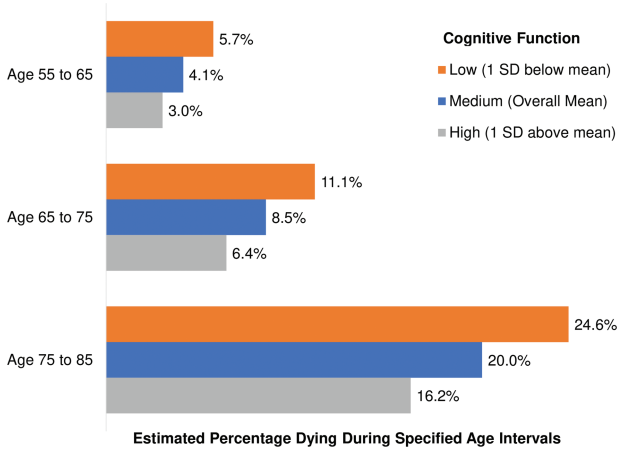

Figure 4. Estimated percentage dying during age intervals 55–65, 65–75, and 75–85 for selected levels of cognition, fully adjusted. Estimates are based on Model 5 (Supplementary Table 3) where cognition is set to the specified value and all other covariates are fixed at the sample mean. *SD* = standard deviation.

cognition (Supplementary Table 3). Further adjustment for social contact and depression has virtually no effect on the association between cognition and mortality (Supplementary Table 3, Model 6, HR = 1.4 at age 55, 95% CI, 1.1–1.7). Limiting the follow-up to 5 years after the measurement of cognitive function also has a negligible effect on its HR. Furthermore, the association between cognition and mortality does not differ significantly by the length of time since cognitive testing (<2, 2–4, 5–9, and 10 or more years). This result suggests that cognition remains a valuable predictor of mortality even more than a decade later.

Cause-Specific Mortality

In auxiliary analyses, we investigate the association between cognition and mortality from broad causes of death. In fully adjusted models (Supplementary Table 5), lower cognition is most strongly associated with mortality from AD, dementia, and other nervous system diseases (HR = 2.4, 95% CI, 1.8–3.2). There was also a strong association with the residual category of causes, although the effect diminished with age: The HR was 2.1 (95% CI, 1.4–3.0) at age 55, but much smaller and only marginally significant by age 75 (HR = 1.2, 95% CI, 1.0–1.5). The associations with mortality from cardiovascular disease, cancer, and respiratory diseases were weak and did not reach statistical significance.

Discussion

Our results demonstrate that worse cognition is associated with mortality throughout midlife and late life. In fact, the HR associated with cognitive function is even stronger in midlife than in late life. The association weakens after adjusting for relevant control variables, but the association remains substantial and statistically significant. The finding that cognition continues to have prognostic value for mortality more than a decade later suggests that it could help identify individuals early in the trajectory leading to premature death, even at working ages when dementia is rare.

The reasons for the association between low cognitive function and mortality, especially premature mortality, remain incompletely understood. Among older adults, low cognition may reflect a decline from higher levels of cognitive function earlier in life and could be a clinical manifestation of neurodegenerative or cerebrovascular disease processes that are known to increase mortality risk. In midlife, the decline in cognition relative to the level in early adulthood is likely to be much smaller, and at these younger ages, clinical symptoms of neurodegenerative, cerebrovascular, or other chronic diseases are much less prevalent. Yet, we find that worse cognition is associated with higher mortality even at younger ages and despite extensive controls for potential confounders including SES, health behaviors, and measures of physical health.

Several other factors may have contributed to the increased risk of premature mortality among persons with worse cognition. As suggested by Zhu and Liao (2), poorer self-care is a potential mechanism through which cognition could affect mortality. Individuals with lower cognitive function may be more prone to medication mismanagement and have more difficulty managing chronic illnesses. For example, diabetic patients who are unable to effectively control their glucose levels can suffer damage to their blood vessels, nerves (neuropathy), and kidneys (nephropathy). Lower levels of cognition may also reduce one's capacity to recognize and seek timely treatment for infections (eg, pneumonia and urinary tract infections) or other health problems. Poor cognition may also compromise the ability to maintain adequate nutrition and hydration, which can have serious health consequences. Another possible mechanism linking lower cognition with higher mortality rates is increased susceptibility to accidents and falls (2). External causes accounted for the largest share (25%) of deaths in the residual category, but there were still too few deaths from falls and other accidents (N = 19) to model that cause separately. Finally, the quality of caregiver support may be worse for individuals with cognitive impairment because they are more vulnerable to abuse (36) or because their caregivers are more overburdened than other caregivers (37).

One strength of this study is the availability of data from a large, diverse sample of both middle-aged and older adults with long-term mortality follow-up. Additional strengths include the use of a validated cognitive assessment and extensive information on potential confounders.

An important limitation of this study is the inability to determine whether the association with cognition reflects a causal process or whether cognitive function is merely a marker of other unobserved factors. Our analyses of cause-specific mortality revealed that the association was strongest for mortality from AD, dementia, and other nervous system diseases. However, lower cognition was also strongly associated with mortality from a residual category of all other causes. That association may be because our measures of morbidity (eg, heart problems, stroke, diabetes, cancer, lung problems) were strong predictors of more specific causes of death (ie, cardiovascular disease, cancer, respiratory diseases), but did not fully capture the underlying health conditions that led to death from the heterogeneous set of causes in the residual category. The reported underlying cause of death for people suffering from dementia is often only indirectly related to cognition (eg, pneumonia, sepsis, and blot clots) (38,39). For example, dysphagia (ie, difficulty swallowing) is common among persons with dementia and can cause aspiration pneumonia (40). A recent meta-analysis concluded that the risk of pneumonia-associated death was twice as high for people with dementia than those without dementia (41).

The second weakness is a long interval (~9 years) between follow-up waves, which may have contributed to attrition and nonresponse for the repeat assessment of cognitive function and confounder variables. Third, our ability to model cause-specific mortality is also limited by the number of deaths in our sample. Fourth,

some of our potential confounders could also be mediators. For example, poor cognitive development during childhood could lead to lower SES throughout midlife and to the adoption of unhealthy behaviors, which, in turn, affect the level of cognition in midlife and other health outcomes including mortality. If we had early life measures of cognition and more frequent follow-ups, we might be able to establish the temporal ordering of educational attainment and other components of SES, health behaviors, incident morbidity, and changes in cognition. Fifth, the MIDUS sample is predominantly White; the replication of these results using more diverse samples would be valuable, particularly for understanding the extent to which the results may vary by race and ethnicity. Sixth, some variables have a lot of missing data. For example, 39% were missing data for household income owing to the complexity of the questions used to capture the variety of income sources from all household members. The proportion of missing data was lower for wages/salary of the respondent (<15%) and spouse/partner (<10%), but higher for other income sources, especially for other family members in the household. In the multiple imputation process, we used a wide array of auxiliary variables in the prediction equations to impute missing data (see Supplementary Text 4). Finally, our measure of cognition (BTACT) has not been used in any other nationally representative sample of the United States that could be used as a comparison to gauge the normative performance of the MIDUS sample relative to the U.S. population as a whole. Nor do we have any gold standard with which to compare scores on the BTACT to determine a cutoff indicating cognitive impairment. DiBlasio et al. (42) state that (p. E238), "the BTACT is a brief cognitive assessment tool and has not been validated for clinical use or diagnosis."

Conclusion

Given that many adults living with dementia have not been formally diagnosed (5), cognitive function may be a valuable early warning sign of premature mortality. Poor cognition in midlife may have prognostic value for mortality risk, even if death does not occur until many years later. At working ages, a diagnosis of dementia is unlikely and mortality is rare, but poor cognition could be a harbinger of adverse outcomes that may not become evident until much later.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This work was supported by the National Institute on Aging (P01 AG020166, U19AG051426, R00AG052458). The study was also supported by funding from the Graduate School of Arts and Sciences, Georgetown University. The funders played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of Interest

None declared.

Acknowledgments

We are grateful to the staff and participants of the Midlife in the United States study for their vital contributions.

Author Contributions

D.A.G. led the study, designed the methodology, conducted the statistical analysis, wrote the original draft of the manuscript, and created the data visualizations. C.F.M.L., C.L., and M.W. helped edit and critically revise the manuscript. M.W. helped secure funding support and served as the project administrator. All authors contributed to the conceptualization of the study and approved the final version.

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