HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Psychosom Med. 2023 April 01; 85(3): 231–237. doi:10.1097/PSY.0000000000001168.

Race and APOE-e4 Status Differences in the Association between Loneliness and Cognitive Decline

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Abstract

Objective: To examine race and APOE-e4 status differences in the longitudinal associations between loneliness and cognitive decline.

Methods: The study sample is comprised of participants (N=7,696, 64% Black participants and 36% White participants) from the Chicago Health and Aging Project, a population-based cohort study. Mixed effects regression models were conducted to examine the longitudinal associations between loneliness on global cognitive function and individual tests of cognitive function. Models were also stratified by race and APOE-e4.

Results: A greater percentage of Black participants (17%) reported loneliness at baseline visit compared to White participants (12%). Black and White participants who were lonely individuals had a similar rate of decline in global cognitive function at 0.075 (95% Confidence Interval (CI) = −0.082, −0.068) standard deviation unit (SDU) per year for Black participants and at 0.075 (95% CI = −0.086, −0.063) SDU per year for White participants. Lonely participants with APOE-e4 had a higher rate of global cognitive decline at −0.102 (95% CI = −0.115, −0.088) SDU per year than for lonely participants without APOE-e4 at −0.052 (95% CI = −0.059, −0.045) SDU per year.

Conclusions: The burden of loneliness and its relation to cognitive decline is higher among participants with APOE-e4, compared to those without APOE-e4. Loneliness is associated with cognitive decline in both Black and White participants.

Keywords

cognitive decline; Alzheimer's disease; loneliness; APOE-e4; race differences; cognitive function

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There are no conflicts of interest to disclose other than NIH funds received by some co-authors.

Introduction

An estimated 30 to 43% of U.S. older adults are lonely.[1–4] Loneliness is defined as a feeling or perception of social isolation and/or experiencing a negative feeling due to a difference in actual compared to expected need for relationships.[1, 3,5] We found thirteen studies that have longitudinally examined loneliness and cognitive decline in older adults.[6–24] These studies did not focus on examining race differences.[6–24] Seven studies showed that loneliness was associated with increased rate of cognitive decline or risk of dementia.[6–12, 15, 17–18, 21–24] However, six studies did not.[13–14, 16, 19–21] We are aware of only one longitudinal study of loneliness and cognition in Black participants. This study used data from the U.S. Census Bureau to evaluate associations between loneliness and semantic memory and found that increased loneliness was associated with improved performance in semantic memory.[19] Thus, it is uncertain whether loneliness is associated with cognitive decline in Black persons. It is important to identify and better understand modifiable factors, such as loneliness, to reduce AD risk, especially among Black older adults, who experience a prevalence of AD that is two times greater than White older adults.[25] Interventions that incorporate cognitive behavioral therapy (CBT) or aspects of it are beneficial to combat loneliness.[26] However, we were unable to find previous research which evaluated the effectiveness of strategies to reduce loneliness by race. Examining the variability in feelings of loneliness in older adults may point to intervention targets to reduce both AD prevalence and AD disparities, given that loneliness is a risk factor for AD.[6–12, 15, 17–18, 21–24, 27]

There are several potential mechanisms by which loneliness may contribute to cognitive decline and development of AD. The loneliness model indicates that lonely individuals view social interactions negatively, and persons who interact with lonely individuals substantiate expectations, resulting in lonely individuals distancing themselves socially. The feelings associated with this process initiate mechanisms that are both behavioral and neurobiological, which in turn, result in poor outcomes, such as cognitive decline or AD. These mechanisms pertain to health behaviors, sleep, and physiological functioning. Loneliness may minimize the ability to self-regulate and manage health behaviors, as well as the restorative aspects of sleep. Further, loneliness may be associated with neuroendocrine sequel. Feeling lonely is related to an increase in total peripheral resistance which is associated with greater systolic blood pressure. Loneliness also seems to worsen immune function and cellular immunity. Gene transcription can vary by loneliness status. Lonely individuals may be more likely to have markers of inhibition of cell cycle and inflammatory processes.[28] More research is needed to better understand the interplay between social and biological characteristics and their impact on cognitive decline or impairment. Loneliness has been linked with cortical burden in amyloid among older adults that are cognitively normal.[29] It is associated with increased tau pathology in the right entorhinal cortex, suggesting that loneliness may be a symptom that occurs during the pre-clinical course of AD.[30] A review conducted by Lam and colleagues (2021) evaluated (N=41) neurobiological studies of loneliness.[31] They found loneliness to be related to factors such as structural abnormalities with gray or white matter, irregular activities in various brain regions including the amygdala, prefrontal cortex, posterior superior temporal cortex, insula, and hippocampus, and variability in networks of activation in attention, visual, and default mode.

The directionality and temporal sequence of changes in the brain related to loneliness and AD requires more specificity. The social environment is important to account for when assessing well-being that is cognitive, and loneliness can moderate the relationship between APOE-e4 and cognitive functioning.[32]

In the present study, we examine the association of loneliness with change in cognitive function across18 years of observation among older, Black and White residents of a geographically defined urban community. Secondly, we evaluate the relationships between loneliness and APOE-e4 status and cognitive decline in the same cohort. We test the hypothesis that loneliness is associated with more rapid cognitive decline in Black participants and White participants. We expect that among participants with APOE-e4, loneliness contributes to more rapid cognitive decline than those who do not report loneliness. We also hypothesize that the association between loneliness and global cognitive decline differs between Black and White participants, stratified by APOE-e4. Among participants with and without APOE-e4, Black participants will experience faster cognitive decline than White participants.

Methods

Participants

Participants in the Chicago Health and Aging Project (CHAP) were 10,082 older residents (age 65 years or older at enrollment) of four adjacent neighborhoods on the south side of Chicago. Eligibility for the current analyses required completion of the baseline visit interview and at least one of five follow-up interviews, which occurred at 3-year intervals. Analyses were conducted with data collected from 7,696 participants (76%). Of the remaining 3,106 participants, a total of 1,732 persons died before the first follow-up assessment; 284 could not be followed because their baseline visit assessment was in the final cycle of the study; 136 had missing data; and 954 were lost to follow up for other reasons.

Study Design and Procedures

CHAP is a population-based cohort study. Participants were recruited through door-to-door census. Data was collected from 1993–2012 in three-year cycles. Participants completed in-home interviews. Cognition was assessed with a battery of brief tests. Clinical evaluations were completed with a randomly selected sample that was stratified.[33] Requests for data, code/scripts, and other materials will be reviewed on a case-by-case basis. CHAP is approved by the Rush University Medical Center Institutional Review Board. Participants were consented to take part in the study.

Measures

Loneliness—Loneliness was measured using a single item from the modified version of the Center for Epidemiologic Studies-Depression (CESD) Scale: *I felt lonely*. For each item, the scale asks: *Have you felt this way much of the time during the past week?* with *1=Yes and 2=No*.[34–36]

Demographics—Demographic information including date of birth/age, sex, race, and education level was obtained from participant self-report.

Apolipoprotein E (APOE)—The hME Sequenom MassARRAY platform was used to measure APOE genotype by the Broad Institute for Population Genetics. The APOE-e4 variable was categorized as any e4-allele versus none.

Cognitive Function—Global cognitive function and individual tests were conducted during in-home interviews. Global cognitive function was assessed using the East Boston Tests of Immediate Memory and Delayed Recall, which measures episodic memory, the Symbol Digit Modalities Test (modified, oral version), which measures perceptual speed, and the Mini-Mental State Examination (MMSE).[37–40] The z-score for each test was determined utilizing means and standard deviations at baseline visit for the total CHAP sample. Z-scores of the tests were then averaged to obtain global cognitive function.[41] Our primary outcome is global cognitive function and secondary outcomes include episodic memory and perceptual speed.

Data Analyses

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive analysis was conducted on the baseline visit sample data, in total and categorized by race and by loneliness status. Separate mixed effects linear regression models tested the interactions of loneliness with race and time and with APOE-e4 and time on global cognitive function. Additional models were conducted to evaluate the associations between loneliness and global cognitive function and individual tests for episodic memory and perceptual speed over time, by race and by APOE-e4. Race stratified models adjusted for age, sex, education, and time, and interactions with time for each demographic characteristic. APOE-e4 stratified models adjusted for age, sex, race, education, and time and interactions with time for each demographic characteristic. Further, mixed effects linear regression models were conducted to examine the relationship between race and loneliness on global cognitive decline, stratified by APOE-e4 status (yes versus no). These models additionally adjusted for age, sex, education, and time, and interactions with time for each demographic characteristic. The estimates of cognitive decline per group were based on mixed effects linear regression models. The estimates for loneliness assume that the other covariates are set to zero. Age and education are centered at 75 years and 12 years. Sex and race variables are categorical.

Results

Table 1 describes the baseline visit characteristics in all participants and stratified by race and by loneliness. In our sample, 15% of participants reported loneliness. A greater percent of Black participants (17%) were lonely at baseline visit compared to White participants (12%) ($p < .001$). Black participants were also on average three years younger than White participants ($p < .001$). The frequency of women (62%) did not differ between Black and White participants. Black participants had an average of 12 years of education, whereas, the average for White participants was 14 years. White participants had higher cognitive

function scores at baseline visit compared to Black participants. More participants who reported being lonely at baseline visit were female, African American, older, had lesser education, APOE-e4, and lower cognitive function scores than those who were not lonely.

The models testing the interactions of loneliness with race and time and loneliness with APOE-e4 and time on global cognitive decline were not statistically significant. We conducted models which were stratified by race and sex. Results consistently showed statistically significant associations between loneliness and each outcome, among Black men and women but not among White men and women.

Table 2 describes longitudinal associations between loneliness and decline in global cognition, episodic memory, and perceptual speed, stratified by race. Black participants who were lonely had a rate of decline at −0.075 (95% Confidence Interval (CI) = −0.082, −0.068) standard deviation unit(s) (SDU) per year for global cognition, compared to Black participants who were not lonely who had a rate of −0.060 (95% CI= −0.064, −0.056) SDU per year. Lonely White participants had a rate of global cognitive decline at −0.075 (95% CI = −0.086, −0.063) SDU per year, as opposed −0.071 (95% CI = −0.076, −0.065) SDU per year for non-lonely White participants. To determine whether loneliness was related to decline in some forms of cognition but not others, we conducted similar analyses of change in episodic memory and perceptual speed. Black participants who were lonely had a rate of decline in episodic memory at −0.058 (95% CI= −0.067, −0.050) SDU per year and in perceptual speed at −0.055 (95% CI= −0.062, −0.049) SDU per year, compared to non-lonely Black participants with a rate of −0.044 (95% CI= −0.049, −0.039) SDU per year and −.049 (95% CI= −0.053, −0.045) SDU per year, respectively. Lonely White participants had a rate of decline that was −0.057 (95% CI = −0.070, −0.044) SDU per year for episodic memory and −0.075 (95% CI = −0.087, −0.064) SDU per year for perceptual speed, as opposed to non-lonely White participants who had a rate of decline at −0.048 (95% CI = −0.054, −0.042) SDU per year for episodic memory and −0.076 (95% CI = −0.082, −0.071) SDU per year for perceptual speed.

Figure S1 (Supplemental Digital Content) illustrates the change in global cognitive function over years in the study among lonely versus non-lonely participants by race and is based on the regression models. The figure shows that Black participants have a lower baseline visit cognitive function score than White participants. The rate of global cognitive decline is similar in Whites who are lonely and not lonely. Black participants who were lonely had a faster rate of cognitive decline over time than Black participants who were not lonely.

Table 3 shows longitudinal associations between loneliness and global cognitive decline and decline in episodic memory and perceptual speed, stratified by APOE-e4 status. Among participants with APOE-e4, those who were lonely had a rate of decline in global cognitive function at −0.102 (95% CI = −0.115, −0.088) SDU per year versus participants who were not lonely with a rate of −0.084 (95% CI= −0.094, −0.074) SDU per year. For participants with no APOE-e4, the rate of global cognitive decline for individuals who were lonely was −0.052 (95% CI = −0.059, −0.045) SDU per year compared to those who were not lonely who had a rate of −0.044 (95% CI = −0.049, −0.040) SDU per year. Participants with APOE-e4 who were lonely had a rate of decline in episodic memory at −0.084 (95%

CI = −0.101, −0.067) SDU per year and perceptual speed at −0.091 (95% CI= −0.104, −0.781) SDU per year, compared to participants with APOEe4 who were not lonely who had a rate of decline in episodic memory at −0.067 (95% CI = −0.079, −0.055) SDU per year and in perceptual speed at −0.078 (95% CI = −0.087, −0.070) SDU per year. Figure S2 (Supplemental Digital Content) depicts annual global cognitive decline among lonely and non-lonely individuals, with and without APOE-e4. Lonely individuals with APOE-e4 had the most pronounced decline of all four groups. Among participants with APOE-e4, lonely individuals had a quicker rate of decline than individuals who were not lonely. Similarly, for those without APOE-e4, participants who were lonely had a steeper decline in the figure than participants who were not lonely.

Table 4 shows the longitudinal associations between the interaction of loneliness and race on global cognitive function, stratified by APOE-e4 status. Among participants with APOE-e4, Black participants who were lonely had a rate of decline at −.091 (95% CI = −.105, −.078) SDU per year compared to White participants who were lonely who had a rate of decline at .114 (95% CI = −.138, −.089) SDU per year. For participants without APOE-e4, Black participants who were lonely had a rate of decline at −.058 (95% CI = −.105, −.078) SDU per year, as opposed to White participants who were lonely who had a rate of decline at −.045 (95% CI = −.138, −.089) SDU per year.

Figure S3 (Supplemental Digital Content) shows the yearly change in global cognitive decline among participants with APOE-e4. Black participants and White participants who were lonely have the steepest decline compared to Black and White participants who were not lonely.

Discussion

Loneliness was more prevalent in Black participants than White participants at baseline visit. Among Black and White participants, individuals who were lonely had a quicker rate of decline in global cognitive function, episodic memory, and perceptual speed than individuals who were not lonely. Among participants with APOE-e4, lonely individuals had faster rates of decline in global cognitive function, episodic memory, and perceptual speed, in contrast to those who were not lonely. White participants with APOE-e4 had a faster rate of decline than Black participants with APOE-e4. Whereas, Black participants without APOE-e4 had a quicker rate of global cognitive decline than White participants without APOE-e4.

Little is known about the role of race in the relationship between loneliness and cognitive decline. Although studies which examine cognitive decline as an outcome often adjust for APOE-e4, we were unable to find a longitudinal study which focused on the association between loneliness and cognitive decline, stratified by APOE-e4 status. Results of previous studies examining associations between loneliness and cognitive decline have been mixed. Prior U.S. research in this area has been conducted with predominantly White groups of older persons and/or evaluation of race differences has not been given enough emphasis. Our findings contribute to addressing these gaps by evaluating the associations between loneliness and cognitive decline in a large sample of Black and White participants over time.

Implications

Our findings suggest that loneliness negatively impacts Black and White participants' cognitive function over time and loneliness is related to a faster rate of cognitive decline among participants with APOE-e4, compared to those without APOE-e4. Loneliness may be modifiable and intervening on loneliness may result in decreasing rate of cognitive decline. It is critical to understand the causal pathways between loneliness and cognitive decline and screen for loneliness in order to effectively intervene.[42, 43] Several interventions exist to combat loneliness. However, the quality of findings is not strong, and limited information exists regarding the effectiveness of methods to intervene on loneliness.[44] It is important to evaluate the types of interventions which benefit population subgroups of older adults.[45] Potential methods to reduce loneliness include: using public health messages to promote social connectedness, leveraging resources and networks in the community and among family members, utilizing technology, and implementing strategies in health care which target and treat loneliness.[46] Implementing strategies for changing *maladaptive social cognition*, that promote communication, are in the community, and that have an educational component have promise for success.[26, 44, 47] Race and APOE-e4 are important to consider when evaluating risk of loneliness and developing interventions to combat loneliness. More research is needed to understand the impact of tailored intervention strategies for slowing rate of cognitive decline in older adults.

Additional research is needed to increase understanding of mechanisms underlying loneliness and negative health outcomes such as cognitive decline.[48] For instance, there is limited information related to mechanisms that are molecular and their influence on associations between loneliness and poor health outcomes. Focusing on certain gene sets may provide opportunity for positive impact.[49] Animal and human mechanistic studies related to loneliness have occurred separately. There may be important questions answered related to underlying mechanisms of loneliness through synthesizing findings.[50]

Study results indicate that APOE-e4 may not be as detrimental to Black participants as White participants. This finding may be unwarranted because the interactions between loneliness, race, and time and loneliness, APOE-e4, and time were not statistically significant. However, perhaps these results suggest that Black race as a social construct represents resiliency, which dampens the effect of APOE-e4. While APOE-e4 has long been established as a risk factor for AD, most of this research is with White populations. The Healthy Aging in Neighborhoods of Diversity across the Life Span study found an association between APOE-e4 and decline in verbal memory for White participants but not Black participants.[51] This finding aligns with ours. More research needs to be done to evaluate race differences in the associations between APOE-e4 and cognitive decline.

Limitations

Only one item to measure loneliness was available and used to conduct this analysis. A single item will not capture the different dimensions of loneliness. Future research should examine loneliness, using more robust measurement, with the addition of items, including ways to distinguish between acute versus chronic loneliness.[26] Only two racial groups from a selected area of the U.S. made up the study sample. There is a possibility that loneliness

may be under-reported, given feelings of stigma.[52] We did not find statistically significant associations when testing the interaction of loneliness with race and time and of loneliness with APOE-e4 and time on global cognitive decline. The reasons for this are unclear but could be because loneliness is a strong enough predictor of decline in global cognitive function, irrespective of race or APOE-e4. Loneliness and depressive symptoms have a strong correlation of .63. Therefore, we did not include depressive symptoms in our models due to concerns regarding collinearity. Although depression and loneliness are two separate concepts, they are related. Our study examined APOE-e4 only and not other haplotypes, such as APOE-e2 or APOE-e3. Previous research indicates that APOE-e2 decreases AD risk compared to APOE-e3.[53] More research should be conducted to examine race differences in the relationship between APOE-e2 and cognitive function.

Strengths

This study includes multiple measurement points over time among a large, bi-racial population-based sample. A unique contribution of this study is its large proportion of Black participants, who are unduly burdened by AD, and therefore, are of particular interest in terms of modifiable AD risk factors such as loneliness. Loneliness was associated with cognitive decline among Black and among White participants, and this finding supports the generalizability of loneliness as an important modifiable risk factor on which to intervene.

Loneliness is a public health issue in itself,[54] and the coronavirus disease 2019 (COVID-19) pandemic will result in long-term, negative consequences, with the exacerbation of loneliness being one them. It is critical, now more than ever, to develop feasible, accessible, and creative strategies for minimizing loneliness and the potential for subsequent, poor outcomes.[43, 46]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work is supported by NIH grant numbers: R01AG051635, RF1AG057532, R01AG073627, and R01AG058679. We thank the study participants, Chicago communities that participated, and the study team.

Abbreviations:

AD	Alzheimer’s disease
APOE-e4	Apolipoprotein E - e4 allele
CESD	Center for Epidemiologic Studies-Depression
CHAP	Chicago Health and Aging Project
CBT	cognitive behavioral therapy
COVID-19	coronavirus disease 2019

CI	Confidence interval
MMSE	Mini-Mental State Examination
SDU	Standard deviation unit(s)
SE	Standard error
U.S.	United States

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Table 1.

Baseline Visit Sample Characteristics by Race

Mean (SD) or % (n)	Total (n=7696)	Whites (n=2757)	Blacks (n=4939)
Age	72.22 (6.22)	74.17 (6.96)	71.14 (5.47)
Education	12.42 (3.53)	13.98 (3.25)	11.55 (3.38)
Global Cognition	0.29 (0.70)	0.57 (0.59)	0.14 (0.71)
Episodic Memory	0.29 (0.83)	0.49 (0.74)	0.18 (0.85)
Perceptual Speed	0.35 (0.93)	0.84 (0.80)	0.08 (0.88)
MMSE	0.29 (0.63)	0.48 (0.47)	0.18 (0.68)
Female	4813 (63)	1716 (62)	3097 (63)
Lonely	1177 (15)	326 (12)	851 (17)

Baseline Visit Sample Characteristics by Loneliness		
Mean (SD)	**Not Lonely (n=6519)**	**Lonely (n=1177)**
Age	71.98 (6.08)	73.56 (6.80)
Education	12.63 (3.50)	11.25 (3.52)
Global Cognition	0.34 (0.68)	0.06 (0.78)
Episodic Memory	0.32 (0.81)	0.10 (0.91)
Perceptual Speed	0.42 (0.91)	−0.003 (0.93)
MMSE	0.32 (0.60)	0.10 (0.79)
%(n)		
Female	61 (3945)	74 (868)
African American	63 (4088)	72 (851)
APOE-e4	33 (1442)	34 (245)

Baseline characteristics include means and standard deviations or frequencies and percents

Table 2.

Longitudinal Associations between Loneliness and Decline in Global Cognitive Function, Episodic Memory, and Perceptual Speed by Race

	Global Cognitive Decline						Episodic Memory						Perceptual Speed					
	Black Participants			White Participants			Black Participants			White Participants			Black Participants			White Participants		
Status	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**
Not Lonely	−0.060	0.002	(−0.064, −0.056)	−0.071	0.003	(−0.076, −0.065)	−0.044	0.003	(−0.049, −0.039)	−0.048	0.003	(−0.054, −0.042)	−0.049	0.002	(−0.053, −0.045)	−0.076	0.003	(−0.082, −0.071)
Lonely	−0.075	0.004	(−0.082, −0.068)	−0.075	0.006	(−0.086, −0.063)	−0.058	0.004	(−0.067, −0.050)	−0.057	0.006	(−0.069, −0.044)	−0.055	0.003	(−0.062, −0.049)	−0.075	0.006	(−0.087, −0.064)

Linear Mixed Effects Regression Models are adjusted for age, sex, education, time, and interactions with time for each demographic characteristic.

SDU = Standard Deviation Units per Year

SE = Standard Error

95% CI = 95% Confidence Interval

Table 3.

Longitudinal Associations between Loneliness and Decline in Global Cognitive Function, Episodic Memory, and Perceptual Speed by APOE-e4

	Global Cognitive Decline						Episodic Memon						Perceptual Speed					
	APOE			No APOE			APOE						APOE			No APOE		
Status	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**	**SDU**	**SE**	**95% CI**
Not Lonely	−0.084	0.005	(−0.094, −0.074)	−0.044	0.002	(−0.049, −0.040)	−0.067	0.006	(−0.079, −0.055)	−0.030	0.003	(−0.036, −0.024)	−0.078	0.005	(−0.087, −0.069)	−0.058	0.002	(−0.063, −0.053)
Lonely	−0.102	0.007	(−0.115, −0.088)	−0.052	0.004	(−0.059, −0.045)	−0.084	0.009	(−0.101, −0.067)	−0.040	0.005	(−0.050, −0.031)	−0.091	0.007	(−0.104, −0.078)	−0.058	0.004	(−0.066, −0.050)

Linear mixed effects regression models are adjusted for age, race, sex, education, time, and interactions with time for each demographic characteristic.

APOE = APOE-e4

SDU = Standard Deviation Units per Year

SE = Standard Error

95% CI = 95% Confidence Interval

Table 4.

Race Differences in the Longitudinal Associations between Loneliness and Decline in Global Cognitive Function, by APOE-e4

Global Cognitive Decline								
	APOE-e4: Yes				APOE-e4: No			
	SDU	SE	95% CI		SDU	SE	95% CI	
Non Lonely Black	−0.077	0.004	−0.085	−0.069	−0.046	0.002	−0.085	−0.069
Non Lonely White	−0.082	0.005	−0.092	−0.073	−0.045	0.002	−0.092	−0.073
Lonely Black	−0.091	0.007	−0.105	−0.078	−0.058	0.004	−0.105	−0.078
Lonely White	−0.114	0.012	−0.138	−0.089	−0.045	0.006	−0.138	−0.089

Additional adjustments to linear mixed effects regression models include: age, sex, education, time, and interactions with time for each demographic characteristic.

APOE = APOE-e4

SDU = Standard Deviation Units per Year

SE = Standard Error

95% CI = 95% Confidence Interval