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Depression is associated with earlier onset of cognitive impairment in a population-based longitudinal cohort

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Depression is associated with earlier onset of cognitive impairment in a population-based longitudinal cohort

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2021

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An abstract of

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Abstract:

Introduction: Many community-based studies have shown an association between depression and the development of cognitive impairment. In this study, we investigated whether depression was associated with differing incidence rates of cognitive impairment in individuals aged 50 or older and whether depression was associated with an earlier onset of cognitive impairment. We also investigated if genetic liability for depression, as represented by polygenic risk score (PRS) for depression, was associated with cognitive impairment.

Methods: Participants were recruited by the Health and Retirement Study, a population-based longitudinal survey of United States individuals that collects data on various sociodemographic and psychological measures using validated measures. Inclusion criteria for the current study was the availability of measures of depression, cognitive status, and availability of genotyping. PRS for depression was estimated using PRSice-2. Analyses were conducted using adjusted logistic regression, Cox proportional hazards, and linear regression.

Results: A total of 6656 participants were included in this study who were assessed every two years for depression and cognitive status for a median of 16 years. Participants with depression had a significantly higher hazard for cognitive impairment compared to those without (HR = 1.9, 95% CI: (1.58,2.27)). Depression was associated with an earlier onset age of cognitive impairment (β = 2.4 years, 95% CI: (1.52, 3.22). Finally, depression PRS was not significantly associated with hazard of developing cognitive impairment (HR = 0.99; 95% CI (0.88, 1.13)).

Discussion: Mid-to-late-life depression was associated with i) a higher hazard of developing cognitive impairment and ii) early onset of cognitive impairment. These findings suggest mid-to-late-life depression may be an early indicator of future cognitive decline. Future work ought to focus on identifying the causes of cognitive decline associated with depression.

Depression is associated with earlier onset of cognitive impairment in a population-based longitudinal cohort

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Introduction:

Depression is a major public health problem. It has become one of the most common illnesses globally and one of the most diagnosed mental illnesses among adults. The prevalence of depression has increased over the last 25 years[1]. As of 2020, it was estimated that 9.2% of Americans aged ≥ 12 experienced a major depressive episode in the prior year[2]. More severe depression is inversely related to quality of life[3]. Depression has also been shown to be associated with cognitive decline and cognitive impairment in the middle-aged and elderly population[4].

Mild cognitive impairment (MCI) is defined as cognitive decline greater than expected for an individual's age and education level, but does not interfere notably with daily life activities. MCI diagnosis is established by evidence of memory impairment, preservation of feneral abilities and absence of diagnosed dementia[5,6].The Centers for Disease Control and Prevention (CDC) studied subjective cognitive decline (SCD) in which individuals self-report experiences of worsening or more frequent memory loss. It was found that 11.1% or 1 in 9 adults experience SCD, with 10.8% of aged 45-64 years experiencing SCD and 11.7% of adults aged 65 or older experiencing SCD[7]. Depression is a common feature of cognitive impairment as pre-morbid depression has been shown to approximately double the risk of subsequent dementia[8]. Therefore, it is imperative to understand the link between depression and cognitive impairment, as impaired cognition can adversely affect an individual's health and overall well-being.

Studies have been performed to better understand the link between depression and the development of cognitive impairment. Multiple large community-based prospective cohort studies have found that experiencing mid-life or late-life depression in the absence of dementia was associated with a higher risk of subsequent development of Alzheimer's disease (AD) and vascular dementia by two to three folds[8-13]. Late-life depression in these studies referred to depression that manifests after age 50 or after age 60[14]. These studies suggest that depression,

specifically late-life depression, may be a risk factor or prodrome for cognitive impairment, or both.

Genome-wide association studies (GWAS) of depression and Alzheimer's disease (AD) have shown that depression and AD have a shared genetic basis[15]. This is worth noting as MCI can progress to dementia and eventually AD[6]. The shared genetic architecture between depression and AD shows that roughly half of the individuals living with mild cognitive impairment or AD experience depressive symptoms[16,17]. AD has a 10-20 year prodromal period resulting in most at-risk individuals being 50 and 70 years old[18,19]. Polygenic risk scores (PRS) provide us with an estimate of an individual's genetic propensity to a trait and are estimated using GWAS data and can lead to recommendations of medical treatments and behavioral modifications to reduce risks. However, it is unknown whether genetic liability for depression, represented by PRS, contributes to the development of cognitive impairment.

Hence, in this study, we aimed to investigate the effect of depression, including its genetic liability, in individuals aged 50 or older on the incidence and onset age of cognitive impairment. To this end, we analyzed data from a population-based longitudinal cohort recruited by the Health and Retirement Study (HRS) to determine whether depression manifesting after age 50 among cognitively normal individuals was associated with a higher hazard and earlier onset age for cognitive impairment. We also investigated whether higher PRS for depression was associated with a higher risk of developing cognitive impairment.

Methods:

The Health and Retirement Study (HRS) Cohort

The HRS is a longitudinal survey comprising 37,000 individuals in 23,000 households in the United States. The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan[20]. It is a nationally representative cohort of Americans aged 50 years or older who have all provided written informed consent for the study. The survey has collected data every two years since 1992[21]. Our analyses focused on participants aged 50 or older with genetic data, who were cognitively normal at baseline, whose cognitive status did not change in the reverse direction (cognitive impairment to normal cognition), and who were of European ancestry. We focused only on those of European descent because the lack of depression GWAS for other ancestries limits our ability to estimate their depression PRS accurately. After applying these criteria, 6656 participants were included in the analyses.

Assessment of cognitive performance

Cognitive status in HRS participants was assessed every 2 years between 1996 and 2016 over the phone or in person via a modified Telephone Interview for Cognitive Status (mTICS), a frequently used screening measure of cognition in aging studies[22], which included 10-word immediate and delayed recall (0–20 points; assessing memory), serial 7 subtraction (0–5 points; assessing working memory), and backward counting (0–2 points; assessing attention and processing speed)[23]. The score of mTICS ranged from 0 to 27, with higher scores indicating better cognitive function. Following the psychometrically validated cut-points developed by Langa and Weir[23], we classified participants scoring between 0 and 11 as having cognitive impairment, while those who scored between 12 and 27 were classified as cognitively normal.

Those who scored between 0 and 11 on mTICS at baseline were excluded from the analyses as we aimed to study how long it took for cognitively normal individuals to develop cognitive impairment. Those who were cognitively impaired at baseline were censored and those who developed cognitive impairment at each follow-up visit were censored prior to the subsequent follow-up visit.

Assessment of depression

Depressive symptoms in HRS were also assessed every two years between 1996 and 2016 using the psychometrically validated 8-item Center for Epidemiologic Studies of Depression (CES-D) scale[24]. The CES-D has been widely used to characterize depressive affect in community populations, including among individuals of advanced age[25]. The CES-D scale ranged from 0 to 8, with higher scores indicating more depressive symptoms. Only participants who responded to all eight questions at each assessment were considered. Participants were divided into two groups: i) cases had clinically significant depression based on average psychometrically determined threshold CES-D score ≥ 3 across all follow-up visits, and ii) controls were those without clinically significant depression based on average CES-D < 3 across all follow-up visits[26,27].

Genome-wide genotyping in the HRS cohort

The publicly available genotype data from the HRS includes data from 15,708 participants in phases 1 to 3. Participants were genotyped on the Illumina HumanOmni2.5-4v1 array in phases 1 and 2 and on the Illumina HumanOmni2.5-8v1 array in phase 3. Genotype data from the combined dataset, which included 2,315,518 overlapping, non-discordant single-nucleotide polymorphisms (SNPs), were obtained from the Database of Genotypes and Phenotypes

(dbGaP). Additional quality control was performed on the genotype data using PLINK v. 1.90b53[28]. Participants with genotype missingness >10%, sex mismatches, or those who were closer than second-degree relatives were excluded. Moreover, variants that deviated from Hardy-Weinberg equilibrium ($P < 10^{-7}$), had a missing genotype rate >10% or minor allele frequency (MAF) < 1%, or were an ambiguous variant were removed. To confirm European ancestry for individuals who self-reported as White, we used multidimensional scaling analysis to compare to the CEU samples from the HapMap project (i.e., U.S. Utah residents with ancestry from northern and western Europe)[29]. Only participants clustering with the HapMap CEU samples (within 6 standard deviations [SD]) were kept. Imputation was performed using the 1000 Genome Project Phase 3[30] and the Michigan Imputation Server[31]. SNPs with imputation $R^2 > 0.8$ were kept. After quality control, 9102 individuals of European ancestry were retained. Of the 9102 remaining, participants were selected based on normal cognition at baseline (mTICS ≥ 12), consistent progression of cognitive performance without back-and-forth fluctuation of cognitive status, and availability of depressive symptom scores. After applying the selection criteria, 6656 individuals were included in the analyses.

Calculation of polygenic risk score (PRS)

PRS is the weighted sum of an individual's genotypic profile weighted by effect-size estimates from a GWAS of a trait or disease of interest[32-34]. It can be interpreted as one's cumulative genetic predisposition to the trait or disease. The PRS for depression was calculated using the PRSice-2 software[32,35]. Default parameters were utilized. To calculate the PRS for depression, we used the depression GWAS in 807,553 participants of European descent[36]. Clumping was performed in 250 Kb windows to keep SNPs with the smallest P-values while removing SNPs in linkage disequilibrium ($r^2 > 0.1$). Genome build GRCh37 was used for GWAS and genotype data. With PRSice-2, SNPS with GWAS p-values below a specified threshold are included in the PRS

estimation, while all other SNPs were excluded[32,34]. The association of PRS with a trait was tested for each of the GWAS p-value thresholds and the optimal P-value threshold (GWAS p-value threshold = 0.0131001) chosen was the one that resulted in the best PRS model fit (R^2)[35].

Statistical Analysis

The association between depression and cognitive impairment was estimated using logistic regression. Depression was treated as a binary variable (case versus control) using the abovementioned CES-D thresholds. Additionally, we utilized the Cox Proportional Hazards model to ascertain if depression status and/or depression PRS were associated with the development of cognitive impairment. In the model that studied the effect of depression PRS on the development of cognitive impairment, depression PRS was transformed into a binary variable (low versus high) by median dichotomization. Both Cox Proportional Hazards models used the time from baseline observation to the onset of cognitive impairment as the outcome. When studying the effect of depression status on the development of cognitive impairment, sex-specific analysis using self-assigned sex was also tested. After the Cox-Proportional Hazards model provided us with information about an individual's risk of developing cognitive impairment at each follow-up visit, we sought to determine if depression was associated with an earlier onset of cognitive impairment using linear regression. All models were adjusted for age at baseline, sex, and education, while the depression PRS Cox Proportional Hazards model also adjusted for the ten principal genetic components. All analyses were performed using R (version 4.1.3) with the packages dplyr (1.0.10), readr (2.1.3), survival (3.4-0), knitr (1.41), kableExtra (1.3.4), sjmisc (2.8.9), finalfit (1.0.5), and survminer (0.4.9).

Results:

Characteristics of cohort

Our study sample comprised 6656 HRS participants with available genotype data and normal cognitive status at baseline. The median age at baseline was 56.0 years and 75% of the study participants were between 50 and 65 years old at baseline. The majority of the participants (59%) was female (n = 3912; Table 1). Educational attainment ranged from less than high school to more than college-level education. Median follow-up time was 14 years (range 0-20; Table 1) for participants overall, with a median follow-up of 12 years and 16 years for those who did and did not develop cognitive impairment, respectively. During the study period, 16.5% (n=1096) of the participants developed cognitive impairment and 9.4% (n=626) of participants developed clinically significant depression, which is consistent with the prevalence of depression in people aged 50 years or older[37].

Participants who experienced depression were more likely to develop cognitive impairment

Among participants with normal cognitive status at baseline (i.e., mTICS > 13), those who experienced clinically significant depression during the follow-up years (average CESD >= 3) were more likely to develop cognitive impairment in subsequent years (odds ratio [OR] = 1.5; p = 0.0007; n=6656; 95% CI: (1.2, 1.9)) after adjusting for age at baseline, sex, and education using logistic regression.

Participants who experienced depression had a greater hazard of cognitive impairment

After finding that those with depression were more likely to develop cognitive impairment over the course of the study, we wanted to understand the risk associated with depression and the development of cognitive impairment at each follow-up visit after adjusting for age at baseline, sex, and education. Using the Cox proportional hazards model, we found that those who experience depression were nearly two times more at risk of developing cognitive impairment at each visit compared to those without depression (hazard ratio [HR] = 1.9; 95% CI (1.6, 2.3); p = 3.9E-12; n = 6634; Figure 1). Sex-specific analysis was performed in each sex separately to determine if there was any difference between males and females in the relationship between depression and cognitive impairment. After adjusting for age at baseline and education, we found that the association between depression and hazard for cognitive impairment was similar between depressed males and females compared to males and females without depression (males HR = 1.89; 95% CI (1.37, 2.62), p = 0.0001, n = 2734; females HR = 1.91; 95% CI (1.54, 2.38), p = 5.83e-09, n = 3900; Figure 2).

Participants with depression had an earlier age at the onset of cognitive impairment

Seeing that individuals with depression were at an increased hazard for cognitive impairment, we performed a linear regression on those who developed cognitive impairment (n = 1096) to estimate the effect of depression on the time to onset of cognitive impairment. After adjusting for age at baseline, sex, and education, we found that those who experienced depression had a 2.4 years earlier onset of developing cognitive impairment compared to those without depression (p = 6.43e-08, 95% CI: (1.52, 3.22)).

Depression PRS was not significantly associated with the risk of cognitive impairment

PRS allows us to determine an individual's genetic liability for a trait or disease[34]. We wanted to understand how the genetic liability for depression impacts the development of cognitive impairment. After accounting for the effects of age at baseline, sex, education, and ten genetic principal components, we did not observe a significant association between depression PRS and the incidence of cognitive impairment (hazard ratio [HR] = 0.99; 95% CI (0.88, 1.13); p = 0.97; n = 6634; Figure 3).

Discussion:

This study utilizes a population-based longitudinal approach to determine whether depression in individuals aged 50 or older is associated with an increased hazard of developing cognitive impairment and if it is associated with earlier onset of cognitive impairment. We found that those who had depression were nearly two times more likely to develop cognitive impairment at each follow-up visit compared to those without depression after adjusting for age at baseline, age, and education. Furthermore, we found that among individuals who developed cognitive impairment during the study period, the onset of impairment was 2.4 years earlier in individuals with depression after adjusting for age at baseline, sex, and education. This is the first study to find to show that depression is associated with earlier onset of cognitive impairment. However, genetic liability for depression, as shown by depression PRS, was not significantly associated with the development of cognitive impairment, likely due to lack of sufficient power to detect a significant association. It is important to note that depression was based on a biennial longitudinal assessment for up to 20 years (median 14 years). Furthermore, we only considered those individuals with normal cognitive performance at baseline to study the effect of depression on cognitively normal individuals. The findings from the analyses suggest that depression

manifesting from age 50 onwards in cognitively normal persons may represent the early signs of prodrome for future cognitive decline. However, further research should be conducted to study whether treating depression in subjects aged 50 years or older in cognitively normal individuals can alter one's risk of developing cognitive impairment.

These findings are notable as we have found a strong association between depression and the development of cognitive impairment in the population-based HRS cohort. Our study showed that individuals with depression had higher odds of developing cognitive impairment, a finding that is consistent with other prospective cohort studies that show that older adults with depression are more likely to develop cognitive impairment[38-41]. Our study builds on this by providing a hazard ratio. The hazard ratio can tell us the odds that a depressed person will develop cognitive impairment faster compared to individuals who are not depressed while providing us an idea of the study subject's risk of developing cognitive impairment at each follow-up visit. However, it does not convey information about how much faster this may occur[42].

Because the Cox proportional hazards model did not provide us insight into how much faster depression can cause cognitive impairment, we performed a linear regression on cognitively impaired individuals to determine if depression caused a more rapid cognitive decline. We found that individuals experiencing depression were estimated to have a 2.4 year earlier onset of cognitive impairment compared to those who were not depressed. This is the first study to show that depression is associated with earlier onset of cognitive impairment. This novel finding contributes to the literature by providing more information about the effects of depression on the development of cognitive impairment. Together, these findings suggest that depression is a factor in the development and can lead to an earlier onset of cognitive impairment after accounting for age, sex, education, and age at baseline.

However, we did not observe an association between high depression PRS and the development of cognitive impairment. A reason for this could be is that the PRS for depression accounts for only a small percentage of the variance of depression and does not consider that depression can be caused by several other environmental or genetic factors[43].

The results of this study should be interpreted in the context of its limitations. First, we focused on participants of European ancestry because of the lack of sufficiently powered GWAS data for individuals of non-European ancestry. This may limit the generalizability of the findings to those of European ancestry. Second, the only available large-scale measure of cognitive performance in HRS was mTICS, which precludes a detailed classification of cognitive dysfunction. Moreover, mTICS only showed a modest association when compared to other neuropsychological tests, bringing its validity into question[22]. However, the cut-off score we utilized in this study for mTICS was based on the Langa-Weir recommended score, which has been psychometrically validated and shown to have an 87.2% concordance with the classification based on the detailed psychological testing in the HRS cohort. Third, self-reported depression may miss individuals who underreport their depression. However, the self-report CES-D scales are very sensitive in detecting depression, compared to depression diagnosed by a clinician[27]. Fourth, this study did not have data to determine whether the reported depressive symptoms represented new or recurrent depressive symptoms[24].

Despite some limitations, this study has several strengths. First, the population-based longitudinal approach allows us to generalize our findings to the elderly population of European ancestry while also allowing us to detect changes in the characteristics of the study population over time and account for censored data. Second, our analysis was of a nationally representative cohort of 6656 Americans of European descent who were aged 50 years or older. This cohort is optimal in determining whether depression is a prodrome for the development of cognitive impairment and for an earlier onset of cognitive impairment, since all participants in this study

had normal cognitive performance at baseline, with 75% of them between ages 50 and 64 at baseline, which is the typical time frame for a prodromal period for cognitive impairment. Third, depression and cognitive performance were assessed longitudinally every 2 years, for up to 20 years, which is useful in helping us evaluate the relationship between these risk factors in the development of cognitive impairment[44]. Fourth, CES-D scores were censored once a participant developed cognitive impairment, so that depression case-control status was determined using only observations made during visits where the participant was cognitively normal. This is important since CES-D score becomes less reliable once an individual has developed cognitive impairment, as it may become difficult to obtain responses from these individuals once they have developed cognitive impairment due to lack of remembrance[45].

In summary, depression may contribute to an increased hazard of developing cognitive impairment while leading to an earlier onset of cognitive impairment in cognitively normal persons of European ancestry aged 50 years or older. These findings can help in developing early interventions to prevent future cognitive decline. However, future research must be conducted to determine if depression interventions can slow cognitive decline.

Tables and Figures:

Table 1: Characteristics of the 6656 participants from the Health and Retirement Study (HRS).

	Developed Cognitive Impairment (n = 1096)			Did Not Develop Cognitive Impairment (n = 5560)			Total (n = 6656)		
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
Age at Baseline	67.0 (9.0)	67 (60-74)	50–92	57.8 (7.3)	55 (52-61)	50–97	59.3 (8.3)	56 (53-64)	50–97
Age at Cognitive Impairment	79.2 (8.7)	80 (74-85)	54–101	-	-	-	-	-	-
Number of Follow-Up Visits	6.1 (2.6)	6 (4-8)	1–10	7.2 (2.7)	8 (6-10)	0–10	7.0 (2.7)	7 (5-9)	0–10
Number of Follow-Up Years	12.2 (5.1)	12 (8-16)	2–20	14.4 (5.3)	16 (12-20)	0–20	14.0 (5.3)	14 (10-18)	0–20
Average Depression Score	1.3 (1.5)	0.9 (0.3-1.9)	0–8	0.6 (1.3)	0.7 (0.2-1.5)	0–8	1.1 (1.3)	0.7 (0.2-1.5)	0–8
		N (%)			N (%)			N (%)	
Depression Status									
Case		139 (12.7)			487 (8.8)			626 (9.4)	
Control		957 (87.3)			5073 (91.2)			6030 (90.6)	
Sex									
Male		448 (40.9)			2296 (41.3)			2744 (41.2)	
Female		648 (59.1)			3264 (58.7)			3912 (58.8)	
Educational Attainment									
Less than High School/GED		234 (21.4)			392 (7.1)			626 (9.4)	
High School/GED		406 (37.0)			1811 (32.6)			2217 (33.3)	
Some College		263 (24.0)			1455 (26.2)			1718 (25.8)	
College		103 (9.4)			891 (16.0)			994 (14.9)	
More than College		90 (8.2)			989 (17.8)			1079 (16.2)	

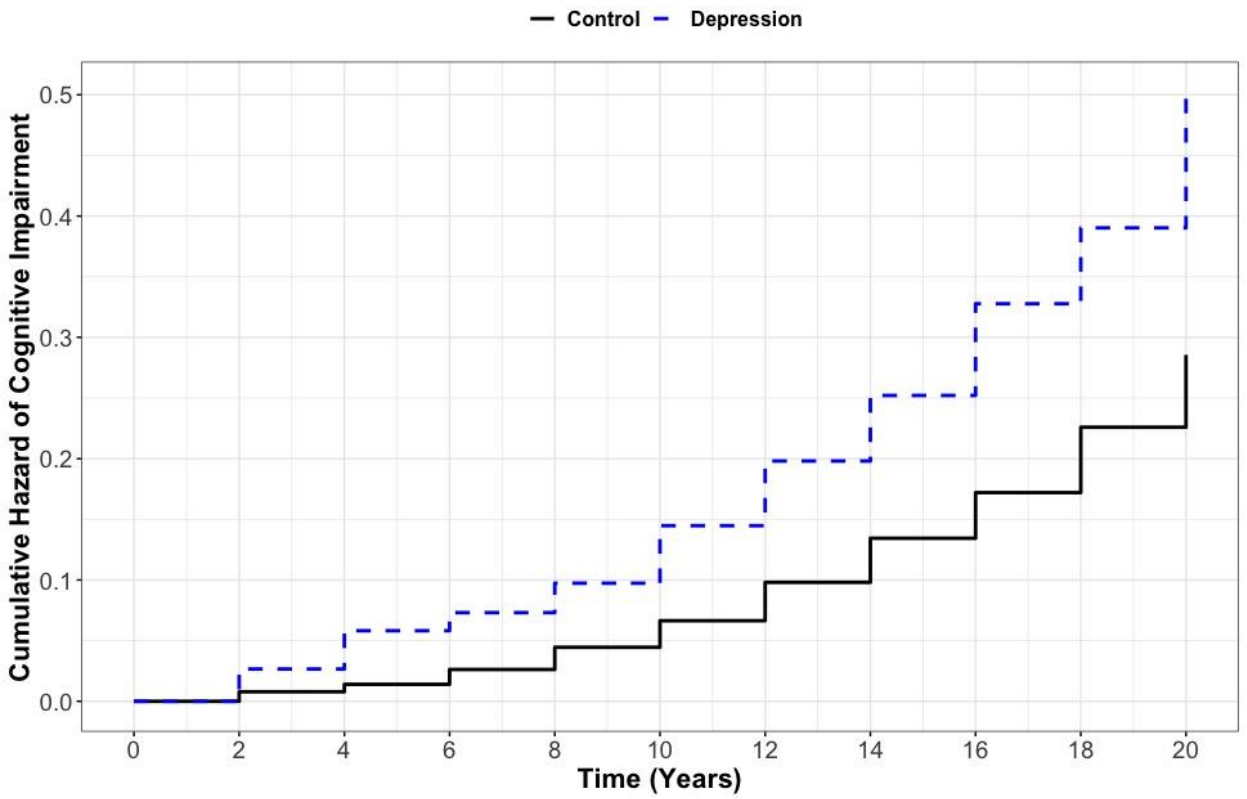

Figure 1: Cumulative hazard plot measuring the time to cognitive impairment for HRS participants with clinically significant depression (depression; dashed blue line) compared to those without clinically significant depression (controls; solid black line). The cumulative hazard for cognitive impairment (y-axis) indicates the proportion of participants in each group (clinically significant depression vs. control) who developed cognitive impairment throughout the study period. After the cognitive performance was assessed, the cumulative hazard for cognitive impairment was calculated every two years at each follow-up visit (x-axis) in 6634 participants. Those with depression were at an increased hazard for developing cognitive impairment (HR = 1.9, 95% CI: (1.58,2.27)).

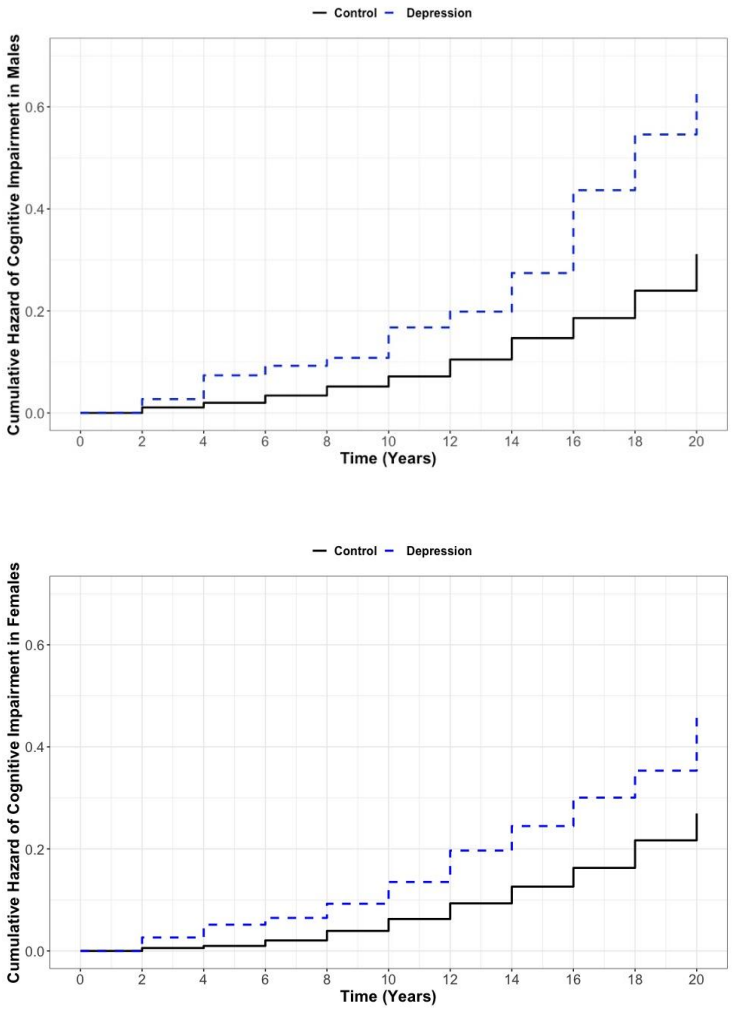

Figure 2: Cumulative hazard plot measuring the time to cognitive impairment for HRS participants with clinically significant depression (depression; dashed blue line) compared to those without clinically significant depression (controls; solid black line) in males (top) vs females (bottom). The cumulative hazard for cognitive impairment (y-axis) indicates the proportion of participants in each group (clinically significant depression vs. control) who developed cognitive impairment throughout the study period. After the cognitive performance was assessed, the cumulative hazard for cognitive impairment was calculated every two years at each follow-up visit (x-axis) in male and female participants. Both males and females were at an increased hazard for developing cognitive impairment (males HR = 1.89; 95% CI (1.37, 2.62), p = 0.0001, n = 2734; females HR = 1.91; 95% CI (1.54, 2.38), p = 5.83e-09, n = 3900).

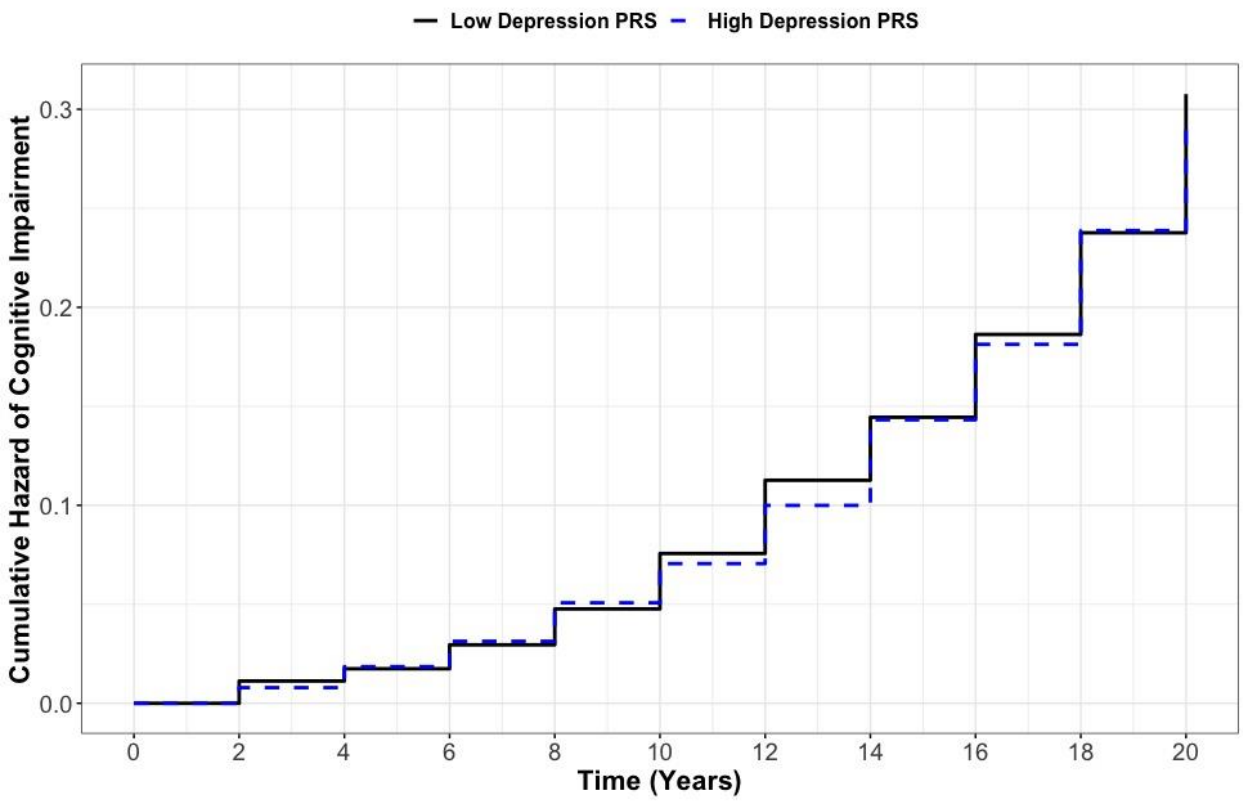

Figure 3: Cumulative hazard plot measuring the time to cognitive impairment for HRS participants with high depression PRS (High Depression PRS; dashed blue line) compared to those with low depression PRS (Low Depression PRS; solid black line). PRS was transformed into a binary variable (low versus high) by median dichotomization. The cumulative hazard for cognitive impairment (y-axis) indicates the proportion of participants in each group (high versus low depression PRS) who developed cognitive impairment throughout the study period. After the cognitive performance was assessed, the cumulative hazard for cognitive impairment was calculated every two years at each follow-up visit (x-axis) in 6634 participants. Higher depression PRS was not associated with an increased hazard of developing cognitive impairment (HR = 0.99, 95% CI: (0.88, 1.13)).

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