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Research paper

Bidirectional association between depressive symptoms and mild cognitive impairment over 20 years: Evidence from the Health and Retirement Study in the United States

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ABSTRACT

Background: Research examining the association between depressive symptoms and mild cognitive impairment (MCI) has yielded conflicting results. This study aimed to examine the bidirectional association between depressive symptoms and MCI, and the extent to which this bidirectional association is moderated by gender and education.

Methods: Data come from the US Health and Retirement Study over a 20-year period (older adults aged ≥50 years). Competing-risks regression is employed to examine the association between baseline high-risk depressive symptoms and subsequent MCI (N = 9317), and baseline MCI and subsequent high-risk depressive symptoms (N = 9428). Interactions of baseline exposures with gender and education are tested.

Results: After full adjustment, baseline high-risk depressive symptoms were significantly associated with subsequent MCI (SHR = 1.20, 95%CI 1.08–1.34). Participants with baseline MCI are more likely to develop subsequent high-risk depressive symptoms than those without baseline MCI (SHR = 1.16, 95%CI 1.01–1.33). Although gender and education are risk factors for subsequent depression and MCI, neither moderates the bidirectional association.

Limitations: Items used to construct the composite cognitive measure are limited; selection bias due to missing data; and residual confounding.

Conclusions: Our study found a bidirectional association between depressive symptoms and MCI. High-risk depressive symptoms are related to a higher risk of subsequent MCI; and MCI predicts subsequent high-risk depression. Though neither gender nor education moderated the bidirectional association, public health interventions crafted to reduce the risk of depression and MCI should pivot attention to older women and those with less formal education.

1. Introduction

With an increasingly global aging population, the co-occurrence of depression and cognitive decline is a major public health issue in the United States (US) and worldwide, as it constitutes enormous personal, social, and financial ramifications (World Health Organization, 2022). There are approximately 280 million people worldwide suffering from depression (Institute of Health Metrics and Evaluation, 2019) and the incidence is on the rise (National Institute of Mental Health, 2022; Vos et al., 2016; Yu et al., 2020). Approximately 8.4 % of all US adults (21 million) had at least one episode of major depression in 2020 (National Institute of Mental Health, 2022). Depression is the second leading cause of disability in the US (Vos et al., 2016), with rates of major depression surging among older Americans (Yu et al., 2020). Moreover, untreated depression is the leading cause of disability worldwide, a major contributor to the overall global burden of disease, associated with decreased life expectancy, and at its worst also can lead to suicide (World Health Organization, 2021b).

Concomitantly, the incidence of cognitive decline, including mild cognitive impairment (MCI), also rises with age (Livingston et al., 2020;

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World Health Organization, 2021a, 2021b). MCI refers to abnormalities in the higher intellectual processes associated with learning and memory, as well as thinking and judgement, resulting in severe learning and memory impairment, accompanied by changes such as apraxia, agnosia, aphasia, or deficits associated with executive function (Staff et al., 2004; Langa and Levine, 2014). MCI is considered as an intermediate condition between "normal aging" and dementia (Petersen et al., 2014). Globally, the prevalence of MCI, which ranges from 7 % to 25 % in adults aged 60 to 84, continues to increase with advancing age (Petersen et al., 2018). Though not all those with MCI develop dementia, individuals with MCI endure a greater risk for Alzheimer's Disease (AD) and other forms of dementia (Alzheimer's Association, 2022). By 2060, the number of individuals aged 65 and older with AD worldwide, likely to grow twofold, is expected to reach 13.8 million (Alzheimer's Association, 2022). Aside from being a risk factor for AD and related dementias, MCI represents an increased likelihood of disability and dependency, stigma, and increased health care costs for older adults and their families worldwide (World Health Organization, 2021a).

Worth pointing out is the high rate of co-occurrence of depression and MCI (Petersen et al., 2018) that seems to inflate the risk for persistent cognitive impairment and dementia (Ma, 2020). Studies showed that the prevalence of depression among older adults with MCI was 32 %, while 37 % of those with depression reported MCI. Despite the co-occurrence of the two conditions, the order in which these conditions occur remains largely unknown. That is, does depression precede MCI or does it manifest post MCI? Establishing this chronology is critical to unraveling the mechanisms driving this association, which consequently are critical to creating interventions.

Two hypotheses explain the potentially bidirectional association between depressive symptoms and MCI. According to the scarring hypothesis, depressive episodes predispose people to cognitive deficiencies that often linger after affective symptoms have subsided (Schaefer et al., 2017; Lu et al., 2021). The chronic alterations in the body's physiological and neurochemical components that start with the onset of depression and continue to impede cognitive function are what lead to the cognitive deficiencies observed in depressed people (Schaefer et al., 2017; Lu et al., 2021). Alternatively, the cognitive reserve hypothesis contends that higher intelligence early in life is linked to reduced risk for depression in later life (Schaefer et al., 2017; Lu et al., 2021). Higher-ordered cognitive processes, and superior neurological integrity could explain this association. Moreover, those with higher early life intelligence are likely to report higher literacy, socioeconomic status, and consequently, are better equipped to avoid or cope with stressors, access quality health care, and secure formal diagnosis and treatment (Wraw et al., 2016). Thus, the association between depression and MCI could be bidirectional.

Some previous studies have explored the bidirectional association between depressive symptoms and cognitive function. The results of these studies can be divided into four categories. First, depressive symptoms and cognitive decline could, indeed, be bidirectionally linked (Wu et al., 2021; Yin et al., 2019). For example, Wu et al. (2021) in their cross-lagged design study consisting of 90 respondents with late-life depression explored the association between cognition and depressive symptoms over time at two points (baseline and 1-year follow-up). They found that decreased information processing speed predicted depressive symptoms and depressive symptoms increased the risk for cognitive decline (Wu et al., 2021). Second, depression predicts memory deficits, but memory deficits do not predict depression (Zahodne et al., 2014; John et al., 2021; Teles and Shi, 2021; Zainal and Newman, 2022). This was found in a community-based longitudinal study of aging and dementia in northern Manhattan where early depressive symptoms predicted a decline in memory scores at the second follow-up and exacerbated memory deterioration over the course of the trial. However, memory deficits were not indicative of future depressive symptoms (Zahodne et al., 2014). Third, cognitive impairment predicts depression, but depression does not predict cognitive impairment (Bhang et al., 2019; Brailean et al., 2016; Yu et al., 2017). For example, in a 13-year longitudinal study on aging from Amsterdam, Brailean et al. (2016) found that age-related memory impairment resulted in an increase in depressive symptoms. Yet, depressive symptoms at baseline did not influence the rate of cognitive deterioration (Brailean et al., 2016). Finally, some research reports that neither depression nor cognitive decline predicts the other. Gale et al. (2012), for instance, failed to find any evidence of association between the depression and MCI.

In addition to the inconsistency in findings, previous studies on the link between depression and MCI are fraught with other limitations. First, some studies have focused on overall affective symptoms including depression, anxiety, and physical and social dysfunctional signs (Yin et al., 2019; John et al., 2021). Thus, the bidirectional association assessed is not between cognitive impairment and depression, but instead cognitive impairment and an array of affective symptoms. Second, studies with smaller sample sizes admittedly lack sufficient power to adequately detect a true linkage between depressive symptoms and long-term modifications in cognitive functioning (Wu et al., 2021). Third, while some research, including the recent prospective network analysis by Zainal and Newman (2022) is racially diverse, the sample is exclusively female and the findings, consequently, are limited in generalizability (Zainal and Newman, 2022). Finally, existing studies have yet to consider the moderating influence of conceptually relevant covariates in the bidirectional link between depression and cognitive impairment. In particular, given gender disparities both in depression (Linnemann and Lang, 2020; Yang et al., 2021; Dal Forno et al., 2005; Heser et al., 2020) and later life cognitive decline (Lee et al., 2012; World Health Organization, 2021a), and the widely documented link between education and brain health (Yang et al., 2021), it is only reasonable to assess the extent to which the bidirectional association between depressive symptoms and MCI is moderated by older adults' gender and educational attainment. In fact, some data show that relative to their female counterparts with depression, men with depression are more likely to develop subsequent cognitive decline (Linnemann and Lang, 2020; Dal Forno et al., 2005; Heser et al., 2020). And one study showed that having $\geq$8 years of education largely reduced the risk of dementia in participants with depression in later life. Similarly, $\geq$8 years of education also largely reduced the risk of depression in participants with dementia (Yang et al., 2021).

The available evidence on cognitive function and depression is inconsistent and limited. Furthermore, very few studies have addressed MCI alone, an important intermediate stage in the progression from normal aging to severe pathology. In the present study, we employed 20 years' worth of data from the US Health and Retirement Study (HRS) to examine (a) the bidirectional longitudinal association between depressive symptoms and MCI and (b) the extent to which the potential bidirectional association between depressive symptoms and MCI is moderated by gender and education.

2. Methods

2.1. Study sample

Data come from the HRS cohort. The HRS is a longitudinal survey of US individuals aged 50 or over since 1992 (Fisher and Ryan, 2017). Ethical approval for the HRS cohort was obtained from the University of Michigan Institutional Review Board and the study has been conducted according to the principles expressed in the Declaration of Helsinki.

At the time of initiating this study, HRS has collected data of 15 waves between 1992 and 2020. But it was only in 1998 that the HRS began adding new cohorts every 6 years (e.g., in 1998, 2004, 2010, 2016, etc.). We set 1998 as the study baseline and tracked the risk of outcome in these baseline participants over the following 20 years. This study therefore included the sub-cohort in 1998 only. We use the 1998 as it is the first time HRS to include refresh samples. And an early version of the 15th wave (HRS 2020) with incomplete data for cognition was

released by the completion of this study (Health and Retirement Study Survey Research Center, 2021). Finally, depressive symptoms and MCI were measured in each wave.

Thus, this study used HRS data over a 20-year period (1998–2018; Waves 4–14). 20,567 participants were interviewed in the 1998 survey. A sample of 20,012 core participants at baseline was obtained by excluding those who did not respond at the baseline interview, had died or were living in a nursing home (baseline weight = 0). We further excluded samples who already reported outcome of interest (MCI/dementia; high-risk depressive symptoms) at baseline, missing data on continuous outcome measures across waves before the end of follow-up (see Supplements I and II for detailed explanation) and missing data on primary exposures (high-risk depressive symptoms; MCI) and covariates at baseline. At subsequent visits, those participants who scored in the 'dementia' range have been excluded. Finally, the analytical sample sizes are 9317 for the association between baseline depressive symptoms and subsequent MCI, and 9428 for the association between baseline MCI and subsequent high-risk depressive symptoms. Supplements I and II show detailed sample selection procedures.

Sample sizes had been defined in this study. For the main association between baseline high-risk depressive symptoms and subsequent MCI, the power of baseline high-risk depressive symptoms for a given sample size was determined by comparing the proportion of participants without baseline high-risk depressive symptoms to those with baseline high-risk depressive symptoms who subsequently developed MCI. For the main association between baseline MCI and subsequent high-risk depressive symptoms, the power of baseline MCI was determined by comparing the proportion of participants without baseline MCI to the proportion of those with baseline MCI who subsequently exhibited high-risk depressive symptoms. A power of 80 % was considered satisfactory. Power of examining the two associations was found to be 99.99 % and 99.68 %. The proportion of incident events, sample size and calculated efficacy are shown in Supplement III.

2.2. Depressive symptoms

A modified version of the Centre for Epidemiological Studies-Depression (CES-D) scale (8-item scale; yes/no; 0–8) was used to measure depressive symptoms. Higher scores reflect higher level of depressive symptoms. High-risk depressive symptoms are indicated when the total score is ≥4 (Mojtabai and Olfson, 2004). We used binary variables for high-risk depressive symptoms as the outcome (subsequent high-risk depressive symptoms) and the primary exposure (baseline high-risk depressive symptoms), respectively.

2.3. Cognition

MCI is measured by a composite cognitive score (0–27) developed using HRS data (Crimmins et al., 2011). The composite cognitive measure consists of an immediate word recall test (verbal memory; 0–10) and delayed word recall (verbal memory; 0–10), the serial 7 s (working memory; 0–5) and counting backwards (attention and working memory; 0–2). Higher scores indicate better cognitive ability. When the total scores were between 0–6, 7–11 and 12–27, participants were considered to have dementia, MCI without dementia, and normal respectively (Crimmins et al., 2011). We used binary variables for MCI as the outcome (1 = subsequent MCI [including cases with subsequent dementia, assuming subsequent MCI occurred in the midterm between baseline and dementia occurrence]; 0 = normal) and the primary exposure (1 = baseline MCI; 0 = normal), respectively.

2.4. Covariates

Based on previous literature and data availability in HRS (Wu et al., 2021; Yin et al., 2019; Zahodne et al., 2014; John et al., 2021; Zainal and Newman, 2022; Bhang et al., 2019), baseline variables (1998, Wave 4) including age (years), gender (Male; Female), race (White/Caucasian; Black/African American; Other), marital status (Married/partnered; Separated/divorced/single/spouse absent; Widowed), education (First stage of tertiary education or above; Upper secondary education; Lower secondary education; Primary education or below), total household wealth ($), father with 8+ years of education (Yes; No), smoking (Non-smokers; Ex-smokers; Current smokers), frequency of alcohol consumption (days per week), physical activity (Yes; No), BMI (Normal weight; Pre-obesity; Obesity), and long-term conditions (Yes; No) were considered to be covariates. Gender and education were also treated as potential effect modifiers (Linnemann and Lang, 2020; Yang et al., 2021; Dal Forno et al., 2005; Heser et al., 2020). Deciles of total household wealth still were used as a continuous variable in statistical analyses. The variable for whether having any long-term conditions was derived by if the participant had any of the chronic conditions including high blood pressure, stroke, heart problems, lung diseases, diabetes, cancer, and arthritis.

In HRS, specific dates of interviews/events are unavailable, but the month and year of each interview/event have been provided. For outcomes of interest detected at follow-up (incident MCI/high-risk depressive symptoms), the time to incident event was calculated using the year and month of onset minus the year and month of the baseline interview. For alive individuals without outcomes of interest occurring during follow-up, they were right considered on December 2018. For censored cases, their years of follow-up were calculated using the year and month of censoring minus the year and month of the baseline interview. For competing cases, their years of follow-up were calculated using the year and month of death minus the year and month of the baseline interview.

2.5. Statistical analysis

First, for the associations between baseline high-risk depressive symptoms and the subsequent MCI, and between baseline MCI and the subsequent high-risk depressive symptoms, unadjusted, minimally, and fully adjusted models were considered. The minimally adjusted model controlled for age and gender. The fully adjusted model additionally controlled for other covariates.

Competing-risks regression was applied. Participants were divided into three groups. In the first investigation, 0 = censored – by the end of follow-up the participant was still alive and had never experienced subsequent MCI; 1 = subsequent MCI; and 2 = other competing events – the participant died without a subsequent MCI occurring during follow-up. Similarly, in the second investigation, 0 = censored – by the end of follow-up the participant was still alive and had never experienced subsequent high-risk depressive symptoms; 1 = subsequent high-risk depressive symptoms; and 2 = other competing events – the participant died without subsequent high-risk depressive symptoms occurring during follow-up. Sub-distribution hazard ratios (SHRs) with 95 % confidence intervals (CI) were calculated. Significant SHR changes imply that the primary exposure or covariate contributes to the occurrence of the outcome, either without an event (censored) or experiencing a competing event (Austin and Fine, 2017).

Second, based on the literature (Linnemann and Lang, 2020; Yang et al., 2021; Dal Forno et al., 2005; Heser et al., 2020), the interaction between gender and each main exposure, and between education and each main exposure was added to the fully adjusted models to test whether gender and education were effect modifiers for the main associations. Significant interaction suggests the extent to which main associations are significantly different between males and females, and between the group of the first stage of tertiary education or above and other groups of education.

Third, there were missing data for covariates. Apart from showing the percentages of missingness, baseline sample characteristics between the analysed and excluded samples were compared to assess whether selection bias existed (see Supplement IV).

2.6. Sensitivity analysis

First, we used continuous variables for depressive symptoms (CES-D scores) and cognitive functioning (composite cognitive scores) and performed multilevel growth curve modelling (considering random intercepts and slopes; timing metric was age) for the longitudinal associations between baseline CES-D scores and trajectories of cognitive functioning and between baseline cognitive scores and trajectories of depressive symptoms over the years.

Second, intermediate models were developed without adjusting for behavioral variables (smoking, alcohol consumption, physical activity, and BMI) and marital status, as they might be influenced by depression and/or cognition. Therefore, we tested whether they were mediators rather than confounders for the bi-directional association.

Third, we performed multiple imputation using chained equations to deal with missing data for baseline depressive symptoms/MCI and covariates. Based on the imputed datasets, we re-built the unadjusted, minimally adjusted, and fully adjusted models, as well as the fully adjusted models after considering interaction with gender/education.

All analyses were performed in Stata version 17.1.

3. Results

3.1. Descriptive results

For the association between baseline high-risk depressive symptoms and subsequent MCI (N = 9317), 4296 incident cases of MCI and 1910 competing events were identified; and 3111 participants were right censored. The mean year of follow-up was 11.0 years (standard deviation = 6.8). For the association baseline MCI and subsequent high-risk depressive symptoms (N = 9428), 2828 incident cases of high-risk depressive symptoms and 2831 competing events were identified; and 3769 participants were right censored. The mean year of follow-up was 11.4 years (standard deviation = 6.9).

In Table 1, the mean age was 64 and 65 years in the analytic sample for subsequent MCI and high-risk depressive symptoms, respectively. In both samples, the median days of alcohol consumption per week was 0, and the interquartile range (IQR) was 2. The median values of total household wealth were $177,500 and $177,000 respectively, and the IQR were $343,000 and $346,000 respectively. The majority of the participants were females, White/Caucasian, pre-obese, married or partnered and ex-smokers, and had upper secondary education, vigorous physical activity, long-term chronic conditions, and fathers receiving education for over 8 years. In the analytic sample for subsequent MCI, 12.0 % of participants had baseline high-risk depressive symptoms. In the analytic sample for subsequent high-risk depressive symptoms, 10.7 % of participants had baseline MCI.

In both investigations, excluded participants tended to have baseline exposures, less problematic drinking, lower household income, normal weight, lower education level, vigorous physical activity, long-term conditions, and fathers with less than eight years of education and be male, Black/African American and current smoker compared to analytic participants (see Supplement IV).

3.2. Bi-directional associations

Table 2 shows unadjusted, minimally, and fully adjusted models for the association between baseline high-risk depressive symptoms and subsequent MCI. Participants with high-risk depressive symptoms at baseline were more likely to have MCI at subsequent follow-up (SHR = 1.38, 95%CI 1.25–1.53). After controlling for age and gender, baseline high-risk depressive symptoms were significantly associated with subsequent MCI (SHR = 1.37, 95%CI 1.24–1.52). After controlling for other covariates, this association attenuated but was still significant (SHR = 1.20, 95%CI 1.08–1.34).

Results also mirrored what we have found in Table 3. Participants

Table 1
Baseline sample characteristics.

Variables	Analytical sample for subsequent MCI (N = 9317)	Analytical sample for subsequent high-risk depressive symptoms (N = 9428)
	Mean (S.E.)	Mean (S.E.)
Age (years)	64 (0.2)	65 (0.2)
Days of alcohol consumption per week		
1st quartile	0	0
2nd quartile (Median)	0	0
3rd quartile	2	2
Total household wealth ($)		
1st quartile	68,500	68,000
2nd quartile (Median)	177,500	177,000
3rd quartile	411,500	414,000
	%	%
Gender		
Male	3873 (41.6 %)	4054 (43.0 %)
Female	5444 (58.4 %)	5374 (57.0 %)
Race		
White/Caucasian	8620 (92.5 %)	8655 (91.8 %)
Black/African American	475 (5.1 %)	537 (5.7 %)
Other	223 (2.4 %)	236 (2.5 %)
Days of alcohol consumption per week		
None	5950 (63.9 %)	6016 (63.8 %)
1 day	977 (10.5 %)	996 (10.6 %)
2 days	593 (6.4 %)	607 (6.4 %)
3 days	437 (4.7 %)	434 (4.6 %)
4 days	226 (2.4 %)	225 (2.4 %)
5 days	205 (2.2 %)	208 (2.2 %)
6 days	108 (1.2 %)	99 (1.0 %)
7 days	821 (8.8 %)	843 (8.9 %)
BMI		
Normal weight	3375 (36.2 %)	3458 (36.7 %)
Pre-obesity	3695 (39.7 %)	3777 (40.1 %)
Obesity	2247 (24.1 %)	2193 (23.3 %)
Marital status		
Married or partnered	6319 (67.8 %)	6416 (68.1 %)
Separated, divorced, single or spouse absent	1353 (14.5 %)	1306 (13.9 %)
Widowed	1645 (17.7 %)	1706 (18.1 %)
Education		
First stage of tertiary education or above	2611 (28.0 %)	2582 (27.4 %)
Upper secondary education	5327 (57.2 %)	5289 (56.1 %)
Lower secondary education	1173 (12.6 %)	1284 (13.6 %)
Primary education or below	206 (2.2 %)	273 (2.9 %)
Smoking		
Non-smokers	3794 (40.7 %)	3897 (41.3 %)
Ex-smokers	4072 (43.7 %)	4164 (44.2 %)
Current smokers	1451 (15.6 %)	1367 (14.5 %)
Vigorous physical activity		
No	4410 (47.3 %)	4536 (48.1 %)
Yes	4907 (52.7 %)	4892 (51.9 %)
Long-term conditions		
Yes	7960 (85.4 %)	8032 (85.2 %)
No	1357 (14.6 %)	1396 (14.8 %)
Father's education (8+ years)		
Yes	6807 (73.1 %)	6786 (72.0 %)
No	2510 (26.9 %)	2642 (28.0 %)
High-risk depressive symptoms		
No	8195 (88.0 %)	–
Yes	1122 (12.0 %)	
MCI		
No	–	8423 (89.3 %)
Yes		1005 (10.7 %)

S.E.: Standard Error; MCI: Mild Cognitive Impairment; BMI: Body Mass Index.

with MCI at baseline were more likely to have high-risk depressive symptoms at subsequent follow-up (SHR = 1.28, 95%CI 1.13–1.45). After accounting for age and gender, participants with baseline MCI faced a greater hazard of high-risk depressive symptoms (SHR = 1.42, 95 % CI 1.25–1.62). This high risk persisted after further controlling for other covariates (SHR = 1.16, 95 % CI 1.01–1.33).

3.3. Interaction with gender and education

Table 4 shows fully adjusted models for the association between baseline high-risk depressive symptoms and subsequent MCI, considering interaction of baseline high-risk depressive symptoms with gender and education. There was no significant interaction, suggesting that the associations between baseline high-risk depressive symptoms and subsequent MCI were similar in males and females, and across groups of education. The association between gender and subsequent MCI was still non-significant, and the association between education and subsequent MCI still statistically significant. The incidence was higher for participants with primary education or below than for those with first stage of tertiary education or above (SHR = 3.67, 95%CI 2.87–4.69).

Table 5 shows fully adjusted models for the association between baseline MCI and subsequent high-risk depressive symptoms, considering interaction of baseline MCI with gender and education. There was no significant interaction, suggesting that the associations between baseline MCI and subsequent high-risk depressive symptoms were similar in males and females, and across groups of education. The associations of gender and education with subsequent high-risk depressive symptoms were still significant, with women more likely to have subsequent high-risk depressive symptoms than men (SHR = 1.50, 95%CI 1.35–1.66), and participants with primary education or below were more likely to subsequently develop high-risk depressive symptoms than those with first stage of tertiary education or above (SHR = 1.39, 95%CI 1.04–1.84).

3.4. Sensitivity analysis

First, as the results in Supplements V and VI show, in unadjusted, minimally adjusted, and fully adjusted models, participants with higher CES-D scores at baseline were more likely to have decreased trajectories of cognitive functioning at subsequent follow-up; and participants with higher composite cognitive scores at baseline were more likely to have decreased trajectories of depressive symptoms at subsequent follow-up. All interactions built on the fully adjusted models were still non-significant, except for the interaction with education, in the

Table 2
Unadjusted, minimally and fully adjusted models for the association between baseline high-risk depressive symptoms and subsequent MCI.

	Unadjusted model		Minimally adjusted model[a]		Fully adjusted model[b]	
	SHR (95%CI)	P-value	SHR (95%CI)	P-value	SHR (95%CI)	P-value
High-risk depressive symptoms						
No	Reference		Reference		Reference	
Yes	1.38 (1.25, 1.53)	<0.001	1.37 (1.24, 1.52)	<0.001	1.20 (1.08, 1.34)	0.001
Age			1.05 (1.04, 1.05)	<0.001	1.05 (1.04, 1.05)	<0.001
Gender						
Male			Reference		Reference	
Female			1.02 (0.96, 1.10)	0.49	0.96 (0.88, 1.03)	0.27
Race						
White/Caucasian					Reference	
Black/African American					1.83 (1.63, 2.06)	<0.001
Other					1.35 (1.05, 1.74)	0.020
Marital status						
Married or partnered					Reference	
Separated, divorced, single or spouse absent					0.93 (0.83, 1.04)	0.216
Widowed					0.90 (0.82, 1.001)	0.051
Education						
First stage of tertiary education or above					Reference	
Upper secondary education					1.47 (1.35, 1.61)	<0.001
Lower secondary education					2.11 (1.87, 2.38)	<0.001
Primary education or below					3.68 (2.98, 4.54)	<0.001
Total household wealth					0.97 (0.95, 0.98)	<0.001
Smoking						
Non-smokers					Reference	
Ex-smokers					0.98 (0.91, 1.06)	0.664
Current smokers					1.01 (0.90, 1.14)	0.811
Days of alcohol consumption per week					0.99 (0.97, 1.001)	0.097
Vigorous physical activity						
No					Reference	
Yes					0.93 (0.87, 1.001)	0.053
BMI						
Normal weight					Reference	
Pre-obesity					1.01 (0.93, 1.10)	0.770
Obesity					1.03 (0.94, 1.13)	0.541
Long-term conditions						
Yes					Reference	
No					0.86 (0.77, 0.94)	0.002
Father's education (8+ years)						
Yes					Reference	
No					1.13 (1.04, 1.22)	0.003

SHR: Sub-distribution Hazard Ratio; 95%CI: 95 % Confidence Interval; MCI: Mild Cognitive Impairment; BMI: Body Mass Index.

[a] Adjusted for age and gender.

[b] Adjusted for age, gender, race, marital status, education, total household wealth, smoking, alcohol consumption, physical activity, body mass index, long-term conditions and father's education.

Table 3
Unadjusted, Minimally and fully adjusted models for the association between baseline MCI and subsequent high-risk depressive symptoms.

	Unadjusted model		Minimally adjusted model[a]		Fully adjusted model[b]	
	SHR (95%CI)	P-value	SHR (95%CI)	P-value	SHR (95%CI)	P-value
MCI						
No	Reference		Reference		Reference	
Yes	1.28 (1.13, 1.45)	<0.001	1.42 (1.25, 1.62)	<0.001	1.16 (1.01, 1.33)	0.032
Age			0.99 (0.98, 0.99)	<0.001	0.99 (0.98, 0.99)	<0.001
Gender						
Male			Reference		Reference	
Female			1.49 (1.36, 1.63)	<0.001	1.49 (1.35, 1.65)	<0.001
Race						
White/Caucasian					Reference	
Black/African American					0.96 (0.84, 1.11)	0.622
Other					0.93 (0.71, 1.22)	0.590
Marital status						
Married or partnered					Reference	
Separated, divorced, single or spouse absent					1.03 (0.90, 1.18)	0.676
Widowed					0.91 (0.80, 1.04)	0.179
Education						
First stage of tertiary education or above					Reference	
Upper secondary education					1.11 (0.99, 1.25)	0.064
Lower secondary education					1.45 (1.25, 1.68)	<0.001
Primary education or below					1.50 (1.19, 1.90)	0.001
Total household wealth					0.96 (0.95, 0.98)	<0.001
Smoking						
Non-smokers					Reference	
Ex-smokers					1.17 (1.07, 1.29)	0.001
Current smokers					1.34 (1.18, 1.53)	<0.001
Days of alcohol consumption per week					0.99 (0.97, 1.01)	0.238
Vigorous physical activity						
No					Reference	
Yes					1.22 (1.12, 1.33)	<0.001
BMI						
Normal weight					Reference	
Pre-obesity					1.03 (0.93, 1.14)	0.538
Obesity					1.15 (1.03, 1.29)	0.015
Long-term conditions						
Yes					Reference	
No					0.67 (0.59, 0.76)	<0.001
Father's education (8+ years)						
Yes					Reference	
No					1.29 (1.17, 1.41)	<0.001

SHR: Sub-distribution Hazard Ratio; 95%CI: 95 % Confidence Interval; MCI: Mild Cognitive Impairment; BMI: Body Mass Index.
[a] Adjusted for age and gender.
[b] Adjusted for age, gender, race, marital status, education, total household wealth, smoking, alcohol consumption, physical activity, body mass index, long-term conditions and father's education.

longitudinal association between baseline composite cognitive scores and trajectories of depressive symptoms (see Supplement VI). However, in this model, the coefficient for baseline composite cognitive scores became statistically non-significant (−0.003, 95%CI -0.01–0.01), suggesting that the model might be overfitting when considering the significant interaction between baseline composite cognitive scores and education.

Second, for the association between baseline high-risk depressive symptoms and subsequent MCI, SHRs for the main exposure were 1.20 (95 % CI 1.08–1.34) in the fully adjusted model and 1.18 (95 % CI 1.06–1.32) in the intermediate model. For the association between baseline MCI and subsequent high-risk depressive symptoms, SHRs for the main exposure were 1.16 (95%CI 1.01–1.33) in fully adjusted model and 1.16 (95%CI 1.01–1.32) in intermediate adjusted model. Comparison between the fully adjusted model and the intermediate model revealed negligible changes in SHRs for main exposures, suggesting that, smoking, alcohol consumption, physical activity, BMI and marital status were not mediators (see Supplements VII and VIII).

Third, results after imputation of the missing data showed minor changes in SHRs for the bidirectional associations in all models (see Supplements IX and X). All interactions built on the fully adjusted models remained statistically insignificant, suggesting that gender and education were not effect modifiers (see Supplements XI and XII).

4. Discussion

Our study found a significant bidirectional association between depressive symptoms and MCI and this association emerged over 20 years of follow-up data and after accounting for a range of theoretically relevant confounders. We also found that gender and education are risk factors for subsequent depressive symptoms and MCI, though neither moderated the bidirectional association between these two conditions.

The bidirectionality between depression and MCI is foreseeable given that the cognitive and emotional information processes in the brain operate in tandem. That is, they interact and are concentrated in the frontoparietal-limbic system (Disner et al., 2011), where cognition controls the downstream pathways to maintain and regulate relevant information, while emotion influences cognition through the upstream of the limbic system (prefrontal and perceptual cortex). Studies have shown that if there is a dysfunction in the frontoparietal cortex, which is closely related to executive function and attention, it can excite the limbic system, leading to a sustained increase in the individual's perception of negative stimuli and attention, thus inducing depressive symptoms or making them recur or worsen (LeMoult and Gotlib, 2019).

Although there is less agreement on what leads persons with high-risk depressive symptoms to MCI, most of the evidence supports the hypothesis of reduced hippocampal volume (Liu et al., 2017; Gujral

Table 4
Fully adjusted models for the association between baseline high-risk depressive symptoms and subsequent MCI, considering the interaction of baseline high-risk depressive symptoms with gender and education.

Considering the interaction with gender	SHR (95%CI)	P-value
High-risk depressive symptoms		
No	Reference	
Yes	1.36 (1.11, 1.66)	0.003
Gender		
Male	Reference	
Female	0.98 (0.90, 1.06)	0.622
Gender * high-risk depressive symptoms		
Female and yes	0.84 (0.66, 1.06)	0.131

Considering the interaction with education	SHR (95%CI)	P-value
High-risk depressive symptoms		
No	Reference	
Yes	1.35 (1.03, 1.77)	0.028
Education		
First stage of tertiary education or above	Reference	
Upper secondary education	1.50 (1.36, 1.64)	<0.001
Lower secondary education	2.12 (1.86, 2.41)	<0.001
Primary education or below	3.67 (2.87, 4.69)	<0.001
Education * high-risk depressive symptoms		
Upper secondary education and yes	0.84 (0.62, 1.14)	0.265
Lower secondary education and yes	0.93 (0.65, 1.32)	0.676
Primary education or below and yes	0.93 (0.59, 1.48)	0.771

SHR: Sub-distribution Hazard Ratio; 95%CI: 95 % Confidence Interval; MCI: Mild Cognitive Impairment.

Table 5
Fully adjusted models for the association between baseline MCI and subsequent high-risk depressive symptoms, considering the interaction of baseline MCI with gender and education.

Considering the interaction with gender	SHR (95%CI)	P-value
MCI		
No	Reference	
Yes	1.19 (0.97, 1.45)	0.096
Gender		
Male	Reference	
Female	1.50 (1.35, 1.66)	<0.001
Gender * MCI		
Female and yes	0.96 (0.75, 1.24)	0.765

Considering the interaction with education	SHR (95%CI)	P-value
MCI		
No	Reference	
Yes	1.44 (0.96, 2.17)	0.081
Education		
First stage of tertiary education or above	Reference	
Upper secondary education	1.13 (1.01, 1.27)	0.040
Lower secondary education	1.48 (1.27, 1.73)	<0.001
Primary education or below	1.39 (1.04, 1.84)	0.025
Education * MCI		
Upper secondary education and yes	0.76 (0.49, 1.19)	0.235
Lower secondary education and yes	0.76 (0.48, 1.21)	0.248
Primary education or below and yes	0.99 (0.57, 1.74)	0.982

SHR: Sub-distribution Hazard Ratio; 95%CI: 95 % Confidence Interval; MCI: Mild Cognitive Impairment.

et al., 2017; Lee et al., 2012; Allison et al., 2019). Structurally, the hippocampus is part of the limbic system and forms neurofibrillary connections with emotion-related brain regions such as the prefrontal cortex and amygdala (Liu et al., 2017). In contrast, depression impairs glucocorticoid receptor function. Increased glucocorticoids cross the blood-brain barrier and exert negative feedback regulation on the hypothalamic-adrenal axis in the hippocampus, affecting normal cellular metabolism and thus leading to hippocampal neuronal death (Liu et al., 2017; Gujral et al., 2017). Empirical studies have found both, a link between depression and reduced hippocampal volume (e.g., Lee et al., 2012) and an association between reduced hippocampal volume and diminished cognitive functioning (e.g., Allison et al., 2019).

Several potential socio-behavioral pathways may also explain the link between depression and MCI. Many studies have reported a positive association between depression and smoking (Fluharty et al., 2016). Depression may increase the risk of smoking through self-medication mechanisms, while remission of depressive symptoms may stimulate the risk of smoking (Fluharty et al., 2016). According to this hypothesis, smoking has been used to cope with depression or to reduce stress. However, smoking can lead to cognitive decline and is a risk factor for MCI (Caffò et al., 2022). On the one hand, smoking may cause oxidative stress or an increase in free radicals, leading to neuronal degeneration and brain cell damage, which can lead to cognitive decline (Hamilton et al., 2021; Duriez et al., 2014). On the other hand, nicotine monoxide, a component of cigarettes, can damage the endothelium of blood vessels, leading to narrowing of blood vessels and platelet aggregation, increasing the risk of blood vessel obstruction, which can lead to stroke or vascular dementia (Hamilton et al., 2021; Duriez et al., 2014).

In addition to smoking, physical activity may also link MCI and depression. MCI can diminish executive abilities, lead to disuse disorder and affect an individual's daily or social abilities. Many studies have shown that aging can have physiological benefits from physical activity, and that regular physical activity can improve cognitive performance and potentially reduce dementia. This is because healthy exercise increases cardiovascular blood flow and transports oxygen to the brain, thereby increasing neuronal formation and maintaining brain volume (Baumgart et al., 2015). On the other hand, a systematic review showed an inverse curve association between physical activity and depressive events (Pearce et al., 2022). Adults who completed 2.5 h of brisk walking per week had a lower risk of depression compared to those who did not engage in physical activity (Pearce et al., 2022). Even small amounts of physical activity, below the level recommended by public health, can significantly improve mental health (Pearce et al., 2022). In summary, physical activity is another potential socio-behavioral pathway linking MCI and depressive symptoms, whether it is MCI-induced low physical activity that increases the occurrence of depression, or depression-induced low physical activity that increases the occurrence of MCI.

Our study complements previous literature on the bidirectional link between depression and cognitive impairment. For example, Desai et al. (2020) found a bidirectional temporal association between depressive symptoms and cognitive decline through cross-lagged analysis of longitudinal data collected online. Similarly, Wu et al. (2021) in their cross-lagged analysis found that higher depressive symptoms predicted poorer cognitive performance in executive function and at follow-up, lower levels of baseline information processing speed predicted symptoms of depression. However, very few longitudinal studies have investigated whether depressive symptoms are the result of a decline in cognitive function. Some of these studies having found no linkage between a precipitously declining cognitive functionality and high-risk depressive symptoms inferred against a path from MCI to depressive symptoms (Zahodne et al., 2014; John et al., 2021; Teles and Shi, 2021; Zainal and Newman, 2022). Conversely, the present study provides evidence for a bidirectional association between cognitive decline and depressive symptoms, both at the participant and temporal levels. The constant updating of the definition of MCI may account for the heterogeneity in the results of these studies.

Interestingly, we did not find gender and education to moderate the bidirectional association between depressive symptoms and MCI. This presents inconsistency with the findings in previous studies. For instance, Heser et al. (2020) found that for women, but not men, the baseline depressive symptoms led to a nearly twofold increase in the likelihood of cognitive impairment over 13 years. Ng et al. (2009) in their study found that depressive symptoms were associated with

subsequent increased risk of cognitive impairment over two years, but among older men and not their female counterparts. While our study departs from previous studies given no gender moderation effect, we do find some interesting findings in the fully adjusted models when gender is treated as a confounder. In fully adjusted model, women are at higher risk of experiencing subsequent depressive symptoms compared to men. The underlying mechanisms that contribute to this phenomenon are complex. Two complementary hypotheses explain the gendered patterns in mental distress, namely depression. The *vulnerability hypothesis* posits that relative to their male counterparts, women react more intensely to stressful conditions. Women's greater vulnerability is attributed to both, biological predispositions, and a higher susceptibility to everyday stress (McLeod and Kessler, 1990). The *exposure hypothesis* suggests that women simply are exposed to a greater number of stressors than their male peers. For instance, the distribution of psychosocial risks and resources both, in families and workplaces are gendered. Moreover, women are faced with unequal opportunities and daily discrimination (McDonough and Walters, 2001). In addition, given the lingering social stigma attached to mental health conditions, relative to women, men may be less likely to report symptoms of depression (Chatmon, 2020; McKenzie et al., 2022). Reporting or seeking care for depression may be particularly difficult for men given that being mentally distressed, for instance, is not characteristic of what it means to be masculine and resilient (Courtenay, 2000; O'Brien et al., 2005). Depression, instead, may be deemed as a sign of weakness or failure (Chatmon, 2020; McKenzie et al., 2022). From a socio-epidemiological perspective, both hypotheses and processes of social stigmatization may illuminate underlying mechanisms linking gender to high-risk depressive symptoms.

This study also showed that there was insufficient evidence to support that education was an effect modifier of the bidirectional association between depression and MCI. And this finding, too, differs from those found in previous research. For example, Geerlings et al. (2000) in their study on Dutch older adults aged 65 to 84 years found that depression was nearly four times more likely to lead to subsequent cognitive impairment among older adults with over 8 years of education. However, no association between depressive symptoms and cognitive impairment was observed in participants with $\leq$8 years of education (Geerlings et al., 2000). Similarly, Yang et al. (2021) found that having $\geq$8 years of education protected older adults with depression against cognitive deficits over 18 years (Yang et al., 2021). Alternatively, the present study did not find education to be an effect modifier for the association between depressive symptoms and MCI. However, like in the case of gender, in the fully adjusted model of the bidirectional association between depressive symptoms and MCI, education emerged as a strong risk factor. Higher education is linked to lower risk of MCI. This is intuitive given that education is linked to developed brain structure, biochemical metabolism, and synaptic system, which increase the cognitive reserve of the aging brain (Yang et al., 2021; Geerlings et al., 2000). At the same time, high levels of cognitive reserve may help to maintain neuronal activity or improve the compensatory capacity necessary to maintain cognitive function during brain neurodegeneration (Yang et al., 2021; Geerlings et al., 2000). Thus, higher education may reduce MCI associated with depression in old age by improving cognitive reserve in early life. Higher educational attainment also mitigates the effect of baseline MCI on the subsequent high-risk depressive symptoms. Ample evidence based on the social comparison theory suggests that depression stems from feelings of relative inferiority and deprivation (Thornton et al., 2016). Well-educated older adults are less likely to experience inferiority and deprivation relative to their counterparts with less education. Moreover, well-educated older adults are more likely to have greater access to social and economic resources, which means they are likely to experience fewer chronic stressors and possess wider and stable social networks and as such support. Alternatively, lack of a detected interaction does not necessarily mean that the interaction does not exist. Even if the sample seems sufficient, it is likely not given the much greater uncertainty in interaction effects (Gelman et al., 2018).

This study has several strengths. First, the HRS dataset is a large, nationally representative dataset that provides rich data on health-related aspects of older people. As such, this dataset provides a wide range of covariates available for analysis to allow for full adjustment. Second, after screening, this study ended up with over 9000 participants entering the study. Efficacy was calculated separately for high-risk depressive symptoms and MCI. The power was found to be >95 % in all cases, meaning that the likelihood of a Type II error in the results of this study was minimal. Thus, the large sample allowed sufficient power to detect a bidirectional association between depressive symptoms and MCI. Third, this study is based on a longitudinal cohort study with clear temporality, minimising the possibility of reverse causality. Fourth, this study is the first to include data from a 20-year follow-up to explore the bidirectional association between depressive symptoms and MCI. This compensates for the confounding of prodromal symptoms and causes in previous studies due to the short follow-up period. Finally, the study used competing risk models to account for competing risks for other outcomes and more accurately estimate the subsequent MCI and high-risk depressive symptoms.

That said, the present study also is limited in some ways. First, although the use of a composite cognitive score developed by the HRS to assess cognitive function is effective in reducing the reporting bias, measures such as these are based on the default 'fact' that the faster or more severe the cognitive decline, the worse the memory. However, a diagnosis of MCI or dementia may not be directly equated with memory loss. Although memory assessment is performed as part of a cognitive diagnosis, some of these diagnoses, such as in non-amnesic MCI and frontotemporal dementia, do not require the presence of memory impairment. The measurement criteria for MCI remains an unresolved issue (Petersen et al., 2014). Second, selection bias may exist due to attrition and non-responsiveness. According to results in Supplement IV, those in excluded sample were more likely to have baseline exposure, but less likely to have higher education (i.e., higher cognitive reserve) than analytical samples. This means that the excluded sample had more participants at high risk of depressive symptoms/MCI at baseline, as well as participants with low levels of education. These excluded samples tended to be in poorer health or poorer psychological status, with lower levels of education. Thus, the included cohort was relatively presented as a healthier cohort, leading to a weaker association between depressive symptoms and MCI. Thus, findings may be limited in representing the overall aging population in the US. Nevertheless, results based on imputed data revealed miniscule changes.

Third, although the HRS provided a considerable number of covariates for this study, the possibility of residual confounding still cannot be ruled out. Additionally, sensitivity analyses suggest that smoking, alcohol, exercise, BMI, and marital status may not be mediators of this two-way association, but behavioral variables and marital status were collected at baseline, so this study does not really determine whether they are mediators. Further research is needed to consider this point in the future.

Fourth, two separate models were run which are conceptually related to each other. However, our model only captures the effect of the risk factor at baseline on the emergence of the subsequent outcome. We did not consider whether the occurrence of MCI during the follow-up period would have exacerbated the original depression of the participant. While both show clear associations, it is difficult to determine bidirectionality without considering directional pathways in both directions in one model.

Fifth, the specificity and sensitivity of these cut-offs for the CES-D ($\geq$4 to define high-risk depressive symptoms) and cognitive scores (7–11 to define MCI) have been developed, assessed, and endorsed by the HRS team itself (Crimmins et al., 2011; Steffick, 2000). These cut-offs have been used in previous studies to identify prevalent/incident cases with high-risk symptoms or MCI (Crimmins et al., 2011; Mojtabai and Olfson, 2004; Lu et al., 2021). However, dichotomies may result in

loss of information and hide any non-linearity and therefore reduce the statistical power to detect relationships between covariates and outcomes (Altman and Royston, 2006). We re-run all statistical models using continuous CES-D and composite cognitive scores. Results were consistent with the original results based on dichotomous variables. Sixth, we set 1998 as the study baseline and did not include new subcohorts after 1998. This may have resulted in a less representative sample. Finally, the usability of our findings is limited by the lack of clinically based data due to the community-based nature of the HRS data collection sites.

In conclusion, this study is the first to examine the bidirectional and longitudinal association between depressive symptoms and MCI using a competing-risks model. Findings support the bidirectional link between depressive symptoms and MCI. High-risk depressive symptoms are related to a higher risk of subsequent MCI; and MCI predicts subsequent high-risk depression. Though neither gender nor education moderate the bidirectional association, both emerge to be strong risk factors for subsequent depressive symptoms and MCI. As such, public health policies and programs to reduce the risk of depression and MCI among older Americans should pivot their attention to women and those with less formal education.

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CRediT authorship contribution statement

WL designed the study. YG performed the statistical analysis and wrote the first draft of the manuscript. MP, BX and WL contributed to the writing and revising of the manuscript. All authors provided critical feedback on the multiple drafts of the manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.046.

References

Allison, S.L., Koscik, R.L., Cary, R.P., Jonaitis, E.M., Rowley, H.A., Chin, N.A., Zetterberg, H., Blennow, K., Carlsson, C.M., Asthana, S., Bendlin, B.B., Johnson, S.C., 2019. Comparison of different MRI-based morphometric estimates for defining neurodegeneration across the Alzheimer's disease continuum. NeuroImage Clin. 23, 101895 https://doi.org/10.1016/j.nicl.2019.101895.

Altman, D.G., Royston, P., 2006. The cost of dichotomising continuous variables. BMJ 332 (7549), 1080.1. https://doi.org/10.1136/bmj.332.7549.1080.

Alzheimer's Association, 2022. 2022 Alzheimer's disease facts and figures. Alzheimers Dement. 18 (4) https://doi.org/10.1002/alz.12638.

Austin, P.C., Fine, J.P., 2017. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat. Med. 36 (27), 4391–4400. https://doi.org/10.1002/sim.7501.

Baumgart, M., Snyder, H.M., Carrillo, M.C., Fazio, S., Kim, H., Johns, H., 2015. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement. 11 (6), 718–726. https://doi.org/10.1016/j.jalz.2015.05.016.

Bhang, I., Mogle, J., Hill, N., Whitaker, E.B., Bhargava, S., 2019. Examining the temporal associations between self-reported memory problems and depressive symptoms in older adults. Aging Ment. Health 24 (11), 1864–1871. https://doi.org/10.1080/13607863.2019.1647135.

Brailean, A., Aartsen, M.J., Muniz-Terrera, G., Prince, M., Prina, A.M., Comijs, H.C., Huisman, M., Beekman, A., 2016. Longitudinal associations between late-life depression dimensions and cognitive functioning: a cross-domain latent growth curve analysis. Psychol. Med. 47 (4), 690–702. https://doi.org/10.1017/s003329171600297x.

Caffò, A.O., Spano, G., Tinella, L., Lopez, A., Ricciardi, E., Stasolla, F., Bosco, A., 2022. The prevalence of amnestic and non-amnestic mild cognitive impairment and its association with different lifestyle factors in a south Italian elderly population. Int. J. Environ. Res. Public Health 19 (5), 3097. https://doi.org/10.3390/ijerph19053097.

Chatmon, B.N., 2020. Males and mental health stigma. Am. J. Mens Health 14 (4), 155798832094932. https://doi.org/10.1177/1557988320949322.

Courtenay, W.H., 2000. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Social Sci. Med. (1982) 50 (10), 1385–1401. https://doi.org/10.1016/s0277-9536(99)00390-1.

Crimmins, E.M., Kim, J.K., Langa, K.M., Weir, D.R., 2011. Assessment of cognition using surveys and neuropsychological assessment: the health and retirement study and the aging, demographics, and memory study. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 66B (Supplement 1), i162–i171. https://doi.org/10.1093/geronb/gbr048.

Dal Forno, G., Palermo, M.T., Donohue, J.E., Karagiozis, H., Zonderman, A.B., Kawas, C. H., 2005. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann. Neurol. 57 (3), 381–387. https://doi.org/10.1002/ana.20405.

Desai, R., Charlesworth, G.M., Brooker, H.J., Potts, H.W.W., Corbett, A., Aarsland, D., Ballard, C.G., 2020. Temporal relationship between depressive symptoms and cognition in mid and late life: a longitudinal cohort study. J. Am. Med. Dir. Assoc. 21 (8) https://doi.org/10.1016/j.jamda.2020.01.106.

Disner, S.G., Beevers, C.G., Haigh, E.A.P., Beck, A.T., 2011. Neural mechanisms of the cognitive model of depression. Nat. Rev. Neurosci. 12 (8), 467–477. https://doi.org/10.1038/nrn3027.

Duriez, Q., Crivello, F., Mazoyer, B., 2014. Sex-related and tissue-specific effects of tobacco smoking on brain atrophy: assessment in a large longitudinal cohort of healthy elderly. Front. Aging Neurosci. 6 https://doi.org/10.3389/fnagi.2014.00299.

Fisher, G.G., Ryan, L.H., 2017. Overview of the health and retirement study and introduction to the special issue. Work Aging Retire. 4 (1), 1–9. https://doi.org/10.1093/workar/wax032.

Fluharty, M., Taylor, A.E., Grabski, M., Munafò, M.R., 2016. The association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tob. Res. 19 (1), 3–13. https://doi.org/10.1093/ntr/ntw140.

Gale, C.R., Allerhand, M., Deary, I.J., 2012. Is there a bidirectional relationship between depressive symptoms and cognitive ability in older people? A prospective study using the English Longitudinal Study of Ageing. Psychol. Med. 42 (10), 2057–2069. https://doi.org/10.1017/s0033291712000402.

Geerlings, M.I., Bouter, L.M., Schoevers, R.A., Beekman, A.T.F., Jonker, C., Deeg, D.J.H., Van Tilburg, W., Adèr, H.J., Schmand, B., 2000. Depression and risk of cognitive decline and Alzheimer's disease. Br. J. Psychiatry 176 (6), 568–575. https://doi.org/10.1192/bjp.176.6.568.

Gelman, A., Cook, S., Carpenter, B., Jakulin, A., Price, P., O'Rourke, K., Simpson, D., Vehtari, A., Lee, D., Hullman, J., Gabry, J., Novik, E., Betancourt, M., Thomas, J., Yao, Y., Wolkovich, L., Mitchell, S., Kennedy, L., Bafumi, J., Weber, S., 2018. You need 16 times the sample size to estimate an interaction than to estimate a main effect. In: Statistical Modeling, Causal Inference, and Social Science. Statmodeling.stat.columbia.edu. https://statmodeling.stat.columbia.edu/2018/03/15/need-16-times-sample-size-estimate-interaction-estimate-main-effect/ (March 15).

Gujral, S., Aizenstein, H., Reynolds, C.F., Butters, M.A., Erickson, K.I., 2017. Exercise effects on depression: possible neural mechanisms. Gen. Hosp. Psychiatry 49 (49), 2–10. https://doi.org/10.1016/j.genhosppsych.2017.04.012.

Hamilton, O.K.L., Cox, S.R., Okely, J.A., Conte, F., Ballerini, L., Bastin, M.E., Corley, J., Taylor, A.M., Page, D., Gow, A.J., Muñoz Maniega, S., Redmond, P., Valdés-Hernández, M. del C., Wardlaw, J.M., Deary, I.J., 2021. Cerebral small vessel disease burden and longitudinal cognitive decline from age 73 to 82: the Lothian Birth Cohort 1936. Transl. Psychiatry 11 (1). https://doi.org/10.1038/s41398-021-01495-4.

Health and Retirement Study Survey Research Center, 2021. About | Health and Retirement Study. Umich.edu. https://hrs.isr.umich.edu/about.

Heser, K., Kleineidam, L., Pabst, A., Wiese, B., Roehr, S., Löbner, M., Hajek, A., van der Leeden, C., Angermeyer, M.C., Scherer, M., König, H.-H., Maier, W., Riedel-Heller, S. G., Wagner, M., 2020. Sex-specific associations between depressive symptoms and risk for subsequent dementia. J. Alzheimers Dis. 74 (1), 151–161. https://doi.org/10.3233/jad-190770.

Institute of Health Metrics and Evaluation, 2019. GBD Results Tool | GHDx. Ghdx.healthdata.org. http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b.

John, A., Rusted, J., Richards, M., Gaysina, D., 2021. Bidirectional relation between affective symptoms and cognitive function from middle to late adulthood: a population-based birth cohort study. Aging Ment. Health 25 (9), 1642–1648. https://doi.org/10.1080/13607863.2020.1758916.

Langa, K.M., Levine, D.A., 2014. The diagnosis and management of mild cognitive impairment. JAMA 312 (23), 2551. https://doi.org/10.1001/jama.2014.13806.

Lee, G.J., Lu, P.H., Hua, X., Lee, S., Wu, S., Nguyen, K., Teng, E., Leow, A.D., Jack, C.R., Toga, A.W., Weiner, M.W., Bartzokis, G., Thompson, P.M., Alzheimer's Disease

Neuroimaging Initiative, 2012. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. Biol. Psychiatry 71 (9), 814–821. https://doi.org/10.1016/j.biopsych.2011.12.024.
LeMoult, J., Gotlib, I.H., 2019. Depression: a cognitive perspective. Clin. Psychol. Rev. 69 (69), 51–66. https://doi.org/10.1016/j.cpr.2018.06.008.
Linnemann, C., Lang, U.E., 2020. Pathways connecting late-life depression and dementia. Front. Pharmacol. 11 https://doi.org/10.3389/fphar.2020.00279.
Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., Cui, R., 2017. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural Plast. 2017, 1–11. https://doi.org/10.1155/2017/6871089.
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A., Orgeta, V., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396 (10248), 413–446.
Lu, W., Pai, M., Scholes, S., Xue, B., 2021. Do depressive symptoms link chronic diseases to cognition among older adults? Evidence from the Health and Retirement Study in the United States. J. Affect. Disord. 294, 357–365. https://doi.org/10.1016/j.jad.2021.07.012.
Ma, L., 2020. Depression, Anxiety, and Apathy in Mild Cognitive Impairment. Current Perspectives. Frontiers in Aging Neuroscience 12. https://doi.org/10.3389/fnagi.2020.00009.
McDonough, P., Walters, V., 2001. Gender and health: reassessing patterns and explanations. Soc. Sci. Med. 52 (4), 547–559. https://doi.org/10.1016/s0277-9536(00)00159-3.
McKenzie, S.K., Oliffe, J.L., Black, A., Collings, S., 2022. Men's experiences of mental illness stigma across the lifespan: a scoping review. Am. J. Mens Health 16 (1), 155798832210747. https://doi.org/10.1177/15579883221074789.
McLeod, J.D., Kessler, R.C., 1990. Socioeconomic status differences in vulnerability to undesirable life events. J. Health Soc. Behav. 31 (2), 162. https://doi.org/10.2307/2137170.
Mojtabai, R., Olfson, M., 2004. Major depression in community-dwelling middle-aged and older adults: prevalence and 2- and 4-year follow-up symptoms. Psychol. Med. 34 (4), 623–634. https://doi.org/10.1017/s0033291703001764.
National Institute of Mental Health, 2022. Major depression, National Institute of Mental Health. https://www.nimh.nih.gov/health/statistics/major-depression.
Ng, T.P., Niti, M., Zaw, M.H., Kua, E.H., 2009. Depressive symptoms and incident cognitive impairment in cognitively well-functioning older men and women. J. Am. Geriatr. Soc. 57 (6), 1058–1063. https://doi.org/10.1111/j.1532-5415.2009.02262.x.
O'Brien, R., Hunt, K., Hart, G., 2005. 'It's caveman stuff, but that is to a certain extent how guys still operate': men's accounts of masculinity and help seeking. Soc. Sci. Med. (1982) 61 (3), 503–516. https://doi.org/10.1016/j.socscimed.2004.12.008.
Pearce, M., Garcia, L., Abbas, A., Strain, T., Schuch, F.B., Golubic, R., Kelly, P., Khan, S., Utukuri, M., Laird, Y., Mok, A., Smith, A., Tainio, M., Brage, S., Woodcock, J., 2022. Association between physical activity and risk of depression: a systematic review and meta-analysis. JAMA Psychiatry 79 (6). https://doi.org/10.1001/jamapsychiatry.2022.0609.
Petersen, R.C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., Fratiglioni, L., 2014. Mild cognitive impairment: a concept in evolution. J. Intern. Med. 275 (3), 214–228. https://doi.org/10.1111/joim.12190.
Petersen, R.C., Lopez, O., Armstrong, M.J., Getchius, T.S.D., Ganguli, M., Gloss, D., Gronseth, G.S., Marson, D., Pringsheim, T., Day, G.S., Sager, M., Stevens, J., Rae-Grant, A., 2018. Practice guideline update summary: mild cognitive impairment. Neurology 90 (3), 126–135. https://doi.org/10.1212/wnl.0000000000004826.
Schaefer, J.D., Scult, M.A., Caspi, A., Arseneault, L., Belsky, D.W., Hariri, A.R., Harrington, H., Houts, R., Ramrakha, S., Poulton, R., Moffitt, T.E., 2017. Is low cognitive functioning a predictor or consequence of major depressive disorder? A test in two longitudinal birth cohorts. Dev. Psychopathol. 1–15 https://doi.org/10.1017/s095457941700164x.
Staff, R.T., Murray, A.D., Deary, I.J., Whalley, L.J., 2004. What provides cerebral reserve? Brain 127 (5), 1191–1199. https://doi.org/10.1093/brain/awh144.
Steffick, D.E., 2000. Documentation of affective functioning measures in the health and retirement study. In: HRS/AHEAD Documentation Report DR-005. Available at. http://www.umich.edu/yhrswww/docs/userg/dr-005.pdf. Available at.
Teles, M., Shi, D., 2021. Depressive symptoms as a predictor of memory decline in older adults: a longitudinal study using the dual change score model. Arch. Gerontol. Geriatr. 97, 104501 https://doi.org/10.1016/j.archger.2021.104501.
Thornton, R.L.J., Glover, C.M., Cené, C.W., Glik, D.C., Henderson, J.A., Williams, D.R., 2016. Evaluating strategies for reducing health disparities by addressing the social determinants of health. Health Aff. 35 (8), 1416–1423. https://doi.org/10.1377/hlthaff.2015.1357.
Vos, T., Allen, C., Arora, M., Barber, R.M., Bhutta, Z.A., Brown, A., Carter, A., Casey, D. C., Charlson, F.J., Chen, A.Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D.J., Dilegge, T., Erskine, H.E., Ferrari, A.J., Fitzmaurice, C., Fleming, T., Forouzanfar, M. H., 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388 (10053), 1545–1602. https://doi.org/10.1016/s0140-6736(16)31678-6.
World Health Organization, 2021a. Dementia. Www.who.int. https://www.who.int/zh/news-room/fact-sheets/detail/dementia.
World Health Organization, 2021b. Depression, World Health Organization; World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression (September 13).
World Health Organization, 2022. Ageing and health, World Health Organization; World Health Organization: WHO. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (October 1).
Wraw, C., Deary, I.J., Der, G., Gale, C.R., 2016. Intelligence in youth and mental health at age 50. Intelligence 58, 69–79. https://doi.org/10.1016/j.intell.2016.06.005.
Wu, Z., Zhong, X., Peng, Q., Chen, B., Zhang, M., Zhou, H., Mai, N., Huang, X., Ning, Y., 2021. Longitudinal association between cognition and depression in patients with late-life depression: a cross-lagged design study. Front. Psychiatry 12. https://doi.org/10.3389/fpsyt.2021.577058.
Yang, W., Li, X., Pan, K., Yang, R., Song, R., Qi, X., Pedersen, N.L., Xu, W., 2021. Association of life-course depression with the risk of dementia in late life: a nationwide twin study. Alzheimers Dement. 17 (8), 1383–1390. https://doi.org/10.1002/alz.12303.
Yin, J., Lassale, C., Steptoe, A., Cadar, D., 2019. Exploring the bidirectional associations between loneliness and cognitive functioning over 10 years: the English longitudinal study of ageing. Int. J. Epidemiol. 48 (6), 1937–1948. https://doi.org/10.1093/ije/dyz085.
Yu, J., Lim, H.-Y., Abdullah, F.N. d/o M., Chan, H.-M., Mahendran, R., Ho, R., Kua, E.-H., Power, M.J., Feng, L., 2017. Directional associations between memory impairment and depressive symptoms: data from a longitudinal sample and meta-analysis. Psychol. Med. 48 (10), 1664–1672. https://doi.org/10.1017/s0033291717003154.
Yu, B., Zhang, X., Wang, C., Sun, M., Jin, L., Liu, X., 2020. Trends in depression among adults in the United States, NHANES 2005–2016. J. Affect. Disord. 263, 609–620. https://doi.org/10.1016/j.jad.2019.11.036.
Zahodne, L.B., Stern, Y., Manly, J.J., 2014. Depressive symptoms precede memory decline, but not vice versa, in non-demented older adults. J. Am. Geriatr. Soc. 62 (1), 130–134. https://doi.org/10.1111/jgs.12600.
Zainal, N.H., Newman, M.G., 2022. A cross-lagged prospective network analysis of depression and anxiety and cognitive functioning components in midlife community adult women. Psychol. Med. 1–12 https://doi.org/10.1017/s0033291722000848.