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Intertwined depressive and cognitive trajectories and the risk of dementia and death in older adults: a competing risk analysis

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ABSTRACT

Background Depressive symptoms and cognitive impairment often interact, rendering their associations controversial. To date, their joint trajectories and associations with dementia and death remain underexplored.

Aims To explore the interactions between depressive symptoms and cognitive function, their developmental trajectories and the associations with all-cause dementia, Alzheimer's disease (AD) and all-cause death in older adults.

Methods Data were from the Health and Retirement Study. Depressive symptoms and cognitive function were measured using the 8-item Centre for Epidemiologic Studies Depression Scale and the Telephone Interview of Cognitive Status, respectively. All-cause dementia and AD were defined by self-reported or proxy-reported physician diagnoses. All-cause death was determined by interviews. The restricted cubic spline, group-based trajectory modelling and subdistribution hazard regression were used.

Results Significant interactions between depressive symptoms and cognitive function in 2010 in their association with new-onset all-cause dementia and AD from 2010 to 2020 were found, especially in women (p for interaction <0.05). Independent trajectory analysis showed that emerging or high (vs no) depressive trajectories and poor or rapidly decreased cognitive trajectories (vs very good) from 1996 to 2010 were at significantly higher risk of subsequent all-cause dementia, AD and all-cause death. 15 joint trajectories of depressive symptoms and cognitive function from 1996 to 2010 were determined, where rapidly decreased cognitive function was more common in those with no depressive symptoms. Compared with older adults with the trajectory of no depressive symptoms and very good cognitive function, those with the trajectory of no depressive symptoms but rapidly decreased cognitive function were much more likely to develop new-onset all-cause dementia and death, with subdistribution hazard ratios (95% confidence intervals) of 4.47 (2.99 to 6.67) and 1.84 (1.43 to 2.36), especially in women.

Conclusions To effectively mitigate the risk of dementia and death, it is crucial to acknowledge the importance of preventing cognitive decline in older adults without depressive symptoms, particularly in women.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depressive symptoms and cognitive impairment interact, rendering their joint trajectories and associations with new-onset dementia and death worth exploring.

WHAT THIS STUDY ADDS

⇒ We found significant interactions between depressive symptoms and cognitive function in their associations with dementia. Among 15 joint trajectories of depressive symptoms and cognitive function, those characterised by rapid cognitive decline and low depressive symptoms were at comparable or even higher risk of all-cause dementia and death compared with those with long-term comorbid high depressive symptoms and poor cognitive function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Concerns about older adults who show significant disparities between mental health and cognitive status can help with the early prevention of dementia and death.

INTRODUCTION

With the global ageing process, the last decades have witnessed a growing interest in the epidemiology of dementia.[1 2] Recent evidence has revealed that Alzheimer's disease (AD)-related dementia is now the fifth leading cause of death worldwide and among adults aged 65 and older in the USA, and its prevalence is increasing.[1 2] Accordingly, implementing primary prevention strategies for dementia and death is of paramount importance.

Depressive symptoms and cognitive impairment among older adults have evolved into serious public health concerns.[3 4] Although emerging meta-analyses have attempted to elucidate the relationship between depressive symptoms and cognitive impairment, the findings have been controversial.[5 6] Previous research suggests that the association

between depressive symptoms and cognitive decline is intricate, with each exerting a reciprocal effect on the other.[5 6] Consequently, incorporating the joint trajectories of depressive symptoms and cognitive function when investigating their interactions may provide new perspectives.

Either depressive symptoms or cognitive impairment, as well as their comorbidity, represent salient risk factors for dementia and death.[7 8] As depressive and cognitive statuses typically deteriorate prior to dementia and death, investigating their interactions during this risk period may offer greater insight into preventing dementia and death. Despite several studies reporting significant interactions between depressive symptoms and cognitive function in their association with olfactory identification (a risk factor for dementia) and anosognosia, their findings are limited by the small sample size and cross-sectional design.[9 10] Related evidence on all-cause death is also limited. Furthermore, there is little research regarding the dynamic trajectories of cognitive function and depressive symptoms, as well as the potential sex differences among older adults in the USA.

To address these research gaps, we conducted a prospective study to explore the interactions between depressive symptoms and cognitive function, their joint trajectories and the associations with new-onset all-cause dementia, AD and all-cause death in older adults based on a US cohort.

METHODS

Study population

The present study relies on data from the Health and Retirement Study (HRS), a nationally representative cohort that collected comprehensive socioeconomic and health information from US adults aged 50 years and older. The baseline survey was conducted in 1992, with subsequent follow-up visits every 2 years. Reinterview rates remained between 80% and 89%, and proxies (9%) were used when respondents were unable to complete the survey on their own. The HRS was supported by the National Institute on Aging (NIA U01AG009740) and was approved by the Institute for Social Research and Survey Research Center of the University of Michigan (IRB Protocol: HUM00061128).[11] All participants provided written informed consent, and detailed information can be found at https://hrs.isr.umich.edu/data-products/restricted-data/available-products/11516.

In this study, we used the HRS 2010 as the baseline, with follow-ups until 2020. The cognitive and depressive trajectories were fitted using the HRS 1996–2010. Figure 1 shows the flowchart of this study. Of the 22 034 participants recruited in 2010, those who were aged <50 or had missing data on education (n=904); who had missing data on depressive symptoms or cognitive function in 2010 (n=1367); and who had prior all-cause dementia or AD (n=341) were excluded, leaving 19 422 analytical samples.

Measurement of depressive symptoms

The depressive symptoms in the HRS were assessed using an 8-item subset of the Centre for Epidemiologic Studies Depression Scale (CESD-8) which consisted of 'yes/no' responses to items including: (1) Felt depressed; (2) Everything was an effort; (3) Sleep was restless; (4) I was happy; (5) Felt lonely; (6) I enjoyed life; (7) Felt sad; and (8) Could not get going. Participants who answered 'yes' were assigned as 1. The validity and reliability of CESD-8 have been confirmed among older adults.[12] The final CESD score, ranging from 0 to 8, was calculated by summing up the participants' responses to each item, with higher scores indicating more severe depressive symptoms. Participants with a CESD score of 4 or higher were defined as having depressive symptoms at baseline.[13]

Subsequently, the CESD scores in 2010 were calculated as z scores based on the mean (standard deviation (SD)) in 2010: (CESD scores: 1.50 (2.01)). Moreover, CESD

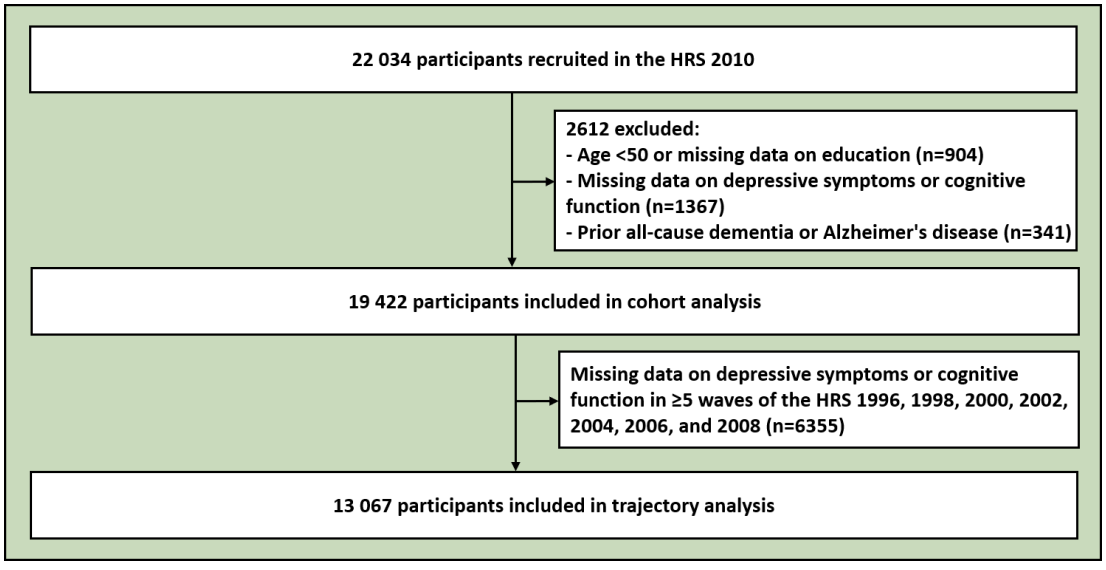

Figure 1 Study flowchart. HRS, Health and Retirement Study.

Table 1 Characteristics of participants included without prior all-cause dementia at baseline

Baseline characteristics	No new-onset all-cause dementia or death (n=14 938)	New-onset all-cause dementia (n=1263)	New-onset all-cause death (n=3221)	χ^2	P value
Age, year	62.0 (56.0–71.0)	76.0 (69.0–82.0)	76.0 (68.0–83.0)	3310.52	<0.001
Sex, n (%)				65.23	<0.001
Men	6086 (40.7)	491 (38.9)	1552 (48.2)		
Women	8852 (59.3)	772 (61.1)	1669 (51.8)		
Race, n (%)				81.46	<0.001
White/Caucasian	10 593 (70.9)	978 (77.4)	2502 (77.7)		
Black or others	4302 (28.8)	284 (22.5)	717 (22.3)		
Missing	43 (0.3)	1 (0.1)	2 (0.1)		
Education, n (%)				305.39	<0.001
Below high school	3223 (21.6)	411 (32.5)	990 (30.7)		
High school	4159 (27.8)	377 (29.8)	1053 (32.7)		
College	3903 (26.1)	247 (19.6)	702 (21.8)		
University or above	3653 (24.5)	228 (18.1)	476 (14.8)		
Household income, n (%)				787.57	<0.001
Bottom tertile	4357 (29.2)	578 (45.8)	1533 (47.6)		
Middle tertile	4906 (32.8)	452 (35.8)	1159 (36.0)		
Top tertile	5675 (38.0)	233 (18.4)	529 (16.4)		
Marital status, n (%)				301.26	<0.001
Married	9999 (66.9)	699 (55.3)	1671 (51.9)		
Single	4934 (33.0)	564 (44.7)	1549 (48.1)		
Missing	5 (0.0)	0 (0.0)	1 (0.0)		
Smoking history, n (%)				147.89	<0.001
Never smoking	6724 (45.0)	566 (44.8)	1076 (33.4)		
Ever smoking	8140 (54.5)	689 (54.6)	2123 (65.9)		
Missing	74 (0.5)	8 (0.6)	22 (0.7)		
Drinking history, n (%)				423.79	<0.001
Never drinking	5790 (38.8)	733 (58.0)	1780 (55.3)		
Ever drinking	9148 (61.2)	530 (42.0)	1441 (44.7)		
Vigorous exercise, n (%)				645.57	<0.001
Never	7516 (50.3)	804 (63.7)	2368 (73.5)		
≤1 day per week	3219 (21.5)	198 (15.7)	396 (12.3)		
>1 day per week	4180 (28.0)	253 (20.0)	445 (13.8)		
Missing	23 (0.2)	8 (0.6)	12 (0.4)		
Body weight index, n (%)				215.92	<0.001
Normal	3715 (24.9)	487 (38.6)	1121 (34.8)		
Abnormal	10 936 (73.2)	755 (59.8)	2045 (63.5)		
Missing	287 (1.9)	21 (1.7)	55 (1.7)		
Number of chronic diseases, n (%)				1123.70	<0.001
0	2987 (20.0)	99 (7.8)	167 (5.2)		
1	4140 (27.7)	239 (18.9)	409 (12.7)		
2 or more	7810 (52.3)	925 (73.2)	2645 (82.1)		
Missing	1 (0.0)	0 (0.0)	0 (0.0)		
Cognitive z scores in 2010	0.15 (−0.58 to 0.73)	−0.52 (−1.25 to 0.21)	−0.13 (−0.86 to 0.57)	475.77	<0.001
Depressive z scores in 2010	−0.25 (−0.74 to 0.25)	−0.25 (−0.74 to 0.75)	−0.25 (−0.74 to 0.75)	295.49	<0.001

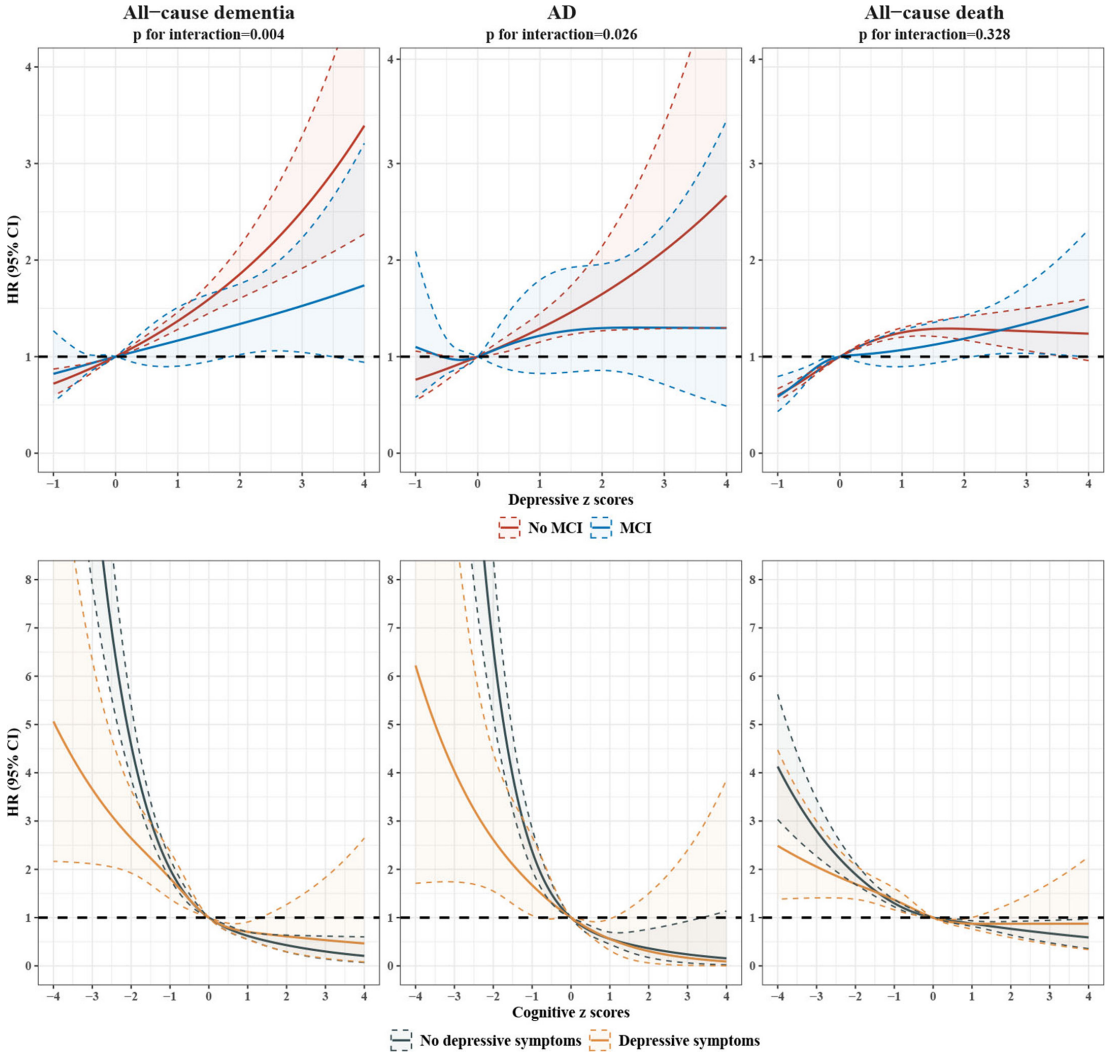

Figure 2 Dose-risk associations of interacted depressive symptoms and cognitive function in 2010 with new-onset all-cause dementia, AD and all-cause death from 2010 to 2020: restricted cubic spline. AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment.

scores from 1996 to 2008 were also converted to z scores based on the mean (SD) in 2010.

Measurement of cognitive function

The cognitive function in the HRS study was measured using a modified version of the Telephone Interview of Cognitive Status, which included episodic memory, serial-7 number subtraction questions and counting backward tests.[14] Episodic memory was determined by the sum of immediate and delayed word recalls using 10 random words. The serial-7 number subtraction questions referred to five serial subtractions of 7 from 100 (0–5). For the counting backward test, participants had to count backward from 20 as fast as possible. Scoring was based on consecutive counts on the first attempt (two points) and successful counts on the second attempt (one point). The total cognitive function score ranged from 0 to 27, with a higher score indicating better cognitive function.

The cognitive scores in 2010 were then calculated as each-5-year-age-stratified and education-stratified z scores ((cognitive scores–means)/SDs) according to online supplemental table S1. Those with a cognitive z score in 2010 of <−1 were defined as having mild cognitive impairment at baseline. Subsequently, the cognitive scores from 1996 to 2008 were converted to z scores based on the means (SDs) in 2010.

Measurement of dementia and death

All-cause dementia and AD were defined by self-reported or proxy-reported physician diagnoses from 2010 to 2020. The vital status of participants was determined by extracting data from the respondent's exit interview or the interview of their spouses/partners, which recorded the year and month of death.

Measurement of covariates

At baseline, information on age, sex (men, women), race (white/Caucasian, black or others), education (below high school, high school, college, university and above), household income (bottom, middle, top tertiles), marital status (married, single), smoking history (ever, never), drinking history (ever, never), vigorous exercise (never,

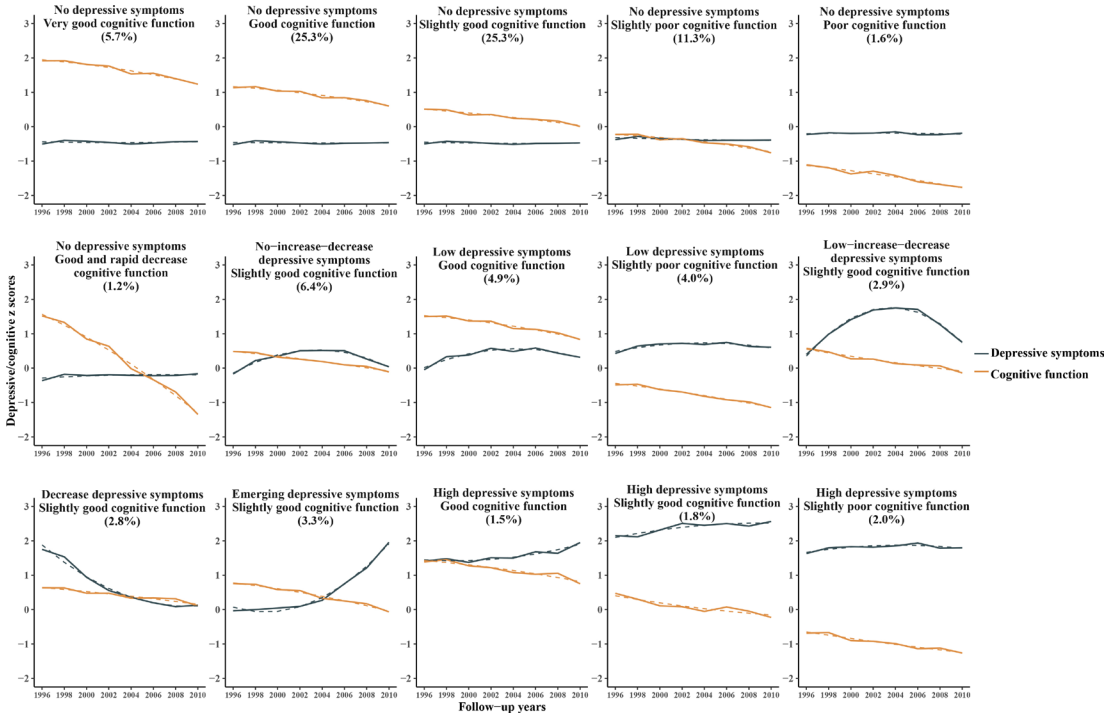

Figure 3 Joint trajectories of depressive symptoms and cognitive function from 1996 to 2010: group-based trajectory model.

≤1 day per week, >1 day per week), weight status (normal (body mass index <25 kg/m^2), abnormal (body mass index ≥25 kg/m^2)) and a number of chronic diseases (hypertension, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems and arthritis, divided into 0, 1, and 2 or more) was collected through questionnaires. Participants who had missing information on race, marital status, smoking history, vigorous exercise, weight status and a number of chronic diseases were classified as 'missing'.

Table 2 Associations of joint trajectories of depressive symptoms and cognitive function from 1996 to 2010 with new-onset all-cause dementia, Alzheimer's disease and all-cause death from 2010 to 2020: subdistribution hazard regression

Joint trajectories		All-cause dementia	Alzheimer's disease	All-cause death
Depressive symptom	Cognitive function	sHR (95% CI)		
No	Very good	Reference	Reference	Reference
No	Good	1.00 (0.74 to 1.36)	1.21 (0.68 to 2.17)	1.00 (0.86 to 1.17)
No	Slightly good	1.37 (1.01 to 1.85)	2.22 (1.25 to 3.94)	1.07 (0.91 to 1.25)
No	Slightly poor	2.23 (1.62 to 3.07)	3.37 (1.87 to 6.08)	1.31 (1.10 to 1.56)
No	Poor cognitive	3.13 (1.87 to 5.22)	5.19 (2.29 to 11.76)	1.88 (1.41 to 2.52)
No	Good and rapid decrease	4.47 (2.99 to 6.67)	6.82 (3.42 to 13.60)	1.84 (1.43 to 2.36)
No-increase-decrease	Slightly good	1.91 (1.35 to 2.70)	2.70 (1.43 to 5.09)	1.23 (1.02 to 1.50)
Low	Good	1.21 (0.82 to 1.78)	1.90 (0.96 to 3.76)	1.18 (0.97 to 1.43)
Low	Slightly poor	3.18 (2.21 to 4.58)	4.79 (2.53 to 9.07)	1.68 (1.36 to 2.08)
Low-increase-decrease	Slightly good	2.34 (1.56 to 3.52)	2.97 (1.42 to 6.22)	1.39 (1.10 to 1.76)
Decrease	Slightly good	1.53 (0.96 to 2.44)	1.69 (0.71 to 4.02)	1.39 (1.10 to 1.75)
Emerging	Slightly good	1.73 (1.14 to 2.63)	2.15 (0.99 to 4.66)	1.57 (1.26 to 1.96)
High	Good	1.82 (1.09 to 3.04)	1.63 (0.59 to 4.51)	1.24 (0.93 to 1.64)
High	Slightly good	3.06 (1.91 to 4.91)	2.78 (1.11 to 6.95)	1.54 (1.16 to 2.06)
High	Slightly poor	4.44 (2.94 to 6.69)	10.22 (5.34 to 19.55)	1.52 (1.15 to 2.02)

All models were adjusted for age, sex, race, education, household income, marital status, smoking history, drinking history, vigorous exercise, weight status and number of chronic diseases.
CI, confidence interval; sHR, subdistribution hazard ratio.

Statistical analysis

The baseline characteristics of included participants were described as medians with interquartile ranges for continuous variables given their non-normal distribution and frequency and percentage (%) for categorical variables. To compare characteristics, differences in continuous or ordered categorical variables were assessed by Kruskal-Wallis tests while those of binary or unordered categorical variables were assessed by χ^2 tests.

Based on the 'rms' package in R,[15] the Cox proportional hazard regression-based restricted cubic spline (RCS) was used to investigate the dose-risk associations (hazard ratio (HR) and 95% confidence interval (CI)) of depressive and cognitive z scores in 2010 with new-onset all-cause dementia, AD and all-cause death from 2010 to 2020. The RCS used four knots at prespecified locations according to the percentiles of the distribution of exposure: 5%, 25%, 50% and 75%. Subsequently, the mild cognitive impairment-stratified dose-risk associations of depressive z scores in 2010 with new-onset all-cause dementia, AD and all-cause death from 2010 to 2020, and depressive symptoms-stratified dose-risk associations between cognitive z scores in 2010 and these outcomes were also explored using the RCS. The interactions between depressive and cognitive z scores were assessed using their multiplication term, that is, 'depressive z scores|cognitive z scores'. The p values of the multiplication term less than 0.05 referred to significant interactions. All these associations were fully adjusted for age, sex, race, education, household income, marital status, smoking history, drinking history, vigorous exercise, weight status and number of chronic diseases. Furthermore, stratified analyses of men and women were conducted to explore the sex differences in these associations.

Group-based trajectory modelling (GBTM) was further conducted to analyse the independent trajectories of depressive symptoms and cognitive function from 1996 to 2010. In this study, participants with four or more time-point depressive and cognitive data were used to conduct GBTM, based on the 'proc traj' procedure in the SAS.[16] Two-order and three-order trajectory models were set to explore the 14-year developmental trajectories of depressive symptoms and cognitive function. Models with lower Bayesian information criteria, lower Akaike's information criterion and higher entropy were selected. Furthermore, the fully adjusted associations (subdistribution HR (sHR) and 95% CI) of independent depressive and cognitive trajectories with new-onset all-cause dementia, AD and all-cause death were investigated using the subdistribution hazard regression. Subdistribution hazard regression is a type of competing risk analysis introduced by Fine and Gray, which is preferable when estimating actual risks and prognosis.[17] In this study, we viewed all-cause death as the competing event of all-cause dementia and AD to conduct the subdistribution hazard regression, based on the 'cmprsk' package in R.[18] Sensitivity analysis based on complete-case analysis was further conducted to verify the robustness of the data imputation.

Subsequently, the GBTM was used to identify the joint trajectories of depressive symptoms and cognitive function from 1996 to 2010. The orders of depressive and cognitive trajectories were the same as those selected in the independent trajectory analysis. The fully adjusted associations of the joint trajectories with new-onset all-cause dementia, AD and all-cause death after 2010 in total participants, men, and women were also investigated using subdistribution hazard regression.

Reporting of this study was done under Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Analyses were performed using SAS (V.9.4, SAS Institute, licensed to Peking University School of Public Health-R&D LIC) and R statistical software V.4.2.3 (R Project for Statistical Computing). All analyses were two-sided.

RESULTS

Of 19 422 participants (41.9% men) aged 65.0 (57.0–74.0) without prior dementia in 2010, 1263 developed all-cause dementia (475 cases of AD) and 3221 developed all-cause death during the 10 years of follow-up. Table 1 shows the baseline characteristics of the participants included after accounting for the competing risks of all-cause death.

Online supplemental figure S1 shows significant dose-risk associations of depressive symptoms and cognitive function in 2010 with new-onset all-cause dementia, AD and all-cause death, which remain more evident in women. Significant interactions between depressive symptoms and cognitive function in 2010 in their associations with all-cause dementia and AD, but not all-cause death, are shown in figure 2. For instance, decreased cognitive function tends to exhibit higher risks of all-cause dementia and AD in older adults with no depressive symptoms than in those with depressive symptoms. Sex-stratified analysis in online supplemental figure S2 further indicates that the interactions are more pronounced in women (p for interaction=0.007 for all-cause dementia).

The fitted statistics for independent depressive and cognitive trajectories are shown in online supplemental table S2. Four three-order depressive trajectories and seven two-order cognitive trajectories were determined. Corresponding growth parameters and trajectories are shown in online supplemental table S3 and online supplemental figure S3. Online supplemental table S4 demonstrates that older adults who developed high or emerging (vs no) depressive trajectories and who developed worse or decreased (vs very good) cognitive trajectories were more likely to develop all-cause dementia, AD and all-cause death, which remained similar in sensitivity analysis based on complete-case analysis (online supplemental table S5).

Furthermore, 15-class joint trajectories were selected, as shown in online supplemental table S6. Corresponding growth parameters and trajectories are shown in online supplemental table S7 and figure 3. Rapidly decreased cognitive function seems to be more common in older

adults with no depressive symptoms. When compared with older adults with the trajectory of no depressive symptoms and very good cognitive function, they are at significantly higher risks of all-cause dementia, AD and all-cause death, with sHRs (95% CIs) of 4.47 (2.99 to 6.67), 6.82 (3.42 to 13.60) and 1.84 (1.43 to 2.36), respectively (table 2). Interestingly, older adults with no depressive symptoms but poor cognitive function seem to exhibit comparable or even higher risks of all-cause dementia and death than those with long-term poor depressive and cognitive statuses, especially in women (online supplemental table S8).

DISCUSSION

Main findings

In this cohort study, we found that rapid cognitive decline was more common in older adults with lower depressive symptoms. Interestingly, older adults who showed significant disparities between depressive status and cognitive status, such as no depressive symptoms but poor cognitive function, exhibited comparable or even higher risks of dementia and all-cause death when compared with those who had long-term comorbid depressive symptoms and cognitive decline, particularly evident among women.

Existing research has established the positive associations of increasing depressive symptoms and accelerated cognitive decline with subsequent dementia and death.[7 8] Depressive symptoms and cognitive decline are both associated with changes in brain structure and function. The reduced cortical thickness and surface area can contribute to cognitive decline.[19] Depressive symptoms, on the other hand, affect brain regions involved in emotional regulation and cognitive processing.[20] All of these are precursors or risk factors for dementia. Furthermore, depressive symptoms and cognitive decline can lead to chronic stress and trigger an inflammatory response.[21] Elevated inflammation and oxidative stress can further increase the risk of dementia by damaging neurons and promoting the formation of harmful proteins in the brain.[22 23] Additionally, depressive symptoms and cognitive decline can result in social isolation and a lack of mental stimulation, which, in turn, can contribute to cognitive decline and heighten the risk of developing dementia.[24]

This study further underscored the significance of cognitive decline in older adults without depressive symptoms as a comparable or even more potent risk factor for subsequent dementia and death. Older adults with depressive symptoms have been found to display abnormal levels of neurotransmitters, such as dopamine, norepinephrine and serotonin, in their brains, which have a consequential impact on their brain function.[20 25] In addition, those with depressive symptoms are more susceptible to chronic stress, sleep disorders and other issues that may negatively impact brain health.[21 26] Therefore, cognitive decline in them may be more closely associated with the depressive symptoms themselves and the biological changes they elicit, rather than being directly related to the development of dementia. On the other hand, those without depressive symptoms may not experience these depression-related biological changes. Consequently, if they experience cognitive decline, it may be more attributable to age-related and gene-related biological changes, including neuronal apoptosis and brain atrophy, which may be more directly associated with the development of dementia.[27] In addition, older adults with depressive symptoms may seek medical attention or make lifestyle changes due to their symptoms and thus reverse their accumulated risk factors and reduce their subsequent risk of dementia and death. Conversely, those without depressive symptoms may not display any apparent symptoms before their cognitive decline occurs, thus potentially missing the optimal treatment window, which may also help explain why the cognitive decline in older adults without depressive symptoms is associated with a higher risk of dementia and death.

Notably, the interactions between depressive symptoms and cognitive function in associations with dementia exhibited greater significance in women compared with men. Women are more susceptible to experiencing depressive symptoms and are typically more attuned to their mental health status than men.[28] As mentioned above, depressive symptoms can contribute to cognitive-related problems, such as attention and memory problems. Consequently, women with depressive symptoms may be more inclined to recognise cognitive decline and seek medical intervention. However, in women without depressive symptoms, cognitive decline may be less noticeable, leading to a progressive deterioration of cognitive function. In addition, the decline in oestrogen levels after menopause may expedite cognitive decline and neurodegeneration in women, thereby amplifying their risk of developing dementia.[29] Finally, sex differences in social roles may also make sense. For instance, women typically undertake more caregiving responsibilities at home,[30] which can result in greater stress and reduced opportunities to engage in cognitive activities, potentially increasing the risk of cognitive decline and dementia.

To the best of our knowledge, this is the first and most comprehensive population-based cohort study to explore the interactions and joint trajectories of depressive symptoms and cognitive function in their associations with all-cause dementia, AD and all-cause death in older US adults. In contrast to prior evidence, the current study is groundbreaking in examining the dynamic interactions between depressive symptoms and cognitive function before new-onset dementia and death. Specifically, we identified a high-risk population characterised by significant disparities between depressive status and cognitive status. Furthermore, 15 common joint trajectories of depressive symptoms and cognitive function were identified in this study. The complex statistical methods, including RCS curves, GBTM and competing risk analysis, guarantee the robustness of our conclusions. The sex-stratified analysis in this study helps explore sex differences and ensures the reliability of the findings. The large sample size and excellent population representation of the HRS further ensure the extrapolation of our findings.

Limitations

Several limitations of our study need to be acknowledged. First, the diagnosis of dementia and AD relied on self-reported or proxy-reported physician diagnoses, which may result in an underestimation of the prevalence. Second, we were not able to adjust for certain potential confounders due to data limitations, such as waist circumference. Lastly, the apolipoprotein E allele was not adjusted in our analysis to retain a larger sample size.

Implications

In conclusion, our findings suggest that older adults with significant disparities between depressive and cognitive status, such as low depressive symptoms but poor cognitive function, are at comparable or even higher risk of subsequent dementia and all-cause death, relative to those with long-term comorbid depressive symptoms and poor cognitive function. It is crucial to recognise the importance of depressive and cognitive trajectories and their interactions in the early prevention of dementia and all-cause death among older adults.

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Contributors JL and ZR designed the study. ZR managed and analysed the data. ZR prepared the first draft. ZR, LN and YD reviewed and edited the manuscript, with comments from JL. All authors were involved in revising the paper. JL accepted full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The Health and Retirement Study was supported by the National Institute on Aging (NIA U01AG009740) and was approved by the Institute for Social Research and Survey Research Centre of the University of Michigan (IRB Protocol: HUM00061128). All participants provided written informed consent and detailed information can be found at https://hrs.isr.umich.edu/data-products/restricted-data/available-products/11516. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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