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Dual Trajectories of Depression and Cognition: A Longitudinal Population-Based Study

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Abstract

Objectives—To examine the relationships over time between dual trajectories of depressive symptoms and several cognitive domains.

Design—5-year longitudinal study.

Setting—Population-based cohort.

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LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1. pdf
Supplemental Digital Content 2. pdf
Supplemental Digital Content 3. pdf
Supplemental Digital Content 4. pdf
Supplemental Digital Content 5. pdf

Participants—1978 randomly selected individuals aged 65+ years at recruitment and assessed annually.

Measurements—Repeated measures of (1) depressive symptoms on the modified Center for Epidemiologic Studies-Depression Scale; (2) composite scores in the cognitive domains of attention, executive function, memory, language, and visuospatial function. Latent class trajectories were identified for depression and for each cognitive domain, and their associations investigated using dual trajectory modeling. Cognitive trajectories with z scores below −1 were designated as persistently low.

Results—Five depressive symptom trajectories were observed: rarely depressed (60.5%); low-grade, decreasing symptoms (18.5%); low-grade, increasing symptoms (9.6%); moderate-grade symptoms (7.4%); and consistent higher-grade symptoms (4.0%). For each cognitive domain, six trajectories were observed. The rarely depressed and low-grade decreasing symptom groups were the least likely to have persistently low cognition. The symptom trajectory most strongly associated with persistently low functioning in each domain was not the higher-grade group, but rather the low-grade increasing group in the case of attention, and the moderate-grade trajectory in the other four domains.

Conclusions—Consistently higher-grade depressive symptoms are less strongly associated with poor cognitive functioning than with either moderate or low-grade increasing depressive symptom trajectories, over time and across different domains. Examining both depression and cognition longitudinally allows heterogeneity of both to be addressed, revealing latent groups with potential diagnostic and prognostic implications.

Keywords

aging; community; epidemiology; neuropsychological functioning; group-based trajectory model

OBJECTIVES

Depression and cognitive impairment are both common and comorbid in older adults (1,2,3), and have shown consistent cross-sectional associations (4, 5). Evidence is mixed as to whether depression at a given time predicts subsequent cognitive decline, and at least partly depends on study sample and longitudinal methods as well as the specific outcomes assessed (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). Depression has been associated with subsequent cognitive decline in studies with prospective, retrospective, and cross-lagged designs (5, 6, 7, 11, 14, 15). However, some prospective studies have not supported this relationship (9, 12), and in others, results have depended on whether the outcome was general cognitive function or specific cognitive domains (8, 10, 13).

A more dynamic view of the relationship is provided by studies which examine both depression and cognition longitudinally (4, 8, 10, 13, 16, 17, 18, 19, 20). In one study, a prominent association was found between depressive symptoms and cognitive decline amongst individuals who had already experienced cognitive decline, suggesting that depression was a possible reaction to worsening cognitive abilities (16). An association has also been shown between the chronicity of depressive symptoms and cognitive decline (8,

10, 17, 18). To our knowledge, sub-patterns of depressive symptomatology have not been examined longitudinally in relation to cognitive functioning.

Study results would also be expected to vary between study samples composed of patients with depressive disorders found in clinical settings and those comprising individuals in the community with varying degrees of depressive symptoms. There are selection factors that lead some, but not all, individuals with symptoms of depression and/or cognitive impairment to seek clinical services, and additional factors affecting their eligibility for clinic-based research. Clinical studies usually focus on mood disorders rather than on depressive symptoms. The majority of studies examining the relationship between depression and cognition longitudinally have been based on community samples (4, 8, 9, 13, 16, 17, 18, 19, 20). We built on this body of research by investigating trajectories of depressive symptoms and cognitive function in a prospective study of an aging population-based cohort, over five years of follow-up, with the aim of determining whether any particular depressive symptom trajectory was associated with poor cognitive outcome.

METHODS

Participants

As previously reported (21, 22), the Monongahela-Youghiogheny Healthy Aging Team (MYHAT) cohort is an age-stratified random sample drawn from publicly available voter registration lists based in a region of southwestern Pennsylvania. Recruitment criteria included (a) age 65 or older, (b) living within the selected area, and (c) not already living in long-term care institutions. Individuals were ineligible if they were (d) too ill to participate, (e) too severely impaired in vision or hearing, or (f) decisionally incapacitated. After initially recruiting 2036 individuals, we excluded those with moderate to severe cognitive impairment, defined as an age-education-corrected Mini-Mental State Examination (MMSE) (23, 24) score of less than 21 out of 30. The remaining 1982 individuals underwent the complete assessment at baseline and five subsequent annual visits, for a total of six assessments.

Assessment – Neuropsychological Testing

Cognitive functioning was assessed in five domains: (1) attention/processing speed (Trailmaking Test A, digit span), (2) executive function (Trailmaking Test B, initial letter fluency, clock drawing), (3) language (Boston Naming Test, category fluency, modified Token Test), (4) memory (immediate and delayed logical memory and visual reproduction), and (5) visuospatial skill (block design) (21, 22). A composite z-score was created in each cognitive domain by first standardizing each individual test score, i.e. subtracting off the baseline sample mean and dividing by the baseline sample standard deviation, and then taking the arithmetic mean of the standardized scores within each domain for each individual at each time point.

Assessment – Depressive Symptom Screen

Depression was assessed using the modified Center for Epidemiologic Studies-Depression scale (mCES-D) (25, 26). The participant rates 20 symptoms of depression as present or

absent (score 1 or 0) over most of the preceding week, summed to a mCES-D total score between 0 and 20.

Statistical Analyses

To identify distinct trajectory patterns for depression symptoms and cognitive functioning and assess their relationships, we used a latent group-based dual trajectory modeling approach that estimates the probabilistic links between two sets of developmental trajectories (27). Model outputs include (1) determination of the optimal number of distinct trajectory groups and the shapes of the trajectories, (2) estimated proportion of the population belonging to each trajectory group, and (3) estimated joint and conditional probabilities of group membership linking the two sets of trajectories. The model determines a posterior probability of membership in each of the trajectory groups for each individual in the sample, and the maximum posterior probability assignment rule assigns each individual to the trajectory group with the highest probability.

Model-fitting proceeded in two stages: (1) The best univariate trajectory models were found for mCES-D and each of the five cognitive domains based on a combination of optimum Bayesian information criterion (BIC), Wald tests, and clinical plausibility. (2) The dual trajectory models were then fit using starting parameters from the final univariate models. In order to find unadjusted trajectory patterns, trajectory models were fit using mCES-D and cognitive z-scores alone; covariate information was not incorporated. We used a zero-inflated Poisson model (28) for mCES-D and normal models for each of the five cognitive domain z-scores. We examined model diagnostics for all of the univariate and dual trajectory models using three criteria (29): (1) average posterior probability of group membership at least 0.7 for all groups, (2) odds of correct classification greater than 5.0 for all groups, and (3) estimated group probabilities reasonably close to the proportion of the sample assigned to the group based on the maximum posterior probability assignment rule. The SAS procedure TRAJ (30) was used to fit the trajectory models in SAS 9.3, (Cary, North Carolina: SAS Institute Inc, 2011). All other analyses were carried out using R version 3.1.3 (See Supplemental Digital Content 1).

As we will show under Results, we found five unique depressive symptom trajectories. We named them relative to one another using the following terms: rarely depressed; low-grade, decreasing depressive symptoms; low-grade, increasing depressive symptoms; moderate-grade depressive symptoms; and higher-grade depressive symptoms. We emphasize that these are based on a symptom scale and not on clinical diagnoses of depressive disorders.

We calculated descriptive statistics to characterize the sample at baseline, years of follow-up, and antidepressant use during the course of the study, for the overall sample and stratified by depression trajectory group. We performed global tests of association of these variables with the depression trajectory groups and did all pairwise comparisons of proportion antidepressant use among the depression trajectory groups using Holm-adjusted p-values.

With regard to cognition, we defined as “persistently low” the cognitive trajectories with a composite z-score of −1 or lower during the majority of the study period. We performed pairwise comparisons of proportions of persistently low cognitive trajectory membership

among the depression trajectory groups using Holm-adjusted p-values. We also fit logistic regression models for each cognitive domain to model the log odds of persistently low cognition as a function of depressive symptom trajectory group (as an unordered categorical variable), both with and without adjustment for baseline demographics.

Since the high-grade symptom group had a shorter median follow-up time (2 years) than the other groups (4 or 5 years), we refit the five depression group dual trajectory models using only the first four time points (3 year follow-up) in a post-hoc analysis. Also, to determine whether results were influenced by the small group size for the persistently low attention group, we investigated whether expanding it to incorporate the next lowest trajectory altered our conclusions.

See Supplemental Digital Content 1 for a full description of our statistical methods.

RESULTS

Of the 1982 eligible recruited subjects, we excluded four who did not respond to the mCES-D questions at any of the six assessments, resulting in a baseline sample size of 1978. Our sample had mean and standard deviation (SD) age at baseline of 77.7 (7.4) years; 61.1% were women, 94.7% were white, and 58.9% had high school or less education. Their mean (SD) MMSE at baseline was 26.9 (2.4) and mean (SD) mCES-D score at baseline was 0.94 (2.1). The overall median follow-up time based on the mCES-D data was 5 years (range 0–5 years) (Table 1).

Depression trajectory model

We report in this section the estimated values from the univariate model rather than from each of the five dual trajectory models; results were similar although not identical across models (data not shown). Each depressive symptom trajectory group had an estimated population percent group membership (Figure 1): rarely depressed (60.5%); low-grade, decreasing symptoms (18.5%); low-grade, increasing symptoms (9.6%); moderate-grade symptoms (7.4%); and higher-grade symptoms (4.0%).

Baseline characteristics (Table 1). Women and those with lower education were significantly overrepresented among all depressive symptom trajectory groups other than the rarely depressed. The moderate- and higher-grade symptom groups had the lowest mean baseline MMSE scores. Baseline mCES-D scores and baseline antidepressant use also differed significantly across groups.

Follow-up duration differed significantly by symptom group, ranging from a median of 2 years in the higher-grade group to 5 years in the rarely depressed and low-grade, increasing groups (Table 1).

Antidepressant use. Overall, 392 (19.8%) of the 1978 participants reported daily antidepressant use at one or more of the assessments, and proportions differed significantly across symptom groups, ranging from 45.6% in the higher-grade group to 12.8% in the rarely depressed group (Table 1).

Cognitive domain trajectory models

We identified six trajectories for each cognitive domain (Figure 2) which are ranked from lowest (1) to highest (6) composite z-score. The trajectory groups with the lowest mean z-scores tend to show most decline in all domains other than visuospatial skills, which had fairly stable trajectories overall. Memory increases slightly in the four highest trajectory groups, which is consistent with known practice effects associated with repeated memory tests (31).

We designated as persistently low the trajectories with z-scores of −1 (dotted lines in Figure 2) or below for the majority of the study period. This included the lowest trajectory for attention and visuospatial function, and the lowest two trajectories for executive function, language, and memory.

Relationships between depression and cognitive function trajectories

We considered the proportion of individuals in each depressive symptom group who were assigned to the persistently low cognitive trajectories (defined above) for each cognitive domain (Table 2). In the domain of attention, the low-grade increasing group had the highest percent membership in the persistently low attention group. Specifically, 12% of the low-increasing symptom group was classified into the persistently low attention group, compared to 5% of the moderate and higher-grade symptom groups, 3% of the rarely depressed group, and 0% of the low-decreasing symptom group. For the other cognitive domains, the moderate-grade symptom group had the highest percent membership in the persistently low trajectory groups. Individuals in the rarely and low-grade decreasing symptom groups were least likely to be in the persistently low cognitive trajectory groups. Pairwise comparisons of proportions of all groups against the highest-ranked group revealed significant differences between rare and low-grade decreasing symptom groups and the highest-ranked group in each domain. The higher-grade symptom group differed significantly from the highest-ranked group (moderate-grade symptoms) only in executive function. These rank orderings (Table 2) were consistent with results of unadjusted logistic regression models for persistently low cognition among the symptom groups. After adjusting for baseline demographics, the odd ratios for the symptom groups and their rankings did not change substantially. The exception was the memory domain, in which the higher-grade group displaced the moderate-grade group for highest odds ratio for persistently low cognition; however, these odds ratios had overlapping confidence intervals (Supplemental Digital Content 2).

Population estimates of joint and conditional probabilities of depression and cognitive function trajectory group membership are tabulated in Supplemental Digital Content 3.

Model diagnostics

Model diagnostics (Supplemental Digital Content 4) indicated that all of the dual trajectory models satisfied the three diagnostic criteria, with the exception that group 3 of visuospatial had an odds of correct classification (OCC) of 4.69, which is less than the suggested minimum of 5 (29). Given that the other diagnostics for this model satisfied the criteria, and

that the visuospatial domain had more missing data than the other cognitive domains, this is probably close to the best fitting model that can be achieved for the visuospatial data.

Post-hoc analyses

To address potential bias from the shorter median follow-up time for the higher-grade depressive symptom group (2 years) versus the other groups (4 or 5 years), we refit the five depression group dual trajectory models using only the first four rather than all six time points, i.e., restricting follow-up to three years. We found that a moderate depressive symptom group was again ranked highest in all unadjusted and adjusted models including in the attention domain (Supplemental Digital Content 5).

Finally, incorporating the second-lowest trajectory into the persistently low attention group did not change our major conclusions, suggesting that small group size does not explain the results. The low-increasing depression group was again ranked highest, and results of pairwise significance tests were unchanged.

CONCLUSIONS

Examining depressive symptoms over time in our population-based cohort, we identified five distinct trajectories: a rarely depressed group, a low-grade decreasing group; a low-grade increasing group, a moderate-grade group, and a group with consistently higher-grade symptoms. Those with the higher-grade symptoms were more likely to be women, while those rarely reporting depression tended to be men. The rarely depressed group had the largest proportion of individuals with greater than high school education; the reverse was true among individuals with moderate and higher grade depressive symptoms. These results are consistent with our previous study (32).

Our findings were somewhat unexpected regarding our main outcome. Persistently low cognitive function trajectories were not associated the most strongly with the high-grade depressive symptom trajectory. Rather, they were most strongly associated with the low-grade increasing trajectory in the attention domain and the moderate-grade trajectory in the domains of executive function, memory, language, and visuospatial function. This pattern held true even after accounting for the greater attrition in the higher-grade symptom group (by refitting the models using a shorter follow-up time).

A handful of previous studies have examined the relationship between depression and cognitive decline over time. One found an association between depressive symptoms and change in MMSE scores over 13 years; however, this association lost significance when adjusted for potential confounders (13). Other studies have found associations between persistent depressive scores over time and greater risk of cognitive decline (18, 20), specifically, with declines in verbal knowledge and fluency, attention, and memory (8, 10). Unlike ours, these previous studies either dichotomized depression scores from the CES-D or the Geriatric Depression Scale (8, 10) or examined measures of global cognitive function rather than specific cognitive domains (18, 20). Conversely, associations have been found between baseline levels of immediate and short-term verbal memory, verbal abilities, and mental tracking with persistent depression (17). Impairments in processing speed, but not

general cognitive functioning, have also been found to be predictive of depressive symptoms (13).

Our results broadly demonstrate that the initial level of depressive symptoms reveals less about associated cognitive trajectories than the subsequent diverging paths these symptoms take. While depression measured on a given day provides a useful snapshot at a single point in time, it does not tell us where the individual's depression on that day stands in relation to the course of his or her depression, i.e. whether a given depression score is part of a declining, stable, or increasing time course. The same holds true for cognition. By examining both depression and cognition annually for five years, we were able to first identify the latent trajectories of both and then to investigate their relationships with each other. Further, by examining the full range of depressive symptom scores in our cohort, rather than dichotomizing them as in previous studies (8, 10), we were able to identify five latent trajectories of depressive symptoms over time. By investigating – rather than burying – the inherent heterogeneity of depression and cognition, we were able to examine in finer grain the relationships of interest. This approach led us to the unexpected finding that it was the moderate symptom group and not the consistently higher-grade symptom group which was most associated with poor cognitive functioning over time. Notably, both the moderate and low-decreasing symptom groups had initial mCES-D mean scores around 2 (i.e., reported two depressive symptoms over the preceding week.). Similarly, while both the low-grade increasing group and the rarely depressed group started with mean scores around zero, the low-grade increasing group displayed worse subsequent cognitive functioning than the rarely depressed group.

It is plausible to speculate that the persistent higher-grade symptom group, which was our smallest trajectory group, of whom nearly half reported using antidepressant drugs, represents individuals with clinically significant depressive disorders. While such individuals are in the majority as patients seeking care for late life depression in clinical settings, they are in the minority at the population level. In such patients, depression has been associated with impairments in information processing speed, visuospatial functioning, and executive functioning; the slowed processing speed has been proposed to underlie the additional cognitive deficits seen in this group (33).

In addition, in our population-based sample, we are able to identify a larger group of individuals with likely subsyndromal depression, such as our moderate and low-increasing symptom groups, who might not be encountered in the clinical setting but have poor cognition. Potentially, one or more shared processes may underlie both their depressive symptoms and their poor cognitive functioning.

One possible shared process is that persistent depression may be in reaction to continued cognitive decline (16). In a three year prospective study, while depressive symptoms were unrelated to subsequent cognitive functioning, cognitive functioning was related to subsequent depressive symptoms (12). Other studies (34, 35) have shown an association of increasing mood and/or anxiety symptoms with decline in cognitive functioning. This association disappears at a certain point during the process of cognitive decline, perhaps because the individuals have lost awareness of their own decline.

Alternatively, a common neuropathological entity might drive both the depression and cognitive decline. Late onset depression has been associated with more severe cognitive and neurological changes than early onset depression, with late onset depression also associated with a faster rate of hippocampal volume loss than early onset (36). The vascular depression hypothesis argues for a significant relationship between cerebrovascular disease and depression, either through direct lesions or through an accumulation of white matter changes, leading or contributing to a depressive episode (37). Depressive symptoms have been associated with white matter hyperintensities in the frontal and temporal regions (38), although the impact of depressive symptoms on cognitive decline has been shown to be independent of the severity of white matter change and medial temporal lobe atrophy (14). Particular emphasis has also been placed on the role of the frontolimbic and frontostriatal pathways in the depression-executive dysfunction syndrome (37). Interactions between hypercortisolemia related to depression and its effects on hippocampal structure and function as well as the concomitant role of cerebrovascular disease may also help to explain the relationship between depression and cognitive impairment (39). Dementia is also much more strongly associated with depressive symptoms which have developed within a year of the diagnosis of Alzheimer's disease than with depressive symptoms which had developed earlier (40).

Our study had a large, representative, population-based sample and a prospective design with repeated depression symptom screens and detailed cognitive assessments, allowing subtle effects to be detected using appropriate statistical modeling techniques. A sample, when drawn from the community at large, allows the identification of groups who would not be seen in clinical settings, such as those with subsyndromal depression and normal variations in mood. However, in such samples, the assessment of depression relies on self-reported depressive symptoms, rather than on expert diagnosis of depressive disorders as used in clinical research. The increasing proportions of antidepressant usage across increasing depressive symptom trajectories provide added face validity to our trajectory-based classification. Like previous studies (1) we found about 4% of our cohort was in our higher-grade depressive symptom trajectory group. Individuals with low and moderate-grade depressive symptoms may not fulfill entry criteria for clinical research; their exclusion from such research may lead significant interactions and nuanced symptom relationships to remain undetected in the preclinical stages. From a public health perspective these individuals with subsyndromal depressive symptoms warrant further investigation, as they are essential to our understanding of possible emerging disease processes within the population as a whole. Our findings demonstrate the importance of longitudinal population-based studies in understanding the fine-grained relationships between depression and cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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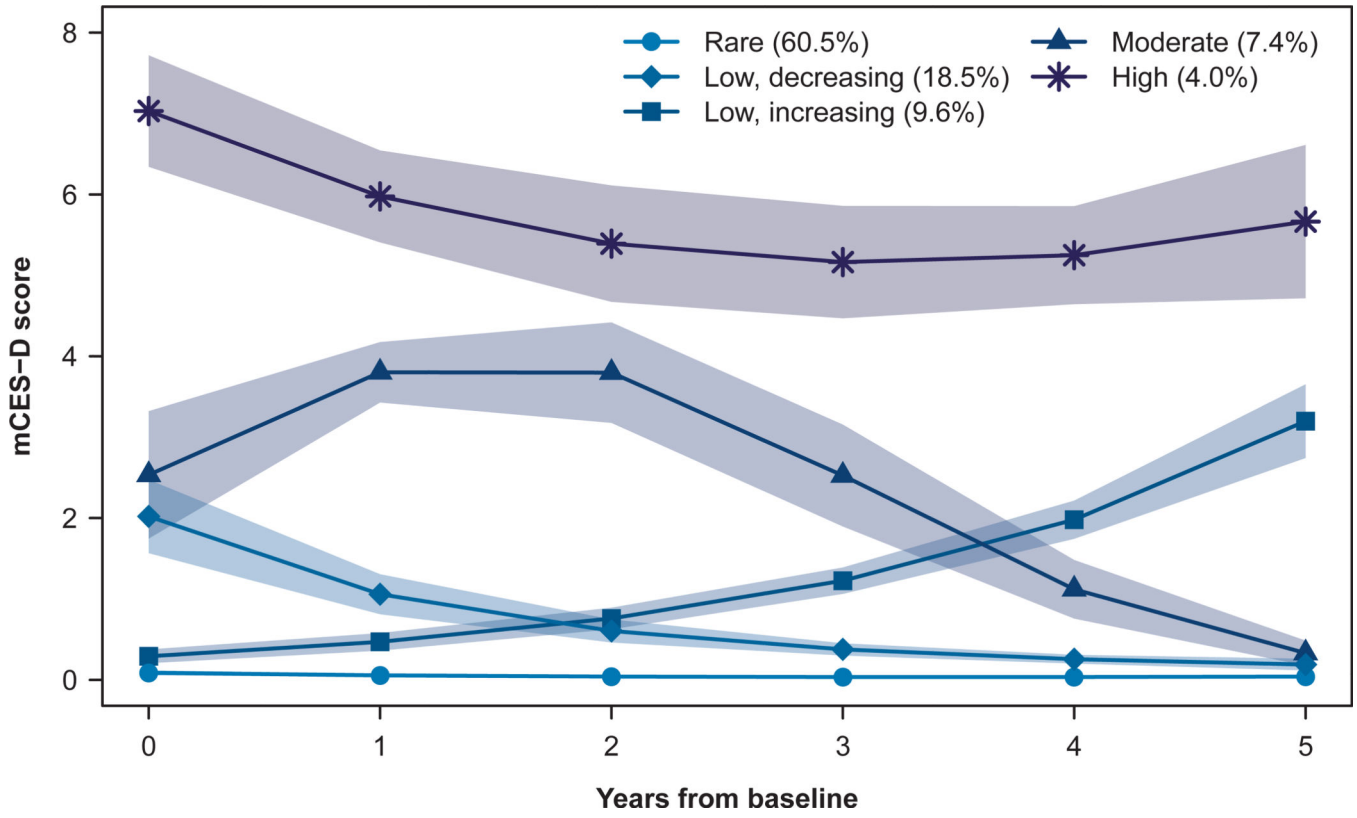

FIGURE 1. Trajectories of depressive symptoms, with 95% confidence bands

Note: mCES-D: modified Center for Epidemiologic Studies-Depression scale.

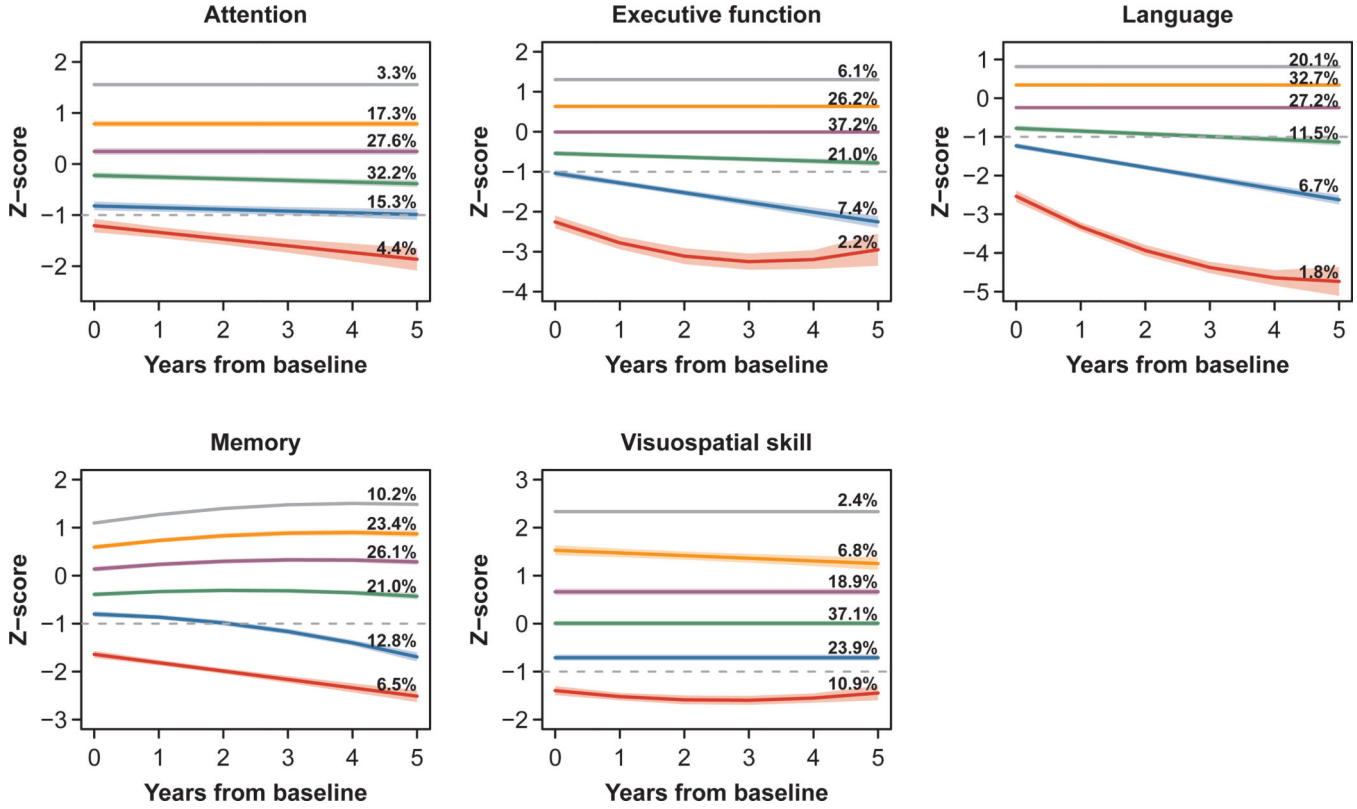

FIGURE 2. Trajectories of cognitive functioning, with 95% confidence bands

Note: Dotted gray lines indicate z-score of −1. Trajectories were designated as persistently low if they had a z-score of −1 or below for the majority of the study period.

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TABLE 1

Characteristics of Participants, Overall and According to Depression Trajectory Group

		Depression Trajectory Groups							
	All Participants (N=1978)	**Rarely (N=1248, 63.1%)**	**Low, Decreasing (N=395, 20.0%)**	**Low, Increasing (N=130, 6.6%)**	**Moderate (N=126, 6.4%)**	**High (N=79, 4.0%)**	**Global Test**		
	N (%)						**Test statistic**	**df**	**p**
Age group at baseline							10.32[a]	8	0.2430
65–74	679 (34.3)	455 (36.5)	125 (31.6)	37 (28.5)	36 (28.6)	26 (32.9)			
74–85	914 (46.2)	570 (45.7)	184 (46.6)	65 (50.0)	60 (47.6)	35 (44.3)			
85+	385 (19.5)	223 (17.9)	86 (21.8)	28 (21.5)	30 (23.8)	18 (22.8)			
Education							20.51[a]	4	0.0004
High school or less	1164 (58.9)	690 (55.3)	246 (62.3)	86 (66.2)	87 (69.0)	55 (69.6)			
More than high school	814 (41.2)	558 (44.7)	149 (37.7)	44 (33.8)	39 (31.0)	24 (30.4)			
Sex							50.21[a]	4	<0.0001
Male	770 (38.9)	556 (44.6)	116 (29.4)	39 (30.0)	44 (34.9)	15 (19.0)			
Female	1208 (61.1)	692 (55.4)	279 (70.6)	91 (70.0)	82 (65.1)	64 (81.0)			
Race							NA[b]	NA	0.0813
White	1873 (94.7)	1189 (95.3)	375 (94.9)	117 (90.0)	120 (95.2)	72 (91.1)			
Non-white	105 (5.3)	59 (4.7)	20 (5.1)	13 (10.0)	6 (4.8)	7 (8.9)			
Antidepressant use									
At baseline[d]	267 (13.5)	115 (9.2)	80 (20.2)	19 (14.6)	27 (21.4)	26 (32.9)	67.47[a]	4	<0.0001
At any time[e]	392 (19.8)	160 (12.8)	108 (27.3)	34 (26.2)	54 (42.9)	36 (45.6)	130.87[a]	4	<0.0001
	Mean (SD)/Median								
Age at baseline	77.7 (7.4)/78	77.3 (7.5)/78	78.1 (7.5)/79	78.6 (6.9)/80	78.4 (7.3)/79.5	78.8 (7.4)/80	11.87[c]	4	0.0183
MMSE at baseline	26.9 (2.4)/27	27.1 (2.2)/27	26.8 (2.6)/27	27.0 (2.7)/28	26.1 (2.8)/26.5	26.1 (2.9)/27	24.87[c]	4	<0.0001
mCES-D at baseline	0.94 (2.1)/0	0.1 (0.3)/0	2.2 (1.9)/2	0.3 (0.7)/0	2.4 (2.6)/2	7.1 (4.0)/7	1241.89[c]	4	<0.0001
	Median (range)								
Years of follow-up	5 (0, 5)	5 (1, 5)	4 (0, 5)	5 (1, 5)	4 (0, 5)	2 (0, 5)	18.31[c]	4	0.0011

Notes: MMSE: Mini-Mental State Examination; mCES-D: modified Center for Epidemiologic Studies-Depression Scale; df: degrees of freedom; SD: standard deviation; KW: Kruskal-Wallis; NA: Not applicable

[a] Chi-squared test

[b] Fisher's exact test

[c] Kruskal-Wallis test

[d] For antidepressant use at baseline, Holm-adjusted pairwise Fisher's exact tests at familywise error rate of 0.05 resulted in significantly greater antidepressant use for all groups with respect to the rarely depressed group ($P_{adjusted} < 0.001$ in each case) with the exception of the low, increasing group ($P_{adjusted} = 0.30$). The high-grade depression group had significantly greater antidepressant use than the low-increasing group ($P_{adjusted}<0.02$). The other comparisons were not significant.

[e] For antidepressant use at any time during the course of the study, Holm-adjusted pairwise Fisher's exact tests at familywise error rate of 0.05 resulted in significantly greater antidepressant use for all groups with respect to the rarely depressed group ($P_{adjusted} < 0.001$ in each case). The moderate-grade and high-grade depression groups had significantly greater antidepressant use than the low-decreasing group ($P_{adjusted}<0.01$ for both) and the low-increasing group ($P_{adjusted}=0.02$ for both). The other comparisons were not significant.

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Table 2

Rank-ordering of Depression Trajectory Groups by Proportion with Persistently Low Cognition

Rank	Attention	Executive	Language	Memory	Visuospatial
1	Low, increasing (12%)	Moderate (28%)	Moderate (21%)	Moderate (32%)	Moderate (27%)
2	Moderate (5%); P=0.0908	*Low, increasing (17%); P=0.0170	High (16%); P=0.2406	High (31%); P=0.4952	High (21%); P=0.1683
3	High (5%); P=0.0908	*High (11%); P=0.0052	Low, increasing (15%); P=0.2349	Low, increasing (23%); P=0.1178	*Low, increasing (13%); P=0.0034
4	*Rare (3%); P<0.0001	*Low, decreasing (9%); P<0.0001	*Low, decreasing (10%); P=0.0042	*Low, decreasing (20%); P=0.0088	*Low, decreasing (11%); P<0.0001
5	*Low, decreasing (0%); P<0.0001	*Rare (6%); P<0.0001	*Rare (6%); P<0.0001	*Rare (16%); P<0.0001	*Rare (6%); P<0.0001

Notes:

*Significant difference (P<0.05) from the Rank 1 group; one-sided Fisher's exact test of difference in proportions.

P-values within each cognitive domain were adjusted using Holm's correction.