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Depressive symptoms and cognitive decline in older adults

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ABSTRACT

Objectives: Few studies have examined the impact of late-life depression trajectories on specific domains of cognitive function. This study aims to delineate how different depressive symptom trajectories specifically affect cognitive function in older adults.

Design: Prospective longitudinal cohort study

Setting: Australia and the United States of America

Participants: In total, 11,035 community-dwelling older adults with a mean age of 75 years

Measurements: Depressive trajectories were modelled from depressive symptoms according to annual Centre for Epidemiological Studies Depression Scale 10 (CES-D-10) surveys. Four trajectories of depressive symptoms were identified: low ("nondepressed"), consistently mild ("subthreshold depression"), consistently moderate ("persistent depression"), and initially low but increasing ("emerging depression"). Global cognition (Modified Mini-Mental State Examination [3MS]), verbal fluency (Controlled Oral Word Association Test [COWAT]), processing speed (Symbol Digit Modalities Test [SDMT]), episodic memory (Hopkins Verbal Learning Test – Revised [HVLT-R]), and a composite z-score were assessed over a subsequent median 2 years.

Results: Subthreshold depression predicted impaired performance on the SDMT (Cohen's d −0.04) and composite score (−0.03); emerging depression predicted impaired performance on the SDMT (−0.13), HVLT-R (−0.09), 3 MS (−0.08) and composite score (−0.09); and persistent depression predicted impaired performance on the SDMT (−0.08), 3 MS (−0.11), and composite score (−0.09).

Conclusions: Depressive symptoms are associated with later impaired processing speed. These effects are small. Diverse depression trajectories have different impacts on cognitive function.

Key words: major depressive disorder, depressive symptoms, cognitive impairment

Introduction

Late-life depression (LLD) and cognitive impairment share a complex and bidirectional link, each influencing and exacerbating the other (van den Kommer *et al.*, 2013). Older individuals with depression often report cognitive difficulties, such as problems with memory, attention and executive function. Furthermore, negative attentional biases can slow information processing (Alexopoulos, 2019). The risk of dementia is more than doubled for both men and women with diagnosed depression (Elser *et al.*, 2023). Conversely, cognitive impairment is a risk factor for the development of depression. The prevalence of depression in individuals with mild cognitive impairment (MCI) living in the community is 25% (Ismail *et al.*, 2017), almost double that of general older population estimates (Mohebbi *et al.*,

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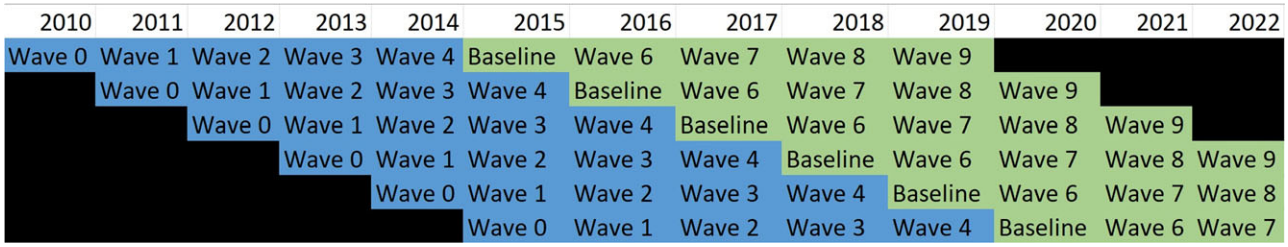

Figure 1. Timeline of when depressive symptoms (blue)* and cognitive outcomes (green)ϕ were measured.
ˣAssessment is relative to the time at which a participant enrolled is ASPREE.
**Depressive trajectories were calculated over a median 3.98 (IQR 3.93–4.02) years.*
ϕCognitive outcomes were measured over a meadian 1.99 (IQR 1.37–2.17) years.

2019). The prevalence of depression in individuals affected by dementia ranges from 37 to 41% (Leung *et al.*, 2021).

We previously reported that emerging depressive symptoms in an initially healthy community-dwelling population are associated with incident dementia (HR 1.42 [95% CI 1.02–1.97]) (Agustini *et al.*, 2022). The current study builds upon a growing body of literature using trajectory modeling to identify the longitudinal relationship between depressive symptoms and cognitive function. This literature includes the Whitehall II prospective cohort study ($n = 774$) that found that those with emerging depressive symptoms later in life had impaired executive function (Demnitz *et al.*, 2020) and the English Longitudinal Study of Aging ($n = 7{,}610$) that found persistent depressive symptoms were associated with global cognitive impairment (Zheng *et al.*, 2018). While most evidence suggests that elevated depressive symptoms are associated with greater incidence of cognitive impairment or dementia (Choi *et al.*, 2019, Demnitz *et al.*, 2020, Formánek *et al.*, 2020, Zheng *et al.*, 2018), there are conflicting findings about how different trajectories of depressive symptoms predict cognitive impairment (Graziane *et al.*, 2016) and which specific cognitive domains are affected. This is important as cognitive decline presents differently in clinical practice depending on the specific domains of cognition affected. This study sought to delineate the specific cognitive domains affected by different depression trajectories. Understanding these associations has implications for clinical practice given global population aging.

Methods

Study design and participants

This study involved secondary data analysis from the ASPREE/-XT study. ASPREE (ASPirin in Reducing Events in the Elderly) was a double-blind, randomized, placebo controlled primary prevention trial to assess whether daily 100 mg aspirin could extend the duration of disability- and dementia-free life in relatively healthy community-dwelling older adults. The trial enrolled 19,111 Australian and American men and women ≥ 70 years of age or older (or ≥ 65 years of age among Blacks and Hispanics in the United States) between 2010 and 2014, and randomly assigned 9,525 to receive aspirin and 9,589 to receive matched placebo. All participants were free from cardiovascular disease, dementia and independence-limiting physical disability on enrollment, and had a score on the Modified Mini-Mental State Examination (3 MS) of at least 78/100 for eligibility. Full details of the trial have been published elsewhere (ASPREE Investigator Group, 2013), including the secondary outcomes related to depression (Berk *et al.*, 2020) and cognitive decline (Ryan *et al.*, 2020).

The ASPREE-eXTension (ASPREE-XT) study is a prospective cohort study following up ASPREE participants to investigate the long-term effects of low-dose aspirin as well as a range of factors that contribute to the maintenance of physical and cognitive health in older adults. All participants in the ASPREE trial were eligible to continue in the ASPREE-XT cohort. Those who did not consent into ASPREE-XT (7%) were slightly older and had lower cognitive scores and more age-related conditions than those who consented (Ernst *et al.*, 2023). A novel analysis was established with a new 'baseline' set, such that depression trajectories were modeled during the clinical trial phase and prior to the new baseline, and cognitive outcomes explored thereafter, as illustrated in Figure 1. All participants who participated at wave 5 (considered 'baseline') and had at least one follow-up in ASPREE-XT were included in the analysis.

Assessment of depressive symptoms and cognitive function

Depressive symptoms were obtained annually using the Center for Epidemiologic Studies Depression

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Scale 10-item (CES-D-10), a reliable measure of depression with high internal consistency (Mohebbi *et al.*, 2018). A battery of cognitive tests was used to measure a range of cognitive processes in the ASPREE-XT cohort. These included the Controlled Oral Word Association Test (COWAT) letter F (Ross, 2003), which measures verbal fluency; the Symbol Digit Modalities Test (SDMT) (Smith, 1973), which measures processing speed; the Hopkins Verbal Learning Test – Revised (HVLT-R) (Benedict *et al.*, 1998), which measures verbal delayed recall; and the Modified Mini-Mental State Examination (3 MS) (Teng & Chui, 1987), which measures a broad range of cognitive functions, and was used as part of the ASPREE participant eligibility assessment. The composite measure was defined as a sum of the z-scores of the four cognitive tests. Impaired performance on each of these measures – 3 MS, COWAT, HVLT-R, and SMDT – has been associated with dementia and persistent physical disability (Wu *et al.*, 2022). Whilst these cognitive assessments were administered to participants at enrollment and then biennially during the trial phase, the novel analysis used to establish preceding depression trajectories required a new baseline to be set, as indicated in Figure 1. Data from cognitive assessments administered after the new baseline were used in this analysis.

Assessment of other covariates

Covariate information was collected annually. Details regarding ascertainment of demographic and clinical information are described elsewhere (ASPREE Investigator Group, 2013). A-priori covariates and potential confounders were selected based on the literature on depressive symptoms (Shin & Cho, 2022, Xiang, 2020) and cognitive functioning (Wu *et al.*, 2021, Zheng *et al.*, 2023) in older individuals. These were age, gender, ethnicity, smoking status, alcohol consumption, education, polypharmacy, and living arrangements. Polypharmacy was defined by the use of five or more medications simultaneously. Information on medical comorbidities was included in a sensitivity analysis and included proxy measures of gastro-oesophageal reflux disease, hypertension, diabetes, chronic kidney disease, dyslipidaemia, respiratory disease, Parkinson's disease, and cancer (see Table 1).

Statistical analysis

The exposure in this study was depressive symptoms. Depressive symptom trajectories were modeled using linear and nonlinear latent class mixed models from annual measures across five annual data collection periods ("waves"), commencing from enrollment into the ASPREE trial (Fig. 1 – area shaded blue). Longitudinal trajectories were used to characterize dynamic change and identify unobserved heterogeneity. These trajectories were significantly different (χ^2 28.7, df 3, $p < 0.0001$). There was a median observation of 3.98 years (IQR 3.93–4.02 years). Four distinct trajectories identified corresponding to low ("nondepressed"), consistently mild ("subthreshold depression"), consistently moderate ("persistent depression"), and initially low but increasing ("emerging depression") CES-D-10 depressive symptoms (Fig. 2). These data are based on the mean CES-D-10 score for each trajectory with statistical analysis details published elsewhere (Agustini *et al.*, 2022). Data on cognitive outcomes were collected over the subsequent period post the new baseline reset (Fig. 1 – area shaded green). Our study sample pertained to those who participated in the final year of the ASPREE trial and had estimates of depression trajectories ($n = 11{,}035$).

Baseline (see Fig. 1) characteristics were analyzed using descriptive statistics, with measures of central tendency using Student's *t*-test for continuous variables and chi-square tests for categorical variables (Table 1).

The association between depressive symptom trajectories and cognitive outcomes was assessed using generalized estimating equations (GEE) with robust variance estimation to handle repeated measures and clustered data. Group-based trajectory modeling enabled an estimation of the probabilities for multiple trajectories rather than only fitting the overall population mean. Full details of the trajectory modeling can be found elsewhere (Agustini *et al.*, 2022).

For the five cognitive outcomes, three models were presented: model 1 was unadjusted, model 2 was adjusted for age and gender (see Supplementary Appendix), and model 3 was adjusted for age, gender, ethnicity, smoking status, alcohol consumption, education, polypharmacy, living arrangements, and baseline cognitive function (Table 2). To provide an estimation of magnitude and facilitate comparison across different cognitive domains, model adjusted Cohen's d scores were calculated (Fig. 3). False discovery rate was controlled for by using the Benjamini-Hochberg correction for multiple comparisons with the FDR set at 5% (Benjamini & Yekutieli, 2001). Three sensitivity analyses were conducted (see Supplementary Appendix). The first excluded those in the study who developed dementia during the exposure period ($n = 218$). The second excluded those taking antidepressants during the exposure period ($n = 1{,}326$), given that antidepressants may have effects on cognition in LLD (Ainsworth *et al.*, 2023). The final sensitivity analysis excluded those without data on medical comorbidities ($n = 4{,}914$).

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Table 1. Baseline characteristics for the nondepressed

	ND* (*N* = 5172)	STD* (*N* = 4304)	ED* (*N* = 673)	PD* (*N* = 886)	TOTAL (*N* = 11,035)	*P*-VALUE
Gender						0.674
Man	44.2%	43.4%	43.8%	42.2%	43.7%	
Woman	55.8%	56.6%	56.2%	57.8%	56.3%	
Age at randomization						0.035
Mean (*SD*)	74.9 (4.1)	75.1 (4.3)	75.1 (4.3)	74.8 (4.0)	75.0 (4.2)	
Range	65.0–93.6	65.1–96.0	65.4–89.8	65.3–88.9	65.0–96.0	
Education level						<0.001
<= 12yrs education	54.5%	57.3%	59.1%	61.7%	56.5%	
>12yrs education	45.5%	42.7%	40.9%	38.3%	43.5%	
Ethnicity[a]						0.017
White	95.7%	94.7%	96.3%	93.8%	95.2%	
African American, Hispanic and Other	4.3%	5.3%	3.7%	6.2%	4.8%	
Body mass index						<0.001
Mean (*SD*)	27.3 (4.5)	27.6 (4.7)	27.4 (4.8)	28.3 (5.2)	27.5 (4.6)	
Range	15.2–50.1	14.5–53.4	15.5–46.9	16.6–48.9	14.5–53.4	
Alcohol consumption[b]						0.136
Heavy	7.1%	7.8%	7.6%	7.9%	7.5%	
Moderate	43.6%	43.8%	43.8%	41.6%	43.5%	
Occasional	31.6%	30.2%	31.5%	35.4%	31.3%	
Nondrinker	17.7%	18.2%	17.1%	15.0%	17.6%	
Smoking status						
Nonsmoker	98.0%	98.0%	97.9%	96.7%	97.9%	
Current smoker	2.0%	2.0%	2.1%	3.3%	2.1%	
Living situation						<0.001
At home with another person	65.9%	61.4%	60.8%	50.1%	62.6%	
At home alone or in a communal residence	34.1%	38.6%	39.2%	49.9%	37.4%	
Polypharmacy[c]						<0.001
Absent	70.4%	61.8%	61.2%	54.0%	65.2%	
Present	29.6%	38.2%	38.8%	46.0%	34.8%	
Cancer or history of cancer[d]	22.5%	23.5%	25.2%	23.8%	23.1%	0.381
Chronic kidney disease[e]	28.5%	29.8%	31.4%	29.1%	29.2%	0.382
Diabetes[f]	11.3%	12.8%	11.4%	16.4%	12.3%	0.001
Dyslipidaemia[g]	64.2%	62.8%	64.8%	62.7%	63.6%	0.670
Gastro-oesophageal reflux disease[h]	21.5%	26.7%	32.2%	33.9%	25.2%	<0.001
Hypertension[i]	70.2%	71.0%	69.0%	70.9%	70.5%	0.687
Parkinson's disease[j]	1.1%	1.7%	1.4%	1.8%	1.4%	0.152
Respiratory disease[k]	9.8%	12.4%	11.3%	16.3%	11.4%	<0.001
Baseline COWAT						<0.001
Mean (*SD*)	13.9 (5.2)	13.5 (5.1)	13.1 (5.0)	13.1 (4.9)	13.6 (5.1)	
Baseline HVLT – R						<0.001
Mean (*SD*)	8.5 (3.2)	8.2 (3.3)	7.8 (3.4)	7.4 (3.5)	8.2 (3.3)	
Baseline SDMT						<0.001
Mean (*SD*)	36.2 (10.2)	34.8 (10.0)	33.0 (10.1)	32.8 (9.9)	35.2 (10.1)	

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Table 1. Continued

	ND* (*N* = 5172)	STD* (*N* = 4304)	ED* (*N* = 673)	PD* (*N* = 886)	TOTAL (*N* = 11,035)	*P*-VALUE
Baseline 3MS						<0.001
Mean (*SD*)	94.3 (5.7)	93.6 (6.0)	93.1 (6.5)	92.8 (6.1)	93.8 (5.9)	
Baseline composite						<0.001
Mean (*SD*)	0.1 (0.8)	−0.0 (0.8)	−0.1 (0.9)	−0.2 (0.8)	0.0 (0.8)	

*ND = nondepressed, STD = subthreshold depression, ED = emerging depression, PD = persistent depression (see Fig. 2 for trajectories).
[a]See detailed demographic information in McNeil et al.[35]
[b]Defined using the National Institute on Alcohol Abuse and Alcoholism guidelines.[36]
[c]Defined as taking ≥ 5 prescription medications daily.
[d]Defined as the diagnosis of any cancer during the study period or a history of a cancer diagnosis.
[e]Defined an estimated glomerular filtration rate of less than 60mL/min/1.73m^2.
[f]Defined as the use of any drug use for the treatment of diabetes, including insulin, or a fasting blood glucose level of greater than or equal to 7mmol/L.
[g]Defined as a total cholesterol level of greater than or equal to 200mg/dL or a low-density lipoprotein level of greater than or equal to 100mg/dL.
[h]Defined as the use of any proton pump inhibitor or H_2-receptor antagonist.
[i]Defined as the use of ACE inhibitors or angiotensin II receptor blockers, centrally acting antiadrenergic agents, beta-blockers or calcium channel blockers or, in the absence of the use of these agents, a systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg.
[j]Defined as the use of any anti-parkinsonian drugs, including anticholinergic agents.
[k]Defined as the use of any drug for chronic obstructive pulmonary disease or asthma, including inhaled beta-adrenergic agents and anticholinergic agents.

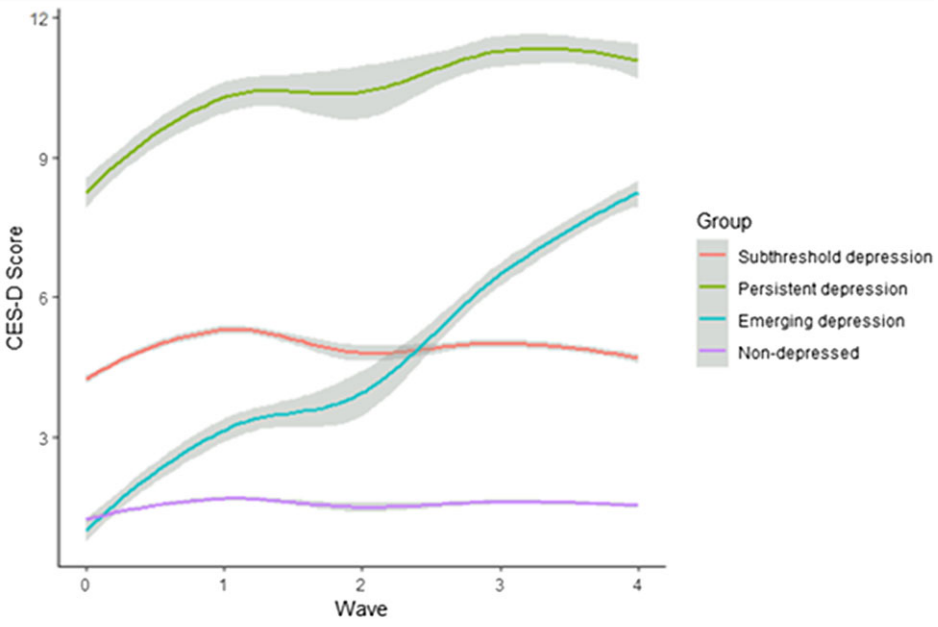

Figure 2. Depressive symptom tragjectories showing subthreshold, emerging, persistent, and nondepressed groups.

Results

Baseline characteristics

At baseline (see Fig. 1), 11,035 participants (56.3% female, mean age at randomization 75.0 ± 4.2 years) were included in the study. Among all participants, 4,304 belonged to the subthreshold trajectory, 886 to the persistent depression trajectory, and 673 to the emerging depression trajectory (Table 1). There were statistically significant differences between depression trajectory groups and education level, ethnicity, body mass index, living situation, polypharmacy, diabetes, gastro-oesophageal reflux disease, and respiratory disease, as well as baseline cognitive measures.

Depression trajectories and risk of cognitive decline

In multiple adjusted GEE models, consistently mild (subthreshold depression), consistently moderate (persistent depression), and emerging depressive symptoms were all associated with composite cognitive impairment. Table 2 and Figure 3 provide

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Table 2. Mean differences in cognitive measures for each depression trajectory in extended follow–up*

	COWAT			SDMT			HVLT-R			3MS			Composite score		
	Est	*CI*	*p*	*Est*	*CI*	*p*	*Est*	*CI*	*p*	*Est*	*CI*	*p*	*Est*	*CI*	*p*
ND	7.44	5.70–9.18	**0.002**	19.67	16.21–23.13	**0.002**	4.83	3.76–5.90	**0.002**	19.68	16.13–23.24	**0.002**	1.03	0.79–1.26	**0.002**
STD	−0.01	−0.18–0.16	0.949	−0.44	−0.75–−0.14	**0.008**	−0.04	−0.14–0.05	0.382	−0.16	−0.32–0.00	0.075	−0.02	−0.04–−0.00	**0.031**
ED	−0.28	−0.61–0.04	0.107	−1.38	−1.97–−0.79	**0.002**	−0.29	−0.49–−0.09	**0.007**	−0.52	−0.89–−0.15	**0.009**	−0.08	−0.13–−0.03	**0.004**
PD	−0.28	−0.58–0.03	0.094	−0.85	−1.42–−0.27	**0.007**	−0.11	−0.30–0.08	0.272	−0.67	−0.98–−0.35	**0.002**	−0.07	−0.11–−0.04	**0.002**

*Model 3: adjusted for age, gender, ethnicity, smoking status, alcohol consumption, education, polypharmacy, living arrangements, and baseline cognitive function (for COWAT, SDMT, HVLT-R, 3 MS and composite score), with p-values corrected via the Benjamini–Hochberg method.

results for model 3, with mean differences and effect sizes presented. The emerging depressive symptom trajectory predicted cognitive decline over time on the SDMT, HVLT-R, 3 MS and composite score with the largest effect size for SDMT (Cohen's *d* −0.13). The persistent depressive symptom trajectory predicted cognitive impairment on SDMT, 3 MS and composite score. The subthreshold symptom trajectory predicted cognitive impairment on SDMT and composite score, albeit with smaller effect sizes. Sensitivity analyses revealed that the exclusion of individuals taking antidepressants was associated with small reductions in magnitude of impairment across all cognitive outcomes in the persistent depressive group only. The exclusion of individuals with dementia did not result in any statistically significant changes in the emerging or persistent depression groups.

Discussion

The evidence that early- and mid-life depression increases the likelihood of dementia is mixed (Elser *et al.*, 2023, Singh-Manoux *et al.*, 2017) but there is robust evidence that indicates that late-life depression increases the likelihood of dementia (Han *et al.*, 2021, Yang *et al.*, 2023). While the link between depression and dementia is established, it is important to note that cognitive decline, even without dementia, is an important concern for older adults.

This study, which to our knowledge is the largest study to date to comprehensively assess different trajectories of depressive symptoms and several cognitive outcomes in a cohort predominantly in their 8th decade, identifying the domains of cognition most affected by depressive symptoms over time. It demonstrates that both persistent (mild and moderate) and emerging depressive symptoms predict small but significant impairments in cognition, most consistently processing speed.

There are few studies that have examined the specific cognitive domains affected by depressive symptoms. In a study of 7,610 adults aged 50 years or older, depressive symptoms were significantly associated with subsequent cognitive decline over a 10-year follow-up period (Zheng *et al.*, 2018). However, this study modeled trajectories on only two time points, limiting its ability to identify potentially clinically relevant depressive trajectories, and did not assess processing speed. An analysis of the Korean Longitudinal Study of Ageing which assessed global cognition using a mini-mental state examination (MMSE) but did not utilize any other cognitive measures, found a similar relationship (Choi *et al.*, 2019). A much larger European study of

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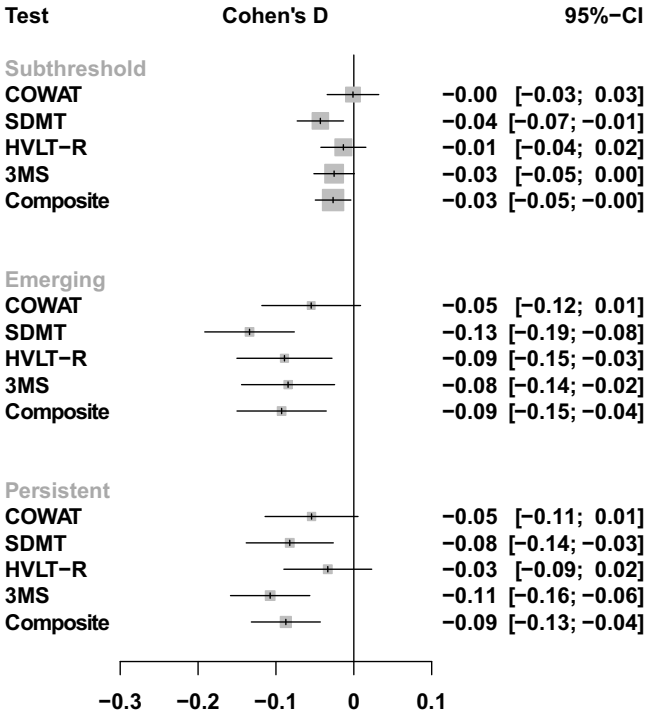

Figure 3. Forest plot of cognitive outcomes with effect size using Cohen's *d* for subthreshold, emerging, and persistent depression groups (compared to the nondepressed group).

69,066 participants found that individuals with persistently high and emerging depressive symptoms experienced linear cognitive decline, but given the large study sample, only a modest battery of cognitive assessments were undertaken (Formánek *et al.*, 2020).

A key strength of our study is its size and the assessment of domain-specific cognitive outcomes. It demonstrates that, in a large sample, cognitive decline occurs across several domains of cognition. These findings are robust to sensitivity analyses excluding individuals taking antidepressants and those with dementia. Another strength is that this study examined a cohort enrolled from a trial, allowing estimation of the impact of depressive symptoms on cognitive outcomes in a group free from clinically apparent cardiovascular disease or dementia at baseline.

There are several possible explanations for the relationship we found between emerging depressive symptoms and persistent depressive symptoms and cognitive decline. Firstly, depressive symptoms may be a prodrome of a dementia. Neuropathological changes in the brain associated with various dementias occur years prior to cognitive symptom onset, thus depressive symptoms occurring de novo in older individuals may represent non-cognitive prodromal features of a dementia (Leoutsakos *et al.*, 2019, Panza *et al.*, 2010). This concept, known as mild behavioral impairment (MBI), is characterized by changes in behavior or personality starting after the age of 50 and persisting, at least intermittently, for six months. The neuropsychiatric symptoms associated with MBI include decreased motivation and affective symptoms (Ismail *et al.*, 2016) and there is considerable overlap with the diagnostic criteria for major depressive disorder (American Psychiatric Association, 2013). This finding is supported by other studies that show emerging depressive symptoms over time increases the risk of cognitive decline (Babulal *et al.*, 2023, Krell-Roesch *et al.*, 2021) and dementia (Kaup *et al.*, 2016, Mirza *et al.*, 2016). The timing of onset of depressive symptoms is important. Ly *et al.* (2021) found that late-onset (first depressive episode $\geq$ 60 years) LLD was associated with a more rapid decline in verbal skills and delayed recall than individuals with early-onset (first depressive episode $\leq$ 60 years) LLD. These late-onset depressive symptoms may be related to cortical amyloid (Gatchel *et al.*, 2019) and neurofilament light levels (Gatchel *et al.*, 2022). A recent study found two different types of LLD: one with relatively preserved brain anatomy and one characterized by widespread brain atrophy and white matter changes, with a higher rate of progression to Alzheimer's disease (Wen *et al.*,

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2022). Interestingly, our study found impairment in delayed recall in the emerging depression group only.

Secondly, it may be the case that the impairments in cognition found in this study relate to ongoing depressive symptoms, particularly given the short period of time between measurement of depressive symptoms and short duration of measurement of cognitive outcomes. It is known that depression is associated with moderate deficits within the domains of executive function, attention and memory (Rock *et al.*, 2014). A meta-analysis of 252 studies found that deficits in selective attention, working memory, and long-term memory persist in remission from a major depressive episode. Older age was associated with lower performance relative to controls on the mini-mental state examination (MMSE), word list learning and delayed recall, logical memory immediate and delayed recall, and the Wisconsin Card Sorting Test (Semkovska *et al.*, 2019). Furthermore, remitted depression is also associated with cognitive deficits in attention, working memory and long-term recall (Semkovska *et al.*, 2019). One caveat regarding this relationship is that Alzheimer's disease could have been a confounder in several studies examining older individuals. Previous research has indicated that it may account for some of the cognitive impairment findings in LLD (Rhodes *et al.*, 2021). Our sensitivity analysis did not find significant differences when those with dementia were excluded during the exposure timeframe.

Interestingly, while executive dysfunction and impaired verbal fluency are common in LLD (Szymkowicz *et al.*, 2023b), this study found no significant decline on the COWAT. This may be due in minor part to the age range of participants. The most pronounced deficits in COWAT are found in those with predominant frontal lobe pathology and the relatively young mean age of onset of frontotemporal dementia means these individuals would not have met inclusion criteria for the ASPREE study. Our study included a measure of verbal delayed recall (HVLT-R), which was impaired only in the emerging depression group, possibly heralding the emergence of Alzheimer's disease, which is typically associated with impairments in encoding and storing new verbal information. However, this cannot be stated unequivocally based on the data and given that impairments in delayed recall also occur in those with recurrent depressive episodes (Gorwood *et al.*, 2008).

The mechanisms underlying the link between depression and cognitive impairment have not been fully elucidated. Neurobiological models of LLD have implicated the accumulation of allostatic load and neurotransmitter dysfunction secondary to senescence, inflammation and vascular disease destabilizing functional brain networks (Szymkowicz *et al.*, 2023a, Taylor *et al.*, 2022). Dopaminergic system dysfunction may be more common in LLD characterized by cerebrovascular damage (Taylor *et al.*, 2022). Depressive symptoms occurring in dementia may relate to neurodegeneration of monoamine pathways and loss of neuroplasticity, and a recent meta-analysis of voxel-based morphometry studies found shared volumetric reductions in the insula, superior temporal gyrus, inferior frontal gyrus, amygdala, hippocampus and thalamus in both individuals with depression and those with MCI (Zacková *et al.*, 2021), suggesting either shared pathophysiology or phenotypic overlap between the two conditions. Similarly, a systematic review of structural magnetic resonance imaging studies found mild frontotemporal volume reduction and widespread white matter changes to be associated with impaired cognition in LLD (Marawi *et al.*, 2023).

In our study, subthreshold depressive symptoms predicted cognitive impairment, albeit with lower effect sizes than the emerging and persistent depressive symptom groups. This finding accords with a pooled analysis of the results of the Health and Retirement Study and English Longitudinal Study of Ageing (Zhu *et al.*, 2022) and the Chinese Health and Retirement Longitudinal Study (Zhang *et al.*, 2022) and suggests a dose effect. Clinically, assessing individual depressive symptoms may be important, even if the symptom threshold for a diagnosis of a major depressive disorder is not met (Fried and Nesse, 2015).

Interestingly, there is evidence from two longitudinal studies suggesting that elevated depressive symptoms do not necessarily lead to accelerated cognitive decline provided that depressive symptoms are reduced (Mirza *et al.*, 2016, Zhu *et al.*, 2022), suggesting a potential protective role for timely and effective treatment intervention (Yu *et al.*, 2020). This epidemiological finding has been shown in a clinical study, with improvement in depressive symptoms associated with improvements in verbal learning, memory and set shifting (Kassel *et al.*, 2022). Clinical subtypes of LLD have recently been identified using a machine learning approach that have different prognoses and may benefit from streamlined interventions (Solomonov *et al.*, 2023). Since it is known that antidepressant medication has limited efficacy in treating depression that occurs in dementia (Costello *et al.*, 2023, Taylor *et al.*, 2021), incorporation of biomarkers to identify dementia processes, and considering information about depressive symptom trajectories, may be of clinical relevance for personalized treatments.

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Our study was limited by its relatively short follow-up period relative to the clinical course of cognition, and its homogenous study sample. Furthermore, we did not include data on some possible mediating factors between depression and impaired cognitive outcomes, including social activities and mobility (Hung *et al.*, 2023), which was only available for a subset of our study sample, and a broader range of medical comorbidities, which were not available for the entire cohort.

In conclusion, this study demonstrates that persistent and emerging depressive symptom trajectories are associated with a subsequent decline in processing speed in a large sample of initially healthy older community-dwelling adults. Further research should consider data-driven depression subtyping.

Conflicts of interest

None.

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Description of author(s)' roles

MF was involved in all aspects of the research and wrote the first draft. ML and MF completed the data analysis under the supervision of MM and AO. RW, SO, TC, BA, JR, and MB were all involved in the design of the cohort study. CR, JR, and MB provided supervision to MF.

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Consent statement

All human subjects provided informed consent.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S1041610224000541.

References

Agustini, B., Lotfaliany, M., Mohebbi, M., Woods, R. L., McNeil, J. J., Nelson, M. R., Shah, R. C., Murray, A. M., Reid, C. M., Tonkin, A., & Ryan, J. (2022). Trajectories of depressive symptoms in older adults and associated health outcomes. *Nature Aging*, 2(4), 295–302.

Ainsworth, N., Marawi, T., Maslej, M., Perivolaris, A., Blumberger, D., Pat McAndrews, M., Pollock, B., & Mulsant, B. (2023). Changes in cognitive function following antidepressant treatment for late-life depression: A systematic review and meta-analysis. *The American Journal of Geriatric Psychiatry*, 31, S48–S49.

Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Transl Psychiatry*, 9(1), 188.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. American Psychiatric Association.

ASPREE Investigator Group (2013). Study design of ASPirin in reducing events in the elderly (ASPREE): A randomized, controlled trial. *Contemporary Clinical Trials*, 36(2), 555–564.

Babulal, G. M., Chen, L., Murphy, S. A., Doherty, J. M., Johnson, A. M., & Morris, J. C. (2023). Neuropsychiatric symptoms and Alzheimer disease biomarkers independently predict progression to incident cognitive impairment. *The American Association for Geriatric Psychiatry*, 31(12), 1190–1199.

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins verbal learning test—Revised: Normative data and analysis of inter-form and test-retest reliability. *Clinical Neuropsychologist*, 12, 43–55.

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *The Annals of Statistics*, 29, 1165–1188.

Berk, M., Woods, R. L., Nelson, M. R., Shah, R. C., Reid, C. M., Storey, E., Fitzgerald, S., Lockery, J. E., Wolfe, R., Mohebbi, M., Dodd, S., Murray, A. M., Stocks, N., Fitzgerald, P. B., Mazza, C., Agustini, B.,

& McNeil, J. J. (2020). Effect of aspirin vs placebo on the prevention of depression in older people: A randomized clinical trial. *JAMA Psychiatry*, 77, 1012–1020.

Choi, D. W., Han, K. T., Jeon, J., Jang, S. I., Kim, S. J., & Park, E. C. (2019). Association between depressive-symptom trajectories and cognitive function in the late middle-aged and older population: Results of the Korean longitudinal study of ageing. *Scientific reports*, 9(1), 7807.

Costello, H., Roiser, J. P., & Howard, R. (2023). *Antidepressant medications in dementia: Evidence and potential mechanisms of treatment-resistance* (pp. 1–14). Psychological Medicine.

Demnitz, N., Anatürk, M., Allan, C. L., Griffanti, L., Mackay, C. E., Mahmood, A., Sexton, C. E., Suri, S., Topiwala, A. G., Zsoldos, E., Kivimäki, M., Singh-Manoux, A., & Ebmeier, K. P. (2020). Association of trajectories of depressive symptoms with vascular risk, cognitive function and adverse brain outcomes: The Whitehall II MRI sub-study. *Journal of Psychiatric Research*, 131, 85–93.

Elser, H., Horváth-Puhó, E., Gradus, J. L., Smith, M. L., Lash, T. L., Glymour, M. M., Toft Sørensen, H., & Henderson, V. W. (2023). Association of early-, middle-, and late-life depression with incident dementia in a Danish Cohort. *JAMA Neurology*, 80(9), 949–958.

Ernst, M. E., Broder, J. C., Wolfe, R., Woods, R. L., Nelson, M. R., Ryan, J., Shah, R. C., Orchard, S. G., Chan, A. T., Espinoza, S. E., Wilson, M., Kirpach, B., Reid, C. M., McNeil, J. J., Williamson, J. D., & Murray, A. M. (2023). Health characteristics and aspirin use in participants at the baseline of the ASPirin in reducing events in the elderly - eXTension (ASPREE-XT) observational study. *Contemporary Clinical Trials*, 130, 107231.

Formánek, Táš, Csajbók, Zófia, Wolfová, K., Kučera, Měj, Tom, S., Aarsland, D., & Cermakova, P. (2020). Trajectories of depressive symptoms and associated patterns of cognitive decline. *Scientific Reports*, 10(1), 20888.

Fried, E. I., & Nesse, R. M. (2015). Depression sum-scores don't add up: Why analyzing specific depression symptoms is essential. *BMC Medicine*, 13(1), 72.

Gatchel, J. R., Yang, H.-S., Mimmack, K. J., Arnold, S. E., Blacker, D., Liu, L., Selkoe, D. J., Johnson, K. A., Sperling, R. A., Marshall, G. A., & Chhatwal, J. P. (2022). Plasma biomarkers of neurodegeneration and Tau in relation to longitudinal depressive symptoms in older adults: Findings from the harvard aging brain study. *Alzheimer's & Dementia*, 18(57), e060979. https://doi.org/10.1002/alz.060979

Gatchel, J. R., Rabin, J. S., Buckley, R. F., Locascio, J. J., Quiroz, Y. T., Yang, H.-S., Vannini, P., Amariglio, R. E., Rentz, D. M., Properzi, M., Donovan, N. J., Blacker, D., Johnson, K. A., Sperling, R. A., Marshall, G. A., & for the Harvard Aging Brain Study (2019). Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Network Open*, 2(8), e198964.

Gorwood, P., Corruble, E., Falissard, B., & Goodwin, G. M. (2008). Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *American Journal of Psychiatry*, 165(6), 731–739.

Graziane, J. A., Beer, J. C., Snitz, B. E., Chang, C. C., & Ganguli, M. (2016). Dual trajectories of depression and cognition: A longitudinal population-based study. *The American Journal of Geriatric Psychiatry*, 24(5), 364–373.

Han, F. F., Wang, H. X., Wu, J. J., Yao, W., Hao, C. F., & Pei, J. J. (2021). Depressive symptoms and cognitive impairment: A 10-year follow-up study from the survey of health. *European psychiatry : the journal of the Association of European Psychiatrists*, 64(1), e55.

Hung, Y. C., Lao, W. L., Yeh, C. J., & Lee, M. C. (2023). The mediating effect of leisure activities in the relationship between depression and cognitive decline in middle age and older adults in Taiwan. *BMC Geriatrics*, 23(1), 315.

Ismail, Z., Elbayoumi, H., Fischer, C. E., Hogan, D. B., Millikin, C. P., Schweizer, T., Mortby, M. E., Smith, E. E., Patten, S. B., & Fiest, K. M. (2017). Prevalence of depression in patients with mild cognitive impairment: A systematic review and meta-analysis. *JAMA Psychiatry*, 74(1), 58–67.

Ismail, Z., Smith, E. E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., Agüera-Ortiz, L., Sweet, R., Miller, D., Lyketsos, C. G., & ISTAART Neuropsychiatric Symptoms Professional Interest Area (2016). Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers & Dementia*, 12(2), 195–202.

Kassel, M. T., Rhodes, E., Insel, P. S., Woodworth, K., Garrison-Diehn, C., Satre, D. D., Nelson, J. C., Tosun, D., & Mackin, R. S. (2022). Cognitive outcomes are differentially associated with depression severity trajectories during psychotherapy treatment for late life major depressive disorder. *International Journal of Geriatric Psychiatry*, 37(8). https://doi.org/10.1002/gps.5779

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., Smagula, S. F., Rubin, S. M., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, 73(5), 525–531.

Krell-Roesch, J., Syrjanen, J. A., Machulda, M. M., Christianson, T. J., Kremers, W. K., Mielke, M. M., Knopman, D. S., Petersen, R. C., Vassilaki, M., & Geda, Y. E. (2021). Neuropsychiatric symptoms and the outcome of cognitive trajectories in older adults free of dementia: The Mayo Clinic study of aging. *International Journal of Geriatric Psychiatry*, 36(9), 1362–1369.

Leoutsakos, J. S., Wise, E. A., Lyketsos, C. G., & Smith, G. S. (2019). Trajectories of neuropsychiatric symptoms over time in healthy volunteers and risk of MCI and dementia. *International Journal of Geriatric Psychiatry*, 34(12), 1865–1873.

Leung, D. K. Y., Chan, W. C., Spector, A., & Wong, G. H. Y. (2021). Prevalence of depression, anxiety, and apathy symptoms across dementia stages: A systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, 36(9), 1330–1344.

Ly, M., Karim, H. T., Becker, J. T., Lopez, O. L., Anderson, S. J., Aizenstein, H. J., Reynolds, C. F., Zmuda, M. D., & Butters, M. A. (2021). Late-life

depression and increased risk of dementia: A longitudinal cohort study. *Translational Psychiatry*, 11(1), 147.

Marawi, T., Ainsworth, N. J., Zhukovsky, P., Rashidi-Ranjbar, N., Rajji, T. K., Tartaglia, M. C., Voineskos, A. N., & Mulsant, B. H. (2023). Brain-cognition relationships in late-life depression: A systematic review of structural magnetic resonance imaging studies. *Translational Psychiatry*, 13(1), 284.

Mirza, S. S., Wolters, F. J., Swanson, S. A., Koudstaal, P. J., Hofman, A., Tiemeier, H., & Ikram, M. A. (2016). 10-year trajectories of depressive symptoms and risk of dementia: A population-based study. *The lancet Psychiatry*, 3(7), 628–635.

Mohebbi, M., Agustini, B., Woods, R. L., McNeil, J. J., Nelson, M. R., Shah, R. C., Nguyen, V., Storey, E., Murray, A. M., Reid, C. M., Kirpach, B., Wolfe, R., Lockery, J. E., Berk, M., & ASPREE Investigator Group (2019). Prevalence of depressive symptoms and its associated factors among healthy community-dwelling older adults living in Australia and the United States. *International Journal of Geriatric Psychiatry*, 34(8), 1208–1216.

Mohebbi, M., Nguyen, V., McNeil, J. J., Woods, R. L., Nelson, M. R., Shah, R. C., Storey, E., Murray, A. M., Reid, C. M., Kirpach, B., Wolfe, R., Lockery, J. E., Berk, M., & ASPREE Investigator Group (2018). Psychometric properties of a short form of the center for epidemiologic studies depression (CES-D-10) scale for screening depressive symptoms in healthy community dwelling older adults. *General Hospital Psychiatry*, 51, 118–125.

Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A. M., Imbimbo, B. P., Santamato, A., Vendemiale, G., Seripa, D., Pilotto, A., Capurso, A., & Solfrizzi, V. (2010). Late-life depression, mild cognitive impairment, and dementia: possible continuum? *The American Journal of Geriatric Psychiatry*, 18(2), 98–116.

Rhodes, E., Insel, P. S., Butters, M. A., Morin, R., Bickford, D., Tosun, D., Gessert, D., Rosen, H. J., Aisen, P., Raman, R., Landau, S., Saykin, A., Toga, A., Jack, C. R., Weiner, M. W., Nelson, C., Mackin, S., & Alzheimer's Disease Neuroimaging Initiative; ADNI Depression Project (2021). The impact of amyloid burden and APOE on rates of cognitive impairment in late life depression. *Journal of Alzheimers Disease*, 80, 991–1002.

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, 44(10), 2029–2040.

Ross, T. P. (2003). The reliability of cluster and switch scores for the controlled oral word association test. *Archives of Clinical Neuropsychology*, 18, 153–164.

Ryan, J., Storey, E., Murray, A. M., Woods, R. L., Wolfe, R., Reid, C. M., Nelson, M. R., Chong, T. T. J., Williamson, J. D., Ward, S. A., Lockery, J. E., Orchard, S. G., Trevaks, R., Kirpach, B., Newman, A. B., Ernst, M. E., McNeil, J. J., Shah, R. C., & on behalf of the ASPREE Investigator Group (2020). Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. *Neurology*, 95(3), e320–e331.

Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., Knittle, H., Ahern, E., & Gload, T. (2019). Cognitive function following a major depressive episode: A systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 851–861.

Shin, J., & Cho, E. (2022). Trajectories of depressive symptoms among community-dwelling Korean older adults: findings from the Korean longitudinal study of aging (2006–2016). *BMC Psychiatry*, 22(1), 246.

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimaki, M., & Sabia, S. (2017). Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry*, 74(7), 712–718.

Smith, A. (1973). *Symbol digit modalities test: Manual*. Western Psychological Services.

Solomonov, N., Lee, J., Banerjee, S., Chen, S. Z., Sirey, J. A., Gunning, F. M., Liston, C., Raue, P. J., Areán, P. A., & Alexopoulos, G. S. (2023). Course of subtypes of late-life depression identified by bipartite network analysis during psychosocial interventions. *JAMA Psychiatry*, 80(6), 621–629.

Szymkowicz, S. M., Gerlach, A. R., Homiack, D., & Taylor, W. D. (2023a). Biological factors influencing depression in later life: Role of aging processes and treatment implications. *Translational Psychiatry*, 13(1), 160.

Szymkowicz, S. M., Ryan, C., Elson, D. M., Kang, H., & Taylor, W. D. (2023b). Cognitive phenotypes in late-life depression. *International Psychogeriatrics*, 35(4), 193–205.

Taylor, W. D., Boyd, B. D., Elson, D., Andrews, P., Albert, K., Vega, J., Newhouse, P. A., Woodward, N. D., Kang, H., & Shokouhi, S. (2021). Preliminary evidence that cortical amyloid burden predicts poor response to antidepressant medication treatment in cognitively intact individuals with late-life depression. *The American Journal of Geriatric Psychiatry*, 29(5), 448–457.

Taylor, W. D., Zald, D. H., Felger, J. C., Christman, S., Claassen, D. O., Horga, G., Miller, J. M., Gifford, K., Rogers, B., Szymkowicz, S. M., & Rutherford, B. R. (2022). Influences of dopaminergic system dysfunction on late-life depression. *Molecular Psychiatry*, 27(1), 180–191.

Teng, E. L., & Chui, H. C. (1987). The modified mini-mental state (3MS) examination. *The Journal of clinical psychiatry*, 48(8), 314–318.

van den Kommer, T. N., Comijs, H. C., Aartsen, M. J., Huisman, M., Deeg, D. J. H., & Beekman, A. T. F. (2013). Depression and cognition: How do they interrelate in old age? *The American Association for Geriatric Psychiatry*, 21(4), 398–410.

Wen, J., Fu, C. H. Y., Tosun, D., Veturi, Y., Yang, Z., Abdulkadir, A., Mamourian, E., Srinivasan, D., Skampardoni, I., Singh, A., Nawani, H., Bao, J., Erus, G., Shou, H., Habes, M., Doshi, J., Varol, E., Mackin, R. S., Sotiras, A., Fan, Y., Saykin, A. J., Sheline, Y. I., Shen, L., Ritchie, M. D., Wolk, D. A., Albert, M., Resnick, S. M., Davatzikos, C., & iSTAGING consortium, ADNI, BIOCARD, and BLSA (2022). Characterizing heterogeneity in neuroimaging, cognition, clinical symptoms, and genetics among patients with late-life depression. *JAMA Psychiatry*, 79(5), 464–474.

https://doi.org/10.1017/S1041610224000541 Published online by Cambridge University Press

Wu, Z., Woods, R. L., Chong, T. T. J., Orchard, S. G., Shah, R. C., Wolfe, R., Storey, E., Sheets, K. M., Murray, A. M., McNeil, J. J., & Ryan, J. (2022). Cognitive trajectories in community-dwelling older adults and incident dementia, disability and death: A 10-year longitudinal study. *Frontiers in Medicine*, 9, 917254.

Wu, Z., Agustini, B., Woods, R. L., McNeil, J. J., Nelson, M. R., Shah, R. C., Nguyen, V., Storey, E., Murray, A. M., Reid, C. M., Kirpach, B., Wolfe, R., Lockery, J. E., Berk, M., & ASPREE Investigator Group (2021). Trajectories of cognitive function in community-dwelling older adults: A longitudinal study of population heterogeneity. *Alzheimer's & Dementia*, 13(1), e12180.

Xiang, X. (2020). Seven-year trajectories of depressive symptoms and their predictors among older Americans. *Journal of Aging and Health*, 32(7-8), 795–806.

Yang, L., Deng, Y. -T., Leng, Y., Ou, Y. -N., Li, Y. -Z., Chen, S. -D., He, X. -Y., Wu, B. -S., Huang, S. -Y., Zhang, Y. -R., Kuo, K., Feng, W., Dong, Q., Feng, J. -F., Suckling, J., Smith, A. D., Li, F., Cheng, W., & Yu, J. -T. (2023). Depression, depression treatments, and risk of incident dementia: A prospective Cohort study of 354,313 participants. *Biological Psychiatry*, 93, 802–809.

Yu, J-T., Xu, W., Tan, C-C., Andrieu, S., Suckling, J., Evangelou, E., Pan, A., Zhang, C., Jia, J., Feng, L., Kua, E-H., Wang, Y-J., Wang, H-F., Tan, M-S., Li, J-Q., Hou, X-H., Wan, Y., Tan, L., Mok, V., Tan, L., Dong, Q., Touchon, J., Gauthier, S., Aisen, P. S., & Vellas, B. (2020). Evidence-based prevention of Alzheimer's disease: Systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *Journal of Neurology, Neurosurgery, and Psychiatry*, 91(11), 1201–1209.

Zacková, L., Jáni, M., Brázdil, M., Nikolova, Y. S., & Marečková, K. (2021). Cognitive impairment and depression: Meta-analysis of structural magnetic resonance imaging studies. *NeuroImage: Clinical*, 32, 102830.

Zhang, B., Lin, Y., Hu, M., Sun, Y., Xu, M., Hao, J., & Zhu, C. (2022). Associations between trajectories of depressive symptoms and rate of cognitive decline among Chinese middle-aged and older adults: An 8-year longitudinal study. *Journal of Psychosomatic Research*, 160, 110986.

Zheng, F., Zhong, B., Song, X., & Xie, W. (2018). Persistent depressive symptoms and cognitive decline in older adults. *The British Journal of Psychiatry*, 213(5), 638–644.

Zheng, H., Cagney, K., & Choi, Y. (2023). Predictors of cognitive functioning trajectories among older Americans: A new investigation covering 20 years of age- and non-age-related cognitive change. *PLoS One*, 18(2), e0281139.

Zhu, Y., Li, C., Xie, W., Zhong, B., Wu, Y., & Blumenthal, J. A. (2022). Trajectories of depressive symptoms and subsequent cognitive decline in older adults: A pooled analysis of two longitudinal cohorts. *Age and Ageing*, 51(1). https://doi.org/10.1093/ageing/afab191

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