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Persistent depressive symptoms and cognitive decline in older adults

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Background

Little is known about the effect of persistent depressive symptoms on the trajectory of cognitive decline.

Aims

We aimed to investigate the longitudinal association between the duration of depressive symptoms and subsequent cognitive decline over a 10-year follow-up period.

Method

The English Longitudinal Study of Ageing cohort is a prospective and nationally representative cohort of men and women living in England aged ≥50 years. We examined 7610 participants with two assessments of depressive symptoms at wave 1 (2002–2003) and wave 2 (2004–2005), cognitive data at wave 2 and at least one reassessment of cognitive function (wave 3 to wave 7, 2006–2007 to 2014–2015).

Results

The mean age of the 7610 participants was 65.2 ± 10.1 years, and 57.0% were women. Of these, 1157 (15.2%) participants had episodic depressive symptoms and 525 participants (6.9%) had persistent depressive symptoms. Compared with participants without depressive symptoms at wave 1 and wave 2, the multivariable-adjusted rates of global cognitive decline associated with episodic depressive symptoms and persistent depressive symptoms were faster by −0.065 points/year (95% CI −0.129 to −0.000) and −0.141 points/year (95% CI −0.236 to −0.046), respectively (*P* for trend < 0.001). Similarly, memory, executive and orientation function also declined faster with increasing duration of depressive symptoms (all *P* for trend < 0.05).

Conclusions

Our results demonstrated that depressive symptoms were significantly associated with subsequent cognitive decline over a 10-year follow-up period. Cumulative exposure of long-term depressive symptoms in elderly individuals could predict accelerated subsequent cognitive decline in a dose-response pattern.

Declaration of interest

None.

Keywords

Depressive symptoms; cognitive decline; trajectory; ELSA.

Depressive symptoms and cognitive impairment are two of the most prevalent psychiatric conditions strongly associated with poor quality of later life and a high social burden.[1–4] Because of its significant clinical and public health importance, the relationship between late-life depressive symptoms and subsequent cognitive decline indicative of dementia has become an increasing focus of contemporary research. A series of cohort studies have suggested that depressive symptoms are associated with cognitive decline or dementia,[5–13] whereas several other studies reported inconsistent findings.[14–17] Studies reporting these inconsistent findings have largely focused on the association between a single-time (mostly baseline) assessment of depressive symptoms and cognitive decline.[5–8,12–16] However, as depressive symptoms tend to fluctuate over time,[18,19] it is likely that these studies may not have fully captured the persistent effect of these symptoms on cognitive decline, affecting our understanding of this relationship. Only a small number of longitudinal studies using repeated assessments of depressive symptoms have been conducted to date, and these studies have typically used small sample sizes over a short time period,[10,11] or in a particular subpopulation, such as women,[9] which may limit the generalisability of the results. Moreover, most prior studies have explored the association between baseline depressive symptoms and incident cognitive impairment,[5–7,10–13,16] rather than the association between depressive symptoms and the trajectory of cognitive decline. The trajectory of cognitive decline, which consists of several assessments of cognitive function, is of great importance for evaluating and monitoring the progression of cognitive deterioration and could therefore be more informative for early intervention.

The English Longitudinal Study of Ageing (ELSA) has involved multiple phases of data collection, representing a golden opportunity for exploring the association between late-life depressive symptoms and the trajectory of subsequent cognitive decline. The objectives of the present study were (a) to determine whether depressive symptoms predict cognitive decline in an elderly population at baseline, and (b) to examine whether people reporting episodic or persistent depressive symptoms show a similar or different association with subsequent cognitive decline.

Method

Study population

This study used data from wave 1 (2002–2003) to wave 7 (2014–2015) of the ELSA study, which is a prospective and nationally representative cohort of men and women living in England aged 50 years and over.[20] A detailed description of the goals, design and methods of the ELSA has been published elsewhere.[21] A flowchart of the cohort is shown in Supplementary Figure 1 available at https://doi.org/10.1192/bjp.2018.155. A total of 12 099 participants took part in the wave 1 survey of the ELSA. Of these, 3226 participants were excluded from this study because they did not attend the wave 2 survey ($n = 2706$), did not complete the cognitive tests at wave 1 or wave 2 ($n = 502$) or had self-reported doctor-diagnosed dementia at wave 1 or wave 2 ($n = 18$). An additional 1263 individuals were excluded because of loss to follow-up from wave 3 to wave 7. The remaining 7610 participants (3272 men and 4338 women) with complete baseline data (wave 2) and at least one reassessment of cognitive function (wave 3 to wave 7) were included in the analyses reported here.

The ELSA study was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91) and informed consent was obtained from all participants.

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Cognitive assessments

The cognitive assessments were conducted as described previously.[22,23] The memory function of each participant was measured with immediate and delayed recall of ten unrelated words. Both immediate and delayed recall scores ranged from 0 to 10, with higher scores indicating better memory performance. Immediate and delayed recall tests have been shown to have good construct validity and consistency.[24] A composite memory score was created by summing the scores of the individual memory tests. Executive function was assessed with a verbal fluency task, in which individuals were required to verbally name as many animals as they could in 60 s. Because of the well-documented reliability and validity of this task, it has already been utilised as a solid indicator of executive function within the ELSA population.[25] The total score on the animal-naming test was the total number of words produced, excluding repetitive words and words outside the animal category. Orientation to time was assessed by asking four questions (one point each for day of month, month, year and day of week). A global cognitive score was created by summing the individual scores on the memory, executive function and orientation assessments. Generally, higher scores indicate better cognitive function.

Depressive symptoms

Depressive symptoms were measured with the eight-item version of the Center for Epidemiologic Studies Depression Scale (CES-D), a widely used self-report measure of depressive symptoms, used to identify people at risk of depression in population-based studies.[22] Participants were asked to think about the past week and the feelings they experienced and to indicate whether each of the following statements was true for them much of the time during the past week: you felt depressed; you felt that everything was an effort; your sleep was restless; you were happy; you felt lonely; you enjoyed life; you felt sad; you could not get going. There were two response options: yes or no. This version of the CES-D has an internal consistency and factor structure that are comparable with longer versions of the scale.[26] As in previous studies, we used a score of ≥4 to define participants with elevated depressive symptoms.[27] To derive a duration of depressive symptoms score, we totalled the number of occasions an individual was recorded as being a case at each wave, resulting in a score range from 0 (never a case) to 2 (a case at both wave 1 and wave 2). The sum of CES-D scores at wave 1 and wave 2, ranging from 0 to 16, was used when modelled as a continuous measure. Participants reporting depressive symptoms at wave 1 or wave 2 were classified as having episodic depressive symptoms, and those reporting depressive symptoms at both waves were classified as having persistent depressive symptoms.

Covariates

According to previous studies, covariates known to be associated with both depression and cognitive function were selected in our analyses.[9,16,28] Blood pressure was measured by the nurse in the right arm of each participant while they were in a sitting position, using the Omron HEM-907.[29] Five minutes elapsed before the first reading was taken. The mean value of three consecutive blood pressure readings was used in our analyses. Hypertension was determined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg, or if the participant was currently using anti-hypertensive drugs. Education level was classified as no qualification, level 1 National Vocational Qualification (NVQ1) or certificate of secondary education, NVQ2 or O-level, NVQ3 or A-level, higher qualification but below degree, and degree level or higher or NVQ4/5. Marital status was classified as single (never married), married, remarried, legally separated, divorced or widowed. We defined cohabitation status as currently living alone or not. Participants were split into two groups: non-smokers (never smoked or ex-smokers) and smokers (current smokers). Alcohol intake was calculated from participant-reported drinking frequency over the previous year (weekly drinking versus occasional or never). Standing height was measured with a portable stadiometer, with participants standing in the centre of the base plate looking straight ahead, and weight was measured by portable electronic scales.[29] Body mass index was calculated with the following formula: weight (kg)/height^2 (m^2). Diabetes was defined as haemoglobin A_{1c} ≥6.5%, fasting blood glucose ≥7.00 mmol/L or current use of anti-diabetic therapy. Measures of chronic disease included lifetime self-reported physician diagnoses of coronary heart disease (angina and heart attack), stroke, chronic lung disease and cancer. The use of antidepressants was measured by asking the participants whether antidepressant medication was recommended by their doctor at wave 2.

Statistical analysis

The results are presented as percentages for categorical variables or mean ± s.d. for continuous variables. The cross-sectional associations between baseline depressive symptoms and cognitive scores at baseline were tested by multiple linear regression models and analyses of covariance. Linear mixed models were used to evaluate the longitudinal associations. Linear mixed models were used to evaluate the longitudinal associations between the sum of CES-D scores (wave 1 and wave 2, range 0–16) and cognitive scores over time. We also ran longitudinal analyses with the duration score of depressive symptoms, with 0 (never a case) as the referent. Linear mixed models use all available data over the follow-up period, take into account the fact that repeated measures on the same participant are correlated with each other and can handle missing data. In these models, both the intercept and the slope were fitted as random effects to account for inter-individual differences at baseline and different rates of change of cognitive function over the follow-up period. The first model included the duration of depressive symptoms (0, 1 or 2), time (years since baseline), time × depressive symptoms interaction, age (years) and gender (male or female). The time × depressive symptoms interaction term indicated differential change of cognitive function by the duration of depressive symptoms from baseline to the end of the study (wave 2 to wave 7). The second model additionally adjusted for baseline body mass index (kg/m^2), education (<NVQ3/GCE A level or ≥NVQ3/GCE A level), marital status (currently living alone or not), current smoking (yes or no), alcoholic drink (less than once per week or once or more per week), antidepressant medication (yes or no), hypertension (yes or no), diabetes (yes or no), depressive symptoms × diabetes interaction, coronary heart disease (yes or no), stroke (yes or no), chronic lung disease (yes or no) and cancer (yes or no). Because Katon *et al* found that the co-occurrence of depression and diabetes was associated with a higher rate of subsequent dementia,[28] we included the depressive symptoms × diabetes interaction in the second model.

To enhance the utility of the findings for clinicians, mild cognitive impairment (MCI) was also considered in our analyses. We defined MCI as a global cognitive score <20 (1.5 s.d. below its mean, as proposed by Petersen *et al*[30]). The status of MCI (yes or no) was allowed to vary over the follow-up period. Poisson regression with PROC GENMOD (DIST = Poisson and LINK = log) was performed to assess the strength of associations (relative risk) between depressive symptoms and MCI, and generalised estimating equations were used to analyse binary repeated measures data.

We used a multiple imputation, chained-equations method to replace missing data for cognitive assessments during follow-up

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(wave 3 to wave 7), and used all available data from 8873 participants in the sensitivity analyses. Variables used to impute the missing values of cognitive scores included participants' baseline information (age, gender, education, marital status, body mass index, current smoking, alcoholic drink, diabetes and stroke) and baseline cognitive scores. For each longitudinal analysis, we created 20 imputed data-sets and combined the results with the MIANALYZE procedure.

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., North Carolina, USA; see https://www.sas.com/en_gb/software/sas9.html). All analyses were two-sided, with an alpha value of 0.05 considered as the threshold for statistical significance.

Results

Baseline characteristics and sample size

The mean age of the 7610 participants was 65.2 ± 10.1 years, and 57.0% of participants were female. Of these, 1157 (15.2%) participants were classified as experiencing episodic depressive symptoms and 525 participants (6.9%) were classified as experiencing persistent depressive symptoms. Table 1 shows the baseline characteristics of participants according to the number of waves with depressive symptoms. In general, compared with those without depressive symptoms, participants who reported a longer duration of depressive symptoms had significantly less favourable characteristics. Study participants reporting a longer duration were older; had higher body mass index; were more likely to be female; had higher percentages of living alone, smoking, diabetes, coronary heart disease, stroke; and chronic lung disease; had lower percentages of higher education and drinking and had worse cognitive function.

Cognitive function was assessed at baseline (wave 2) and reassessed biennially at wave 3 to wave 7. The cohort size was 7610 (wave 2), 7221 (wave 3), 6225 (wave 4), 5763 (wave 5), 5267 (wave 6) and 4573 (wave 7). The mean follow-up duration was 7.9 ± 2.9 years and the mean number of cognitive assessments was 4.8 ± 1.5.

Depressive symptoms and cognitive scores (cross-sectional analyses)

Supplementary Figure 2 shows the multivariable-adjusted cognitive scores according to the number of waves with depressive symptoms. All of the cognitive scores decreased linearly with increasing duration of depressive symptoms (all P for trend < 0.001). As seen in Supplementary Table 1, when modelled as a continuous measure, a one-unit change in the sum of CES-D scores was also associated with the four cognitive scores after adjustment for age and gender (all $P < 0.001$), and these associations were still significant after multivariable adjustment.

Depressive symptoms and cognitive decline (longitudinal analyses)

Table 2 shows the longitudinal associations between the sum of CES-D and rate of change in cognitive scores. After multivariable adjustment, a one-unit increment in the sum of CES-D scores was associated with faster declines in global cognitive scores (–0.012 points/year, 95% CI –0.019 to –0.005, $P = 0.001$), memory scores (–0.004 points/year, 95% CI –0.007 to –0.002, $P = 0.002$), executive function scores (–0.005 points/year, 95% CI –0.011 to –0.001, $P = 0.015$) and orientation scores (–0.001 points/year, 95% CI –0.002 to –0.001, $P < 0.001$).

As shown in Fig. 1, cognitive scores of participants with persistent depressive symptoms significantly deteriorated over time compared with participants without depressive symptoms at wave 1 and wave 2. The multivariable-adjusted rates of global cognitive decline associated with episodic depressive symptoms and persistent depressive symptoms were faster by –0.065 points/year

Table 1 Characteristics of the study participants at baseline (wave 2), according to the number of occasions (wave 1 to wave 2) with depressive symptoms

Characteristic	Number of waves with depressive symptoms			*P* for trend[a]
	0 (*n* = 5928)	1 (episodic, *n* = 1157)	2 (persistent, *n* = 525)	
Age (years)	65.0 ± 10.0	65.5 ± 10.4	66.6 ± 11.1	<0.001
Women (%)	3189 (53.8)	781 (67.5)	368 (70.1)	<0.001
Body mass index (kg/m^2)	27.8 ± 4.2	28.2 ± 4.9	28.5 ± 4.7	<0.001
Systolic blood pressure (mm Hg)	136.2 ± 17.5	135.2 ± 17.2	136.6 ± 17.1	0.589
Diastolic blood pressure (mm Hg)	75.7 ± 10.1	75.1 ± 10.5	75.4 ± 10.3	0.084
Education ≥NVQ3/GCE A-level (%)	2129 (35.9)	295 (25.5)	97 (18.5)	<0.001
Living alone (%)	1683 (28.4)	502 (43.4)	308 (58.7)	<0.001
Current smoking (%)	794 (13.4)	213 (18.4)	144 (27.4)	<0.001
Alcoholic drink ≥once per week (%)	3509 (59.2)	518 (44.8)	190 (36.2)	<0.001
Antidepressant medication (%)	48 (0.8)	39 (3.4)	27 (5.1)	<0.001
Hypertension (%)	2463 (41.6)	485 (41.9)	229 (43.6)	0.391
Diabetes (%)	407 (6.9)	111 (9.6)	59 (11.2)	<0.001
Coronary heart disease (%)	347 (5.9)	98 (8.5)	76 (14.5)	<0.001
Stroke (%)	127 (2.1)	33 (2.9)	36 (6.9)	<0.001
Chronic lung disease (%)	239 (4.0)	75 (6.5)	63 (12.0)	<0.001
Cancer (%)	303 (5.1)	65 (5.6)	28 (5.3)	0.588
Global cognitive scores	35.0 ± 8.5	33.0 ± 8.8	30.0 ± 8.7	<0.001
Memory scores	10.5 ± 3.4	9.7 ± 3.6	8.8 ± 3.7	<0.001
Executive function scores	20.7 ± 6.4	19.5 ± 6.3	17.5 ± 6.1	<0.001
Orientation scores	3.79 ± 0.48	3.76 ± 0.54	3.68 ± 0.61	<0.001
CES-D scores at wave 1	0.74 ± 0.93	3.26 ± 2.18	5.61 ± 1.39	<0.001
CES-D scores at wave 2	0.78 ± 0.93	3.42 ± 2.11	5.75 ± 1.36	<0.001

The results are presented as mean ± s.d., or *n* (%).
CES-D, Center for Epidemiologic Studies Depression; NVQ, National Vocational Qualification.
a. Calculated by linear regression analysis or χ^2-test for trend.

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Table 2 Association between sum of CES-D scores (wave 1 and wave 2, range 0–16) and rate of change in cognitive scores (points/year): longitudinal analyses with linear mixed models

Model terms for cognitive scores	β (95% CI)[a]	*P* value
Global cognitive scores		
Time	−0.212 (−0.241 to −0.182)	<0.001
CES-D scores	−0.287 (−0.339 to −0.234)	<0.001
CES-D scores × time	−0.012 (−0.019 to −0.005)	0.001
Memory scores		
Time	−0.083 (−0.094 to −0.072)	<0.001
CES-D scores	−0.101 (−0.121 to −0.081)	<0.001
CES-D scores × time	−0.004 (−0.007 to −0.002)	0.002
Executive function scores		
Time	−0.091 (−0.114 to −0.069)	<0.001
CES-D scores	−0.178 (−0.219 to −0.138)	<0.001
CES-D scores × time	−0.005 (−0.011 to −0.001)	0.015
Orientation scores		
Time	−0.011 (−0.013 to −0.008)	<0.001
CES-D scores	−0.006 (−0.009 to −0.003)	<0.001
CES-D scores × time	−0.001 (−0.002 to −0.001)	<0.001

CES-D, Center for Epidemiologic Studies Depression.
a. Adjusted for baseline age, gender, body mass index, education, marital status, current smoking, alcoholic drink, antidepressant medication, hypertension, diabetes, depressive symptoms × diabetes interaction, coronary heart disease, stroke, chronic lung disease and cancer.

(95% CI −0.129 to −0.000) and −0.141 points/year (95% CI −0.236 to −0.046), respectively, compared with participants without depressive symptoms (*P* for trend < 0.001; Table 3). Similarly, memory, executive and orientation function also declined faster with increasing duration of depressive symptoms (all *P* for trend < 0.05; Table 3). Compared with the reference category, the multivariable-adjusted rate of memory decline associated with persistent depressive symptoms was faster by −0.048 points/year (95% CI −0.084 to −0.013), and the rates of executive and orientation function decline were faster by −0.074 points/year (95% CI −0.146 to −0.002) and −0.014 points/year (95% CI −0.023 to −0.006), respectively (Table 3).

Depressive symptoms and MCI (longitudinal analyses)

As shown in Supplementary Table 2, compared with participants without depressive symptoms, episodic and persistent depressive symptoms were associated with a 13 and 28% greater risk of MCI, respectively, after multivariable adjustment.

Non-response analyses

A total of 1263 participants (14.2%) with complete baseline data were excluded from the study because they were lost to follow-up. This group of excluded participants were older; had higher levels of systolic blood pressure; higher percentages of living alone, current smoking, diabetes, coronary heart disease, stroke, chronic lung disease, cancer and depressive symptoms; had lower percentages of higher education and drinking and had worse cognitive function (see Supplementary Table 3).

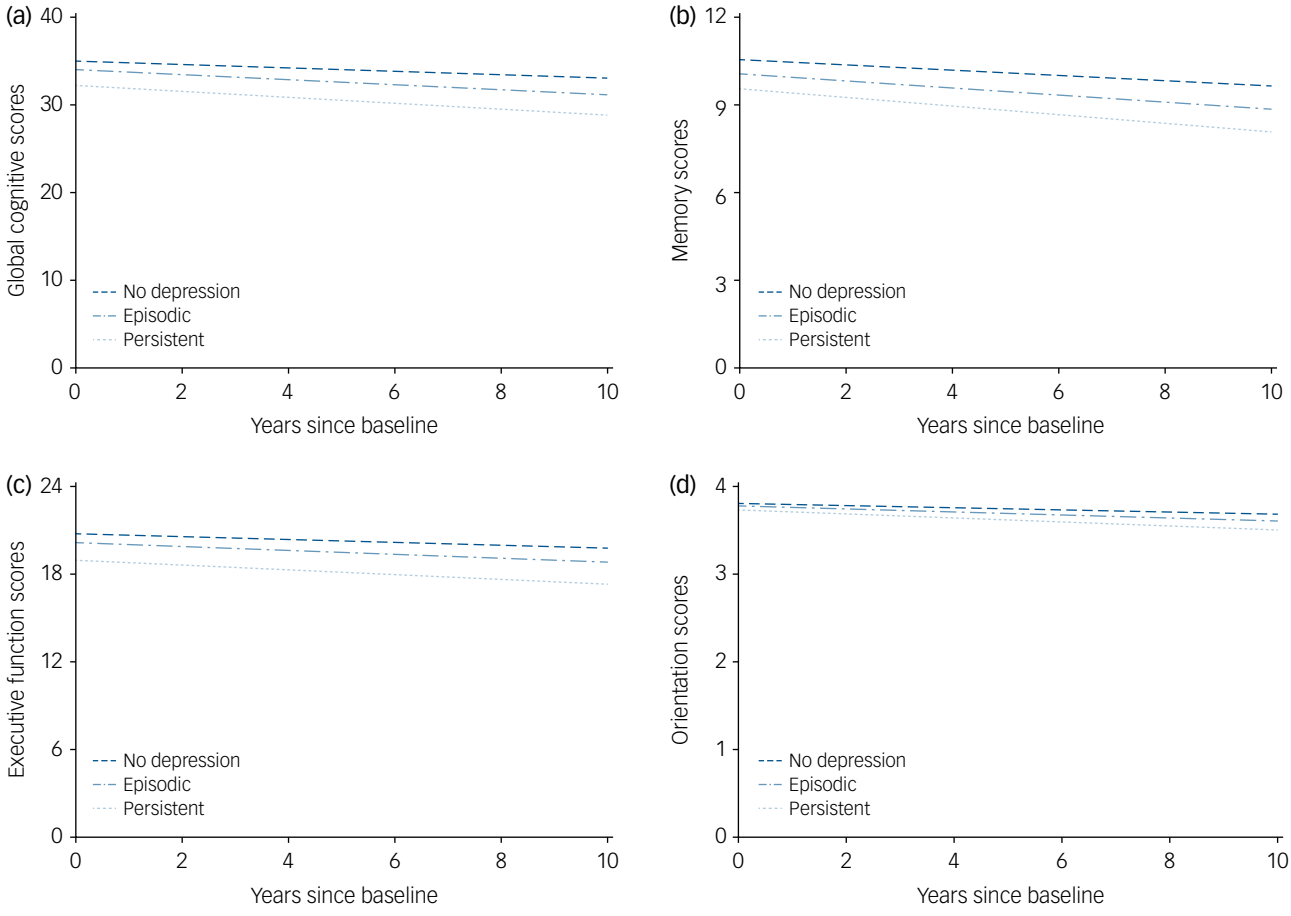

Fig. 1 The trajectories of cognitive scores by the number of waves with depressive symptoms (wave 1 to wave 2), adjusted for baseline age, gender, body mass index, education, marital status, current smoking, alcoholic drink, antidepressant medication, hypertension, diabetes, depressive symptoms × diabetes interaction, coronary heart disease, stroke, chronic lung disease and cancer.

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Table 3 Mean difference in the rate of change in cognitive scores (points/year) comparing the number of waves with depressive symptoms (wave 1 to wave 2): longitudinal analyses with linear mixed models

	Mean difference (95% CI) in rate of change by number of waves with depressive symptoms			*P* for trend
	0 ($n = 5928$)	1 (episodic, $n = 1157$)	2 (persistent, $n = 525$)	
Global cognitive scores				
Model 1[a]	0.000 (ref)	−0.065 (−0.130 to −0.001)	−0.142 (−0.238 to −0.047)	<0.001
Model 2[b]	0.000 (ref)	−0.065 (−0.129 to −0.000)	−0.141 (−0.236 to −0.046)	<0.001
Memory scores				
Model 1[a]	0.000 (ref)	−0.025 (−0.049 to −0.001)	−0.049 (−0.085 to −0.013)	0.001
Model 2[b]	0.000 (ref)	−0.025 (−0.049 to −0.001)	−0.048 (−0.084 to −0.013)	0.002
Executive function scores				
Model 1[a]	0.000 (ref)	−0.030 (−0.078 to 0.019)	−0.075 (−0.147 to −0.003)	0.025
Model 2[b]	0.000 (ref)	−0.029 (−0.078 to 0.019)	−0.074 (−0.146 to −0.002)	0.027
Orientation scores				
Model 1[a]	0.000 (ref)	−0.005 (−0.011 to 0.001)	−0.014 (−0.023 to −0.006)	<0.001
Model 2[b]	0.000 (ref)	−0.005 (−0.011 to 0.001)	−0.014 (−0.023 to −0.006)	<0.001

ref, reference value.
a. Model 1: adjusted for baseline age and gender.
b. Model 2: further adjusted for baseline body mass index, education, marital status, current smoking, alcoholic drink, antidepressant medication, hypertension, diabetes, depressive symptoms × diabetes interaction, coronary heart disease, stroke, chronic lung disease and cancer.

Sensitivity analyses

Longitudinal results with imputed data ($n = 8873$) were similar to those from the main analyses (see Supplementary Tables 4 and 5). Thus, the effect of missing data was likely to be small.

Discussion

In this large ongoing cohort study of an elderly British population, depressive symptoms were associated with baseline cognitive function in a cross-sectional analysis. Moreover, depressive symptoms were associated with subsequent cognitive decline over a 10-year follow-up period in a longitudinal analysis. In addition to this association, we found that the cumulative depressive symptom burden was independently and strongly associated with poorer cognitive performance and could, in a dose-response pattern, predict accelerated subsequent cognitive decline.

This study used previous assessments of depressive symptoms as a baseline to investigate the temporal association between persistent depressive symptoms and the trajectory of subsequent cognitive decline in a large general population, using depressive symptom data collected at wave 1 and wave 2 and cognitive decline data from wave 2 to wave 7. Several cohort studies have been conducted to explore the association between cumulative depressive symptoms and cognitive decline.[9,31,32] However, these studies were unable to confirm the temporal relations involved because it could not be determined with certainty whether a change in mood status preceded the development of cognitive decline based on data collected simultaneously during the same follow-up period. Although a small number of studies have examined the fluctuating nature of depressive symptoms over time, using multiple depressive assessments for statistical analysis, they have typically used incident cognitive decline as the main outcome measure and failed to show an effect on subsequent cognitive trajectory.[10,11] Apart from the methodological differences mentioned above, our results were largely compatible with previous findings,[9–11] demonstrating not only a significant association of depressive symptoms with cognitive decline, but also a greater effect of persistent depressive symptoms on subsequent cognitive deterioration. Importantly, our results are also supported by a recent study with a clinically depressed sample.[33] Nevertheless, it should be noted that only a weak association between depressive symptoms and cognitive decline was observed, in accordance with previous studies.[8,32] Although depressive symptoms may have caused only miniscule annual changes in cognitive function, the phenomenon could play an important role in cognitive decline. As reported in a previous study, even minor differences in cognition can lead to a substantially increased risk of dementia over several years.[34] Because there is currently no cure for dementia, early detection and intervention based on modifiable predictors, such as depressive symptoms, may offer an effective approach for the prevention of cognitive decline, delaying the progression to dementia and reducing its prevalence and associated public health burden.

Depression and cognitive impairment can have severe consequences, including reduced quality of life, elevated needs of social services and increased mortality, and are among the most important mental health problems among elderly people.[1–4] Late-onset depression and MCI occur together at a rate of up to 63%, suggesting a close association between the two disorders.[35] Increasing research attention has focused on elucidating the relationship between depression and subsequent cognitive decline in recent decades, but this research has yielded mixed findings. One possible explanation for the discrepancy in previous findings might be related to the fluctuating nature of depressive symptoms over time. As mentioned above, most previous studies have been limited by their use of a single assessment of depressive symptoms, potentially resulting in underestimation of the association. As such, our study adds more evidence to previous research by exploring the influence of the cumulative burden of repeated measures of depressive symptoms on subsequent cognitive outcomes. In addition, previous studies assessing the association between depressive symptoms and cognitive decline have been heterogeneous in terms of study population, symptom measurement, cognitive assessment, follow-up periods, outcome ascertainment and the reporting of results, which may have contributed to the discrepancies in findings. Furthermore, the magnitude of the dose-response association between the duration of depressive symptoms and faster subsequent cognitive decline was not attenuated by adjusting for these covariates in our linear mixed models, suggesting that depressive symptoms is strongly linked to cognitive decline independently of other social factors and comorbidities. These findings suggest that multiple assessments of depressive symptoms should be taken into account to detect depression and improve prognosis.

Importantly, although our results reveal a significant association of persistent depressive symptoms at wave 1 and wave 2, with subsequent cognitive decline from wave 2 to wave 7, the presence of depressive symptoms at subsequent waves and their potential

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effect on cognitive function should be considered. The observed cognitive decline was related not only to depressive symptoms at wave 1 and wave 2, but also to depressive symptoms in later waves. However, because individuals from the persistent depressive symptoms group would be expected to have a higher risk of depressive symptoms in later waves (see Supplementary Table 6), the persistent depressive symptoms at wave 1 and wave 2 could, to some extent, predict accelerated subsequent cognitive decline.

The mechanisms underlying the association between depressive symptoms and cognitive decline remain under debate, and several different mechanisms have been proposed. Accordingly, depressive symptoms could be a risk factor for subsequent cognitive decline, an early manifestation of cognitive deterioration, a reaction to perceived cognitive decline and functional disability or even a symptom of a related risk factor, such as cerebrovascular disease or neurodegenerative changes.[11,13,16] As summarised by Byers and Yaffe, predominant pathways linking depressive symptoms to cognitive decline include vascular disease, proinflammatory changes and hippocampal atrophy, and those pathways are likely to be multifactorial and not sequential.[36] It should be noted that, because it is not possible to conduct a randomised trial to test the relationship between depressive symptoms and subsequent cognitive decline, conclusions must be based on observational studies, from which causality cannot be established. However, with the current temporal design, we were able to conclude with confidence that, although a causal relationship remains to be determined, depressive symptoms exhibited years before could predict subsequent cognitive decline, and hence could serve as an indicator for early intervention to prevent further exacerbation of cognitive decline.

To our knowledge, the present study is the largest general population-based study exploring the relationship between depressive symptoms and cognitive decline with a long-term follow-up of 10 years. Moreover, cognitive function was repeatedly measured over a long period, providing a more robust measurement of cognitive deterioration. Our study design enabled us to better measure the cumulative burden of depressive symptoms and to estimate the long-term trajectories of cognitive decline. Nevertheless, our findings should be interpreted cautiously in the context of several potential limitations. First, because our study lacked the clinical diagnosis of dementia during follow-up, we could not analyse the temporal relationship between depressive symptoms and dementia. Second, although we adjusted for a number of potential confounders, we could not rule out the possibility of residual confounding factors, such as anxiety, chronic pain, sleep-related issues and prescribed agents that may affect anxiety and cognition. Genetic susceptibility factors, such as the APOE genotype, are also potential confounders. Currently, the moderating effect of the APOE genotype on the association between depressive symptoms and cognitive outcome remains equivocal, with some studies suggesting a synergistic interaction between APOE genotype and depressive symptoms in elevating the risk of further cognitive decline,[6,11] whereas others have not supported the existence of such an effect.[31,37,38] Unfortunately, genetic data are not available in ELSA, so we cannot adjust for the APOE genotype. Third, although we adjusted for the use of antidepressant, it should be noted that the data we used might not represent actual antidepressant use. Fourth, 1263 participants (14.2%) with complete baseline data were excluded from the study because they were lost to follow-up, potentially causing selection bias. Fifth, the study population was healthier than the original ELSA population, which may threaten the internal validity of estimates, potentially limiting the generalisability of our findings to the English population. However, sensitivity analyses with multiple imputation methods revealed similar results, indicating that the effect of attrition was minimal. In addition, cognition was assessed by isolated tasks in this study. Broader assessment of neuropsychological cognitive domain performance may have produced different results. Besides, individuals with depressive symptoms were not identified by a clinical diagnosis of depression made by a psychiatrist according to symptom criteria. The CES-D mainly assesses the depressive symptoms in the past week, which might lead to underestimation of the presence of depressive symptoms. Finally, although we identified the detection of depressive symptoms at both wave 1 and wave 2 as persistent depressive symptoms, it is still possible that what we captured are actually two separate episodes of depressive symptoms. In this case, the effect of persistent depressive symptoms on subsequent cognitive trajectory might represent the cumulative burden of recurrent depressive symptoms.

In conclusion, this study demonstrated that depressive symptoms were significantly associated with both baseline cognitive function and subsequent cognitive decline over a 10-year follow-up period. Cumulative exposure of long-term depressive symptoms in elderly individuals could predict accelerated subsequent cognitive decline in a dose-response pattern. Careful monitoring of depressive symptoms in older adults may benefit early intervention and treatment of those symptoms, delaying the progression of cognitive impairment and the development of late-onset dementia.

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Supplementary material

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