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Breakthroughs in Epidemiology

The impact of depressive symptoms on cognitive function in early old age: a longitudinal fixed-effect study

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Abstract

Depression is associated with cognitive decline, but the causal nature of this association in early old age has not yet been established. We examined the impact of depressive symptoms on changes in cognitive function using data from 27 315 adults aged 50-65 in the Survey of Health, Aging, and Retirement in Europe followed for 8 years (2010/2011-2017/2018), using fixed effect models. Results suggest that an increase in depressive symptoms is associated with a significant decline in overall cognitive function ($\beta = -0.069$, 95% confidence interval (CI), −0.082 to −0.057), episodic memory ($\beta = -0.052$, 95% CI, −0.065 to −0.038), working memory ($\beta = -0.075$, 95% CI, −0.091 to −0.059), and verbal fluency ($\beta = -0.039$, 95% CI, −0.043 to −0.016). Symptoms capturing difficulties to concentrate, loss of appetite, loss of enjoyment, loss of interest, pessimism, sleep problems, and suicidality have stronger effects than depressed mood symptoms such as sadness and tearfulness. Results are robust to an expanded set of controls and to an instrumental variable approach for depressive symptoms. Findings provide novel evidence of a potentially causal relationship between depressive symptoms and cognitive function in early old age.

This article is part of a Special Collection on Cross-National Gerontology.

Key words: dementia; social determinants; depression; mental health; Europe.

Introduction

Depression is a leading cause of disability worldwide, with an estimated economic burden of US$326 billion per year in the United States.[1] Evidence suggests that depression is common in early old age, with approximately 10% of adults aged 45-59 having a probable depressive disorder.[2] Depression has major social and economic costs, including impacts on the health care system and lost productivity.[3]

Several studies have reported a significant association between depression and cognitive impairment in older adults.[4] This relationship may arise from multiple mechanisms: First, depressive symptoms may cause cognitive decline. Second, both depressive symptoms and cognitive decline may share multiple causes. For example, non-communicable disease risk factors such as smoking, physical activity, and obesity may impact both depression and cognitive function. Likewise, declines in physical health and functioning may independently impact both cognition and depression.[5,6] In addition, educational level and other measures of socioeconomic status are associated with both cognitive function and depression.[7-10] Finally, cognitive decline may lead to depressive symptoms.[11]

In light of multiple plausible mechanisms, existing studies have not fully established whether changes in depressive symptoms are causally linked to changes in cognitive function, particularly in early old age. The most rigorous evidence comes from randomized controlled trials (RCTs) showing that use of antidepressants among patients diagnosed with clinical depression improves cognitive function.[12,13] However, at least one large-scale RCT found no impact of antidepressant use on cognitive function among depressed patients.[14] These studies, however, have focused on children and young patients clinically diagnosed with major depression, while less is known about the impact of milder depressive symptoms on cognitive function among otherwise healthy adults of early old age in the general population.[12]

Using data from a representative sample of adults aged 50 years and older in 18 European countries, we examined the relationship between depressive symptoms and cognitive function in adults aged 50-65. We estimate whether depressive symptoms are associated with cognitive function once we control for time-invariant confounding using an individual FE estimator, which exploits within-individual changes in depressive symptoms, while controlling for time-varying confounders. To further

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address potential reverse causality and unmeasured confounding, we implement supplementary FE models that use an instrumental variable for depressive symptoms. To our knowledge, this is the first study that uses FE models to assess the impact of depressive symptoms on cognitive function at ages 50-65.

Methods

Data

We used data from the Survey of Health, Aging and Retirement in Europe (SHARE), a longitudinal household survey with extensive information on health, demographics, and the social and economic wellbeing of adult aged 50 and over, which started in 2004 and assesses individual biennially. We used data from four waves spanning from 2010/11 (wave 4) to 2017/18 (wave 7). We excluded data from Wave 1 because it lacked information on dementia and Alzheimer diagnosis and working memory tests, as well as data from wave 2, which did not include all cognitive assessments. Wave 3 was also excluded as it did not collect cognitive information and focused on life-history data. We focused on countries that entered SHARE in 2004 or 2006 and had at least three waves of follow-up, which included Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, Czech Republic, Poland, Luxembourg, Portugal, Slovenia, and Estonia.

We restricted the sample to respondents aged 50-65 for two reasons. First, focusing on this age group enables us to capture early cognitive decline, which may impact productivity before retirement. Second, focusing on this relatively young group reduces potential reporting bias from memory issues. However, in sensitivity analyses, we also include results for the full sample aged 50 and over.

We include respondents who were interviewed at least twice, as well as those with completed data on depressive symptoms outcomes, yielding a sample of 35 389 individuals. We then excluded individuals with missing values in any of the variables used in the main models, resulting in a final sample of 27 315 individuals.

Cognitive function assessments

Variables used in the analysis are summarized in Table 1. Our primary outcome was a cognitive index that combined scores for episodic memory, working memory, and verbal fluency. Episodic memory was measured by the immediate and delayed word recall tasks.[15] To assess immediate recall, respondents were read a list of 10 words and immediately after asked to recall the words from the list in any order. To assess delayed recall, respondents were asked to say the words from the list after having completed another test. Working memory (short-term integration, processing, disposal, and retrieval of information) was assessed by the serial sevens test, which requires respondents to count backwards from one hundred by sevens. This test is a component of several routinely used screening tools for cognitive impairment, including the Mini Mental State Examination.[16] Verbal fluency is a test of semantic fluency but also measures some aspects of executive function. Respondents were asked to name as many animals as possible within 1 min.[17] They were asked to avoid duplicates and responses outside of the category, under time pressure. Further details of the construction of cognitive scores is summarized in Supplementary files.

Depressive symptoms

Depressive symptoms were assessed using the Euro-Depression (Euro-D) scale, a 12-point battery of depressive symptoms validated in older people in Europe.[18] Respondents were asked to report whether in the past month they experienced any of the following symptoms: depressed mood, pessimism, suicide thoughts, feelings of guilt, loss of interest, irritability, appetite, fatigue, difficulties to concentrate, difficulty to enjoy things, and tearfulness. The EURO-D score is the sum of all symptoms. We used a linear version of the EURO-D score as our main exposure, as well as a binary variable that indicates whether the score is equal or higher than four symptoms, a cutoff shown to predict clinically significant depression.[19]

Covariates

We controlled for time-varying covariates that are likely to simultaneously influence depressive symptoms and cognitive function, including age, labor market status, marital stats, life events, and physical health and function (Table 1). We controlled flexibly for age by including age dummies in our model. We controlled for labor market and marital status changes as important life events potentially correlated with both mental health and cognition.[5] We also adjusted for changes in household income and difficulties in making ends meet, both linked to depression and cognitive function.[20] The onset of a major chronic disease, including Alzheimer's disease[11] may increase risk of depression[21] and cognitive impairment.[22] We therefore control for self-reports of a doctor diagnosis of serious health conditions, including heart attack, stroke, diabetes, high blood pressure, cancer, dementia, and Alzheimer's disease. We included dummies indicating if the respondent suffers from at least one limitation of activities of daily living (ADL), or at least one instrumental ADL. We also controlled for low physical activity (defined as never or almost never engaging into neither moderate nor vigorous physical activity).

Analytical approach

Identifying the effect of depressive symptoms on cognitive function is challenging because many factors are likely to simultaneously influence depressive symptoms and cognitive function. This may be particularly important for time-invariant confounders that affect both outcomes, such as genetic predisposition or early life factors. To address this, we use linear individual FE models with cognitive function as the outcome and depressive symptoms as our main independent variable, controlling for time (wave) effects, and time-varying confounders. To better understand which depressive symptoms drive the relationship with cognitive function, we estimated an FEs model that separately controlled for each of the 12 components of the Euro-D scale. We interpret coefficients based on the impact of a one-standard-deviation (SD) change in the EURO-D score, where the SD is calculated from the full sample distribution.

Sensitivity analyses

We carry out three types of sensitivity analyses: First, we run random effect (RE) models and compare coefficients to those in our FE models (Table S1). Second, we examine the robustness of our results to excluding controls, comparing models that subsequently add different sets of time-varying confounders (Table S1). Third, to address concerns that FE estimates may be biased by unobserved time-varying confounding, reverse causation,[11] or measurement error, we implemented an FE instrumental variable (FEIV) estimator, based on an instrumental variable (IV) inspired by earlier econometric studies on the impact of depression on labor force participation.[23] Specifically, we leverage variation in

Table 1. Description of variables in the SHARE, 50-65 years, 2010-2017, 18 European countries.

Variables	Descriptions
Outcomes	
Total word recall score	Immediate and delayed word recall tasks
Working memory score	Serial 7 subtraction test
Verbal fluency score	Animal names test
Overall cognitive score	Standardized sum of the standardized scores for working memory and fluency scores
Exposure	
Depression scale EURO-D	Number of depressive symptoms (0 to 12)
EURO-D caseness	Depression scale EURO-D of 3 or more
Covariates	
Female	Binary variable for being a female
Age	Age in years
Marital status	Single/widowed, married, divorced
Employment status	Employed, retired, others
Total household income	Log of monthly net household income, estimated based on the sum of all income sources for all household members
Household able to make ends meet	No difficulty, some difficulty, great difficulty
1+ ADL limitations	Limitation with at least one ADL
1+ IADL limitations	Limitation with at least one IADL
Low physical activity	Low level of physical activity defined as never or almost never engaging into neither moderate nor vigorous physical activity
Health conditions	Binary variables for heart attack, high blood pressure, high blood cholesterol, stroke, diabetes, chronic lung disease, cancer, digestive disorders, Parkinson's disease, hip or femoral fracture, Alzheimer's disease or dementia
Instrument and relevant controls	
Mother's death	Binary variable for mother's death between previous and current wave
Father alive	Binary variable for father being alive in current wave
Informal care for mother	Yes, no
Informal care for father	Yes, no
Health of mother	Poor, fair, good
Health of father	Poor, fair, good

Abbreviations: activity of daily living, ADL; Euro-Depression, Euro-D; instrumental activity of daily living, IADL; Survey of Health, Aging, and Retirement in Europe, SHARE.

the timing of maternal death as a potential instrument for depression, restricting the sample to participants whose mother was still alive in their first interview. As illustrated in the directed acyclic graph in the appendix (Figure S1), maternal death from time $_{t-1}$ to time $_{t}$ ($Z_{t-1\,\text{to}\,t}$) serves as an IV, affecting depressive symptoms (X_t) but not cognitive scores (Y_t) directly. Conditional on mother's health (V_{t-1}), $Z_{t-1\,\text{to}\,t}$ as an IV helps address time-varying confounders (U_t) and estimate the effect of depressive symptoms on cognitive function.

FEIV models use individual FEs to control for time-invariant factors like genetics or early life background, which may influence both maternal death timing and cognitive decline. We derived a binary variable, varying over time, indicating whether the respondent lost their mother between the current (t) and previous ($t-1$) wave of the survey. Our choice of the instrument is based on several criteria: first, the death of a respondent's mother is a strong predictor of depressive symptoms, meeting the first IV condition. Second, in our FEIV setting, conditional exchangeability requires that, after conditioning on relevant covariates, maternal death between $t-1$ and t affects changes in cognitive function between t and $t+1$ only through increasing depressive symptoms in the same period. The conditional exchangeability assumption would be violated if maternal death led to other changes, like employment, that independently affect cognition. Therefore, we test the robustness of our results to extensive controls for time-varying factors to ensure our model captures maternal death impacts on cognition only via depressive symptoms. In addition, we provide indirect but reassuring evidence of the potential validity of this assumption by estimating the effect of maternal death on several outcomes that could indirectly affect cognition, including employment, marital status, health, physical inactivity, caring for a surviving father, and types of leisure activities.

A concern is that respondents' mental health may decline before maternal loss due to emotional strain or caregiving burden[24,25,26] Maternal death could also change caregiving behavior and social interactions, potentially affecting depressive symptoms,[25,26] but with unclear effects on cognition.[27] To address this, we implemented models that: 1) controlled for maternal health (fair/poor) and caregiving frequency; 2) controlled for labor market status, income, and health; 3) controlled for whether father was alive and whether respondent provided care to a surviving father (as this may increase after maternal death); and 4) excluded respondents who lived with their parents at any point during the survey. In supplementary analysis, we also test whether maternal loss affects participation in leisure activities.[28]

Importantly, the effect of the instrument on depressive symptoms must be monotonic. While the instrument may not affect everybody's depressive symptoms, the direction of the effect must be the same for all those who are affected. Given that maternal death is generally a stressor, we believe this is a reasonable assumption. While rare cases may exist where it alleviates distress (eg, relief from caregiving), our results remain robust when controlling for caregiving status, supporting the validity of our IV approach.

FE and FEIV leverage different variation in depressive symptoms and therefore offer two different estimands, with the IVFE

being a local average treatment effect that specifically captures the effects of depression on cognition as a result of mother's death. Nevertheless, this approach enables us to address unobserved confounding, offering a potential robustness check of our main FE model results.

Results

Sample characteristics

Table 2 shows main sample characteristics. 56.4% of the sample was female, and the mean age was 60.7. The average EURO-D score was 2.2, and 23.8% of the respondents had a score of four or more symptoms, an indication for probable depression. Over one-third of respondents reported having experienced sadness and difficulty sleeping in the past month, while just over 5% reported having suicidal thoughts and a loss of appetite. 6.5% had limitations with at least one ADL, such as bathing, dressing, or personal hygiene, while 9.6 reported a limitation with IADLs, such as cleaning and maintaining the house, preparing meals, or managing money. 34.8% reported high blood pressure or hypertension and 22.3% cholesterol. Only 0.3% of respondents reported having had a diagnosis of Alzheimer's disease or dementia. Although self-reports are likely an underestimation, this is consistent with evidence that the prevalence of Alzheimer's disease and dementia is low before the age of 65.[29] Supplementary Figure S2 shows the distribution of cognitive scores, while Supplementary Figure S3 shows the correlation matrix for Euro-D components.

Out of all respondents, 15 747 still had a living mother in their first interview. Nearly, 30% (4661) of them lost their mother during follow-up.

As our models include FEs, they rely solely on within-individual variation to estimate the effect of depression on cognition, which minimizes bias from differential attrition. Nevertheless, to test whether lost to follow-up may have altered our sample, we compared descriptives of all respondents interviewed in 2010, to respondents in our analytical sample. Results suggest that our sample was not fundamentally different from a sample of all respondents in 2010 (Table S2). Compared to those included in our analytical sample, people who responded in 2010 were slightly younger (58.0 years old vs 60.7), slightly more likely to be female (56.0 vs 56.7%) and reported slightly higher levels depressive symptoms (Average EURO-D: 2.4 vs 2.2).

Table 2. Descriptive statistics, SHARE, 50-65, 2010-2017, 18 European countries.

	Mean	SD	N
Outcomes			
Total word recall score	10.32	3.358	87 999
Working memory score	4.347	1.204	87 999
Verbal fluency score	22.32	7.499	87 999
Exposure			
Depression scale EURO-D	2.232	2.129	87 999
EURO-D caseness	0.238	0.426	87 999
Covariates			
Female	0.567	0.496	87 999
Age	60.74	5.320	87 999
Married	0.723	0.447	87 999
Divorced	0.111	0.315	87 999
Employed	0.394	0.489	87 999
Retired	0.434	0.496	87 999
Others	0.172	0.378	87 999
Total household income	39661.1	99778.2	87 999
1 + ADL limitations	0.0663	0.249	87 999
1 + IADL limitations	0.0958	0.294	87 999
Physical inactivity	0.0606	0.239	87 999
Heart attack	0.0759	0.265	87 999
High blood pressure or hypertension	0.348	0.476	87 999
High blood cholesterol	0.223	0.417	87 999
Stroke	0.0237	0.152	87 999
Diabetes or high blood sugar	0.109	0.311	87 999
Chronic lung disease	0.0535	0.225	87 999
Cancer	0.0401	0.196	87 999
Stomach or duodenal ulcer, peptic ulcer	0.0392	0.194	87 999
Parkinson disease	0.00341	0.0583	87 999
Cataracts	0.0406	0.197	87 999
Hip fracture or femoral fracture	0.0101	0.100	87 999
Alzheimer's disease, dementia, senility	0.00344	0.0586	87 999
Mother alive in first interview	0.462	0.499	74 616
Mother's death	0.105	0.306	34 350
Helped mother: no	0.815	0.388	34 483
Almost every day	0.0427	0.202	34 483
Almost every week	0.0717	0.258	34 483
Almost every month	0.0409	0.198	34 483
Less often	0.0298	0.170	34 483
Health of mother: fair	0.261	0.439	34 350
Health of mother: poor	0.157	0.364	34 350
Father alive	0.230	0.421	32 292
Helped father	0.0378	0.191	34 483

Abbreviations: activity of daily living, ADL; Euro-Depression, Euro-D; instrumental activity of daily living, IADL; Survey of Health, Aging, and Retirement in Europe, SHARE.
Sample restricted to 50-65 interviewed at least twice.

Individual FE models

In FE models, an increase in depressive symptoms was associated with a significant decline in cognitive function (Figure 1 and full estimates in Supplementary Tables S1 and S3). Adjusting for individual FEs and time-varying confounding factors, we found that one SD increase in the EURO-D scale was associated with a 0.069 (95% confidence interval (CI), 0.057 – 0.082) SD decrease in the composite cognitive score. One SD increase in the EURO-D scale was associated with a 0.075 (95% CI, 0.059 – 0.091) SD decrease in working memory, a 0.052 (95% CI, 0.038 – 0.065) SD decrease in episodic memory and 0.028 (95% CI, 0.016 – 0.043) SD decrease in verbal fluency (Table S3). In sensitivity analyses, results for the full sample aged 50 and over (Table S4) closely align with those for the 50-65 age group (Figure 1 and Table S1).

Difficulty to concentrate was the depressive symptom most strongly associated with the overall cognitive score (Figure 1, full estimates in Appendix Table S5). Holding all other components constant, difficulty to concentrate was associated with a decrease in cognitive function of 0.102 (95% CI, 0.082 – 0.121) SD. Difficulty to concentrate was associated with the three dimensions of cognition, namely episodic and working memory (−0.083, 95% CI, −0.107 to −0.059 and −0.103, 95% CI, −0.128 to −0.079, respectively) and verbal fluency (−0.062, 95% CI, −0.083 to −0.040).

Symptoms that can result in low motivation were also associated with cognitive function. Being pessimistic, not enjoying anything in life, having suicidal thoughts and lacking interest were associated with a decrease in cognitive function of more than 0.05 of a SD. Lacking interest, loss of appetite, and sleep problems were also associated with a significant reduction in cognitive function. Overall, the associations were larger for working and episodic memory than for verbal fluency. By contrast, depressed mood symptoms, such as being sad and tearful, were not significantly associated with changes in cognitive function.

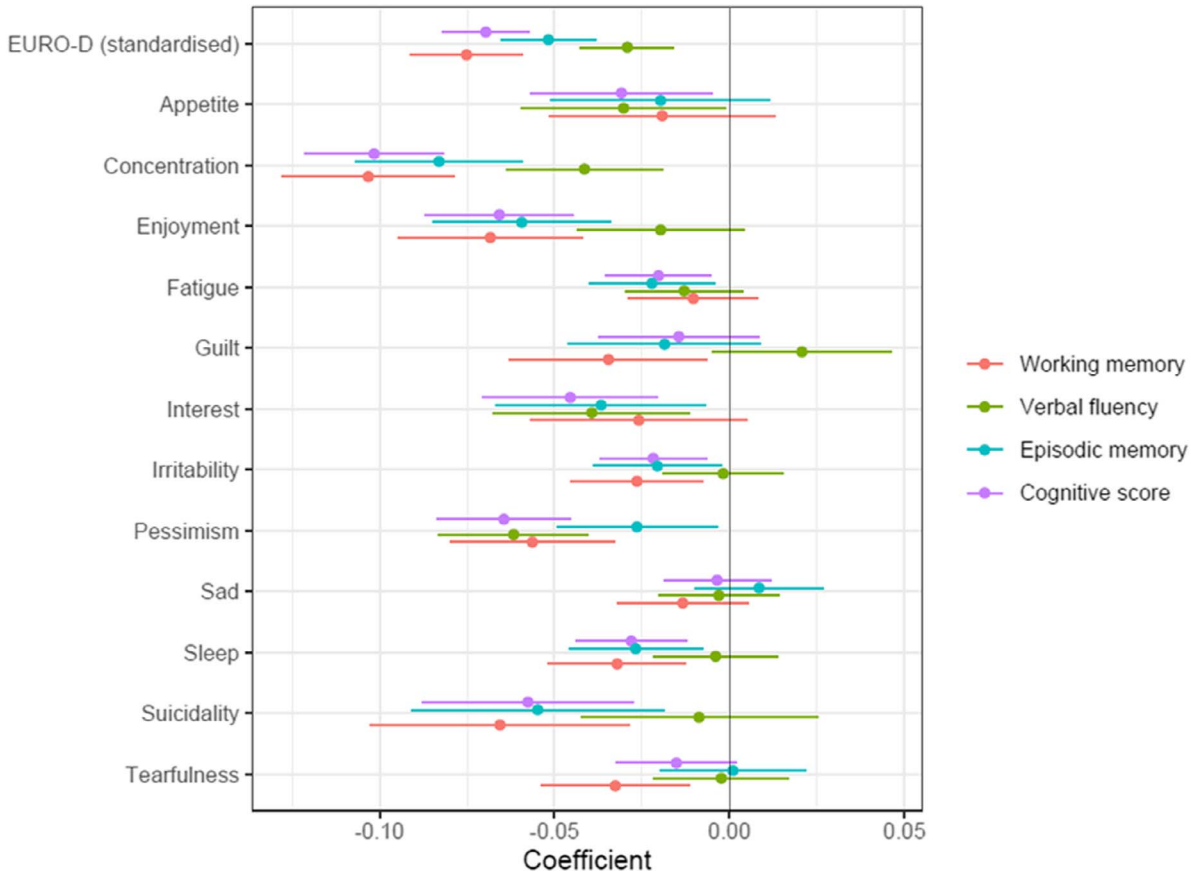

Figure 1. Coefficients of FE models on the association between depressive symptoms and cognitive function: SHARE, 50-65 year, 2010-2017, 18 European countries. Note: coefficients and 95% CI for components of the Euro-D scale. Results from an FE model regressing cognitive score on dummy variables for each Euro-D component. Sample restricted to those aged 50-65 who were interviewed at least twice. All models also include age (in years) wave dummies. Time-varying covariates include log household income, dummies indicating if the respondent is employed, retired, married, divorced, if the household is able to make ends meet, dummies indicating if respondent suffers from at least one limitation of ADL, IADL, has regular physical activity as well as dummies for serious illnesses, including Alzheimer, dementia, and senility. Standard errors clustered at the individual level. Abbreviations: activity of daily living, ADL; confidence interval, CI; Euro-Depression, Euro-D; fixed-effects instrumental variable, FEIV; instrumental activity of daily living, IADL; Survey of Health, Aging, and Retirement in Europe, SHARE.

Sensitivity analyses and robustness checks

Exclusion of controls and RE models

A concern is that time-varying factors like labor market and marital status may mediate the effect of depressive symptoms on cognition. Table S1 shows that controlling only for age and wave (column 1), the association (−0.0751, 95% CI, −0.085 to −0.065) remains similar to Figure 1. Adding time-varying controls (columns 2-3) changes estimates minimally. REs models (columns 4-6) show larger effects, but both RE and FE estimates are in the same direction. Wu–Hausman tests confirm unobserved heterogeneity, supporting fixed over REs.

Instrumental variable FE models

As robustness check, Table 3 presents results from supplementary analyses that used an FEIV approach. First-stage estimates show that maternal death significantly increases depressive symptoms. In column 2, which controls for mother's health and informal care, maternal loss increased EURO-D depressive symptoms by 0.097 SD (95% CI, 0.061 – 0.133). This finding remained consistent across all robustness specifications (columns 3-5). The lag variable of maternal death was close to zero and not significant (0.035, 95% CI, −0.017 to 0.088).

Second-stage estimates (Table 3) show that an increase in depressive symptoms—caused by maternal death—leads to a significant decline in cognitive function. In column 2, which controls for maternal health and caregiving frequency, one SD increase in the Euro-D score reduces cognitive function scores by 0.340 (95% CI, 0.014 – 0.665) of an SD. Second-stage results are consistent across models that control for labor market status, income and health (Table 3, column 3); for whether father was alive and whether respondent provided care to a surviving father (Table 3, column 4); and to the exclusion of respondents who lived with their parents at any point during the survey (Table 3, column 5).

We assume that, conditional on covariates, maternal death affects cognitive function only through depressive symptoms. Although this assumption cannot be tested, it is reassuring that we find no association between maternal death and changes in employment, marital status, health, low physical activity, and caring for a surviving father in FE models (Supplementary Table S6), or with participation in leisure activities (Supplementary Table S7).

Discussion

Results suggest that an increase in depressive symptoms at ages 50-65 is associated with a decrease in cognitive function, even after adjusting for time-invariant and measured time-varying confounders. In our preferred FE specification, one SD increase

Table 3. FEIV estimates of the effect of depressive symptoms on overall cognitive function: SHARE, 50-65 year, 2010-2017, 18 European countries.

	(1)	(2)	(3)	(4)	(5)	(6)
A. First stage: standardized EURO-D score						
Mother death$_t$	0.068 [0.034,0.102]	0.097 [0.061,0.133]	0.093 [0.058,0.128]	0.099 [0.063,0.135]	0.096 [0.059,0.132]	0.109 [0.068,0.150]
Mother death$_{t-1}$						0.035 [−0.017,0.088]
B. Second stage: cognitive score						
Standardized	−0.388	−0.340	−0.340	−0.345	−0.320	0.288 [−0.599,0.023]
EURO-D	[−0.825,0.049]	[−0.665,−0.014]	[−0.665,−0.014]	[−0.661,−0.028]	[−0.652,0.012]	
F-Stat. (excl. Inst.)	15.512	27.750	26.474	28.637	26.327	14.578
z score (diff. FE)	1.402	1.651	1.681	1.777	1.520	1.402
Observations	31 147	31 147	31 147	28 402	29 372	31 147
Individuals	12 462	12 462	12 462	11 752	11 768	12 462
Model	Age, wave FE	+ Mother's health, caring	+ Labor, income and health	+ Father alive, caring	(2), excl. Resp. living with parents	(2)

Abbreviations: activity of daily living, ADL; Euro-Depression, Euro-D; fixed-effects instrumental variable, FEIV; instrumental activity of daily living, IADL; Survey of Health, Aging, and Retirement in Europe, SHARE.
Sample restricted to those aged 50-65 whose mother was alive in first interview and who were interviewed at least twice. Cognitive score and EURO-D scale are standardized with mean 0 and standard deviation 1. Instruments: dummy for mother's death. FE models estimated via 2SLS. All models include wave and age dummies. Labor and marital status include dummies indicating if the respondent is employed, retired, married and divorced. Income includes household income and dummies indicating if the household is able to make ends meet. Health covariates include dummies for suffering from at least one limitation of ADL, IADL, has regular physical activity, as well as dummies for serious illnesses, including Alzheimer, dementia, and senility. Standard errors cluster at individual level. Standard errors cluster at individual level. z scores indicate the difference with FE estimates obtained on the same sample.

in the EURO-D score was associated with a 0.069 SD (95%, CI 0.057 – 0.082) decline in the composite cognitive score. The size of this effect is similar in magnitude to the cognitive decline occurring for each year above the age of 60. We found that this effect is driven primarily by changes in concentration, pessimism, and motivation, while changes in depressed mood symptoms, such as sadness or tearfulness, did not influence cognitive scores. Our results are robust to multiple specifications, including instrumenting depressive symptoms in a IV approach.

Interpretation of results

Our results are consistent with findings from observational epidemiological studies reporting an association between depressive symptoms and cognitive impairment,[4,30,31] as well as between depressive symptoms and self-reported productivity.[32-35] Although these studies may be prone to confounding and reverse causality, our findings provide further support to the hypothesis of a causal relationship between depressive symptoms and cognitive function at the population level. Our analysis of specific symptoms sheds light on some of the potential mechanisms and suggests that symptoms affecting the future outlook (pessimism), decision-making (concentration), and behavior (eg, loss of interest, sleep problems) have stronger effects on cognitive function than depressed mood symptoms such as sadness or tearfulness. Results are also consistent with findings from clinical trials suggesting that antidepressant treatment improves cognitive outcomes of depressed patients[12,13] and workplace productivity.[36] While these studies focus on clinically depressed patients, our findings suggest that depressive symptoms in adults 50-65, which are highly prevalent and not always linked to clinical depression, can also reduce cognitive function.

Several limitations should be considered in our study. First, FE models may be biased by unmeasured time-varying covariates not considered in our models. Although we included a wide range of time-varying confounders, unmeasured confounding may remain, including changes in medication use, social support [36,37], lifestyle factors, unmeasured stressful life events, or changes in sleep patterns.

It is reassuring that robustness results using FEIV models, which capture the specific impact of an increase in depressive symptoms linked to maternal death, were in line with estimates from FE models. A limitation of the IV approach is the assumption that maternal death impacts cognition only via depressive symptoms (exclusion restriction). While this assumption cannot be directly tested, we found that maternal death is uncorrelated with changes in variables potentially linked to cognitive function directly (eg, employment, working status). While these factors could also be in the pathway between depressive symptoms and cognitive function, the fact that they are uncorrelated with maternal death suggests that, in our sample, the timing of maternal death is not associated with major factors linked to cognitive function such as employment or physical activity.

Conclusion

Our study assessed the association between depressive symptoms and cognitive function in early old age. Our results suggest that an increase in depressive symptoms leads to a large and significant reduction in overall cognitive function, as well as on measures of working memory, episodic memory, and verbal fluency. These findings suggest that preventing and treating depressive symptoms in early old age may help reduce age-related cognitive decline, which could potentially delay the onset of Alzheimer's disease and related disorders. This is particularly important given recent increases in depressive symptoms during the Covid-19 pandemic.[38,39] Results call for wider acknowledgement of the link between psychological well-being and cognitive symptoms[40] and policies to identify and address common symptoms of depression as a potential strategy to prevent cognitive decline and improve healthy cognitive aging in older adults.

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Supplementary material

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Conflict of interest

The authors declare no conflicts of interest.

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