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Late-life depression and cognitive function among older adults in the U.S.: The National Health and Nutrition Examination Survey, 2011–2014

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ABSTRACT

Discrepancies exist on the associations of late-life depression with cognition, and synergistic effect of depression and diabetes on cognition among older adults was suggested in literature. We aimed to examine the associations of late-life depression with cognitive function in a representative sample of older adults in the U.S., and to examine the associations among individuals with diabetes. A total of 3101 adults aged 60 and above of the 2011–2014 National Health and Nutrition Examination Survey who completed measurements of depressive symptoms and diabetes were included in cross-sectional analyses. The 9-item Patient Health Questionnaire (PHQ-9) was used to measure depressive symptoms (including overall, somatic and cognitive). Clinically relevant depression (CRD) and clinically significant depression (CSD) were defined by cutoffs of PHQ-9. Domain-specific cognitive function was examined using Delayed Word Recall Test, Digit Symbol Substitution Test, and Animal Fluency Test for memory, executive function/processing speed, and language, respectively. Z scores were created for overall cognition and specific domains. Multivariable linear regression models were applied to examine the association of depressive symptoms and scale-defined depression with cognition z scores. The overall, somatic and cognitive depressive symptoms were associated with lower cognitive function among older adults. Both CRD ($\beta = -0.20$, 95% CI: -0.28, -0.12) and CSD ($\beta = -0.56$, 95% CI: -0.75, -0.37) were associated with lower cognition. A synergistic relationship was found between depression and diabetes on lower cognition. These results suggested that cognition among older adults may be modified by late-life depression, and older adults with both depression and diabetes may be particularly impacted on cognition.

1. Introduction

Late-life depression, defined as depression that occurs at the age of 60 and older, is a heterogeneous syndrome. It is associated with severe health outcomes including higher risk of mortality (Schulz et al., 2000), suicide (Vannoy et al., 2007), physical disability (Koenig and George, 1998), and poor quality of life (Sivertsen et al., 2015). In addition, late-life depression has been largely underdiagnosed and undertreated (Reynolds et al., 2001), and likely to be treatment-resistant (Blazer, 2003). Compared to nondepressed elderly patients, the total ambulatory costs were 43%–52% higher, and total ambulatory and inpatient costs were 47%–51% higher in depressed elderly (Katon et al., 2003). Therefore, late-life depression has become a great burden in public health.

Cognitive deficit often coexists with late-life depression. As estimated by Alzheimer's Disease International, a total of 46.8 million people had dementia in 2015, and this number is projected to reach 131.5 million in the year of 2050 (Alzheimer's, 2015). The worldwide costs of dementia are estimated at 818 billion US dollars, which is larger than 1% of the world's gross domestic product (Wimo et al., 2017). Currently, no drug or therapy is available to cure dementia or delay its onset.

Population-based studies have found that late-life depression and its symptoms are associated with cognitive decline (Paterniti et al., 2002; Wilson et al., 2004; Yaffe et al., 1999), mild cognitive impairment (Kopchak and Pulyk, 2017; Ravaglia et al., 2008; Spira et al., 2012) and

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dementia (Mirza et al., 2016; Saczynski et al., 2010; Spira et al., 2012; van Uden et al., 2016). Poor performance in tests of cognitive function may serve as a precursor of dementia. A few population-based studies have reported that depressive symptoms in late-life are associated with poorer performance in cognitive tests (Dias et al., 2017; Ganguli et al., 2006; Hamilton et al., 2014; Morin and Midlarsky, 2017; Shimada et al., 2014; Yaffe et al., 1999). However, heterogeneity still exists between studies. The studies used varied methods in defining late-life depression and depressive symptoms, as well as different means of testing cognitive function among older adults. In results of findings, although these studies showed a general trend of negative associations between late-life depression and cognitive function, some studies reported associations among all domains of cognitive function while some reported associations only in some of the domains, and some studies only found associations in particular periods of comorbidities.

Depressive symptoms are often categorized into somatic (e.g., sleep, appetite disturbance) and cognitive depressive symptoms (e.g., sadness, pessimism). Compared to depression among young adults, which is often presented with cognitive symptoms, late-life depression is more likely to show somatic depressive symptoms. There are few studies available that reported conflicting results on the associations of somatic and cognitive depressive symptoms with cognitive function among older adults. In one study, both somatic and cognitive symptoms are both associated with inductive reasoning, and somatic symptoms are also associated with lower processing speed (Brailean et al., 2016), while in another study, cognitive depressive symptoms were negatively associated with the delayed verbal memory composite and somatic symptoms were positively associated with the executive function composite (Szymkowicz et al., 2017).

In addition to the various definition of depressive symptoms and cognitive function, all these discrepancies between studies may also be largely due to varied characteristics (e.g., race/ethnicity, comorbidities) of participants in these studies. To find the true burden on cognition among adults brought by depression in population, we aimed to examine the association of depression and depressive symptoms, including somatic and cognitive depressive symptoms with cognition among older adults in a representative population.

Diabetes is an independent risk factor of cognitive impairment and dementia (Strachan et al., 2008), and depression is a common condition in patients with diabetes (Voinov et al., 2013)– the age-adjusted prevalence of major and minor depression is 16.6% in patients with diabetes mellitus in the U.S. (Li et al., 2008). A recent systematic review by Danna et al. indicated that the comorbid depression is associated with poorer cognitive outcomes than for persons with diabetes alone (Danna et al., 2016). In addition, recent studies suggest a synergistic effect of diabetes and depression on outcomes of cognitive function among older adults in the U.S. (Demakakos et al., 2017; Downer et al., 2016; Sullivan et al., 2013; Watari et al., 2006), with magnitudes of associations of comorbid depression and diabetes greater than the sum of diabetes-cognition and depression-cognition associations. However, these results were based on small samples or subjects selected by specific characteristics (e.g., ethnicity), thus the potential synergistic relationship is expected to be examined in general populations of older adults.

Using data of the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014, we estimated the burden on cognitive function that is associated with depressive symptoms (including total, somatic and cognitive) and depression based on cutoff of a standardized scale in older adults in the U.S. In addition, we examined whether diabetes and depression show a synergistic effect on cognition among older adults.

2. Methods and materials

2.1. Study population

NHANES is a serial ongoing cross-sectional survey of the civilian, non-institutionalized U.S. population, conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. Every two years, NHANES randomly selected 5000 participants for a comprehensive health screening to generate a nationally representative sample. The response rates were 72.6% and 71.0% in the 2011–2012 and the 2013–2014 cycles, respectively (Centers for Disease and Prevention, 2014).

The 2011–2012 and the 2013–2014 NHANES performed assessments of cognitive function and depressive symptoms for adults aged 60 years old and above. We combined data from the two survey cycles for a cross-sectional analysis. A total of 19,931 people of all ages were enrolled for NHANES interviews from 2011 to 2014. Among these participants, 3180 participants aged ≥ 60 had at least one cognitive test. After further excluding individuals with missing data on depressive symptoms (n = 79), a total of 3101 participants were included in the current analyses.

The NHANES was carried out in accordance with the recommendations of National Center for Health Statistics Research Ethics Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the National Center for Health Statistics Research Ethics Review Board.

2.2. Assessment of depressive symptoms

Depressive symptoms during the previous 2 weeks of the survey were assessed using the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The score of each item ranges from 0 (not at all) to 3 (nearly every day), adding up to a range of 0–27 points in total. The nine items contain four somatic depressive symptoms (sleep difficulties, fatigue, appetite problems, psychomotor agitation or retardation) and five cognitive depressive symptoms (lack of interest, depressed mood, worthlessness, concentration problems, suicide ideation) (Leavens et al., 2012).

Depression status was defined using validated cutoffs of the PHQ-9 scale. The correlation between PHQ-9 and the Mental Health Professional Validation Interviews within 48 h is 0.48 (Kroenke et al., 2001). Individuals with PHQ-9 total scores of 5–14, and 15 or greater were categorized as clinically relevant depression (CRD, mild depression to moderate depression) and clinically significant depression (CSD, including moderately severe depression and severe depression), respectively (Kroenke et al., 2001a,b). For CRD, physician should use clinical judgment about treatment according to patient's duration of symptoms and functional impairment; for CSD, treatment for depression, including using antidepressant, psychotherapy and/or a combination of treatment is warranted (UMHS, 2011).

2.3. Tests of cognitive function

The cognitive tests of NHANES 2011–2014 include the Delayed Word Recall Test (nested in the Consortium to Establish a Registry for Alzheimer's disease [CERAD] Word Learning subtest), the Animal Fluency Test, and the Digit Symbol Substitution Test (DSST).

The Delayed Word Recall Test (DWRT) is a test of immediate verbal memory. In the DWRT, a set of ten common nouns was presented, one word at a time. Participants are asked to learn a 10-word list and then recall as many words as possible after 5 min. The score of the DWRT is based on the total number of correctly recalled words (Knopman and Ryberg, 1989).

The Animal Fluency Test (AFT) is a test of language ability (Whiteside et al., 2016). Participants are asked to name as many animals as possible in 1 min. A point is given for each named animal, and the total score of the AFT is the number of animals named in 1 min (Howe, 2007).

The DSST is a test of executive function and processing speed. The DSST is conducted using a paper form that has a key at the top

containing 9 numbers paired with symbols. Participants were asked to copy the corresponding symbols in the 133 boxes that adjoin the numbers in 2 min. The score is the total number of correct matches (Centers for Disease and Prevention).

2.4. Covariates

Demographical information (age, sex, race, marital status, and education), lifestyle factors (smoking and physical activity) and comorbidities (hypertension, diabetes, coronary heart disease, and stroke) were obtained through questionnaires. Body height and weight were assessed by trained staff and body mass index was calculated as weight in kilograms divided by height in meters squared.

2.5. Statistical analysis

Descriptive statistics were computed on participants characteristics according to the status of depression (PHQ-9 score ≥ 5). Cognitive test scores were normalized by z scores. Three domain-specific z scores were created using sample mean and standard deviation of the test scores. Standardized global cognition z score was generated by averaging the z scores of all test domains, including memory, language, and executive function/processing speed. Multivariable linear regression models were used to examine the associations of depressive symptoms (including total, somatic and cognitive depressive symptoms) and depression (including overall depression, CRD and CSD) with domain-specific z scores and the global cognition z score. Factors for adjustment included age, sex, race, marital status, education, smoking, body mass index, physical activity, and self-reported hypertension, diabetes, coronary heart disease and stroke. The estimated effect sizes (β) and 95% confidence intervals (CIs) were estimated and presented in the final models. The associations were considered statistically significant if the CIs of the β′s did not include 0. The effect sizes for individuals with depression only, diabetes only, and with both depression and diabetes were calculated, and the effects of depression and diabetes were considered super-additive if the effect size of joint association of depression and diabetes with z scores was greater than the sum of effect sizes of depression and diabetes with z scores. The analysis was weighted for the stratified, multistage probability sampling design of NHANES and survey non-response rate. All analysis was conducted using SAS 9.4 (Cary, NC, USA).

3. Results

Characteristics of the study participants are shown in Table 1. Compared to individuals without depression, those with depression were more likely to be female, Hispanics, and smokers, having smaller amount of time for physical activity, and higher body mass index. Meanwhile, they were more likely to be unmarried, and receive less than high school education; and have comorbid hypertension, diabetes, coronary heart disease, and stroke. Furthermore, individuals with depression had less time for physical activity and a higher body mass index. In addition, individuals with depression had lower average scores for the DWRT, AFT, and DSST.

The PHQ-9 total scores were distributed in a right-skewed manner, with the median of 2 (range: 0–27). The median of somatic symptom score was 1 (range: 0–12), and the median of cognitive symptom score was 0 (range: 0–15). The weighted prevalence of CRD and CSD among older adults during the 2011–2014 cycle was 19.1% and 2.6%, respectively.

The unadjusted linear regression models showed that a higher PHQ-9 total score was associated with lower domain-specific z scores and global cognition z score. After adjusting for demographic and lifestyle factors, as well as self-reported chronic conditions, each increase of standard deviation in PHQ-9 total score was associated with 0.04 (β = −0.04, 95% CI: −0.08, −0.01), 0.07 (β = −0.07, 95% CI: −0.11, −0.04), 0.11 (β = −0.11, 95% CI: −0.14, −0.08), and 0.10 (β = −0.10, 95% CI: −0.13, −0.06) standard deviations lower scores in memory, language, executive function/processing speed, and overall cognition, respectively (Table 2). Categorized by specific cutoffs, overall depression (defined as PHQ-9 ≥ 5), CRD (defined as PHQ-9 ranging from 5 to 14), and CSD (defined as PHQ-9 ≥ 15) were associated with lower overall cognition z scores (for overall depression: β = −0.25, 95% CI: −0.33, −0.17; for CRD: β = −0.20, 95% CI: −0.28, −0.12; for CSD: β = −0.56, 95% CI: −0.75, −0.37) and its domain-specific cognition z scores, with the largest magnitude of associations for executive function/processing speed (for overall depression: β = −0.26, 95% CI: −0.33, −0.19; for CRD: β = −0.22, 95% CI: −0.29, −0.14; for CSD: β = −0.54, 95% CI: −0.71, −0.36) (Table 3).

Components of depressive symptoms were also associated with cognitive function. As shown in Table 2, after adjusting for all potential confounders, each standard deviation increment of somatic depressive symptoms was associated with 0.02 (β = −0.02, 95% CI: −0.04, −0.003), 0.04 (β = −0.04, 95% CI: −0.06, −0.02), 0.06 (β = −0.06, 95% CI: −0.08, −0.04), and 0.05 (β = −0.05, 95% CI: −0.07, −0.04) standard deviations lower z scores in memory, language, executive function/processing speed, and overall cognition, respectively; Similarly, each unit increment in somatic depressive symptoms was associated with lower memory, language, executive function/processing speed, and overall cognition, respectively with the same magnitudes.

The results of interaction between depression and diabetes on cognitive function are presented in Table 4. For the domains of memory (for both depression and diabetes: β = −0.27, 95% CI: −0.41, −0.14; for depression only: β = −0.13, 95% CI: −0.23, −0.04; for diabetes only: β = −0.09, 95% CI: −0.19, 0.02), language (for both depression and diabetes: β = −0.33, 95% CI: −0.47, −0.19; for depression only: β = −0.11, 95% CI: −0.21, −0.01; for diabetes only: β = −0.03, 95% CI: −0.13, 0.07), executive function/processing speed (for both

Table 1
Characteristics of participants included in the analysis from NHANES 2011–2014 (n = 3101).

	All	PHQ-9 ≥ 5	PHQ-9 < 5
Participants number, n (%)	3101	778 (25.1)	2323 (74.9)
Weighted frequency, n (%)	106,454,736	23,086,296 (21.7)	83,368,440 (78.3)
Age, ≥80 years, n (%)	528 (17.0)	123 (15.8)	405 (17.4)
Sex, female, n (%)	1598 (51.5)	490 (63.0)	1108 (47.7)
Race, n (%)			
Non-Hispanic White	1437 (46.3)	332 (41.4)	1115 (48.0)
Non-Hispanic Black	752 (24.3)	199 (25.6)	553 (23.8)
Hispanic	601 (19.4)	202 (26.0)	399 (17.2)
Non-Hispanic Asian	265 (8.6)	44 (5.7)	221 (9.5)
Other	46 (1.5)	11 (1.4)	35 (1.5)
Not married, n (%)	1412 (45.6)	416 (53.5)	996 (43.0)
High school graduate, n (%)	2264 (73.1)	502 (64.5)	1762 (76.0)
Smoking, n (%)	1557 (50.3)	415 (53.3)	1142 (49.2)
Physical activity, minutes/week	304.2 ± 636.7	216.6 ± 466.5	333.5 ± 681.9
Body mass index, kg/m^2	29.1 ± 6.3	30.6 ± 7.4	28.5 ± 5.8
Hypertension, n (%)	1959 (63.3)	556 (71.7)	1403 (60.5)
Diabetes, n (%)	741 (25.1)	256 (34.5)	485 (21.9)
Coronary heart disease, n (%)	284 (9.2)	100 (13.0)	184 (8.0)
Stroke, n (%)	231 (7.5)	83 (10.7)	148 (6.4)
DWRT score	5.8 ± 2.4	5.5 ± 2.4	5.9 ± 2.4
AFT score	16.4 ± 5.5	15.3 ± 5.5	16.7 ± 5.5
DSST score	45.7 ± 17.4	41.4 ± 17.4	47.1 ± 17.1

DWRT: Delayed Word Recall Test; AFT: Animal Fluency Test; DSST: Digit Symbol Substitution Test.

Table 2
Associations between PHQ-9 depressive symptoms with cognitive function as quantified by cognitive tests.

Total PHQ-9 scores			
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Memory	**−0.08 (−0.11, −0.04)**	**−0.05 (−0.09, −0.02)**	**−0.04 (−0.08, −0.01)**
Language	**−0.16 (−0.20, −0.12)**	**−0.09 (−0.12, −0.05)**	**−0.07 (−0.11, −0.04)**
Executive function/processing speed	**−0.20 (−0.23, −0.16)**	**−0.13 (−0.16, −0.10)**	**−0.11 (−0.14, −0.08)**
Overall cognition	**−0.18 (−0.22, −0.14)**	**−0.11 (−0.15, −0.08)**	**−0.10 (−0.13, −0.06)**
Somatic depressive symptoms			
Memory	**−0.04 (−0.06, −0.02)**	**−0.03 (−0.05, −0.01)**	**−0.02 (−0.04, −0.003)**
Language	**−0.09 (−0.11, −0.07)**	**−0.05 (−0.07, −0.03)**	**−0.04 (−0.06, −0.02)**
Executive function/processing speed	**−0.11 (−0.13, −0.09)**	**−0.07 (−0.09, −0.05)**	**−0.06 (−0.08, −0.04)**
Overall cognition	**−0.10 (−0.12, −0.08)**	**−0.07 (−0.09, −0.05)**	**−0.05 (−0.07, −0.04)**
Cognitive depressive symptoms			
Memory	**−0.04 (−0.06, −0.02)**	**−0.03 (−0.05, −0.01)**	**−0.02 (−0.04, −0.003)**
Language	**−0.09 (−0.11, −0.07)**	**−0.05 (−0.07, −0.03)**	**−0.04 (−0.06, −0.02)**
Executive function/processing speed	**−0.11 (−0.13, −0.09)**	**−0.07 (−0.09, −0.05)**	**−0.06 (−0.08, −0.04)**
Overall cognition	**−0.10 (−0.12, −0.08)**	**−0.06 (−0.08, −0.04)**	**−0.05 (−0.07, −0.03)**

Bold indicates results that were statistically significant.Model 1: unadjusted.
Model 2: adjusted for demographic (age, sex, race, education and marital status) and lifestyle factors (body mass index, smoking, physical activity).
Model 3: adjusted for factors in Model 2 and physical conditions (self-reported hypertension, diabetes, coronary heart disease and stroke).

depression and diabetes: β = −0.49, 95% CI: −0.61, −0.37; for depression only: β = −0.25, 95% CI: −0.33, −0.17; for diabetes only: β = −0.22, 95% CI: −0.30, −0.13), and overall cognitive function (for both depression and diabetes: β = −0.47, 95% CI: −0.60, −0.34; for depression only: β = −0.22, 95% CI: −0.31, −0.13; for diabetes only: β = −0.15, 95% CI: −0.24, −0.05), depression and diabetes showed super-additive joint effect.

4. Discussion

In this cross-sectional analysis of a nationally representative sample of older adults in the U.S., we demonstrated robust associations of depressive symptoms and scale-based depression with cognitive function, including memory, language, and executive function/processing speed and the overall cognition. The effect sizes of associations increased with severity of depressive symptoms. In addition, depression and diabetes showed a synergistic relationship with cognitive function among older adults.

A few previous studies have been conducted to examine the associations between depressive symptoms and cognition among older adults. Yaffe et al. showed that a larger number of depressive symptoms are associated with lower scores on Trails B, Digit Symbol, and a modified Mini-Mental State Examination in a population of elderly women aged ≥65 years (Yaffe et al., 1999); Ganguli et al. showed that depression (defined as ≥5 symptoms in modified Center for Epidemiological Studies–Depression Scale) is cross-sectionally associated with poorer performance in CERAD, including Mini-Mental State Examination, immediate retell of the story and immediate learning of the word list, delayed recall of the story and delayed recall of the word list, constructional praxis and clock drawing, Boston Naming Test, initial letter fluency for the letters P and S, and category fluency for the names of fruits and animals, Trail-Making Tests A and B in blue-collar rural community with 1265 adults 67 years and older without dementia at baseline (Ganguli et al., 2006). Shimada et al. reported that compared to individuals with no depressive symptoms (defined as geriatric depression scale-15 (GDS-15)≤5), those with depressive symptoms (defined as GDS-15 ≥ 6) showed poorer performance in word recall, story memory, and Trail-making test part B; those with depression (defined

Table 3
Associations between depression defined by PHQ-9 cutoffs with cognitive function, as quantified by cognitive tests.

CRD (n = 662)			
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Memory	**−0.16 (-0.25, -0.07)**	**−0.15 (-0.24, -0.07)**	**−0.13 (-0.22, -0.04)**
Language	**−0.26 (-0.35, -0.16)**	**−0.17 (-0.26, -0.08)**	**−0.12 (-0.21, -0.04)**
Executive function/processing speed	**−0.32 (-0.41, -0.24)**	**−0.24 (-0.32, -0.17)**	**−0.22 (-0.29, -0.14)**
Overall cognition	**−0.29 (-0.39, -0.20)**	**−0.24 (-0.32, -0.16)**	**−0.20 (-0.28, -0.12)**
CSD (n = 116)			
Memory	**−0.48 (-0.70, -0.26)**	**−0.37 (-0.57, -0.16)**	**−0.30 (-0.50, -0.09)**
Language	**−0.83 (-1.06, -0.60)**	**−0.58 (-0.79, -0.37)**	**−0.45 (-0.66, -0.25)**
Executive function/processing speed	**−0.95 (-1.17, -0.74)**	**−0.61 (-0.79, -0.44)**	**−0.54 (-0.71, -0.36)**
Overall cognition	**−0.94 (-1.17, -0.71)**	**−0.69 (-0.89, -0.49)**	**−0.56 (-0.75, -0.37)**
Overall depression (n = 778)			
Memory	**−0.20 (-0.28, -0.11)**	**−0.18 (-0.26, -0.10)**	**−0.15 (-0.23, -0.07)**
Language	**−0.33 (-0.41, -0.24)**	**−0.19 (-0.27, -0.11)**	**−0.16 (-0.25, -0.08)**
Executive function/processing speed	**−0.40 (-0.48, -0.32)**	**−0.29 (-0.36, -0.22)**	**−0.26 (-0.33, -0.19)**
Overall cognition	**−0.37 (-0.46, -0.28)**	**−0.26 (-0.33, -0.19)**	**−0.25 (-0.32, -0.17)**

Bold indicates results that were statistically significant. CRD: clinically relevant depression, defined as PHQ-9 score ranging from 5 to 14; CSD: clinically significant depression, defined as PHQ-9 score ≥15; overall depression is defined as PHQ-9 score ≥5.
Model 1: unadjusted.
Model 2: adjusted for demographic (age, sex, race, education and marital status) and lifestyle factors (body mass index, smoking, physical activity).
Model 3: adjusted for factors in Model 2 and physical conditions (self-reported hypertension, diabetes, coronary heart disease and stroke).

Table 4
Associations of cognitive function associated with depression, diabetes and joint effect of depression and diabetes.

	With depression only β (95% CI)	With diabetes only β (95% CI)	With both depression and diabetes β (95% CI)
Memory	**−0.13 (-0.23, -0.04)**	−0.09 (−0.19, 0.02)	**−0.27 (-0.41, -0.14)**
Language	**−0.11 (-0.21, -0.01)**	−0.03 (−0.13, 0.07)	**−0.33 (-0.47, -0.19)**
Executive function/processing speed	**−0.25 (-0.33, -0.17)**	**−0.22 (-0.30, -0.13)**	**−0.49 (-0.61, -0.37)**
Overall cognition	**−0.22 (-0.31, -0.13)**	**−0.15 (-0.24, -0.05)**	**−0.47 (-0.60, -0.34)**

Bold indicates results that were statistically significant. Models were adjusted for age, sex, race, education, marital status, body mass index, smoking, physical activity, hypertension, diabetes, coronary heart disease and stroke.

by diagnosis and receiving antidepressant treatment) did poorer in word recall, story memory, Trail-making test part A and symbol digit substitution task in a group of Japanese aged 65 years or older (Shimada et al., 2014); Hamilton et al. that depressive symptoms assessed with GDS-15 are associated with lower scores on measures of memory (California Verbal Learning Test-2), language (30-item Boston Naming Test, Letter and Category Fluency Test), executive functioning and processing speed (Trail-Making Test Parts A and Digit Symbol Forward) in an African American population (Hamilton et al., 2014); Morin and Midlarsky reported that depressive symptoms are associated with poorer memory among older adults after a cancer diagnosis, but not before in the Health and Retirement Study (Morin and Midlarsky, 2017); In a group of community-dwelling individuals aged ≥75 years in Brazil, depression (defined as GDS-15 ≥ 6) is associated with poorer performance on Mini-Mental State Examination (overall and time, spatial orientation, attention/calculation, language), brief cognitive battery (incidental and immediate memory, learning tasks), category fluency test, clock-drawing test and Pfeffer's Functional Activities Questionnaire (Dias et al., 2017). The associations between depressive symptoms and cognition were similar but not for some domains (e.g., language, executive function) or specific tests (e.g., Trail-Making Tests A and B). The different characteristics of the study populations may have largely contributed to the inconsistency. Taking the advantage of the study sample, as well as validated and comprehensive assessment tools of depression and cognitive function, our study showed a picture reflecting the burden on cognitive function associated with late-life depression.

A previous study reported that the rate of cognitive decline among older adults without experiencing substantial cognitive decline is 0.04 standard deviations per year (Hayden et al., 2011). Based on the results of our study, CRD and CSD were associated with 0.21 and 0.56 standard deviations lower of cognitive function, respectively, which are about 5 years and 14 years of decline in cognition. These magnitudes characterized by standard deviations in our study may precisely show a huge impact on cognition by late-life depression among older adults in the U.S., and a higher severity of depression is associated with a lower level of cognition.

It is worth noting that the etiology of late-life depression is highly complex and heterogeneous (Koenig et al., 2014). Late-life depression is largely impacted by vascular disease and its risk factors. Cerebrovascular disease, including cerebral small vessel disease, is likely to contribute to developing late-life depression via structural damage to frontal-subcortical circuits, with cortico-striato-pallido-thalamo-cortical pathways disrupted (Aizenstein et al., 2016; Alexopoulos et al., 1997). This is supported by the evidence that older patients with late-life depression had white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI), and is subsequently associated with poor cognition, particularly executive dysfunctions and lower processing speed (Aizenstein et al., 2016). This was reflected in the results of our study, which showed that among the three domains of cognitive function, executive dysfunctions/processing speed showed the largest magnitudes of associations with late-life depression.

Somatic and cognitive depressive symptoms in our study showed similar contribution to poor cognitive function among older adults. Somatic depressive symptoms were likely to be considered as manifestations of physical disease, such as cardiovascular disease (Carney and Freedland, 2012). We therefore adjusted for physical conditions, such as hypertension, diabetes, coronary heart disease and stroke in our models to minimize the potential confounding effects, and the results suggests that somatic depressive symptoms do have an impact on cognitive function.

A synergistic relationship of late-life depression and diabetes with cognition was found in our study. In addition to the vascular depression hypothesis, stress from psychosocial sources, HPA axis dysregulation and elevated levels of glucocorticoids may also account for the synergistic effect (Demakakos et al., 2017). Given the impact on cognition, it suggests the importance of coordination between health professionals for diabetes and for depression in geriatrics. Geriatric patients with either depression or diabetes may be suggested screening for the other condition, to prevent further deficits in cognitive function. In addition to diabetes, other vascular risk factors could be particularly important since a great proportion of depression and dementia is vascular related, and one feature of vascular depression is its poor treatment outcome (Little et al., 1998).

Our findings have substantial public health relevance. It is necessary to treat individuals with late-life depression, who are at a high risk of cognitive impairment. In addition, to reduce the burden of cognitive decline and dementia, late-life depression should be prevented in population level. From the results of our study, depressive symptoms showed monotonic associations with lower cognitive function, which suggests that no specific cutoff of depressive symptoms is associated with particularly low cognitive function. Instead, efforts should be made to reduce depressive symptoms not just among depressed individuals, but also for those without depression, since they account for majority of older adults, and a “population strategy” that attempts to reduce depressive symptoms among the whole population of older adults is beneficial. Therefore, a combination of “population strategy” and “high-risk strategy” may be a good mode for preventing cognitive impairment through reducing depression.

The main limitation of our study is the cross-sectional design, which precludes causal inferences from depressive symptoms to cognitive function among older adults. Additionally, the definitions of depression were decided by cutoffs of PHQ-9 scale, which might suffer from misclassification bias. However, the misclassification is likely non-differential, which bias the associations towards the null. This in turn indicates the robustness of our study findings. Given the external validity of the PHQ-9 scale, we were still able to use this tool to assess the prevalence of depression and its relationship with cognition. Furthermore, information of physical conditions in our study was obtained through self-report. And the imaging data were not available for studying the role of cerebral small vessel disease in the association b etween depression and cognition among older adults. Future longitudinal studies are expected to examine to what degree that cerebral small vessel disease accounts for the relationship between late-life depression and cognitive impairment.

In conclusion, measures of depressive symptoms and depression are associated with lower cognitive function in a representative sample of older adults in the U.S. Moreover, a synergistic effect is found between

late-life depression and diabetes on cognition among older adults. Since vascular risk factors play an important role in the associations between late-life depression and cognition, it is essential to control cardiovascular disease and cerebrovascular disease risk factors. Depressive symptoms should be reduced among the whole population of older adults for benefits on cognition in population level.

Conflicts of interests

All authors have no conflict of interests.

Disclosures

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JW designed the study, performed data analysis and drafted the manuscript. MY, LX, EKC, HL, TW and CL helped edit the manuscript. All authors reviewed and approved the manuscript.

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