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Effect of depressive disorder on cognitive decline

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ABSTRACT

This study longitudinally investigates the effect of depressive disorder on psychiatric disorder in middle aged and aged population from the Korean Longitudinal Study of Aging. Data from the Korean Longitudinal Study of Aging (KLoSA) from 2006 to 2016 was assessed using longitudinal data analysis and 7515 research samples were included after excluding those with cognitive decline and missing information at baseline (2006). To analyze the association between depressive disorder on cognitive decline in middle aged and aged population, generalized estimating equation (GEE) model and chi-square test were used. The association between depressive symptom during a week and center for epidemiological studies depression (CESD) on cognitive decline was statistically significant, respectively with the following Odds ratio (OR) predicting decreased MMSE score: OR = 0.89 ($p < .0001$) for 5–7 days *vs.* less than a day and B = 0.91 ($p < .0001$) for depression (8–10) *vs.* healthy (zero). In terms of cognitive decline, depressive symptom was higher for 5–7 days (OR = 3.79, $p < .0001$) compared to less than a day. This study shows a statistically significant association between depressive disorder and cognitive decline in a Korean middle aged and aged population. These findings suggest the importance of managing depressive disorder for incident cognitive decline.

1. Introduction

Aging of the population is already a global trend. With population aging, depression is one of the most prevalent psychiatric disorders in the elderly population and it is characterized by cognitive dysfunction and significant psychosocial impairment that persist from weeks to years (American Psychological Association, 2013). In addition, depression is a well-known risk factor and one of the prodromal symptoms of psychiatric diseases such as Alzheimer`s disease (AD) (Byers & Yaffe, 2011; Deckers et al., 2015), especially when depression has its onset late in life and appears close to the onset of dementia (Bennett & Thomas, 2014; Masters, Morris, & Roe, 2015).

Several authors have pointed to the potential of preventing cognitive decline by treating depression (Kessing, 2012; Lyketsos et al., 2011). Previous study (Landro, Stiles, & Sletvold, 1997) reported that patients with depression typically showed a pattern of deficient memory, deficits in psychomotor speed, processing speed and executive function that may accelerate the progression of psychiatric diseases (Gualtieri, Johnson, & Benedict, 2006). Similarly, Suhr (2003) also found that depression was significantly related to memory performance, consistently reporting that depression has a negative impact on cognitive function (Potter & Steffens, 2007).

However, the findings in regards to whether depression accelerates the progression of psychiatric diseases such as AD or dementia are controversial. For instance, a previous study found that depression did not accelerate the progression of dementia among patients with AD (Leoutsakos et al., 2015), whereas other studies reported the opposite (Rapp et al., 2011; Wilson et al., 2002).

Recent biomarker studies for AD, one of the psychiatric diseases, have reported that depression is associated with beta-amyloid burden (Babulal et al., 2016; Wu et al., 2014). However, it is not easy to detect symptoms of psychiatric diseases or early Dementia. Thus, it is important to find early signs of this disease through regular assessment in the community to explore high-risk group and plan for the future long-term care needs.

Therefore, in this paper, we will focus on the depressive symptom during a week and depression measured with center for epidemiological studies depression (CESD) and its relationship to the progression of cognitive decline, measured with Korean Mini-Mental State Examination (K-MMSE), through 10-year follow up database.

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2. Methods

2.1. Data source

We obtained de-identified study data from the first wave of the Korean Longitudinal Study of Aging (KLoSA) in 2006, containing participants' data for Korean community-dwelling Koreans 45 years of age, and older and follow up to 2016. Participants were selected randomly using a multistage, stratified probability sampling design to create a nationally representative sample. As per the KLoSA study protocol, trained surveyors collected informed consents from participants and conducted face-to-face interviews using a computer-assisted personal interviewing program. The data is composed of 7 categories such as population, family, health, employment, income, wealth, subjective expectation and life expectation. This biennial survey involves multistage stratified sampling based on geographical areas and housing types across Korea. Participant selection was performed by the Korea Labor Institute for these rapidly growing populations, including individuals from both urban and rural areas. In case of refusal to participate, another subject was selected from an additional, similar sample from the same district. Out of the public data in Korea, KLoSA was considered as the most suitable data for the analysis involved in the current study. In this study, 7515 participants were included in the analysis after excluding those with cognitive decline at baseline and missing values for the variables of interest (Fig. 1).

2.2. Independent variable

2.2.1. Depressive symptom during a week

Depressive symptoms were assessed for 7 days prior to the interview. Responses to the question were assigned to 1 of 5 subcategories: less than a day, 1–2 days, 3–4 days and 5–7 days.

2.2.2. Depression

The CESD was created in 1977 by Radloff (1977). The scale is well known and remains one of the most widely used instruments in the field of psychiatric epidemiology (Naughton & Wiklund, 1993; Shin et al., 2016). We used the CESD-10 Korean edition for measuring depressive symptoms defined by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-IV). Depression was categorized into four groups based on previous studies (Bjorgvinsson, Kertz, Bigda-Peyton, McCoy, & Aderka, 2013; Mohebbi et al., 2018): healthy (0), mild (1–4), moderate (5–7) and depression (8–10)

2.3. Dependent variable

2.3.1. The korean mini-mental state examination (K-MMSE)

The Korean Mini-Mental State Examination (K-MMSE) included 11 items in 7 categories of cognitive functions, including orientation for time and place, registration, attention & calculation, recall, language, and visual construction (Kang, Na, & Hahn, 1997; Thomas et al., 2005). The total score of the measure ranges from 0 to 30; higher the score, better the cognitive function. The validity of the K-MMSE was reported elsewhere (Kang et al., 1997). Cognitive decline was categorized into two group: normal (K-MMSE $\geq$ 24) or cognitive decline (K-MMSE $\leq$ 23). (Kang et al., 1997; Thomas et al., 2005).

2.4. Control variable

Education level, gender, age, marital status, residential region, type of health insurance, self-rated health, number of chronic diseases, smoking status, economic activity and physical activity were considered as confounding factors. Levels of education were categorized as 'less than elementary school', 'middle school graduate', 'high school graduate', or 'college graduate or beyond'. Three age group categories were used as follows: $\leq$54, 55–64 and $\geq$65 years. Marital status was categorized as 'married' or separated, divorced and 'single' which means 'never married'. The residential regions were categorized into metropolitan (Seoul), urban (administrative divisions of a city: Daejeon, Daegu, Busan, Incheon, Kwangju, or Ulsan) or rural (not classified as

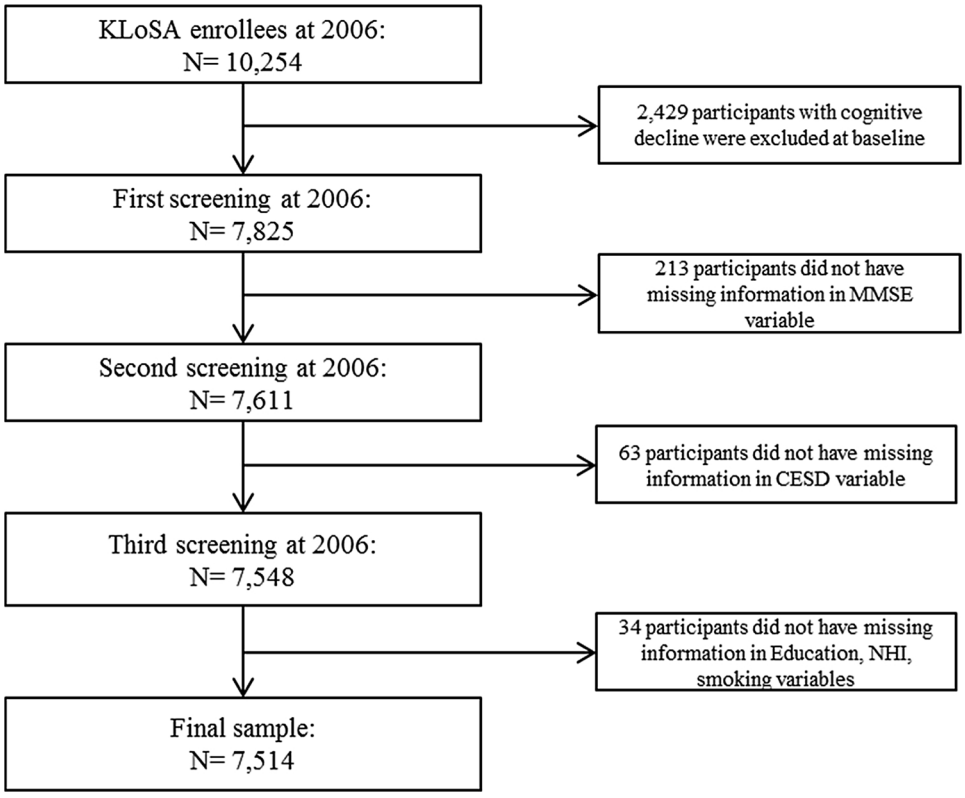

Fig. 1. Flow chart for sample selection.

administrative of a city). The type of health insurance was categorized into National Health Insurance (NHI) (either employee-insured or self-insured) or Medical Aid. Participants were asked to rate their health status on a five-point Likert scale (1 corresponding to "very good" and 5 to "very bad") and self-rate health was categorized into three groups: Good (sufficient or very sufficient), Normal (moderate), or Bad (insufficient' or very insufficient). Self-reported data regarding comorbidities of hypertension, diabetes, cancer, chronic obstructive pulmonary disease, liver disease, cardiovascular disease, cerebrovascular disease, mental illness, and arthritis were included and categorized into three group: 0, 1, and ≥2. Smoking status was categorized into non-smoker who never smoked, former smoker, or smoker, and alcohol use was categorized into drinker or former drinker. Labor means current economic activity and it was categorized as 'employed' or 'unemployed'. Physical activity means regular exercise (more than once a week) and it was categorized "yes" or "no".

2.5. Statistical analysis

In this study, using 2006 as the baseline year and considering the follow-up period until 2016 we employed chi-square test and generalized estimating equation (GEE) model, a clustered model, was performed for this analysis. In GEE, *proc genmod* was used, with *link logit*, *distribution normal*. Cognitive function was the outcome in all GEE models. Covariates of interest from all subjects were added to the model to determine their effects on the odds ratio (OR) of reporting cognitive decline. To determine whether the OR of cognitive decline changed over time, we included time (year) in the model as a categorical covariate; the regression coefficient was used to estimate both the change in OR of cognitive decline and independent variables. SAS statistical software package, version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used in all analyses. All statistical tests were two-tailed, with the null hypothesis of no difference being rejected if $p < 0.05$.

3. Results

3.1. Sample characteristics

Baseline general characteristics of participants are shown in Table 1. Out of the 7151 participants gathered at baseline, mean score of MMSE was 27.93 (SD: 1.88). MMSE score of those who felt depressive symptom for 5–7 days was 27.07 (SD: 1.83) and MMSE score of those who felt depressive symptom for 3–4 days was 26.93 (SD: 1.95). In terms of CESD, MMSE score of those with depression (8–10) was 27.13 (SD: 1.97) and MMSE score of those with moderate (5–7) status was 27.38 (SD: 1.97). (Table 1)

3.2. Relationship between depressive symptom and cognitive functioning

In the fully adjusted model, the association between depressive symptom during a week and MMSE was statistically significant, with the following Odds ratio (OR) predicting decreased MMSE score: OR = 0.97 ($p < .0001$) for 1–2 days with depressive symptom during a week, OR = 0.93 ($p < .0001$) for 3–4 days with depressive symptom during a week, OR = 0.89 ($p < .0001$) for 5–7 days with depressive symptom during a week *vs.* less than a day with depressive symptom during a week. The association between depressive symptom during a week and cognitive decline was also statistically significant, with the following OR predicting increased risk of cognitive decline: OR = 1.64 ($p < .0001$) for 1–2 days with depressive symptom during a week, OR = 2.58 ($p < .0001$) for 3–4 days with depressive symptom during a week and OR = 2.82 ($p < .0001$) for 5–7 days with depressive symptom during a week *vs.* zero depressive symptom during a week. (Table 2)

Table 1
General characteristics of subjects included for analysis.

	Total		MMSE score		P-value
	N	%	Mean	SD	
Depressive symptom during a week					< .0001
Less than a day	5,999	79.8	28.10	1.82	
1-2 days	1,148	15.3	27.39	1.96	
3-4 days	299	4.0	26.93	1.95	
5-7 days	69	0.9	27.07	1.83	
CESD					< .0001
Healthy (0)	1,562	20.8	28.31	1.76	
Mild (1-4)	4,484	59.7	28.01	1.84	
Moderate (5-7)	975	13.0	27.38	1.97	
Depression (8-10)	494	6.6	27.13	1.97	
Education level					< .0001
≤ Elementary school	2,601	34.6	27.04	1.94	
Middle school	1,427	19.0	28.02	1.76	
High school	2,493	33.2	28.46	1.63	
≥ College	994	13.2	28.81	1.49	
Gender					0.633
Male	3,692	49.1	28.11	1.82	
Female	3,823	50.9	27.76	1.92	
Age					< .0001
≤54	3,046	40.5	28.50	1.62	
55-64	2,288	30.5	27.91	1.86	
≥65	2,181	29.0	27.17	1.96	
Marital status					0.968
Married	6,384	85.0	28.03	1.84	
Separated, divorced	1,059	14.1	27.34	2.03	
Single	72	1.0	28.13	1.88	
Residential region					< .0001
Metropolitan	1,386	18.4	28.40	1.84	
Urban	2,247	29.9	27.83	1.86	
Rural	3,882	51.7	27.82	1.88	
National health insurance					0.007
Health insurance	7,192	95.7	27.96	1.87	
Medical aid	323	4.3	27.27	1.92	
Self-rated Health					< .0001
Good	3,435	45.7	28.42	1.68	
Normal	2,476	33.0	27.77	1.89	
Bad	1,604	21.3	27.13	1.94	
Number of chronic disease[a]					0.810
0	4,313	57.4	28.19	1.78	
1	2,051	27.3	27.70	1.94	
≥2	1,151	15.3	27.38	1.94	
Smoking status					0.000
Never	5,112	68.0	27.89	1.91	
Former smoker	785	10.5	27.72	1.84	
Smoker	1,618	21.5	28.17	1.78	
Labor					0.009
Yes	3,477	46.3	28.28	1.73	
No	4,038	53.7	27.63	1.95	
Physical activity					0.914
Yes	3,335	44.4	28.06	1.82	
No	4,180	55.6	27.84	1.92	
Total	7515	100.0	27.93	1.88	

[a] Hypertension, diabetes, cancer, chronic obstructive pulmonary disease, liver disease, cardiovascular disease, cerebrovascular disease, mental illness, arthritis.

3.3. Relationship between depression and cognitive functioning

In the fully adjusted model, the association between CESD and MMSE was also statistically significant, with the following Odds ratio (OR) predicting decreased MMSE score: OR = 0.99 ($p < .0001$) for mild (1–4) in CESD, OR = 0.95 ($p < .0001$) for moderate (5–7) in CESD, OR = 0.91 ($p < .0001$) for depression (8–10) in CESD *vs.* zero for CESD. The association between CESD and cognitive decline was also

Table 2
Adjusted effect between Depressive symptom and cognitive function.

	MMSE score				Cognitive function			
	OR	95% CI		P-value	OR	95% CI		P-value
Depressive symptom during a week								
Less than a day	1.00				1.00			
1–2 days	0.97	0.97	0.98	< .0001	1.64	1.48	1.81	< .0001
3–4 days	0.93	0.92	0.93	< .0001	2.57	2.21	2.98	< .0001
5–7 days	0.89	0.88	0.90	< .0001	2.82	2.18	3.65	< .0001
Education level								
≤Elementary school	0.95	0.94	0.95	< .0001	2.26	1.89	2.69	< .0001
Middle school	0.98	0.98	0.99	< .0001	1.67	1.38	2.01	< .0001
High school	0.99	0.99	0.99	< .0001	1.22	1.01	1.46	0.04
≥College	1.00				1.00			
Gender								
Male	1.00	1.00	1.01	0.50	0.87	0.77	0.99	0.03
Female	1.00				1.00			
Age								
≤54	1.00				1.00			
55-64	1.00	0.99	1.00	0.01	1.53	1.28	1.83	< .0001
≥65	0.95	0.95	0.96	< .0001	3.64	3.05	4.35	< .0001
Marital status								
Married	1.01	1.00	1.03	0.08	0.92	0.60	1.43	0.72
Separated, divorced	1.00	0.98	1.01	0.53	1.17	0.75	1.81	0.50
Single	1.00				1.00			
Residential region								
Metropolitan	1.00				1.00			
Urban	0.99	0.98	0.99	< .0001	1.28	1.11	1.47	0.00
Rural	0.98	0.98	0.99	< .0001	1.42	1.24	1.62	< .0001
National health insurance								
Health insurance	1.00				1.00			
Medical aid	0.99	0.99	1.00	0.05	1.24	1.04	1.47	0.02
Self-rated Health								
Good	1.00				1.00			
Normal	0.99	0.99	1.00	< .0001	2.72	1.00	1.00	< .0001
Bad	0.95	0.95	0.96	< .0001	1.30	1.15	1.46	< .0001
Number of chronic disease*								
0	1.00				1.00			
1	1.01	1.01	1.01	< .0001	0.84	0.75	0.95	0.00
≥2	1.01	1.01	1.01	< .0001	0.85	0.77	0.95	0.00
Smoking status								
Never	0.99	0.99	0.99	< .0001	1.27	1.11	1.45	0.00
Former smoker	0.99	0.98	0.99	< .0001	1.42	1.24	1.62	< .0001
Smoker	1.00				1.00			
Labor								
Yes	1.00				1.00			
No	0.99	0.98	0.99	< .0001	1.53	1.38	1.69	< .0001
Physical activity								
Yes	1.02	1.02	1.02	< .0001	0.58	0.53	0.64	< .0001
No	1.00				1.00			

statistically significant, with the following OR predicting increased risk of cognitive decline: OR = 1.45 ($p < .0001$) for mild (1–4) in CESD, OR = 2.49 ($p < .0001$) for moderate (5–7) in CESD and OR = 3.79 ($p < .0001$) for depression (8–10) in CESD *vs.* zero in CESD. (Table 3)

4. Discussion

In this study, we investigated the relationship between the psychiatric disorder such as depressive symptom during a week measured by self-reported questionnaire and cognitive decline measured by MMSE. This study showed a significant relationship between depressive disorder and cognitive decline after controlling for several factors such as demographic characteristics based on a large population-based sample with 10-year follow-up database. These findings suggest an important role of depressive disorder in cognitive decline and showed that depression is associated with cognitive decline, which was also supported by a previous study (Taylor, 2014).

Controversial findings have been reported in regards to whether depression accelerates the progression of cognitive decline. Several studies have found that depression accelerates dementia progression (Rapp et al., 2011; Wilson et al., 2002), but another study did not (Leoutsakos et al., 2015).

Several mechanisms have been hypothesized for why depression would be associated with faster or greater progression of incident cognitive decline. First, possible explanation for our finding has been shown in a previous study that depression leads to increased circulation of glucocorticoids, which, in turn, could lead to hippocampal atrophy (Byers & Yaffe, 2011; Sheline, Gado, & Kraemer, 2003). One study reported that patients with depression had more medial temporal lobe atrophy (MTA) than patients without depression (Dhikav, Sethi, & Anand, 2014), and a post-mortem study revealed that patients with a history of depression had more neuritic plaques and neurofibrillary

Table 3
Adjusted effect between CESD and cognitive function.

	MMSE score				Cognitive function			
	OR	95% CI		P-value	OR	95% CI		P-value
CESD								
Healthy (0)	1.00				1.00			
Mild (1–4)	0.99	0.98	0.99	< .0001	1.45	1.27	1.66	< .0001
Moderate (5–7)	0.95	0.95	0.96	< .0001	2.49	2.15	2.88	< .0001
Depression (8–10)	0.91	0.91	0.92	< .0001	3.79	3.22	4.45	< .0001
Education level								
≤Elementary school	0.95	0.95	0.96	< .0001	2.17	1.82	2.60	< .0001
Middle school	0.98	0.98	0.99	< .0001	1.65	1.36	1.99	< .0001
High school	0.99	0.99	1.00	0.01	1.19	0.99	1.44	0.06
≥College	1.00				1.00			
Gender								
Male	1.00	1.00	1.01	0.74	0.85	0.75	0.96	0.01
Female	1.00				1.00			
Age								
≤54	1.00				1.00			
55-64	1.00	0.99	1.00	0.09	1.56	1.30	1.87	< .0001
≥65	0.96	0.95	0.96	< .0001	3.76	3.15	4.50	< .0001
Marital status								
Married	1.00	0.98	1.02	0.94	0.94	0.61	1.45	0.78
Separated, divorced	0.99	0.97	1.01	0.18	1.17	0.75	1.81	0.49
Single	1.00				1.00			
Residential region								
Metropolitan	1.00				1.00			
Urban	0.99	0.98	0.99	< .0001	1.30	1.12	1.50	0.00
Rural	0.98	0.98	0.99	< .0001	1.43	1.26	1.64	< .0001
National health insurance								
Health insurance	1.00				1.00			
Medical aid	0.99	0.99	1.00	0.24	1.20	1.01	1.43	0.04
Self-rated Health								
Good	1.00				1.00			
Normal	1.00	0.99	1.00	0.13	1.28	1.13	1.44	< .0001
Bad	0.95	0.94	0.95	< .0001	1.96	1.72	2.25	< .0001
Number of chronic disease*								
0	1.00				1.00			
1	1.01	1.01	1.02	< .0001	0.83	0.74	0.93	0.00
≥2	1.01	1.01	1.02	< .0001	0.85	0.76	0.94	0.00
Smoking status								
Never	0.99	0.98	0.99	< .0001	1.28	1.12	1.47	0.00
Former smoker	0.98	0.98	0.99	< .0001	1.44	1.26	1.64	< .0001
Smoker	1.00				1.00			
Labor								
Yes	1.00				1.00			
No	0.98	0.98	0.99	< .0001	1.49	1.34	1.64	< .0001
Physical activity								
Yes	1.02	1.02	1.02	< .0001	0.58	0.53	0.64	< .0001
No	1.00				1.00			

tangles in the hippocampus than those without a history of depression (Rapp et al., 2006). In addition, cardiovascular factors are risk factors for both depression (Almeida et al., 2007), dementia (Kivipelto et al., 2006) and AD (Almeida et al., 2007). And it is possible that these factors would booster the progression of psychiatric disease in patients with depression. Memory loss was found to be a significant risk factor of cognitive impairment. Memory loss is generally thought of as a normal process of aging, which could be a symptom of a condition called cognitive impairment (Burns & Zaudig, 2002).

Our findings suggest the direct association between depression and cognitive decline. Therefore, the treatment of such conditions, in addition to providing symptomatic relief, may be seen as a form of secondary prevention by slowing the progression of the disease and diminishing the negative consequences of cognitive decline. In addition, antidepressant treatment might reduce the risk of cognitive decline, both indirectly through changes in behavior (*e.g.*, increased activation) and more directly through impact on pathophysiological mechanisms associated with cognitive decline.

This study has some limitations. First limitation is that this study includes the use of self-report measures of health. Although the MMSE and CESD are a widely used and well-validated measures in older adults, respondents' reports are subjective and are potentially affected by false consciousness and adaptation of resources because depression and cognition were determined using a cut-off on a self-report measure of depression and not by clinical evaluation. Another important limitation is that although psychotropic agents or medication use may be an early sign of cognitive decline, we were unable to adjust for medication use due to lack of information. Final limitation is that as a general limitation of observational studies, we were unable to adjust for unknown confounding factors highly associated with the investigated relationship. Nevertheless, there are several major strength of the current study. Participants were followed for nearly 10 years and the study

obtained a large sample size, so the results can be generalized to adults aged 45 years and older within the South Korean population.

In this study, the results showed a significant relationship between depressive disorder and cognitive decline after controlling for several factors such as demographic characteristics based on a large population-based sample with 10-year follow-up database. These findings suggest the importance of management for preventing depressive disorder, which could be protective against cognitive decline, in addition to providing direct symptomatic relief for incident cognitive decline.

Conflicts of interest

No author has any financial or other conflict of interest to declare.

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