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APOE-ε4, Depressive Symptoms, and Cognitive Decline in Chinese Older Adults: Singapore Longitudinal Aging Studies

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Background. The precise relationship between depression and cognitive decline in older adults is unclear. We investigated the influence of apolipoprotein E (APOE)-ε4 genotype in modulating the effect of depressive symptoms on cognitive decline.

Methods. Prospective cohort study of 1,487 cognitively high-functioning Chinese older adults. Depressive symptoms (Geriatric Depression Scale score ≥5) and Mini-Mental State Examination (MMSE) were assessed at baseline, and cognitive decline (at least 1-point drop in MMSE) at 1–2 years after baseline.

Results. There was no significant difference in cognitive decline between depressed (32.9%) and nondepressed (31.5%) participants in the whole sample or among non–APOE-ε4 carriers. Among APOE-ε4 carriers, depressed participants showed more cognitive decline (40.0%) than their nondepressed counterparts (28.6%), odds ratio = 2.89, 95% confidence interval: 1.03–8.12; $p = .04$, after controlling for age, gender, education, vascular risk factors/events, smoking, alcohol drinking, physical functioning, subjective memory complaint, length of follow-up, and baseline MMSE scores (p for interaction = .03).

Conclusions. Our study suggests that the presence of the APOE-ε4 allele significantly enhanced the risk of cognitive decline associated with depressive symptoms. This finding should be independently replicated in future studies.

Key Words: Depression—Cognition—Dementia—Apolipoprotein E.

DEPRESSIVE symptoms and poor cognitive function are highly prevalent and often coexist, but the precise relationship between them is unclear (1). Whether depressive symptoms contribute to the onset or progression of poor cognitive function in later life remains controversial (2–4). A number of prospective studies have found that depressive symptoms are associated with an increased risk of dementia (5–7), cognitive impairment (8), or cognitive decline (9–11). However, other studies have also failed to show such associations (12–23). These inconsistent findings may be partly due to differences in sample size and population characteristics, including genetic factors that modify the association.

Gene × Environment interactions are important in the progression of cognitive impairment and the development of dementia (24). The apolipoprotein E-ε4 (APOE-ε4) genotype is widely investigated for its association with an increased risk of cognitive decline (25–28). Although not a specific risk factor, the presence of the APOE-ε4 allele may render individuals more vulnerable to the influence of a specific environmental risk factor (29). To the best of our knowledge, the role of APOE-ε4 in modulating the effects of depressive symptoms on cognitive decline has not been reported.

In this present prospective cohort study, we examined the association of depressive symptoms with cognitive decline among cognitively high-functioning Chinese older adults living in the community and whether the presence of the APOE-ε4 allele modified such an association. We hypothesized that the association of depressive symptoms with cognitive decline was accentuated in individuals who were carriers of the APOE-ε4 allele.

Methods

Our study participants were from the Singapore Longitudinal Aging Studies cohort, a population-based study of older adults aged 55 years and older living in a geographically defined area in South East Region of Singapore. They were identified from door-to-door census and invited to participate in the study, which was approved by the National University of Singapore Institutional Review Board. A total of 2,804 eligible residents participated, representing a response rate of 78.5%. They provided written informed consent before undergoing extensive face-to-face interviews, assessments, and tests that were performed by trained research nurses to collect baseline information on a wide range of demographic, biological, clinical, psychosocial, and behavioral variables (30). The follow-up interviews were performed 1–2 years after the baseline assessment (mean of 1.5 years).

The participants in the present study were 2,611 Chinese, who were enrolled in the baseline examination in 2004/2005.

In 2005/2006, a total of 1,673 participants completed reinterview at 1–2 years after the baseline interview, 53 died, and 885 were lost to follow-up (15 were unfit to be interviewed, 444 refused, and 426 could not be contacted). Participants who were lost to follow-up were more likely to be men (40% vs 35%, $p = .024$), had poorer mean (standard deviation [*SD*]) baseline cognitive function (26.6 [4.2] vs 27.1 [3.2], $p = .003$), and had more depressive symptoms (16% vs 12%, $p = .004$) than participants who were followed up. No significant differences in age ($p = .73$), education level ($p = .67$), and prevalence of APOE-ε4 carriers ($p = .14$) were observed. In the present analysis, we excluded 169 cognitively impaired participants with Mini-Mental State Examination (MMSE) score ≤23 at baseline and others with missing data for the APOE genotype ($N = 17$), resulting in a final cohort of 1,487 cognitively high-functioning Chinese participants with complete baseline and follow-up data for analysis.

Cognitive Decline

Cognitive performance was assessed using the MMSE (31), a validated and widely used measure of global cognitive functioning on domains of memory, attention, language, praxis, and visuospatial ability. The Chinese translation of the instrument has been validated for local use in Chinese older adults (32). Total scores range from 0 to 30, with higher scores denoting better cognitive performance. Respondents with MMSE scores of 23 or less were classified as cognitively impaired. Cognitive decline was defined as at least 1-point drop in the MMSE test scores between baseline and follow-up assessments.

Depressive Symptoms

The presence of depressive symptoms was determined using a locally validated Chinese version (33) of the 15-item Geriatric Depression Scale (GDS) (34). The 15-item GDS is a highly reliable and valid measure of depressive symptoms in older adults. For the purpose of this analysis, one item tapping on subjective memory complaint ("Do you feel you have more problems with memory than most?") was removed from the GDS. The total score based on the remaining 14 items thus ranged from 0 (no depressive symptoms) to 14 (severe depressive symptoms). A GDS score of 5 or more was used to categorize participants as having depressive symptoms.

Covariates

We collected baseline information on potential confounding or mediating variables that are known to be associated with cognitive decline. They included age (in years), gender, education (0–6 years or more), cigarette smoking (current smokers vs past-smokers or nonsmokers), and alcohol drinking (at least one alcoholic drink daily or less).

Information on vascular risk factors and diseases was ascertained using self-reports of physician diagnoses and cardiac procedures and surgeries; interviewer inspection of medications; and measurements of blood pressure, electrocardiogram (ECG), fasting blood glucose, and lipids. Heart diseases included coronary artery disease, angina, myocardial infarction, cardiac failure (based on self-report of physician diagnoses or procedures and surgeries such as percutaneous transluminal coronary angioplasty, stenting or coronary artery bypass grafting, or cardiac medications use), and atrial fibrillation (ECG); stroke (self-report); hypertension (self-reported history or use of antihypertensive medications or measured sitting blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic); diabetes (self-reported history or antidiabetic medication use or fasting blood glucose >7.0 mmol/L); and hyperlipidemia (self-reported presence of hyperlipidemia or use of lipid-lowering drug or elevated values in total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein cholesterol, and ratio of total cholesterol to HDL).

Physical functioning was assessed by the respondent's level of dependency in performing basic activities of daily living (BADL) (35) and instrumental activities of daily living (IADL) (36). Functional disability was defined as needing personal help in at least one task, and categorized in three ordinal levels (independent, IADL disability only, and BADL disability).

APOE genotyping was identified by polymerase chain reaction (PCR) or PCR amplification followed by restriction endonuclease digestion of the PCR product. Participants with the APOE-ε4 allele (ε2/4, ε3/4, and ε4/4) were classified as carriers and those without it (ε2/2, ε2/3, and ε3/3) as noncarriers.

Statistical Analysis

In univariate analyses, baseline characteristics including baseline MMSE scores were compared between depressed and nondepressed groups, using the independent *t* test for continuous variables (mean/*SD*) and χ^2 trend tests for categorical variables (%). Multivariate analyses of the longitudinal association between depressive symptoms and cognitive decline were performed using binomial logistic regression with covariate adjustment in a saturated model that included relevant confounding and mediating variables, namely age, gender, education, presence of vascular risk factors/events, physical functional status, smoking, alcohol drinking, APOE genotype, length of follow-up, and baseline MMSE score (controlling for "floor effect"). We also included subjective memory complaint ("Do you feel you have more problems with memory than most?") because it is associated with depression and is itself a risk marker of cognitive decline (37, 38). The effect modification by APOE-ε4 status of the association between depression and cognitive decline was assessed by the two-way interaction between depression and APOE-ε4 status, based on a single testing for subgroup effects. The level of statistical significance was set at $p < .05$

Table 1. Characteristics of Study Participants, for Whole Sample and by Depression Status

	Whole Sample	Nondepressed (GDS <5)	Depressed (GDS ≥5)	*p*
Sample size (no., %)	1,487	1,353 (91.0)	134 (9.0)	—
Length of follow-up, yr (mean/*SD*)	1.46 (0.5)	1.45 (0.5)	1.57 (0.5)	.01
Age, yr (mean/*SD*)	65.4 (7.0)	65.4 (7.0)	65.0 (7.2)	.47
Female gender	63.5	63.5	63.4	.99
Education: 6 yr or less	46.6	46.5	47.8	.78
Vascular risk factors/events				
Hypertension	45.8	54.5	51.5	.51
Diabetes	15.3	14.9	20.1	.11
Cardiac diseases*	7.3	7.1	9.0	.43
Stroke	3.0	3.0	3.0	.99
Physical functioning				
IADL dependent	16.0	15.3	22.6	.004
ADL dependent	5.0	4.6	9.0	
APOE-ε4 carrier	18.1	17.5	23.9	.07
Current smokers	5.4	5.2	7.5	.26
Alcohol drinking	7.5	7.5	8.2	.76
Baseline MMSE score (mean/*SD*)	28.0 (1.7)	28.0 (1.7)	27.8 (1.8)	.11
Subjective memory complaint	16.9	12.9	58.2	<.001

Notes: Values are % unless otherwise indicated. APOE-ε4 = apolipoprotein E-ε4; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; *SD* = standard deviation; IADL = instrumental activities of daily living; ADL, activities of daily living.

*Ischemic heart disease or congestive heart failure or atrial fibrillation.

with two-tailed distribution. Odds ratios (ORs) of associations and their corresponding 95% confidence intervals (95% CIs) were computed. All analyses were performed using SPSS statistical software version 15.0 (SPSS, Inc., Chicago, IL).

Results

Baseline Characteristics

In the sample of 1,487 cognitively high-functioning Chinese participants, the mean MMSE score was 28.0 (*SD* 1.7); the mean age was 65.4 years (*SD* 7.3, range: 55–92); 63.5% were women; and 46.6% had 6 years of education or less. Hypertension was present in 54.2% of the participants, diabetes in 15.3%, cardiac diseases in 7.3%, stroke in 3.0%, IADL disability in 16.0%, BADL disability in 5.0%, current smoking in 5.4%, and daily alcoholic drinking in 7.5%. The frequency of APOE-ε4 carriers was 18.1%, and depressive symptoms were reported by 9.0% of the participants. Subjective memory complaint was reported by 16.9% (Table 1).

Depressed participants showed a higher prevalence of functional disability ($p < .001$), had more subjective memory complaint ($p < 0.001$), and were current smokers ($p = 0.02$) than nondepressed participants. No significant differences were observed for age, gender, education level, vascular risk factors/events, alcohol drinking, APOE-ε4 status, and baseline MMSE scores.

Depression and Cognitive Decline

Overall, cognitive decline was observed in 31.6% of the participants. Among those with cognitive decline, MMSE scores dropped from 1 to 8 points (mean drop of 2 points) during follow-up. There was no significant difference in cognitive decline between depressed (32.9%) and nondepressed (31.5%) participants, adjusted OR = 0.95, 95% CI: 0.61–1.48; $p = .83$ (Table 2).

However, a significant association was observed in subgroup analysis of participants stratified by APOE-ε4 status. Among APOE-ε4 carriers, depressed participants showed more cognitive decline than their nondepressed counterparts (40.0% vs 28.6%, respectively). The association was statistically significant (OR = 2.89, 95% CI: 1.03–8.12; $p = .04$), after controlling for relevant baseline characteristics, including age, gender, education, vascular risk factors/events, smoking, alcohol drinking, physical functioning, subjective memory complaint, length of follow-up, and MMSE scores. The test of interaction between APOE status and depressive symptoms on the risk of cognitive decline was significant ($p = .03$).

Discussion

We found in our community-dwelling cohort of cognitively high-functioning Chinese older adults that the presence of the APOE-ε4 allele was a significant factor modifying the association between depressive symptoms at baseline and the subsequent risk of cognitive decline. Among non–ε4-carriers, depressive symptoms were not associated with cognitive decline, but among ε4-carriers, depressive symptoms were associated with a significantly increased risk of cognitive decline, independent of other risk factors. Our findings of a significant interaction between APOE-ε4 status and depressive symptoms have not been reported by previous investigators and may explain the

Table 2. Association of Depression With Cognitive Decline by APOE-ε4 Status*

	Sample Size	Cognitive Decline* (%)	Adjusted OR† (95% CI)	*p*
Depression (GDS score ≥5)				
No	1,353	31.8	1.00	
Yes	134	29.9	0.95 (0.61–1.48)	.83
APOE-ε4 carriers				
No	1,218	31.9	1.00	
Yes	269	30.1	1.10 (0.86–1.41)	.43
Interaction: Depression × APOE status				.03
APOE-ε4 noncarriers				
Nondepressed	1,116	32.4	1.00	
Depressed	102	26.5	0.73 (0.44–1.21)	.22
APOE-ε4 carriers				
Nondepressed	237	28.7	1.00	
Depressed	32	40.6	2.89 (1.03–8.12)	.04

Notes: APOE-ε4 = apolipoprotein E-ε4; GDS = Geriatric Depression Scale; OR = odds ratio; CI = confidence interval.

*At least 1-point drop in Mini-Mental State Examination test scores during follow-up period.

†Adjusted for age, gender, education, vascular risk factors/events (hypertension, diabetes, cardiac diseases, and stroke), smoking, alcohol drinking (APOE status), physical functioning, subjective memory complaint, length of follow-up, and baseline Mini-Mental State Examination score.

variations in findings from many previous studies of the relationship between depression and cognitive decline.

A number of published reports (12–23) have failed to show a significant association of depression with cognitive decline. We also found that when the modifying presence of APOE-ε4 was ignored, there was an overall lack of association between depressive symptoms and cognitive decline in the total sample.

Also, the presence of the APOE-ε4 allele is consistently shown to be a major genetic risk factor for dementia (39), but reports of the associations of APOE-ε4 with global cognitive decline are also variable. Although some studies have shown greater cognitive declines in ε4-carriers (25,26,28), others have observed a lack of association (27). We also observed that overall there was no association between APOE-ε4 and cognitive decline in the whole sample (OR = 1.10, 95% CI: 0.86–1.41). It is possible that the effect of APOE-ε4 on cognitive function is manifested when it is present as a genetic susceptibility factor together with a modifiable risk factor such as depression (Gene × Environmental interaction).

Variations in findings across different studies may be explained by the selection characteristics of the study populations among other reasons such as sample size. Population studies with relatively high concentrations of participants with APOE-ε4 and depression may be more likely to show such a positive association in the whole sample, whereas studies that are selected with relatively low prevalence of APOE-ε4 and depression may show a lack of association without stratified analyses. This was also the case in this study; our cohort showed a low frequency of depressive symptoms as well as subjective memory complaints because of their baseline selection characteristics: Participants in the follow-up study had fewer depressive symptoms than nonparticipants, and they were cognitively well functioning. For these reasons, depressed and nondepressed participants showed little or no differences in gender, age, and vascular factors at baseline, but still showed significantly great differences in activities of daily living dependency and subjective memory complaint.

The biological mechanisms for the modulating effect of the APOE-ε4 genotype on cognitive decline are not fully understood. APOE is a polymorphic 299–amino acids protein, which has critical functions in redistributing lipids among central nervous cells cells, repairing injured neurons, maintaining synapto-dendritic connections, and scavenging toxins (40). Although APOE-ε4 genotype is not a specific risk factor of cognitive decline, its presence may render individuals more vulnerable to a specific environmental risk factor. It has been postulated that APOE-ε4 allele carriers may have less effective neural protection and repair mechanisms (40), which may subsequently make them less protected against the negative impacts of depression on cognitive decline.

So far, the precise underlying mechanisms of the association of depression with cognitive decline, the principal preclinical marker of dementia, remain poorly understood. A risk factor common to both depression and cognitive decline such as vascular diseases (41) may mediate the relationship, but as shown in multivariate analyses in this and other studies (8,42) did not completely explain the relationship. Short-term situational factors such as physical functional disability (43) may also confound the relationship but were also controlled in our multivariate analyses.

A common underlying neurodegenerative process, such as white matter and subcortical abnormalities, may cause depression as well as cognitive decline in elderly participants (44,45). However, there are some evidence to suggest that the association of depressive symptoms with clinical Alzheimer's disease and cognitive impairment appeared to be independent of cortical plaques and tangles (42,46).

Depression may be an early manifestation or prodrome of dementia because of the loss of noradrenergic and cholinergic neurons associated with dementia in the locus coeruleus and substantia nigra (47). In the present study, we excluded cognitively impaired participants at baseline (those with MMSE score ≤23), but this may not completely eliminate the possibility of an intrinsic relationship with incipient dementia. Finally, it is possible that depression in old age may be an independent risk factor of cognitive decline, operating via the "glucocorticoid cascade" pathway in the hypothalamic-pituitary-adrenal axis (48), to increase cortisol level, ultimately leading to hippocampal atrophy.

The strengths of this prospective cohort study included an adequately large sample size and statistical adjustment for a wide range of potential confounders. A limitation is possible attrition bias. We observed that those who remained in the study had better baseline cognitive function and were less depressed; hence, our findings were likely to be biased toward underestimating the negative association of depression and cognitive decline. Cognitive decline was based on changes in global cognitive function measured by the MMSE; hence, our findings did not pinpoint declines in specific cognitive domains, nor did they amount to a diagnostic determination of dementia. Also, we used the GDS to determine the presence of depressive symptoms, not clinical depression. Although self-report of somatic conditions have been shown to have good validity (49,50), differential self-reporting of somatic conditions by depression (possible overreporting) and cognitive status (possible underreporting) may potentially bias the results in unknown ways. As the principal finding was based on subgroup analysis of a small number of APOE carriers with depression ($n = 32$), this finding should be replicated in future studies in a different population.

In conclusion, the risk of cognitive decline associated with depressive symptoms was significantly enhanced among APOE-ε4 carriers. This may have implications for identifying depressed individuals with higher risk of cognitive decline, who could be selected for more targeted treatment.

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