APOE ε4 Allele Modulates The Differential Effects of Education on Cognition in Alzheimer's Continuum: The SILCODE Study

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Research

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Abstract

Background: Elders with subjective cognitive decline (SCD) in the absence of objective cognitive impairment are at increased risk of developing mild cognitive impairment (MCI) or Alzheimer's disease (AD). Previous study has reported that higher education was associated with better performance in cognitive performance in elderly people with SCD. However, it is not clear whether there is a differential effect of education on cognition between healthy controls (HC), individuals with SCD and patients with cognitive impairment (CI).

Methods: We performed a cross-sectional study that included 186 HC, 279 SCD subjects and 79 patients with CI from the Sino Longitudinal Study on Cognitive Decline (SILCODE) project. A series of neuropsychological tests of memory, executive, language, and general cognitive function were used to assess the subjects cognitive performance. We performed multiple linear regression models to examine the effect of education on neuropsychological test scores in the total sample and then described differences in the effect according to three different groups. In addition, we presented the effect of education on total test score expressed as a global composite z-scores in the total sample and three different groups, respectively. Furthermore, we examined whether apolipoprotein E ε4 allele (*APOE ε4*) status would regulate the effect of education on the global composite score among three different groups.

Results: Education has a positive effect on cognition in the total sample. Stratification for different groups showed that the positive effect of education on cognition is found in HC and SCD group, while education has a negative effect on cognition in the CI group. Furthermore, we found the *APOE ε4* allele does not modify the positive effect of education on cognition in the HC group, but the *APOE ε4* allele weaken that beneficial effect in the SCD group and maintain the negative effect in the CI group.

Conclusions: High education may delay the progression from SCD to cognitive impairment and yield differential effects on cognition across the spectrum of AD. Furthermore, that differential effects are subjected to modulation by the *APOE ε4* status.

Introduction

Alzheimer's disease (AD) is the leading cause of dementia, which was characterized by a progressive deterioration in memory, language, and logical thinking [1]. Currently, there is no disease-modifying treatment for patients with AD [2]. A consensus has been reached regarding that AD has a long preclinical stage, as its pathology like β-amyloid (Aβ) and tau start to accumulate as early as 15 to 20 years before symptom onset, which indicated that AD can be considered as a continuum [3–5]. This asymptomatic stage of AD may offer a golden opportunity for successful prevention and treatment of dementia. What's more, several potentially modifiable risk factors for AD and dementia have been identified by epidemiological studies [6, 7]. Among them, less education is a very important risk factor. It was estimated that the population-attributable risk (PAR) of AD of low educational attainment was the highest

around the world (19.1%, 95% CI 12.3–25.6) [8]. A study based on Mendelian randomisation analysis supported that higher educational attainment is associated with a reduced risk of AD [9]. Evidence obtained in recent years suggests that the prevalence and incidence of dementia in some Western countries are stable or declining, which may be interpreted by reductions in absolute inequalities including improvement in education [10].

Subjective cognitive decline (SCD) refers to a condition that cognitively normal individuals reported they have a reduced cognitive function [11, 12]. There is growing evidence supports that individuals with SCD are at an increased risk of developing AD or dementia [13–15]. In addition, previous studies confirmed that SCD is associated with AD pathology [16, 17]. Therefore, individuals with SCD may be a potential target population for AD prevention. A recent study by our group found that higher education was associated with better performance in all cognitive domains in elderly people with SCD and apolipoprotein E ε4 (*APOE ε4*) status does not modify the beneficial effect of education on cognition [18]. However, it is not clear whether there is a differential influence of education on cognition between cognitively normal older adults without SCD, individuals with SCD and patients with cognitive impairment.

Here, we used data from the Sino Longitudinal Study on Cognitive Decline (SILCODE) project to examine the effect of education on cognition in cognitively normal older adults without SCD (normal control), subjects with SCD and cognitive impairment, respectively. Furthermore, we explored whether the *APOE ε4* status would modify those effects.

Methods

Standard protocol approvals, registrations and patients consents

The study protocol was approved by the medical ethics committee of Xuanwu Hospital of Capital Medical University, Beijing, China, and all the participants gave their written informed consent before any study procedures began.

Participants

We included 544 participants in the present study. The sample was selected from the SILCODE project, an observational longitudinal study carried out in Beijing, which was registered at ClinicalTrials.gov (number NCT03370744). Recruitment of SILCODE started in April 2017 and, at time of data extraction for the present study (August 2020), was still ongoing. The goal of SILCODE is to collect longitudinal data including clinical and imaging data from older adults with SCD and then to develop a model for the ultra-early diagnosis of AD. In addition, SILCODE also recruit healthy controls (HC) and patients with mild cognitive impairment (MCI) and AD dementia. The detailed protocol for the SILCODE project has been published elsewhere [19]. All participants underwent a standardized clinical evaluation at baseline visit including a medical history interview, physical and neurological examinations, neuropsychological testing, laboratory tests, and brain magnetic resonance imaging (MRI) scanning and as well as optional

[^{18}F] florbetapir (AV-45) positron emission tomography (Aβ-PET) or [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET). The same examinations will be performed by each participant during the 15-month follow-up. The HC group had to achieve unimpaired cognitive performance according to the results of standard neuropsychological assessments and no self-reported persistent decline in cognition. The SCD group was defined by the presence of self-perceived continuous cognitive decline compared to a previous normal status and unrelated to other diseases or conditions that would lead to cognitive decline, and failure to meet the following criteria for MCI and AD. The CI group was consisted of both patients with MCI and AD. The diagnostic criteria for MCI are defined by an actuarial neuropsychological method proposed by Jak and Bondi [20] and the clinical diagnostic criteria for AD according to diagnostic guidelines established by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21]. All the participants were required to be aged between 60 and 80 years old and had at least 6 years of education. Further requirements were Mandarin- speaking and right-handed. Here, we included n=186 HC, n=279 SCD subjects and n=79 CI patients for the present study. For details see figure 1 as a flowchart.

Clinical and cognitive function assessments

A paper-printed case report form (CRF) was used to record demographic features (name, birthdate, sex, education, occupation, ethnic origin, residential address and contact information etc.), medical history (particularly including history of hypertension, diabetes, dyslipidemia, etc.), biochemical examination, results of a battery of neuropsychological tests and clinical diagnosis for each participant at the baseline and at different visits.

A standardized neuropsychological test battery was used to assess performance in 3 cognitive domains: episodic memory (Auditory Verbal Learning Test-Huashan version long-delayed free recall [AVLT-H-N5] and recognition [AVLT-H-N7]) [22], speed/executive function (Shape Trailing Test A [STT-A] and B [STT-B]) [23], language (Animal Fluency Test [AFT]; Boston Naming Test [BNT]) [24,25]. And Montreal Cognitive Assessment-Basic (MoCA-B) scores were used as an index of global cognitive condition [26]. To obtain a total test score of cognitive performance, all raw neuropsychological test scores were first converted into Z scores calculated by subtracting the score from the mean test score and dividing it by the standard deviation of initial test scores, and then the total test score was expressed as a global composite z-scores created by averaging all neuropsychological test z-scores.

APOE genotyping

A fasting blood sample was drawn from each participant in the department of laboratory, Xuanwu Hospital of Capital Medical University at the baseline visit. A part of the blood sample was used for analysis of the level of blood glucose, blood lipids, anti-syphilis, homocysteine, folic acid, vitamin B12, thyroid hormone, hemoglobin, blood coagulation and the other part was used to determine the apolipoprotein E (*APOE*) gene polymorphism status. *APOE* was genotyped using the standard Sanger sequencing method (Sangon, Shanghai, China) with the following primers: 5'-

ACGCGGGCACGGCTGTCCAAGG-3' (forward) and 5'-GGCGCTCGCGGATGGCGCTGA-3' (reverse). *APOE* was amplified using the following conditions: 1 cycle at 98 °C for 10 s, 35 cycles at 72 °C for 5 s, and 1 cycle at 72 °C for 5 min. Polymerase chain reaction (PCR) was performed in a final volume of 30 μl containing 10 pmol of forward and reverse primers, and 50 ng of genomic DNA template using PrimeSTAR HS DNA polymerase with GC Buffer (Takara Bio, Kusatsu Shiga, Japan). In the present study, *APOE* genotype was dichotomized into individuals with 1 or 2 copies of the *ε4* allele (*APOE ε4* carriers) and those without any copies of the *ε4* allele (*APOE ε4* non-carriers).

Statistical analyses

First, Shapiro-Wilk test was used to test continuous variables for normality. Means and standard deviations were reported for normally distributed variables, while non-normally distributed variables were described as median (range). Categorical variables were expressed as number (%). Statistical differences between the three groups were analysed using one-way analysis of variance (*ANOVA*), *Kruskal-Wallis* test or *Chi-square* test. Second, the method of simple linear correlation analysis was employed to measure the association between education and raw score of all neuropsychological tests including AVLT-H-N5, AVLT-H-N7, STT-A, STT-B, AFT, BNT and MoCA-B. Third, we used multiple linear regression model, adjusted for age, sex, the presence of hypertension, diabetes, dyslipidemia, and *APOE ε4* status, to examine the effect of education on cognition in the total sample with the raw score of neuropsychological tests as the dependent variable and education as independent variable. Next, we examined whether the effect of education on cognition differed according to different groups, by performing previous multiple linear regression analysis in HC group (n=186), SCD group (n=279), and CI group (n=79). Then, we presented the effect of education on the global composite score of cognitive performance in the total sample and three different groups, respectively. Furthermore, we explored whether the *APOE ε4* status would modify the effect of education on the global composite score among three different groups. Regression diagnostics were performed to ensure the assumptions for linear regression were met. Residuals were normally distributed. Durbin-Watson test statistics indicated independence of observations and heteroscedasticity was in conformance with test assumptions (results not shown). The “PerformanceAnalytics”, “tableone”, “forestplot” and “effects” packages in R 3.6.3 software (https://www.r-project.org) were used to perform all the analyses. The significant level was set at $p< 0.05$ (2-sided).

Results

Subject characteristics

In Table 1, we showed the demographic and clinical characteristics of the total sample and according to three different groups. The sample consisted predominantly of women (64.5%). The average age was 66 years. The mean years of education was 12.3. The proportion of *APOE* ε4 carriers was 24.4%. There were no differences in the prevalence of hypertension, diabetes mellitus and dyslipidemia between the three groups. However, significant differences in sex, age, education and all of neuropsychological measures

were observed between groups. Specifically, post-hoc tests showed that the proportion of women in the SCD group was higher than the other two groups, while the years of education in the CI group were lower than the other two groups. Regarding age, the CI group was older than the SCD group, but there was no difference between HC and SCD group, nor between HC and CI group. Overall, the CI group performed worse than other two groups on all neuropsychological tests. In addition, there was a relatively poor performance in AVLT-H-N5, BNT and MoCA-B in the SCD group when compared with the NC group.

Effects of education on neuropsychological test scores

Simple linear correlation analysis revealed a modest association between education and all neuropsychological test scores in the total sample (AVLT-H-N5: r=0.21, AVLT-H-N7: r=0.16, STT-A: r=-0.27, STT-B: r= -0.20, AFT: r=0.29, BNT: r=0.33, MoCA-B: r=0.33, all p<0.001), in HC group (AVLT-H-N5: r=0.17, AVLT-H-N7: r=0.16, STT-A: r=-0.18, STT-B: r= -0.28, AFT: r=0.19, BNT: r=0.35, MoCA-B: r=0.23, all p<0.05), in the SCD group (AVLT-H-N5: r=0.19, AVLT-H-N7 r=0.14, STT-A: r=-0.18, STT-B: r= -0.12, AFT: r=0.36, BNT: r=0.2, MoCA-B: r=0.32, all p<0.05), while there was a significant correlation between education and AVLT-H-N5 (r=-0.25, p<0.05), AVLT-H-N7 (r=-0.23, p<0.05) and STT-A (r=-0.23, p<0.05) in CI group.

Multiple regression analyses with adjustment for age, sex, the presence of hypertension, diabetes, dyslipidemia, and *APOE ε4* status revealed a positive effect of on all neuropsychological test scores for total subjects (all p<0.001; Figure 2). Then, we stratified the sample according to three different groups and performed multiple regression analyses with adjustment for age, gender, the presence of hypertension, diabetes, dyslipidemia in three subgroups. Subgroup analyses revealed that education showed a positive effect on all neuropsychological test scores in HC and SCD group (p<0.05; Figure 3), except for the effect of education on STT-A in the HC group (p=0.069, Figure 3). And there was no significant association between education and all neuropsychological test scores in the CI group (p>0.05, Figure 3), except for there was a positive effect of education on STT-A (p=0.013, Figure 3).

Next, we presented the effect of education on the total test score expressed as a global composite z-scores in the total sample and according to three different groups, respectively. As years of educational attainment increased, the total test score increased in the total samples (Figure 4a), HC and SCD group (Figure 4b). However, as years of educational attainment increased, the total test score decreased in the CI group (Figure 4b). Finally, we explored whether the *APOE ε4* status would modify those effects of education on cognition among three different groups. Figure 5 shows that there was a similar effect of education on cognition in the HC group regardless of the *APOE ε4* status. However, the *APOE ε4 allele* does attenuate the positive effect of education on cognition in *APOE ε4* carriers with SCD group in comparison with the *APOE ε4* non-carriers with SCD group. And the negative effect of education on cognition was maintained in *APOE ε4* carriers with CI group when compared with the *APOE ε4* non-carriers with CI group.

Table 1
Demographic and clinical characteristics of the study participants

	Total sample (n = 544)	HC (n = 186)	SCD (n = 279)	CI (n = 79)	*P* value	Post-hoc paired comparisons		
						SCD VS HC	CI VS HC	CI VS SCD
Female, n(%)	351 (64.5)	108 (58.1)	203 (72.8)	40 (50.6)	**< 0.001**†	**0.002**	0.293	**0.001**
Age, y	66 (63, 69.3)	66 (63, 70)	65 (62, 69)	67 (63, 72)	**0.009**‡	0.052	0.234	**0.024**
Education, y	12.3 (2.9)	12.3 (3)	12.5 (2.8)	11.4 (3)	**0.01**§	0.362	**0.026**	**0.003**
AVLT-H-N5	6.4 (2.5)	7.2 (2)	6.8 (2.1)	3.4 (2.7)	**< 0.001**§	**0.019**	< **0.001**	**< 0.001**
AVLT-H-N7	22 (21, 24)	23 (22, 24)	22 (22, 24)	18 (6.5, 21)	**< 0.001**‡	0.566	**< 0.001**	< **0.001**
STT-A	60 (50, 76)	59 (50, 73)	57 (48, 71.5)	93 (69, 120)	**< 0.001**‡	0.216	< **0.001**	< **0.001**
STT-B	143 (118, 178)	141.5 (115, 167.5)	136 (114.5, 159.5)	222 (168, 259.5)	< **0.001**‡	0.414	< **0.001**	< **0.001**
AFT	18.5 (4.6)	19.1 (4.3)	19.2 (4.5)	14.9 (4.3)	< **0.001**§	0.739	< **0.001**	< **0.001**
BNT	25 (23, 27)	26 (24, 28)	25 (23, 27)	22 (19, 24)	< **0.001**‡	**0.015**	< **0.001**	< **0.001**
MoCA-B	25 (23, 27)	26 (24.3, 27)	26 (24, 27)	21 (20, 23)	**< 0.001**‡	**0.029**	**< 0.001**	**< 0.001**
Hypertension, n(%)	203 (37.3)	66 (35.5)	100 (35.8)	37 (46.8)	0.166†			
Diabetes, n(%)	76 (14)	26 (14)	37 (13.3)	13 (16.5)	0.77†			
Dyslipidemia, n(%)	215 (39.5)	62 (33.3)	121 (43.4)	32 (40.5)	0.093†			
APOE ε4 status[a], n(%)	127 (24.4)	34 (19.2)	67 (24.5)	26 (36.6)	**0.015**†	0.227	**0.019**	0.088

	Total sample (n = 544)	HC (n = 186)	SCD (n = 279)	CI (n = 79)	*P* value	Post-hoc paired comparisons		
						SCD VS HC	CI VS HC	CI VS SCD

HC healthy controls, *SCD* subjective cognitive decline, *CI* cognitive impairment, *AVLT-H-N5* Auditory Verbal Learning Test-Huashan Version for long-delayed free recall, *AVLT-H-N7* Auditory Verbal Learning Test-Huashan version long-delayed free recognition, *STT-A* Shape Trail Test A, *STT-B* Shape Trail Test B, *AFT* Verbal Fluency Test (animal), *BNT* Boston Naming Test, *MoCA-B* Montreal Cognitive Assessment-Basic. *APOE ε4* apolipoprotein *ε4*.

[a] *APOE ε4* status included 521 total samples, 177 HC, 273 SCD subjects and 91 CI patients.

[†]The p value was calculated using *Chi-square* test.

[‡]The p value was calculated using *Kruskal-Wallis* test.

[§]The p value was calculated using one-way *ANOVA*.

Discussion

In the present study, we investigated whether the education shows a different effect on cognitive performance in HC, SCD and CI group. Furthermore, this study examined whether the *APOE ε4* allele regulates those effects among three different groups. The main findings of our study are (1) education has a positive effect on cognition in the total sample, (2) the positive effect of education on cognition is found in HC and SCD group, while education has a negative effect on cognition in CI group that as years of educational attainment increased, the cognitive performance deteriorated, (3) the *APOE ε4* allele has a differential role in regulating the effect of education on cognition in three different groups. Specifically, the *APOE ε4* allele does not modify the positive effect of education on cognition in the HC group, but the *APOE ε4* allele weaken that beneficial effect in the SCD group and maintain the negative effect in the CI group.

In a recently published work, we found that high education has a beneficial impact on cognition in subjects with SCD [18]. We extend on that finding by demonstrating that high education has a differential effect on cognition across the spectrum of AD, as high education has a positive effect on cognition in HC, SCD group and a negative effect on cognition in the CI group. Such difference in the effect of education on cognitive symptoms during different disease stage of AD can be explained by the theory of cognitive reserve (CR). The concept of CR grew out of a marked disjunction between an individual's clinical manifestation and the degree of brain pathology or damage [27]. Foe example, among individuals matched for the amount of AD neuropathologic process, some people develop cognitive impairment while others do not, which can be attributed to differences in CR [28]. The concept of CR refers to an ability that uses alternate paradigms or functional brain process more efficiently to maintain function in response to brain changes or damage [27, 29]. As CR is a theoretical construct, it is not measured directly but rather the more general sociobehavioral indices like years of education, IQ, occupational attainment,

leisure activities, and other protective factors used as a surrogate [29]. According to the theory of CR in AD [30], individuals with high CR can tolerate more AD pathology in the absence of clinical symptoms and therefore, the point at which cognitive performance begin to decline will be delayed. However, the rate of decline in cognition is more rapid in individuals with high CR than those with low CR after they present with the clinical presentation of AD. Indeed, longitudinal studies have confirmed that greater CR attenuated clinical progression at an early stage of AD, while accelerated cognitive decline at an advanced stage AD [31, 32]. In particular, a 7-year follow-up study found that high CR delayed progression to MCI about 9 years in SCD subjects in comparison to SCD subjects with low CR, while high CR was a risk factor for progression to AD dementia in MCI patients with *APOE ε4* [32]. Therefore, our findings that education has a dual role at different stages of AD are in line with the theory of CR.

We further found that the differential effect of education on cognition is subjected to regulation by the *APOE ε4* allele across the spectrum of AD. The *APOE ε4* allele imposed no regulatory action in HC group, while the beneficial effect of education is reduced in SCD group with *APOE ε4* and the negative effect of education is retained in CI group with *APOE ε4*. Genetically, *APOE ε4* allele represents a strongest risk factor for AD [33, 34]. Previous studies reported that individuals with *APOE ε4* heterozygosity were at 3-4-fold increased risk of AD, and with *APOE ε4* homozygosity was at 9-15-fold increased risk [35, 36]. The mechanism that link *APOE ε4* status with AD risk is might be mediated by Aβ-dependent and Aβ-independent pathways including tau pathology, inflammatory responses and breakdown of the blood–brain barrier [37–39]. Therefore, one explanation for our findings modulated by the *APOE ε4* status is that subjects with *APOE ε4* allele who may harbour severe pathological lesions is more sensitive to the depletion of CR than *APOE ε4* non-carriers. Previous study has identified that the beneficial effect of education on cognitive function can not be modified by the *APOE ε4* status in healthy older adults with more than 4-year period follow-up [40]. In individuals with SCD, the *APOE ε4* allele significantly increased the risk of conversion to AD dementia [41], while at the symptomatic stage, the *APOE ε4* allele accelerate progression from MCI to AD dementia only in *APOE ε4* carriers [32]. However, further studies will be required to understand the mechanisms underlying the role of *APOE ε4* allele in regulating the effect of education on cognition across the spectrum of AD.

Limitation

The strength of this study was a relatively large sample size and comprehensive neuropsychological assessment. However, the study also has its limitations. First, current study was a cross-sectional design, and therefore, longitudinal data is needed to further confirm whether high education has a differential effect on cognition in Alzheimer's continuum and that could be regulated by the *APOE ε4* allele. Second, the present study is lack of biomarkers of AD. It is a very important issue to clarify if different AD pathology profiles are differentially related to education and cognitive change or clinical outcomes. Third, the participants in our study were relatively well-educated and females were relatively over represented. Therefore, such differences need to be taken into account when those results are extrapolated to other populations.

Conclusions

Our data indicates that high education may delay the progression from SCD to cognitive impairment, while it could accelerate cognitive deterioration in patients with cognitive impairment, which are in line with the model of CR. Furthermore, the differential effect of education on cognition in Alzheimer's continuum is regulated by the *APOE ε4* status. Therefore, no effective treatment available for AD makes it urgent to improve the popularization of education, which may be a potentially promising approaches to preventing AD.

Abbreviations

AD: Alzheimer's disease, Aβ: β-amyloid, Aβ-PET: [^{18}F] florbetapir (AV-45) positron emission tomography, APOE: apolipoprotein E, AFT: Verbal Fluency Test, ANOVA: analysis of variance, AVLT-H-N5: Auditory Verbal Learning Test-Huashan version long-delayed free recall, AVLT-H-N7: Auditory Verbal Learning Test-Huashan version long-delayed free recognition, BNT: Boston Naming Test, CRF: case report form, CI: cognitive impairment, FDG-PET: [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography, HAMA: Hamilton Anxiety Scale, HAMD: Hamilton Depression Rating Scale, HC: healthy controls, MCI: mild cognitive impairment, MoCA-B: Montreal Cognitive Assessment-Basic, MRI: magnetic resonance imaging, NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, PAR: population-attributable risk, PCR: Polymerase chain reaction, SCD: Subjective cognitive decline, SILCODE: the Sino Longitudinal Study on Cognitive Decline. STT-A: Shape Trail Test A, STT-B: Shape Trail Test B.

Declarations

Ethics approval and consent to participate

The protocol of the study was approved by the medical ethics committee of Xuanwu Hospital of Capital Medical University. Beijing, China, and all participants gave their written informed consent before any study procedures began.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GC collected, analyzed, interpreted the data and drafted this manuscript. KY revised this manuscript. YH designed this study and revised this manuscript. All authors read and approved the final manuscript.

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Figures

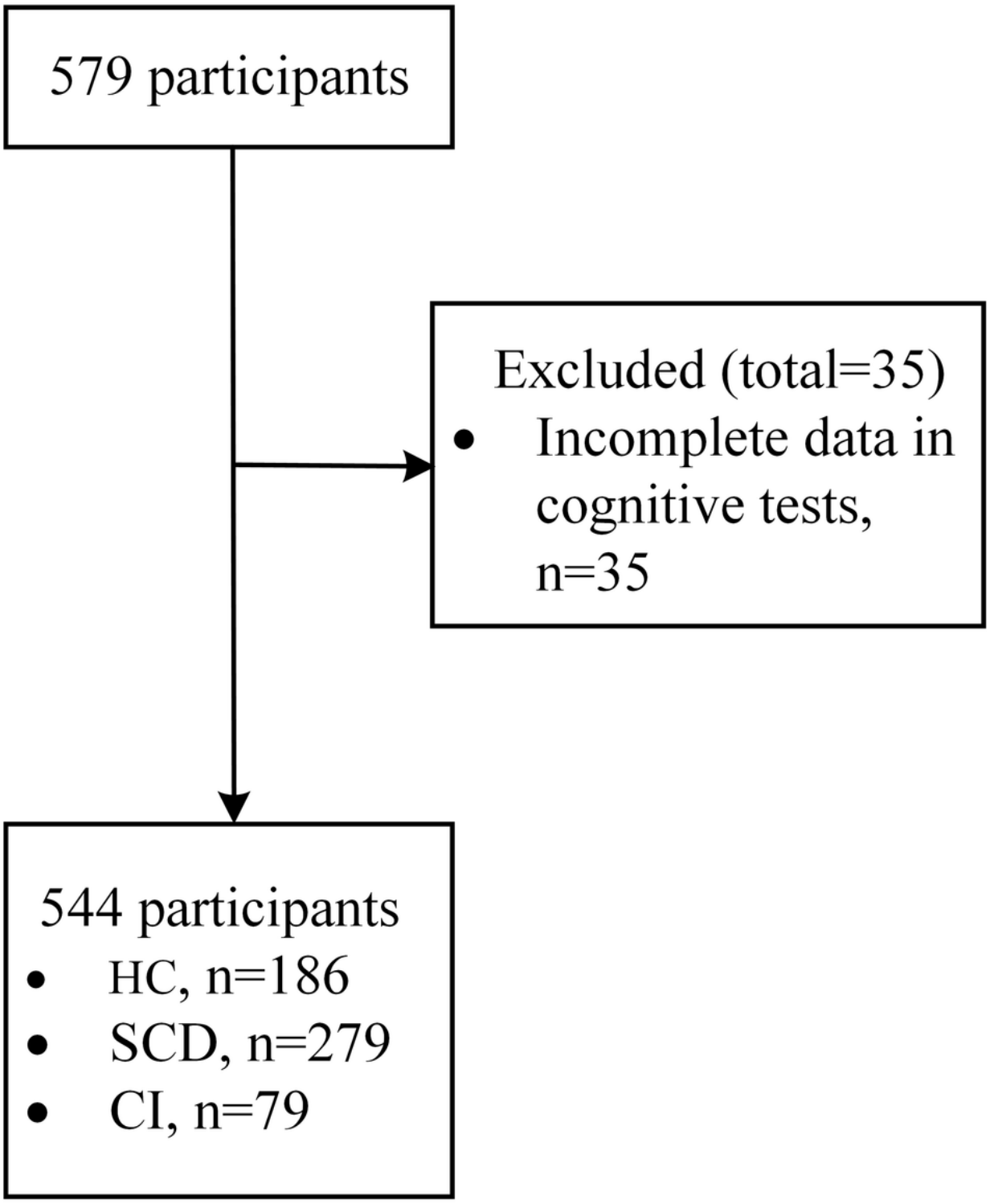

Figure 1

Flowchart of the sample selection. HC healthy controls, SCD subjective cognitive decline, CI cognitive impairment.

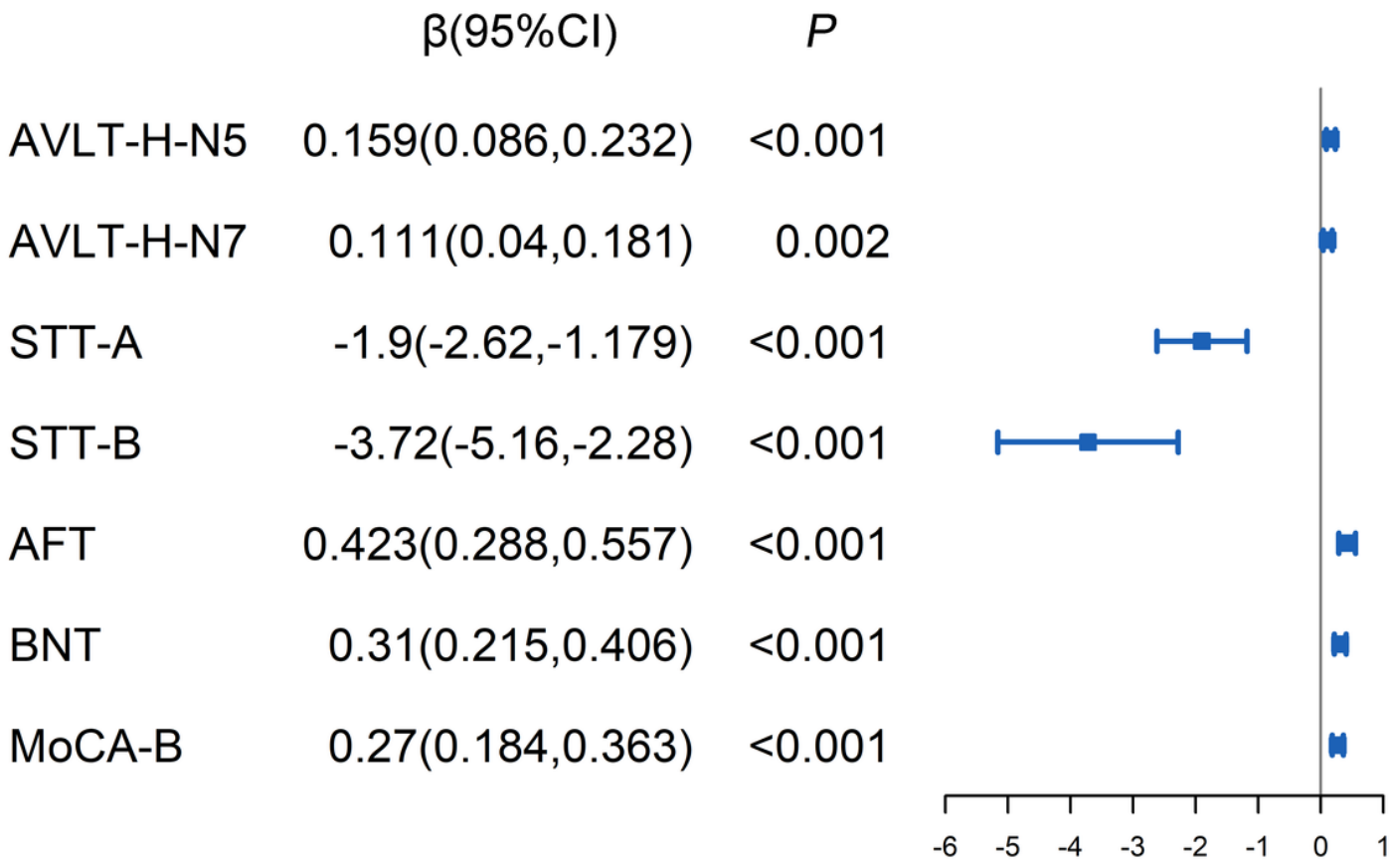

Figure 2

Effect sizes of education on neuropsychological tests in the total sample. β partial regression coefficients, CI confidence interval, AVLT-H-N5 Auditory Verbal Learning Test-Huashan Version for long-delayed free recall, AVLT-H-N7 Auditory Verbal Learning Test-Huashan version long-delayed free recognition, STT-A Shape Trail Test A, STT-B Shape Trail Test B, AFT Verbal Fluency Test (animal), BNT Boston Naming Test, MoCA-B Montreal Cognitive Assessment-Basic.

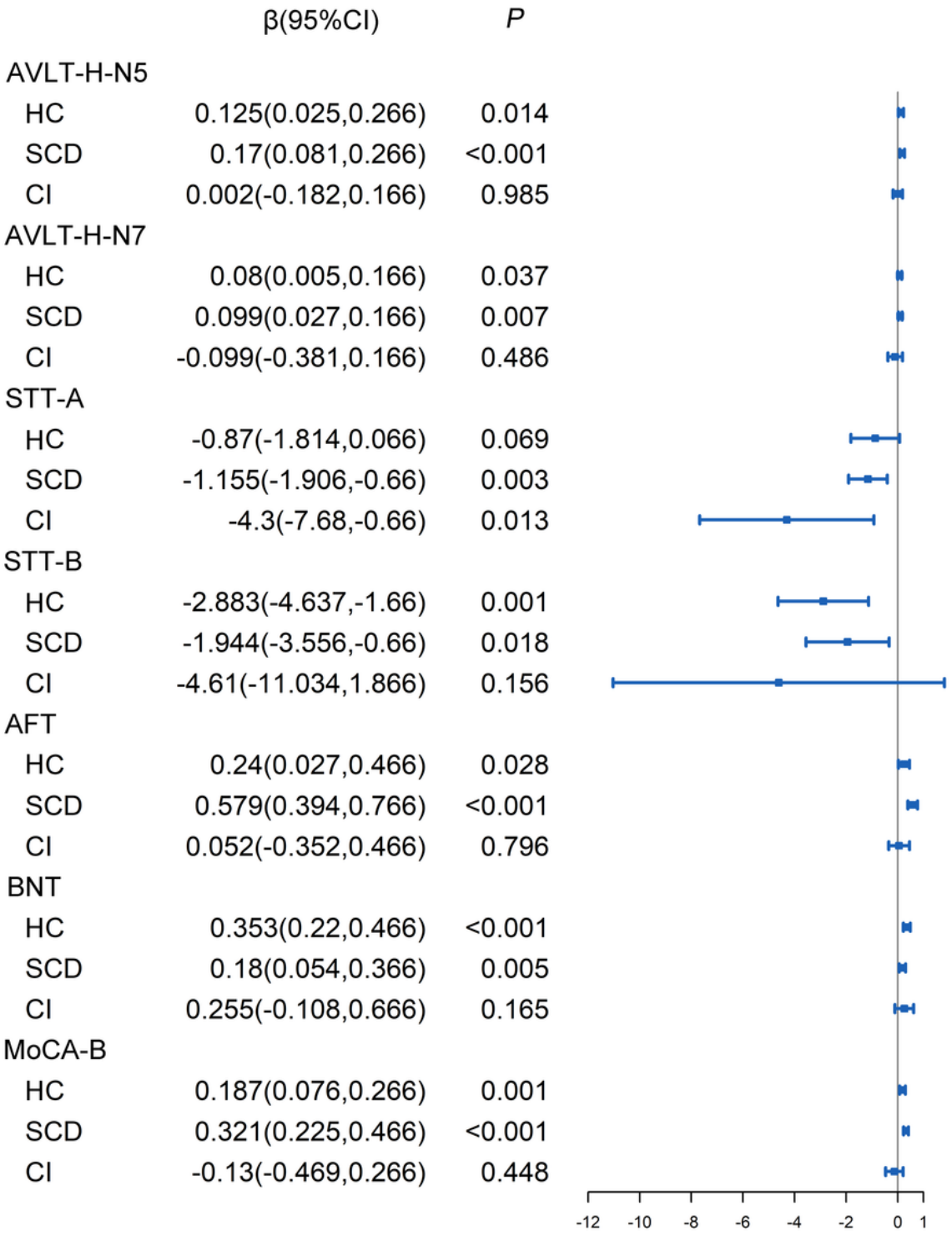

Figure 3

Effect sizes of education on neuropsychological tests in HC, SCD and CI group. β partial regression coefficients, CI confidence interval, AVLT-H-N5 Auditory Verbal Learning Test-Huashan Version for long-delayed free recall, AVLT-H-N7 Auditory Verbal Learning Test-Huashan version long-delayed free recognition, STT-A Shape Trail Test A, STT-B Shape Trail Test B, AFT Verbal Fluency Test (animal), BNT Boston Naming Test, MoCA-B Montreal Cognitive Assessment-Basic.

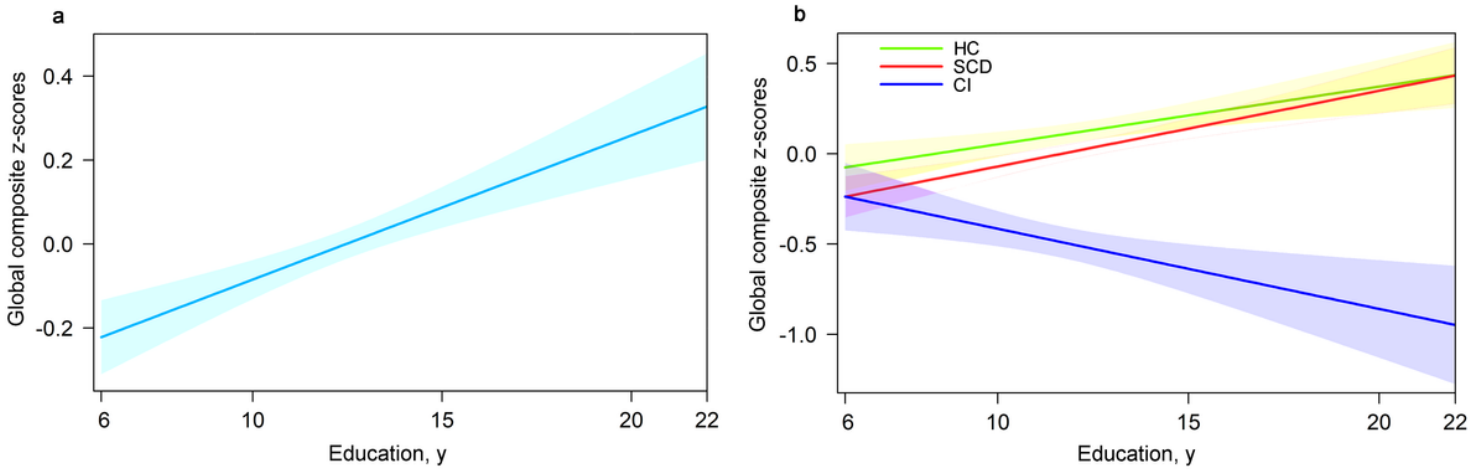

Figure 4

Predicted global composite z-scores. a For the total sample, b For the three subgroups. HC healthy controls, SCD subjective cognitive decline, CI cognitive impairment.

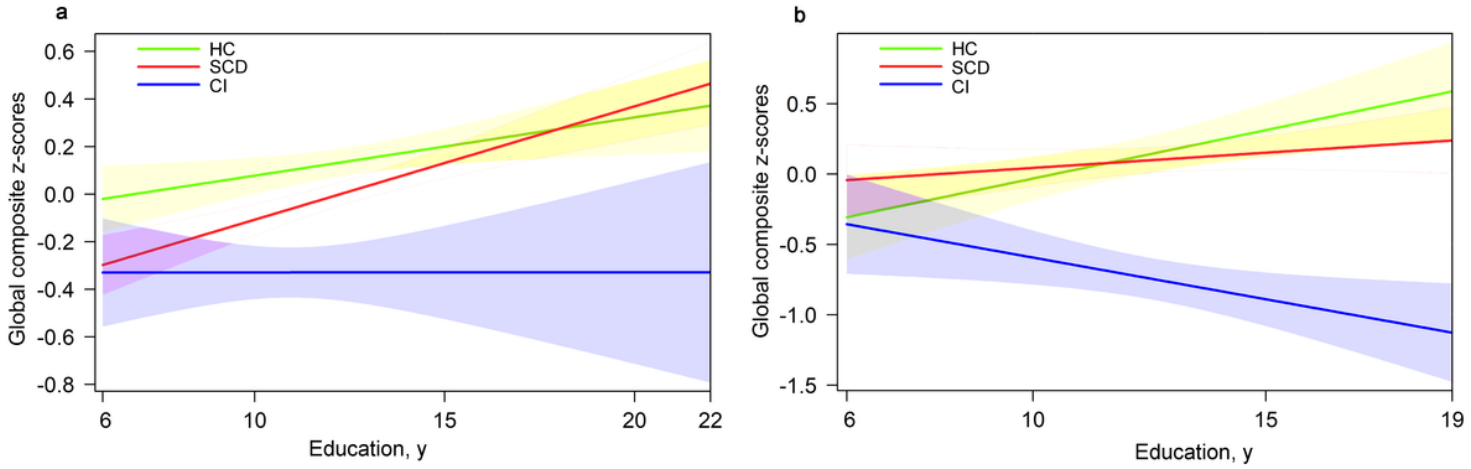

Figure 5

Predicted global composite z-scores among the three subgroups according to the APOE ε4 status. a APOE ε4 non-carriers, b APOE ε4 carriers. HC healthy controls, SCD subjective cognitive decline, CI cognitive impairment.