Association of apolipoprotein E epsilon 4 and cognitive impairment in adults living with human immunodeficiency virus: a meta-analysis

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Abstract

Background: It is controversial whether the apolipoprotein E epsilon 4 allele (*APOE ε4*) is a risk gene for human immunodeficiency virus (HIV)-related neurocognitive impairment. This meta-analysis aimed to summarize evidence of the associations between *APOE ε4* and cognitive impairment in people living with HIV (PLWH).

Methods: Our study conducted a systematic literature search of PubMed, Web of Science, Embase, Google Scholar, and ProQuest for studies published before April 11, 2022 that evaluated associations between *APOE ε4* and cognitive impairment in adult PLWH (aged ≥18 years). We calculated pooled odds ratios (ORs) of global cognitive impairment and 95% confidence intervals (CIs) and standardized mean differences (SMDs) for specific cognitive domains between *APOE ε4* carriers and non-carriers. Subgroup meta-analyses were used to evaluate the result profiles across different categorical variables.

Results: Twenty studies met the inclusion criteria, including 19 that evaluated global cognitive impairment. *APOE ε4* was significantly associated with global cognitive impairment in PLWH (OR = 1.36, 95% CI = [1.05, 1.78], number of estimates [k] = 19, $P = 0.02$, random effects). Subgroup meta-analysis based percentage of females showed evident intergroup differences in global cognitive performance between ε4 carriers and non-carriers ($P = 0.015$). *APOE ε4* carriers had lower cognitive test scores than non-carriers in all seven cognitive domains, including fluency (SMD = −0.51, 95% CI = [−0.76, −0.25], $P < 0.001$, $k = 4$, $I^2 = 0\%$), learning (SMD = −0.52, 95% CI = [−0.75, −0.28], $P < 0.001$, $k = 5$, $I^2 = 0\%$), executive function (SMD = −0.41, 95% CI = [−0.59, −0.23], $P < 0.001$, $k = 8$, $I^2 = 0\%$), memory (SMD = −0.41, 95% CI = [−0.61, −0.20], $P < 0.001$, $k = 10$, $I^2 = 36\%$), attention/working memory (SMD = −0.34, 95% CI = [−0.54, −0.14], $P = 0.001$, $k = 6$, $I^2 = 0\%$), speed of information processing (SMD = −0.34, 95% CI = [−0.53, −0.16], $P < 0.001$, $k = 8$, $I^2 = 0\%$), and motor function (SMD = −0.19, 95% CI = [−0.38, −0.01], $P = 0.04$, $k = 7$, $I^2 = 0\%$).

Conclusions: Our meta-analysis provides significant evidence that *APOE ε4* is a risk genotype for HIV-associated cognitive impairment, especially in cognitive domains of fluency, learning, executive function, and memory. Moreover, the impairment is sex specific.

Meta analysis registration: PROSPERO, CRD 42021257775.

Keywords: Apolipoprotein E epsilon 4; Cognition; Gene; Human immunodeficiency virus; Meta-analysis

Introduction

According to a report from the United Nations Program on human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), there were 1.5 million new HIV infections and 37.7 million people living with HIV (PLWH) at the end of 2020.[1] With the widespread use and earlier initiation of antiretroviral therapy (ART), the life expectancy of PLWH has approached the general population with suppression of viral replication and restoration of immune function.[2,3] However, HIV-associated neurocognitive disorder (HAND), which results in poorer life quality and a rising death rate of PLWH, remains an unsolved problem and increases the public health burden with the meta-analyses reporting prevalence over 40%.[4,5] The underlying mechanisms remain unclear, and several possible explanations include neuroinflammation, ART toxicities, cerebrospinal fluid (CSF) HIV ribonucleic acid (RNA) escape and HIV persistence, lifestyle factors, aging, comorbidities, mental health and stigma, and legacy effects from HIV and its

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complications.[6-8] Recently, Alzheimer's disease (AD)-like perturbations in the neuropathogenesis of HAND have been noticed.[9] Additionally, an increasing number of studies have begun to elucidate the mechanism of cognitive impairment caused by HIV infection from the perspective of AD.

Apolipoprotein E epsilon 4 allele (*APOE ε4*) is a known genetic risk factor for late-onset sporadic AD, atherosclerosis, and worse clinical outcomes after traumatic brain injury.[10] In people not living with HIV, *APOE ε4* can reduce amyloid-β (Aβ) clearance,[11-13] increase Aβ production,[11-13] and induce central nervous system (CNS) phosphorylated tau (p-tau) protein accumulation,[14-16] which is the dominant framework of AD pathology.[13] Similarly, studies on HAND have revealed that *APOE ε4* moderates abnormal brain Aβ and p-tau metabolism, which may be associated with neurocognitive impairment.[17-19] In PLWH, CSF Aβ is reduced in individuals suffering from neuronal complications;[20] although HIV protein or particle exposure to the brain influences the regulation of Aβ and p-tau metabolism pathways directly or indirectly;[21-24] the role of *APOE ε4* in HAND has always been of interest. Moreover, resting-state functional magnetic resonance imaging (MRI) confirmed that *APOE ε4* is associated with reduced memory and functional connectivity within the memory network in PLWH.[25] On the other hand, *APOE ε4* moderates the relationship between inflammatory responses, brain structural and functional networks, and cognitive function of HIV-seronegative people.[26,27] Furthermore, systemic inflammation and neuroinflammation are very common in HAND. Studies have also reported that *APOE ε4* may decrease brain volumes and enhance the systemic progression of HIV infection.[28-30] Therefore, the *ε4* gene may promote the development of neurocognitive impairment in PLWH by enhancing the inflammatory response. Although the molecular mechanism of *APOE ε4* in HAND has remained unclear up to the present, taken together, it seems that *APOE ε4* may be associated with HAND by regulating the Aβ, p-tau, and inflammation pathways.

However, the associations between ε4 and HAND in cohort and cross-sectional studies have been inconsistent: some results found that ε4 is associated with a higher risk of neurocognitive impairment or dementia,[31-34] while others found no associations.[29,35-39] In addition, the progression of ε4-related effects may start in specific cognitive domains in HAND and eventually become a global neurocognitive disorder. For example, impaired episodic memory is the cognitive hallmark in AD, and ε4 is associated with reduced episodic memory in HIV-uninfected and HIV-infected "cognitively normal" adults,[25,40-43] suggesting the presence of early neural injury to the memory network in some of the "cognitively normal" ε4 carriers. Moreover, reduced executive function is also highly prevalent.[34,40,42,44] Therefore, focusing on the relationships between particular cognitive domain impairments and ε4, rather than global cognitive impairment and ε4 based on diagnostic criteria, may be more sensitive for discovering the role of ε4 in the pathogenesis of HAND.

Thus, we conducted this meta-analysis to assess the relationships between *APOE ε4* and global and domain-specific cognitive impairments in PLWH. We aimed to explore whether *APOE ε4* is a risk genotype for HAND and whether neurocognitive performance is significantly different between *APOE ε4* carriers and non-carriers in PLWH.

Methods

This work is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [Supplementary Table 1, http://links.lww.com/CM9/B373].[45] The protocol was registered and is available at PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021257775). The PICOS method was used to develop our research questions[46]: (A) Is there an association between the *APOE ε4* genotype and global cognitive impairment in adult PLWH? (B) Which cognitive domains are the most adversely affected by the *APOE ε4* genotype in PLWH?

Search strategy

We searched five electronic databases, including PubMed, Embase, Google Scholar, Web of Science, and ProQuest, from their inception to April 11, 2022. The language was limited to English. The search terms were (APOE OR "apolipoprotein E") AND (HIV OR "human immunodeficiency virus" OR "AIDS" OR "Acquired Immune Deficiency Syndrome"). When screening Google Scholar results, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions Reference, the first 1000 relevancy-ranked list of identified papers were screened to supplement the database searches, avoiding potential missed data sources.[47,48] When screening ProQuest, we only searched academic dissertations to cover the gray literature. The reference lists of selected articles and related reviews were screened to avoid missing entries.

Eligibility criteria

Studies were included in the meta-analysis if they met the following eligibility criteria: (1) all participants were adults (aged ≥18 years) who were able to complete a neuropsychological test; (2) the study reported cognitive outcomes stratified by *APOE ε4* carriers and non-carriers among PLWH; and (3) the study reported quantitative data that allowed for the calculation of odds ratios (ORs) or standardized mean differences, such as the proportion of cognitive impairment or mean and standard deviation (SD) of scores measured by neuropsychological tests. We excluded studies that (1) were animal research; (2) were duplicate studies; (3) lacked cognitive assessment outcome data; (4) used a single test to screen participants' cognitive abilities; and (5) were case reports, review articles, theoretical articles, or non-peer-reviewed materials.

Two independent reviewers conducted the initial screening process, which involved screening the titles, abstracts, and keywords based on the preset eligibility. Full-text papers were downloaded and assessed whenever the title,

abstract, and keywords suggested that the paper was likely related to our research topic. Final eligibility was assessed based on full-text reviews, and disagreements were resolved by discussion.

Data extraction

The extracted information included first author, publication year, country, sample size, mean age, factors associated with HAND and *APOE ε4* function (including proportion of female participants, education years, current and nadir CD4$^+$ T cell counts, proportion using ART, percent with hepatitis C virus (HCV) coinfection, HIV duration, and proportion with undetectable virus load),[25,49-54] cognitive domain(s) assessed, neuropsychological tests, number of individuals with cognitive impairment, mean and SD values for neuropsychological test results, and other salient factors for each included study. ORs were calculated from the raw numbers of individuals with cognitive impairment or other data that could be pooled for both *APOE ε4* carriers and non-carriers among PLWH. Standard mean differences (SMDs) were calculated from original data for cognitive domain evaluation. We only extracted and recorded baseline data for cohort or longitudinal studies. Data were independently extracted by two reviewers (TTM and JQW) and then compared and aggregated to ensure accuracy.

Statistical analysis

Data analysis was performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA), and the funnel plot was constructed using Review Manager Software, version 5.4 (Cochrane Collaboration, Copenhagen, Denmark). We aimed to compare the global and domain-specific cognitive abilities of *APOE ε4* carriers and non-carriers. The ORs of having cognitive impairment between carriers and non-carriers were used in global cognitive meta-analyses. As cognitive domain performance was measured by different instruments across our included studies, we selected SMDs to combine continuous data for the cognitive domain meta-analyses.[55] We measured heterogeneity among studies using Cochrane's Q test and I^2 test.[56] According to Cochrane's strategies for addressing heterogeneity,[57] we performed these meta-analyses using the random effects model. Publication bias was evaluated by Begg's funnel plot and Egger's linear regression test.[58] Potential publication bias was adjusted by the trim and fill method. The threshold for statistical significance was two-tailed $P < 0.05$.

Quality assessment

Two reviewers independently evaluated the methodological quality of the included studies using the modified 11-item Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[59] This assessment tool consists of 14 items providing a total quality score of information bias, selection bias, confounding bias, and measurement bias.[59] Based on the original condition of the included articles, the checklist entries could be answered with "yes," "no," "cannot determine," "not reported," or "not applicable."

As some of the items in this checklist are only applicable to cohort studies and not to cross-sectional studies, we eliminated the non-applicable items and adjusted the total scores to 11 instead of the original 14.[60,61] The number of "yes" determined the research quality of each study, and sufficient quality was considered to have been attained when the score reached ≥6 points.[61]

Subgroup analysis

To investigate the heterogeneity in the global cognitive impairment meta-analysis, we conducted subgroup meta-analyses with the following factors: (1) age (<50 *vs.* ≥50 years), (2) education level (<12 *vs.* ≥12 years), (3) mean/median of nadir CD4$^+$ T cell counts (<200 *vs.* ≥200 cells/μL), (4) current mean/median CD4$^+$ T cell counts (<500 *vs.* ≥500 cells/μL), (5) female percent, (6) undetectable virus percent, (7) ART proportion, (8) HIV duration, and (9) HCV positive percent. The median was used based on data distributions in studies with continuous variables in the subgroup meta-analyses.

We divided the age subgroups at age 50 based on several studies exploring the association between *APOE ε4* and HAND and identifying ε4-related cognitive decline risk at older ages (≥50 years),[25,38,44,62] but not at younger ages (<50 years).[34] The allocation of the education subgroups was in line with Frascati criteria, which indicated that norm education level (schooling ≥12 years) could drop the cognitive impairment rate.[50] Moreover, nadir CD4$^+$ T cell count <200 cells/μL and current CD4$^+$ T cell count <500 cells/μL indicate a history of or current immunosuppression, both of which are suspected risk factors for HAND.[51] In addition, as female *APOE ε4* carriers may be more likely to develop AD in the HIV-seronegative population,[49] we evaluated the influence of differences in the percentage of female participants. Other indices, such as the proportion using ART, percent with undetectable virus, HIV duration,[52] and HCV status,[63] are likely relevant to the subjects' health condition and influence the progression of neurocognitive decline. Thus, these factors cannot be ignored when analyzing global cognitive differences.

We also conducted a subgroup meta-analysis across cognitive domains to assess differences in specific cognitive domain function between *APOE ε4* carriers and non-carriers among PLWH.

Results

Selection processes

Our research strategy identified a total of 3196 records. After duplicates were removed, 2661 records remained for the title, abstract, and keyword screening process. Title and abstract screening excluded 2619 records for unrelated research topics. Then 42 entries remained for full-text viewing. We excluded 22 items for not matching the inclusion criteria or lacking data. Finally, we identified 20 eligible studies for this meta-analysis. Figure 1 shows the flowchart of study selection.

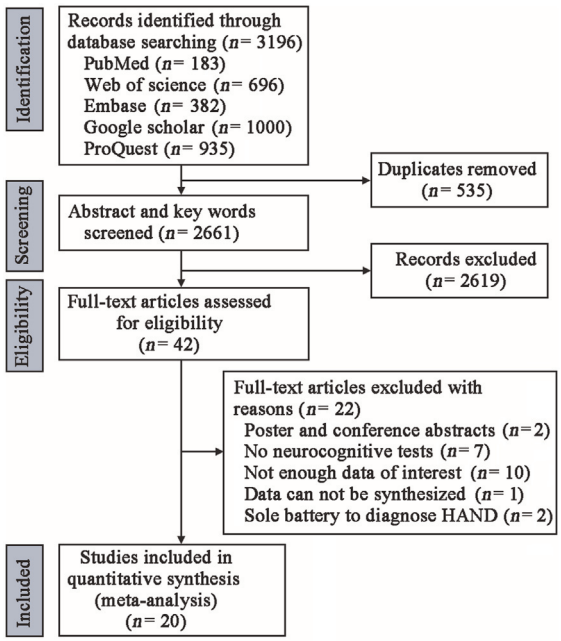

Figure 1: Flow chart of literature search. HAND: Human immunodeficiency virus-associated neurocognitive disorder.

Study characteristics and participants

Of the 20 studies, 19[17,18,25,28,31,33,34,36-38,41-44,62,64-68] were identified as conducting a global cognitive impairment analysis, and 10[25,28,34,41-44,64,65,68] as conducting a cognitive domain analysis. The characteristics of these studies are summarized in Table 1. There were 2671 participants from the 20 studies; 828 were HIV-positive and *APOE ε4* carriers, and the remaining 1843 were HIV-positive and *APOE ε4* non-carriers. Of all studies included in the meta-analysis, 16 were carried out in high-income countries and four in upper-middle income countries. In addition, all included studies were high-quality ones, since all of them obtained ≥9 points. Supplementary Table 2, http://links.lww.com/CM9/B373 provides the quality assessment results of the 20 studies.

Neuropsychological tests

All 20 articles used comprehensive cognitive evaluation tools when assessing global or domain-specific cognitive function. Of the 19 studies included in the global cognitive impairment meta-analysis, 17 studies adopted classic criteria for HAND diagnosis, one adopted comprehensive neuropsychological tests to evaluate the differences in cognitive function, and one defined cognitive impairment according to scores >1.5 SD below the education-, sex-, and age-matched norm in at least two cognitive domains. The classic criteria were the Frascati criteria ($n = 12$),[50] American Academy of Neurology (AAN) criteria ($n = 2$),[69] and global deficit score (GDS) ($n = 3$).[70] However, the thresholds for the GDS criteria were different (2 considered that damage existed when GDS > 0.5 and 1 considered a threshold >0.25).

The GDS considers the number and severity of impairments across all measures, and generally, GDS ≥ 0.5 is classified as having global cognitive impairment.[70] We recognized the reasonableness of three studies with different GDS thresholds because of the different actual conditions of their subjects. The 1991 AAN criteria defined two levels of neurologic manifestations, HIV-associated dementia (HAD) and minor cognitive motor disorder (MCMD), in HIV-infected individuals. According to these criteria, both HAD and MCMD must have marked abnormalities in work or activities of daily living; moreover, mild severe HAD overlapped with MCMD, but they all overlooked the existence of an earlier neurocognitive impairment stage, which may not have developed to the point of interfering with work or daily life. In 2007, the National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke reviewed the adequacy and utility of the AAN criteria and promoted the Frascati criteria, an updated version, to address the issues that restricted a HAND diagnosis.

In addition to global cognitive analysis, we also explored the association between *APOE ε4* and domain-specific cognitive functions. Supplementary Table 3, http://links.lww.com/CM9/B373 provides the detailed cognitive domains and evaluation tools used in the included studies.

Meta-analysis of APOE ε4 and global cognitive impairment

We found a significant association between *APOE ε4* and global cognitive impairment in PLWH (OR = 1.36, 95% confidence interval [CI] = [1.05, 1.78], number of estimates [k] = 19, $P = 0.02$, random effects). Cochrane's Q test and I^2 test showed moderate heterogeneity ($I^2 = 46\%$, $P = 0.01$). Figure 2 shows the pooled OR value and weight for each study. The funnel plot [Supplementary Figure 1, http://links.lww.com/CM9/B373] and Egger's test results (intercept = 1.14, two-tailed $P = 0.21$) showed no significant publication bias in these studies.

Subgroup meta-analyses (global cognitive impairment)

We carefully checked the relevant data to judge the applicability of the literature for subgroup analyses. A significant intergroup result was observed only for the factor female percent ($P_2 = 0.015$). The risk was significantly higher in the group with <11% females (OR = 2.02, 95% CI = [1.45, 2.81], $P < 0.001$, $k = 9$) than in the group with ≥11% females (OR = 1.10, 95% CI = [0.76, 1.58], $P = 0.624$, $k = 9$). This indicated that men with *APOE ε4* had an increased risk of HAND. Other subgroups presented mixed results, all of which had P-values >0.05. Detailed results regarding these intergroup effects and heterogeneity are shown in Table 2.

Meta-analyses of cognitive domain impairments

We conducted assessments of impairments in seven cognitive domains in our meta-analysis. They were executive function, speed of information processing/perceptual speed/psychomotor speed, memory, motor function, attention/working memory, fluency, and learning.

All seven domains showed notably poorer cognitive performance in *APOE ε4*-carrier PLWH ($P < 0.05$).

Table 1: Characteristics of studies included in the meta-analysis.

Study	Country	Design	Diagnostic criteria	Sample size (*n*)	Age (years)	Female (%)	Education (years)	Current/Nadir CD4 (cells/μL)	ART (%)	HCV (%)	HIV duration (months)	Undetectable virus load (%)	Study quality score
Corder *et al*[31]	USA	Longitudinal study	NR*	11 *vs.* 33	32.1	4.5	13.3	377/NR	NR	NR	NR	NR	9
Valcour *et al*[62]	USA	Cohort study	AAN†	52 *vs.* 130	NA‡	10.4	NA§	457/NR	75	NR	NR	56	10
Spector *et al*[33]	China	Longitudinal study	GDS > 0.5‖	43 *vs.* 158	40.2	39.3	5.5	349/252	57	93	NR	36.8	10
Joska *et al*[37]	South Africa	Cross-sectional study	Frascati‖	71 *vs.* 73	29.5	74	10	188/NR	0	NR	NR	NR	10
Sun *et al*[36]	USA	Cross-sectional study	>1.5 SD¶	11 *vs.* 33	50.3	0	14.4	355/NR	100	0	202.8	NR	9
Morgan[64]	USA	Longitudinal study	Frascati	97 *vs.* 179	43	21.3	13.2	NA/NA	67.4	21	NR	43.8	10
Andres *et al*[65]	USA	Cross-sectional study	Frascati	15 *vs.* 33	46.7	6.3	14.3	463/188	NR	NR	142.7	NR	10
Chang *et al*[28]	USA	Cross-sectional study	Frascati	22 *vs.* 47	47.8	8.7	14.6	349/196	79.7	NR	146.3	62.3	10
Soontornniyomkij *et al*[18]	USA	Cohort study	Frascati	15 *vs.* 57	44.4	10.9	12.3	NR/NR	79.1	37.6	NR	NR	10
Bol *et al*[66]	USA	Cohort study	Frascati	74 *vs.* 210	40	NR	NR	108/NR	NR	NR	NR	NR	9
Morales *et al*[41]	USA	Longitudinal study	AAN	5 *vs.* 15	41.4	100	12.9	635/412	80	20	NR	100	10
Hoare *et al*[43]	South Africa	Cross-sectional study	NR	24 *vs.* 19	27.8	73.3	8.8	202/NR	0	NR	NR	NR	10
Morgan *et al*[38]	USA	Cross-sectional study	Frascati	144 *vs.* 322	44.1	46.9	13	NR/175	69.5	27	124.8	46.9	10
Panos *et al*[34]	USA	Cross-sectional study	Frascati	77 *vs.* 182	42.6	15.4	13.3	219/NR	84.6	18.5	NR	NR	10
van Brakel[67]	South Africa	Longitudinal study	GDS > 0.25	55 *vs.* 59	30	80	10	177/NR	0	NR	NR	NR	10
Chang *et al*[42]	USA	Cross-sectional study	Frascati	23 *vs.* 57	47.3	8.8	14.9	452/181	92.5	NR	218.7	58.8	10
Cysique *et al*[17]	Australia	Cross-sectional study	GDS > 0.5	13 *vs.* 29	56.7	11	13.8	597/198	100	NR	246	95.5	9
Mukerji *et al*[68]	USA	Longitudinal study	Frascati	31 *vs.* 77	50	0	NA	514/387	95	14.3	NR	100	10
Wendelken *et al*[44]	USA	Cross-sectional study	Frascati	19 *vs.* 57	64	3.9	16.1	536/206	93.4	NR	240.6	88	10
Yang *et al*[25]	USA	Cross-sectional study	Frascati	26 *vs.* 73	55.6	23.2	14.3	631/187	98	NR	312	81.8	10

* The HIV-1 cohort had been examined for neurologic and other symptoms twice yearly for up to 10 visits during 1988–1993 (AIDS Neurologic Center, Department of Neurology, the University of North Carolina at Chapel Hill), but there was no clear description regarding the definition of global neurocognitive impairment. † AAN criteria (1991). ‡ There were two age groups of all subjects in this study: 85 adults aged ≤40 years in the younger group and 97 adults aged ≥50 years in the older group. § The educational characteristics of the population were as follows: high school or less (≤12 years) = 90, some college (12–16 years) = 79, and college or greater (≥16 years) = 15. ‖ Updated AAN criteria – Antinori *et al*[50]. ¶ The neuropsychological evaluation results were adjusted for educational level, sex, and age. Raw scores were transformed to age-corrected and (where applicable) education-corrected standard scores. Cognitive impairment was categorized according to scores >1.5 SD below the norm in at least two cognitive domains. AAN: American Academy of Neurology; AIDS: Acquired immune deficiency syndrome; *APOE ε4*: Apolipoprotein E epsilon allele; ART: antiretroviral therapy; GDS: global deficit score; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; NA: Not available; NR: Not reported; SD: Standard deviation. *vs.* = *APOE ε4* carriers *vs.* non-carriers among people living with HIV.

According to the meta-analyses, there were differences in fluency (SMD = −0.51, 95% CI = [−0.76, −0.25], $k = 4$, $I^2 = 0\%$), learning (SMD = −0.52, 95% CI = [−0.75, −0.28], $k = 5$, $I^2 = 0\%$), executive function (SMD = −0.41, 95% CI = [−0.59, −0.23], $k = 8$, $I^2 = 0\%$), memory (SMD = −0.41, 95% CI = [−0.61, −0.20], $k = 10$, $I^2 = 36\%$), attention/working memory (SMD = −0.34, 95% CI = [−0.54, −0.14], $k = 6$, $I^2 = 0\%$), speed of information processing (SMD = −0.34, 95% CI = [−0.53, −0.16], $k = 8$, $I^2 = 0\%$), and motor function (SMD = −0.19, 95% CI = [−0.38, −0.01], $k = 7$, $I^2 = 0\%$). According to the effect sizes of the SMDs, the top four domains were learning, fluency, executive function, and memory. Table 3 provides the detailed results for each domain. In addition, Supplementary Figures 2 to 8, http://links.lww.com/CM9/B373 provide the forest plots for the cognitive domain meta-analyses.

Discussion

This is a rare meta-analysis to assess the associations between the *APOE ε4* genotype and neurocognitive impairment in adult PLWH. We identified 20 studies with approximately 2671 participants relevant to our research purpose. Our results suggested that *APOE ε4* carriers had a significant association with global cognitive impairment among PLWH and was one of the risk factors for developing HAND. Subgroup meta-analyses found significant intergroup differences in the factor female percent. Moreover, the meta-analyses of domain-specific cognitive impairments found that *APOE ε4* carriers were significantly associated with poorer performance in all seven domains, namely memory, executive function, information processing speed, learning, fluency, attention, and motor function. There was no publication bias in the present work, and all included studies were of high quality.

Previous reports have found significant associations between *APOE ε4* and HAND. *APOE ε4* carriers showed greater atrophy in subcortical gray matter structures and white matter.[28] In addition, in the brains of postmortem PLWH, both *APOE ε4* and older age increased the likelihood of cerebral Aβ plaque deposition (as diffuse plaques and mild to moderate amyloid angiopathy, but

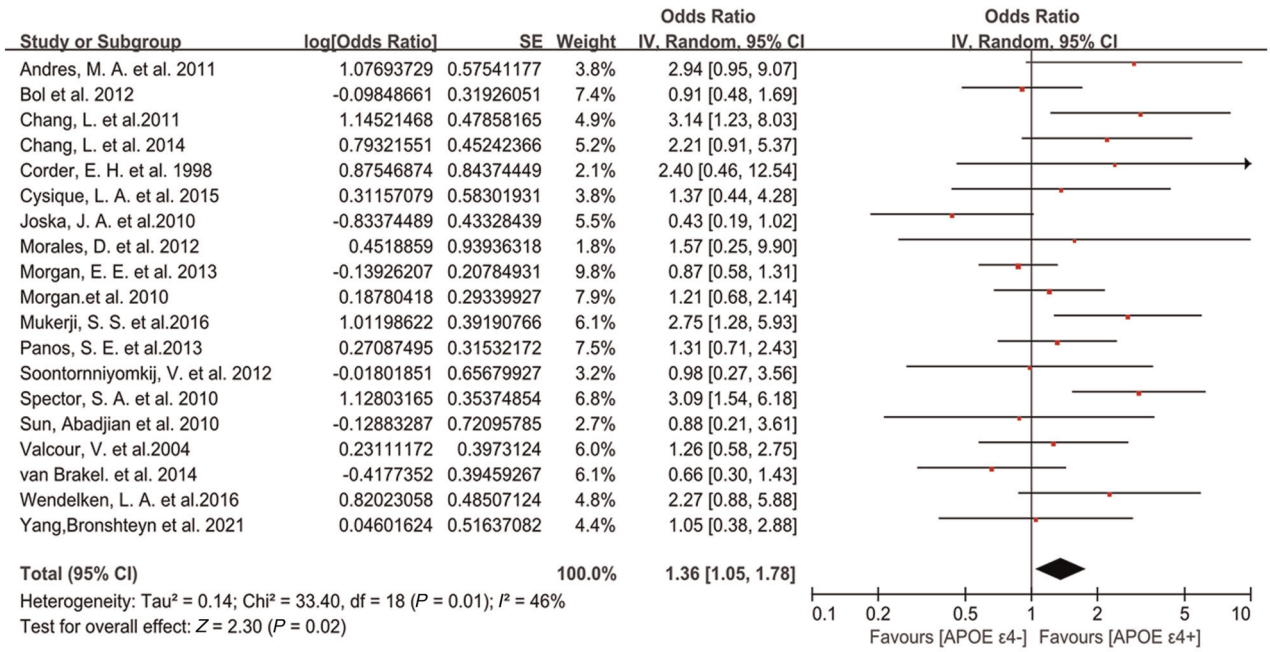

Figure 2: Results of *APOE ε4* and global cognitive impairment meta-analyses in PLWH. *APOE ε4*: Apolipoprotein E epsilon 4 allele; CI: Confidence interval; PLWH: People living with HIV; SE: Standard error.

Table 2: Subgroup meta-analysis outcomes of *APOE ε4* and global cognitive impairment.

Subgroup	*N*	OR (95% CI)	P_1	I^2 (%)	P_2
Age					0.055
<50 years	13	1.07 (0.78, 1.47)	0.673	44	
≥50 years	8	1.86 (1.17, 2.98)	0.009	26	
Education					0.534
<12 years	3	0.98 (0.29, 3.28)	0.970	86	
≥12 years	15	1.45 (1.14, 1.84)	0.003	15	
Nadir CD4 T cell counts					0.126
<200 cells/μL	6	1.58 (0.95, 2.64)	0.080	53	
≥200 cells/μL	4	2.68 (1.73, 4.16)	<0.001	0	
Current CD4 T cell counts					0.336
<500 cells/μL	11	1.39 (0.93, 2.09)	0.111	59	
≥500 cells/μL	5	1.87 (1.19, 2.95)	0.007	0	
Female*					0.015
<11%	9	2.02 (1.45, 2.81)	<0.001	0	
≥11%	9	1.10 (0.76, 1.58)	0.624	52	
Undetectable virus*					0.890
<80%	6	1.63 (1.02, 2.59)	0.042	65	
≥80%	5	1.70 (1.08, 2.68)	0.022	0	
ART proportion					0.120
<90%	10	1.20 (0.83, 1.73)	0.345	58	
≥90%	6	1.84 (1.24, 2.74)	0.003	0	
HIV duration*					0.860
<211 months	4	1.57 (0.72, 3.43)	0.258	67	
≥211 months	4	1.71 (1.04, 2.79)	0.034	0	
HCV positive*					0.598
<20.5%	4	1.63 (1.04, 2.54)	0.031	0	
≥20.5%	4	1.34 (0.74, 2.41)	0.334	69	

* Since these subgroups lacked a clinically defined threshold, we chose the median of the included studies as the basis for subgroup analysis. P_1: *P* value from the random effects model. P_2: *P* value for subgroup difference. *APOE ε4*: Apolipoprotein E epsilon 4 allele; ART: Antiretroviral therapy; CI: Confidence interval; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; *N*: Number of studies; OR: Odds ratio.

Table 3: Results from the meta-analysis of *APOE ε4* and cognitive domain impairment.

Domain	*N*	Participants	SMDs (95% CI)	*P* values	I^2 (%)
Attention	6	663	−0.34 (−0.54, −0.14)	0.001	0
Executive function	8	759	−0.41 (−0.59, −0.23)	<0.001	0
Fluency	4	296	−0.51 (−0.76, −0.25)	<0.001	0
Learning	5	555	−0.52 (−0.75, −0.28)	<0.001	0
Memory	10	943	−0.41 (−0.61, −0.20)	<0.001	36
Motor	7	565	−0.19 (−0.38, −0.01)	0.040	0
Speed of information processing	8	759	−0.34 (−0.53, −0.16)	<0.001	0

APOE ε4: Apolipoprotein E epsilon 4 allele; CI: Confidence interval; *N*: Number of studies: SMDs: Standardized mean differences.

sparse phospho-tau neurofibrillary tangles), and only *APOE ε4* carriers with Aβ plaques had a greater probability of HAND.[18] CSF APOE protein was elevated only in *APOE ε4* carriers among PLWH, and the levels correlated with the severity of cognitive deficits,[65] suggesting that the aberrant *APOE ε4* protein could not clear Aβ and contributed to HAND. Moreover, a low $CD4^+$ T cell count nadir exacerbated the impacts of *APOE ε4* on functional connectivity and memory in adults with HIV,[25] which indicated that *APOE ε4* is involved with the immune system, and immune reconstitution is likely to prevent HAND. However, due to the low gene frequency of *APOE ε4*, it is not conducive to collect a sufficient sample size, which has caused considerable difficulties in the development of cohort studies or longitudinal studies. Our meta-analysis suggests only a significant association between *APOE ε4* and the increased prevalence of HAND, but it still lacks the data necessary to prove causal relationships between them.

Our subgroup analysis results found only that the groups based on percent of females showed statistically significant differences. When the female percentage was <11%, the pooled OR was >2 (the lower 95% CI was >1). A previous meta-analysis reported that women *APOE ε4* carriers have an increased AD risk at younger ages than men because of menopause and decreased estrogen levels after 50 years of age.[49] However, our findings did not show this same relationship. The reason may be that our original study samples were too young or involved too many men, limiting the accuracy of the results. Our study did not find HIV-related clinical indicators (such as nadir/current $CD4^+$ T cell counts, HIV duration, ART use status, and HIV RNA load) impacting the relationship between *APOE ε4* and HAND. There were significant trends in nadir $CD4^+$ T cell counts and proportion using ART subgroups (P_2 = 0.126 and 0.120), but the included studies did not provide sufficient data to confirm this trend. Additionally, neuropsychiatric side effects have been reported with the non-nucleoside reverse transcriptase inhibitor efavirenz and integrase-strand transfer inhibitors[8]; however, almost no included studies reported ART types. Moreover, many studies suggest that the cognitive impairments associated with *APOE ε4* are more evident at older ages. Our study did not find a significant effect, perhaps because the original study samples were too young (with an average age >50 years, but not all subjects were aged >50 years).

With regard to the meta-analyses across cognition domains, we found that function in all seven cognitive domains was significantly poorer for the *APOE ε4* carriers among PLWH. The most severely impacted cognitive domains were learning, fluency, executive function, and memory. Previous meta-analyses found that *APOE ε4* was associated with worse episodic memory and executive function in preclinical AD adults.[71] Additionally, comparing PLWH with people not living with HIV, the most significant deficits in cognitive domains were motor function, attention/working memory, executive function, and processing speed.[61,72,73] Aβ deposition sites and p-tau pathology regions may explain this phenomenon. In the AD brain, the plaques (originating in the hippocampus) are predominantly located in the extracellular space and tend to arise primarily in neocortical areas[74]; however, plaques are typically dispersed in brain somas, extracellular space, and axonal tracks with preferred locations in the basal ganglia, frontal lobe, and hippocampus in HIV-infected patients.[75-77] However, p-tau shows a similar disease process in PLWH and those with AD, which usually forms in the entorhinal cortex and hippocampus and later expands to adjacent areas.[78,79] The learning domain aims to assess mental skills and the acquisition of knowledge of the individual. Memory is the process of storing and then remembering information. Both are regulated by the hippocampus. The fluency cognitive domain reflects language function. The left inferior frontal and left temporopolar regions are the brain regions that control language abilities.[80] Executive function refers to advanced cognitive skills that control and coordinate other cognitive abilities and behaviors. Furthermore, the brain region responsible for executive functioning is the prefrontal cortex. Amyloid positron emission tomography (PET) scans may help determine whether amyloid deposition is more prominent in the above brain regions, similar to studies in AD research.[81,82] Moreover, computerized cognitive training may help to delay the decline in function in these cognitive domains.[83]

Similar to HIV-uninfected individuals, *APOE ε4* carrier-status can increase the risk of developing neurodegeneration among PLWH. However, the role of *APOE ε4* is weaker in PLWH, because the OR value for developing cognitive impairment is higher in *APOE ε4* carrier of HIV-uninfected individuals than our result.[49,84] Moreover, previous meta-analyses showed that PLWH aged >50 years were more susceptible to cognitive disorder than

healthy controls.[61] Thus, we conclude that HIV infection is dominant in neurocognitive impairment causes of PLWH. In addition, our cognition domain analyses results demonstrating a whole-brain cognitive disruption of *APOE ε4* in PLWH differ from a previous study[85] that claimed *APOE ε4*-associated cognitive network disruption centering at hippocampus region and causing memory problems in people not living with HIV. These findings suggest that the involvement of *APOE ε4* is somewhat specific in HAND.

This study has limitations. First, the HAND diagnostic criteria and cognitive evaluation tools used in the studies included in the meta-analysis were not identical, which may have influenced the results. Second, almost all the studies included were conducted in the United States, making it impossible to analyze the effect of ethnicity. Third, many original studies did not provide comprehensive cognitive domain results and may have preferentially reported positive results, potentially contributing to false-positives in our analysis. Fourth, the lack of sufficient clinical data reported in the original studies made it impossible for subgroup analyses to find potential influencing factors (eg, HCV coinfection, ART condition, nadir/current $CD4^+$ T cell counts, time living with HIV, age, and education level). Fifth, no studies separately reported cognitive information for *APOE ε4* homozygous carriers among PLWH, making it impossible to analyze whether *APOE ε4* dose dependency is present in neurocognitive impairment among PLWH.

In conclusion, the current meta-analysis indicated that *APOE ε4* is significantly associated with HAND prevalence. Moreover, cognitive domain meta-analyses showed that all seven domains, namely fluency, learning, executive function, memory, speed of information processing, attention/working memory, and motor function, were significantly poorer in *APOE ε4* carriers. Therefore, the data support the notion of *APOE ε4* as a risk genotype for neurocognitive impairment among PLWH. Subgroup analysis results found that pooled OR values showed intergroup differences based on percentage of female patients. This suggested that effects of *APOE ε4* on HAND showed sex differences. Future studies are needed to clarify whether *APOE ε4* promotes cognitive decline in PLWH. In addition, more studies that provide information on potential confounders, such as age, education level, ART type, nadir/current $CD4^+$ T cell counts, years of PLWH, and comorbidities, are needed to further validate.

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Conflicts of interest

None.

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