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MRI phenotype mediates the association between APOE4 and AD: A cross-sectional study

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Abstract. Background: Alzheimer's disease (AD) is a prominent factor in mortality among older people. The precise biological mechanisms linking APOE4 and cognitive impairment in AD are still unclear, despite significant research efforts. Thus, our study aimed to explore the potential mediating role of MRI phenotypes in the relationship between APOE4 and cognitive impairment in AD. **Methods:** The white mass volume of MRI phenotypes was measured in 1721 older adults based on the ADNI. Linear regression was employed to explore the association of cognitive impairment and MRI phenotype with the APOE4 allele, respectively. Furthermore, the researchers performed mediation analyses to explore the potential mediating effect of the MRI phenotype on the relationship between the APOE4 allele and cognitive ability indicated by the MMSE score. The researchers also stratified the results by gender and by age to ensure comprehensiveness. **Results:** The research indicated that both the mean causal mediating effect (ACME) and the mean direct effect (ADE) of LH, RH, LA, and RA in relation to the APOE4 and MMSE score associations were negative. Besides, the white matter volume of the MRI phenotype mediated the relationship between APOE4 and MMSE scores, with mediation proportions of 47.5%, 43.7%, 33.1%, and 28.3%, respectively. Notably, the proportion mediated was higher in the hippocampus than in the amygdala, and it was also higher in the left hemisphere compared to the right hemisphere. All of these findings were statistically significant (p-value < 0.05). Additionally, when stratified by age, the older half of the participants exhibited higher ACME levels compared to the younger half, and when stratified by gender, females demonstrated higher ACME levels than males. **Conclusions:** The mediation analysis showed a good fit with previous studies. The model presents a promising target for further future studies on clinical diagnosis and potential therapeutic targets related to APOE4.

Keywords: Alzheimer's Disease, APOE4, MMSE, MRI, Mediation Analysis

1. Background

1.1. Alzheimer's Disease

Dementia, which encompasses a range of disorders characterized by effects on memory, cognitive function, and daily activities, stands as a prominent contributor to mortality rates among the elderly population. More than 55 million people worldwide suffer from dementia, and Alzheimer's disease (AD), a neurological illness that causes brain degradation, contributes to up to 70% of incidents. With the expansion of lifespans and the escalating challenge of an aging population, the prevalence of AD is increasing [1,2].

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The main pathologic features of AD are β-amyloid plaque deposits and NFT aggregations. The two phenomena correspond to the prevalent AD pathology hypotheses: the amyloid cascade hypothesis and tau hyperphosphorylation [2]. In the amyloid-beta hypothesis, plaques develop due to the proteolysis of amyloid precursor protein, resulting in the creation of oligomers that eventually aggregate into toxic plaques [3]. While the Tau Hypothesis focuses on the functions of hyperphosphorylated microtubule-related protein tau in AD, which causes normal tau protein to change into PHF-tau (paired helical filament) and NFTs [3]. The downstream consequences of these pathological processes encompass neuroinflammation, neuronal degeneration, and synaptic impairment. It is worth noting that a combination of these pathologies often manifests, especially in the older population.

1.2. APOE4

Although most cases of Alzheimer's disease appear to be sporadic, hereditary mutations in certain genes, such as APP, PSEN1, and PSEN2, contribute to a small percentage (about 5% to 7%) of all AD instances [4]. This often develops between individuals younger than 65, which is categorized as EOAD, or early-onset Alzheimer's disease. Unlike EOAD, most sporadic AD develops in people older than 65 and is hence often categorized as LOAD, or late-onset Alzheimer's disease. LOAD is mainly caused by an intricate combination of genes and the environment, and it is the major factor that contributes to LOAD susceptibility. Apolipoproteins serve an essential function in the regulation of lipid metabolism, specifically in the redistribution of cholesterol and other lipids via apolipoprotein receptors, as well as in lipolysis and, additionally, in lipolysis and the transfer of lipids to the extracellular space.

Carriers of APOE4, one of three polymorphic variants of the APOE gene, have a higher likelihood of developing AD. In contrast, APOE2 is 'protective' whereas apoE4 is 'toxic' in AD development. Up to 80% of people with AD have at least one APOE4 gene [5]. The chance of developing AD is increased by 2-3 times in carriers of one APOE4 allele and by as much as 15 times in carriers of two alleles [6].

1.3. MRI

Today, numerous researchers have conducted investigations on brain morphometry via magnetic resonance imaging (MRI). It is widely recognized as a reliable method to assess atrophy in Alzheimer's disease, serving both in clinical diagnosis as well as monitoring disease progression in research studies [7]. High-resolution MRI, which has millimeter-level spatial resolution, enables the accurate assessment of neurodegeneration in targeted sections of the brain's gray matter (GM), including the cortex and subcortex. This quantification includes measurements of volume loss, structural alterations, and cortical thinning.

The hippocampus, situated within the limbic lobe and comprising the dentate gyrus and portions of the Cornu Ammonis, assumes a pivotal role in cognitive processes, particularly learning and memory. Its subregions contribute significantly to the formation of episodic memory. However, it is noteworthy that AD has a significant impact on the hippocampus. Among the fundamental biomarkers recognized in the context of the disease, hippocampal atrophy stands as the most solidified and verified marker [7,8]. This marker is instrumental in staging AD progression throughout the entire spectrum of the disease. Numerous MRI investigations conducted by research groups worldwide have consistently reported a significant reduction in hippocampal volume. Clinical Alzheimer's disease patients had a mean total hippocampus volume that was about 30% less than that of healthy controls [9]. Remarkably, even in the initial stages, there is a notable reduction of 15-30% in the volume of the hippocampus, and the prevalence of amnestic MCI declines by 10-15% [10].

The amygdala is also within the initial brain regions affected by NFT generation in Alzheimer's disease. Research conducted on affected brains shows substantial atrophy and cell loss in the amygdala [11]. From a therapeutic perspective, the amygdala is known to have a significant impact on the enhancement of explicit memory via its modulation of the encoding and consolidation processes. Previous research on amygdala atrophy in AD has shown widely varying results about the extent of atrophy, with estimates of atrophy spanning from 15% to 41% [12]. In addition, the research found that amygdala volume, as determined by visual inspection using MRI, showed a sensitivity of 88% and a

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specificity of 69% in differentiating between those with AD and healthy controls [8]. However, this relationship has received little attention, and further research is needed.

1.4. Study Hypothesis

Despite extensive efforts, the biological mechanisms underlying Alzheimer's disease (AD) remain uncertain. The most popular and powerful predictors in AD models include APOE4, MRI, MMSE scores, etc. Nevertheless, probable paths or processes behind the association between these features have not been completely examined, since there is a scarcity of research that specifically delves into the connection between these biomarkers or tests. Therefore, the primary objective of this study is to explore the potential mediation effect of MRI phenotypes on the relationship between APOE4 and cognitive impairment in AD, as assessed by the Mini-Mental State Examination (MMSE). A parallel casual mediation analysis model is constructed based on datasets from the ADNI (Fig. 1).

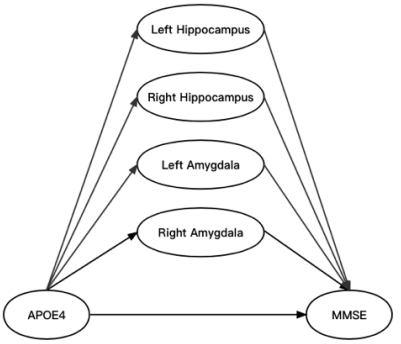

Figure 1. Study Model: Parallel casual mediation analysis of the relationship between the APOE4 gene and MMSE score through imaging phenotypes in AD

According to previous studies suggesting a possible correlation between the APOE4 allele and AD pathophysiology [13], including anatomical abnormalities like hippocampus and amygdala atrophy [14], three hypotheses have been put forward:

H1: APOE4 negatively correlates with the MMSE score.

H2: APOE4 is negatively associated with imaging phenotypes.

H3: The MRI phenotype mediates the relationship between APOE4 and the MMSE score.

To provide a more comprehensive understanding of the mediation analysis, we stratified the data by sex (male and female) and age (into 4 quartile groups) and hypothesized that the stratified results would be similar to the unstratified results.

2. Methods

2.1. Study Population

The TADPOLE Challenge Data subset comprises a compilation of participants who had previously enlisted in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (https://adni.loni.usc.edu/). These individuals have already contributed data to prior studies conducted by the ADNI and have consented to supply further data for the follow-up study. In this investigation, we limited mediation analyses of cross-sectional investigations to baseline participants (n = 1737). We excluded 16 individuals due to missing MRI data, resulting in a total enrollment of 1721 participants (Fig. 2).

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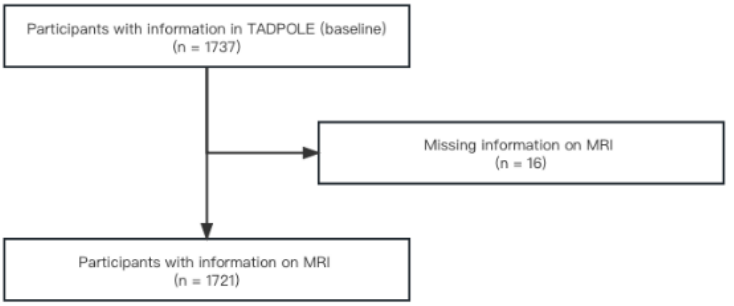

Figure 2. Flow chart for selecting the study population

2.2. Instruments

In this study, we assessed various key variables and instruments. The number of APOE4 alleles was obtained for each participant (n = 0, 1, or 2). Regarding imaging phenotype assessment, we focused on the hippocampus and amygdala as regions of interest, using the volume of white mass as the variable for assessing atrophy, as indicated by the MRI result. Cognitive ability was quantitatively assessed using MMSE scores, which range from 0 to 30 [15]. The MMSE is a standard set of 11 questions commonly utilized by researchers to assess cognitive function, encompassing aspects such as thinking, communication, comprehension, and memory. Furthermore, a comprehensive record of the patient's diagnoses was documented, encompassing a range of cognitive states, including cognitive normal (CN), subjective memory concerns (SMC), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and Alzheimer's disease (AD). Other demographic characteristics in the dataset included age (birth year), gender (male = 0), education (year of education), ethnicity (Hisp/Latino, not Hisp/Latino, or unknown), marriage (married, widowed, divorced, never married, or unknown), etc.

2.3. Study Model

All analyses were conducted using R (version 4.3.1). Mediation analysis was employed to examine whether the covariance between two variables could be attributed to a third variable, referred to as the mediator. In line with our hypothesis, the independent variable was the APOE4 genotype, while the dependent variable was the MMSE score, serving as an indicator of cognitive ability. The proposed mediators in the indirect pathway were the imaging phenotypes, including the left hippocampus (LH), right hippocampus (RH), left amygdala (LA), and right amygdala (RA). The investigation relies on the measurement of the white matter volume in these cerebral areas. The statistical analyses controlled for covariates, including gender, age, and education.

Given the observed association between the independent variable (APOE4 genotype) and the dependent variable (MMSE score), linear regression analyses were initially conducted before proceeding with the mediation analysis. The potential mediating effects of imaging phenotypes on the relationships between the APOE4 and MMSE as an indicator of cognitive ability were assessed using a causal mediation model implemented with the R package "mediation". To assess the significance of the mediation, a bootstrap approach was employed, involving 1,000 random samplings.

3. Results

3.1. Demographic Features

Among the 1721 participants, 920 are diagnosed with APOE carriers (APOE4+). Table 1 provides a comprehensive examination of the demographic characteristics of the study population stratified by clinical diagnosis. Overall, sex, age, education, APOE4 genotype, and MMSE scores were statistically significant among each class.

Remarkably, the MMSE scores displayed a consistent decline as the severity of the participants' disease diagnoses escalated. This decrease ranged from a mean score of 29.06 (SD = 1.12) in the CN

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group to 23.21 (SD = 2.06) in the AD group, which underscores the efficacy of MMSE as a reliable indicator of cognitive ability.

Table 1. Descriptive statistics of the study population

	Overall	CN	SMC	EMCI	LMCI	AD	P
N	1721	413	106	304	561	337	
Sex = Female (%)	772 (44.9)	205 (49.6)	62 (58.5)	137 (45.1)	217 (38.7)	151 (44.8)	<0.001
Age (Mean (SD))	73.77 (7.17)	74.75 (5.73)	72.20 (5.56)	71.20 (7.41)	74.01 (7.50)	74.96 (7.78)	<0.001
Education (Mean(SD))	15.90 (2.86)	16.27 (2.73)	16.76 (2.52)	15.96 (2 .68)	15.88 (2.94)	15.16 (3.00)	<0.001
APOE4 = Positive (%)	920 (53.5)	301 (72.9)	71 (67.0)	177 (58.2)	257 (45.8)	114 (33.8)	<0.001
MMSE(Mean (SD))	27.17 (2.66)	29.06 (1.12)	29.02 (1.19)	28.34 (1.54)	27.18 (1.80)	23.21 (2.06)	<0.001

Note: Cognitive Normal (CN); Subjective Memory Concerns (SMC); Early Mild Cognitive Impairment (EMCI); Late Mild Cognitive Impairment (LMCI); and Alzheimer's Disease (AD); Mini-Mental State Examination (MMSE)

3.2. Mediational Analysis

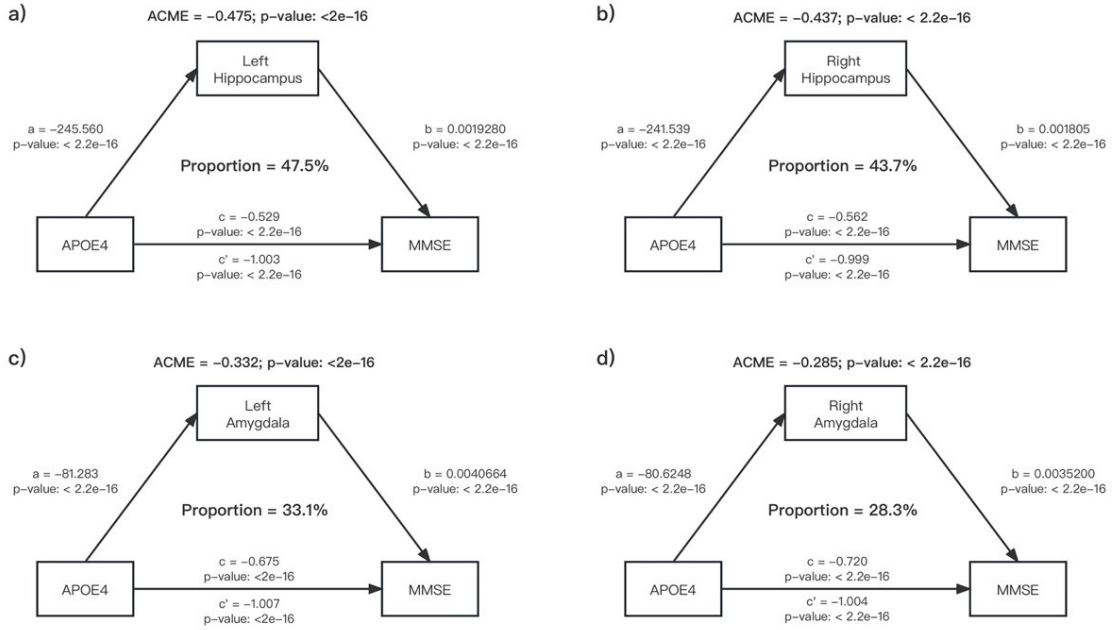

Figure 3. Estimated proportion of the association APOE4 gene and MMSE score mediated by the white mass volume of left hippocampus (a), right hippocampus (b), and left amygdala (c) and right amygdala (d). Note: Models were adjusted for sex, age, and education. ACME, Average Causal Mediation Effects; a, indirect effect of exposure on mediator; b, indirect effect of mediators on outcome; c, the estimate of the average direct effect (ADE) of exposure on outcome; c', the estimate of the total effect; proportion, proportion mediated.

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Fig. 3 offers a concise summary of the parallel casual mediation analysis conducted to explore the potential mediation effects of white mass volume in the left hippocampus (Fig. 3a), right hippocampus (Fig. 3b), and left amygdala (Fig. 3c) and right amygdala (Fig. 3d) on the relationships between APOE4 and MMSE scores. The findings demonstrate that the ACME of LH, RH, LA, and RA on the associations between APOE4 and MMSE scores is consistently negative, with respective values of -0.475, -0.437, -0.332, and -0.285. Besides, APOE4 exhibits a negative ADE on MMSE scores across all imaging phenotypes, specifically LH (c = -0.529), RH (c = -0.562), LA (c = -0.675), and RA (c = -0.720). Overall, the results show that the connections between APOE4 and MMSE scores are significantly mediated by the white mass volume of LH, RH, LA, and RA, with proportions mediated of 47.5%, 43.7%, 33.1%, and 28.3%, respectively. The proportion mediated was generally higher in the hippocampus than in the amygdala. All results are statistically significant, where p-value < 0.05.

3.3. Stratify by Age

Table 2. Mediation analysis results after stratifying the data by age

		ACME	P-VALUE	ADE	P-VALUE	PROP. MEDIATED	P-VALUE
LH	**G1**	-0.411	0	-0.485	0	0.457	0
	G2	-0.62	0	-0.67	0	0.482	0
	G3	-0.379	0	-0.635	0.002	0.374	0
	G4	-0.396	0.002	-0.581	0.002	0.404	0.002
RH	**G1**	-0.485	0	-0.403	0.008	0.545	0
	G2	-0.56	0	-0.722	0	0.438	0
	G3	-0.306	0	-0.694	0	0.304	0
	G4	-0.305	0.002	-0.687	0.002	0.308	0.002
LA	**G1**	-0.375	0	-0.508	0	0.421	0
	G2	-0.342	0	-0.951	0	0.262	0
	G3	-0.267	0	-0.735	0	0.265	0
	G4	-0.28	0.008	-0.705	0	0.284	0.008
RA	**G1**	-0.366	0	-0.532	0	0.408	0
	G2	-0.291	0	-1.007	0	0.223	0
	G3	-0.271	0	-0.742	0	0.265	0
	G4	-0.147	0.034	-0.829	0	0.147	0.034

Note: G1, first quartile age group (participants in the lower 25% of the age range); G2, second quartile age group (participants in the 25th and 50th percentiles of the age range); G3, third quartile age group (participants in the 50th and 75th percentiles of the age range); G4, fourth quartile age group (participants in the upper 25% of the age range).

To examine whether similar mediating effects of imaging phenotypes could be observed across various age subgroups, we expanded our analysis to encompass four quartile age groups (Table. 2). Similarly, all results related to the ACME and ADE exhibited negative values. However, the trend indicating that the Hippocampus had a higher proportion mediated, as observed in the unstratified data, does not entirely align with the trend revealed after age stratification. In this stratified analysis, there was no significant observable trend in the proportion mediated. All results are statistically significant (p-value < 0.05) except for G4 data for LA and RA.

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3.4. Stratify by Sex

Table 3. Mediation analysis results after stratifying the data by sex.

	ACME	P-VALUE	ADE	P-VALUE	PROP. MEDIATED	P-VALUE
LH_M	-0.582	0	-0.422	0	0.581	0
LH_F	-0.396	0	-0.601	0	0.396	0
RH_M	-0.613	0	-0.384	0.006	0.617	0
RH_F	-0.325	0	-0.671	0	0.327	0
LA_M	-0.396	0	-0.61	0	0.393	0
LA_F	-0.282	0	-0.712	0	0.284	0
RA_M	-0.373	0	-0.647	0	0.366	0
RA_F	-0.215	0	-0.779	0	0.216	0

Note: index: LH_M (white mass volume of the left hippocampus of males).

Additionally, we conducted further analyses by stratifying the data by sex. Similarly, the ACME of imaging phenotypes and the ADE of APOE4 on MMSE exhibited negative values, consistent with the unstratified findings. Furthermore, a corresponding pattern emerged, indicating that the proportion mediated is higher in the hippocampus compared to the amygdala (e.g., LH_M = 58.1%; LA_M = 39.3%). Remarkably, females displayed a higher proportion mediated than males. All results are statistically significant (p-value < 0.05).

4. Discussion

Understanding the association between APOE4 and cognitive impairment in AD is crucial for identifying potential targets for innovative treatments. Prior research has established the significant role of APOE4 in AD development [5,6]. Brain atrophy, particularly in the hippocampus [7-10] and amygdala [7,11,12], has also been linked to disease progression and cognitive function. Both APOE4 alleles and brain imaging phenotypes are vital predictors or biomarkers for AD diagnosis and disease monitoring. However, few studies have explored the relationship between these variables. Therefore, our study aims to expand on previous findings by investigating whether imaging phenotypes mediate the correlation between APOE4 and cognitive impairment in AD.

Our parallel casual mediation model exhibited a good fit to the data, providing support for all three of the proposed hypotheses. As predicted, the number of APOE4 alleles is negatively correlated to MMSE scores, indicating that APOE4 plays a role in cognitive impairment in AD. This finding aligns with a recent systematic review [16], which reported that AD patients with APOE4 carriers exhibit a more pronounced amnestic cognitive profile compared to those without the APOE4 allele. However, it is worth noting that the research results regarding the impact of APOE4 on the speed of cognitive decline are inconsistent. While some studies suggest that APOE4-positive AD patients indeed experience a swifter cognitive decline, others propose that there may be no discernible relationship between the two.

The results also indicated a negative correlation between APOE4 carrier status and the volume of white matter in both the left and right hippocampus (LH and RH) and amygdala (LA and RA), aligning with our second hypothesis. This observation is consistent with prior research that has alluded to a potential relationship between the APOE4 allele and AD pathophysiology [13], especially the link evident in MRI markers such as atrophic hippocampal and amygdala volumes [14].

Given the significant link between APOE4 and cognitive impairment, as well as its association with brain atrophy, our results further elucidate this crucial relationship. Consistent with our third hypothesis, brain atrophy partially mediates the correlation between APOE4 and the MMSE score. This suggests that the pattern of brain atrophy induced by APOE4 does indeed impact cognitive performance. This aligns with findings from other literature, although these studies only mention the correlation without specifying the exact role during this process [14,17]. All our data demonstrate statistically significant mediating effects across various brain regions (LH, RH, LA, and RA) (Fig. 1). It is believed that

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individuals who have the APOE4 allele exhibit a more significant decrease in brain volume, as measured by MRI, and a higher level of amyloid plaques within the cerebral cortex. Besides, APOE4 carriers exhibit higher levels of tau protein and neurofibrillary tangle accumulation. These factors are thought to contribute to the enhanced severity of cognitive impairment [17].

Noteworthy, the hippocampus exhibited a more pronounced mediating influence, with ACME values of -0.475 in LH and -0.437 in RH, compared to the amygdala ACME values of -0.332 in LA and -0.285 in RA. This observation may be related to the degree of atrophy in these brain regions among Alzheimer's patients. In other words, higher average casual mediation effects are potentially linked to greater levels of brain atrophy. According to Laako's study [14], individuals diagnosed with Alzheimer's disease had significantly reduced volumes of the left and right hippocampus, with a loss of around 38%. While the observed reductions in the dimensions of the right amygdala (14%) and the left amygdala (18%) did not reach statistical significance. These findings show that the hippocampus may endure a more severe degree of atrophy compared to the amygdala. Additional work is required to understand these trends.

Besides, left-brain regions exhibit a higher degree of mediating influence relative to the right brain. This left-right brain lateralization may be linked to the compensatory mechanisms proposed by Laurence O'Dwyer et al [18]. Although this lateralization contradicts our findings, it suggests that older ApoE4 carriers may compensate for loss of episodic memory by increasing activity in the right hemisphere of the brain. However, the underlying causes and mechanisms of this bias require further confirmation.

After stratifying the data by age, the findings remained in line with the unstratified results, showing negative ACME and ADE outcomes. Even though there is no clear age trend in the observed mediation effects across different age groups and no apparent hemisphere or brain region preference, the results show that the two younger groups (G1 and G2) have higher ACME levels than the two older groups (G3 and G4). Despite the G4 data for LA and RA, all data points are statistically significant. Whether the mediating effect of the imaging phenotype is stronger in younger patients requires further study.

The results after stratifying by sex are consistent with the unstratified data. Remarkably, the mediation effect of the imaging phenotype is stronger in females than in men. This phenomenon may be elucidated by existing studies indicating that the risk of developing AD associated with the APOE4 gene variant is more pronounced in females [19].

4.1. Strengths and Limitations

The study possesses various strengths, such as a substantial sample size, the examination of multiple mediators in four parallel mediation models, stratification by sex and age, consideration of the exact number of APOE4 alleles, and the use of MRI. Nevertheless, it is crucial to acknowledge the limitations inherent in our results when evaluating the study.

First of all, our study employed a cross-sectional design, which does not determine the order of the mediators throughout time. Although a cross-sectional design is a valid foundation, future research using longitudinal designs is essential for establishing causal relationships.

Additionally, our mediational model was developed based on previous studies. However, this model is just one of several plausible options for understanding the relationships among the variables of interest. To ensure the validity of our findings, it is necessary to conduct comparisons with alternative models, such as incorporating other brain regions as mediators.

Furthermore, it is important to consider the potential influence of test bias on our findings, specifically in relation to the MMSE score. Educational disparities may impact MMSE performance, possibly as a result of test bias [20]. Although the educational levels within each clinical diagnostic group show little variation (Table. 1), the cognitive abilities of our sample, as indicated by their MMSE scores, exceed the typical range observed in the EMRI (typically between scores 20 and 25 [15]). Additionally, the MMSE is a general assessment of cognitive function, lacking the ability to identify specific areas that may be impacted. Additional research is necessary to enhance comprehension of the precise cognitive functions impacted.

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Our findings confirm the overall importance of the suggested mediators, but further research is needed to determine their validity in more specific populations. The sample used in our study may not accurately represent the general population due to potential biases in recruitment and participant retention. Hence, further study is required to ascertain the generalizability of our result to different populations.

5. Conclusion

Extending previous findings, our study demonstrates that the MRI phenotype mediates the correlation between APOE4 genotype and cognitive impairment in AD. This has significant clinical implications, including the potential for genotype-based interventions to address brain atrophy and cognitive impairment in AD patients. Furthermore, understanding how specific brain imaging markers relate to cognitive function can enhance risk assessment, enabling more informed counseling and early intervention for APOE4 carriers.

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