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Research Report

The Association of Body Mass Index with Cognition and Alzheimer's Disease Biomarkers in the Elderly with Different Cognitive Status: A Study from the Alzheimer's Disease Neuroimaging Initiative Database

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Abstract.
Background: The association of body mass index (BMI) with cognition and Alzheimer's disease (AD) biomarkers of the elderly remains inconclusive.
Objective: To investigate the relationship between BMI and cognition as well as AD biomarkers in the elderly with different cognitive status.
Methods: Participants with cognitively normal (CN) were included as the CN group. Participants with mild cognitive impairment and mild dementia were included as the cognitive impairment (CI) group. The relationship between BMI and AD biomarkers (cerebrospinal fluid $A\beta_{42}$ and p-tau181, hippocampal volume [HV]), global cognition (Mini-Mental State Examination [MMSE]), memory, and executive function were explored.

[1]These authors contributed equally to this work.

[2]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators is available at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Results: In the CI group, BMI was associated with MMSE ($\beta = 0.03$, $p = 0.009$), $A\beta_{42}$ ($\beta = 0.006$, $p = 0.029$), p-tau181/$A\beta_{42}$ ratio ($\beta = -0.001$, $p = 0.011$), and HV ($\beta = 0.05$, $p < 0.001$). However in the CN group, BMI exhibited associations with p-tau181 ($\beta = 0.012$, $p = 0.014$) and memory composite score ($\beta = -0.04$, $p = 0.038$), but not with p-tau181/$A\beta_{42}$ ratio and HV. Moreover, mediation analysis showed that in the CI group, the positive effect of BMI on HV and MMSE score was partially mediated by diastolic blood pressure.

Conclusions: The association of BMI with cognition and AD biomarkers varies across different cognitive status. In particular, a lower BMI was associated with worse cognition, higher Aβ burden, and lower HV in individuals with CI. Clinical practice should strengthen the monitoring and management of BMI in patients with AD.

Keywords: Alzheimer's disease, body mass index, cognition, hippocampus

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia. Its pathological hallmark is the accumulation of amyloid-β (Aβ) senile plaques and hyperphosphorylated tau (p-tau) tangles [1]. The presence of Aβ and tau pathology can be detected by Aβ and tau positron emission tomography (PET), or through analysis of cerebrospinal fluid (CSF) biomarkers, including $A\beta_{42}$ and p-tau181 [1]. Currently, available medications for dementia and AD have limited effectiveness and do not significantly alter the progression of the disease. However, research has shown that around a third of AD cases worldwide may be attributed to potentially modifiable risk factors [2]. This suggests that prevention strategies targeting such factors may be promising in reducing the risk of dementia and AD. Moreover, the FINGER clinical trial has demonstrated that targeting preventive interventions in individuals at risk of developing dementia from the general population could improve or maintain cognitive function [3]. Therefore, intervening on modifiable factors has emerged as an alternative strategy to reduce the risk of developing dementia and AD.

Late-life body mass index (BMI) is a well-known modifiable factor for many diseases [4]; however, its relationship with AD has always been controversial. Some studies have reported an association between higher BMI and an increased risk of AD [5, 6]. Conversely, other studies have suggested an association between higher BMI and a reduced risk of AD [7]. The underlying mechanisms by which BMI influences AD are unclear. Among these, the hippocampus may be an important factor linking BMI and AD [8]. Several studies found that late-life BMI has a different association with hippocampal volume (HV) depending on its corresponding cognition status. In individuals with cognitive impairment (CI), there was a positive association between BMI and HV [8]. Conversely, in individuals with cognitively normal (CN), BMI exhibited a negative correlation with HV [9]. CSF $A\beta_{42}$ and p-tau181 are also important biomarkers of AD and are associated with HV [10]. Whether the relationship between BMI and other AD biomarkers (CSF $A\beta_{42}$ and p-tau181) varies with cognitive status remains unknown.

Vascular risk factors (VRFs), an integral component of modifiable risk factors, which include diabetes mellitus, hypertension, and midlife obesity, can increase the risk of dementia, including AD [2]. However, recent investigations have shown that VRFs are not associated with AD pathology [11]. Lane et al. also found that VRFs, as indicated by the office-based Framingham Heart Study–cardiovascular risk (FHS) score, showed no association with the Aβ status detected by PET [12]. The FHS score is commonly used to assess the risk of cardiovascular disease, which includes the weighted contribution of BMI as a risk factor [13]. Due to the potential protective effect of late-life BMI on AD [14], is there a difference in the association between the FHS score (which does not include the weighted score of BMI) and AD pathology?

The *APOE* ε4 genotype is the strongest genetic risk factor for late-onset AD [15]. There is evidence to suggest that the effect of late-life BMI on AD biomarkers and cognition varies depending on *APOE* ε4 status [16, 17]. Blautzik et al. investigated the relationship between BMI and Aβ positivity in CN and mild cognitive impairment (MCI) individuals and found that in *APOE* ε4 carriers, BMI was negatively associated with Aβ burden in the cerebral cortex and recent cognitive function decline, whereas in non-carriers, BMI was not correlated with Aβ burden or cognitive performance [16]. However, they did

not conduct subgroup analyses based on different cognitive groups. It was later further revealed that only in *APOE* ε4 carriers, a drop in BMI over five years strongly predicted cognitively healthy elders' conversion to MCI or dementia [17]. To date, the effect of both *APOE* ε4 status and Aβ status on the relationship between BMI and AD biomarkers in individuals with different cognitive status remains unclear.

We investigated the relationship between late-life BMI and cognition as well as AD biomarkers across different cognitive status in the present study. We hypothesized that 1) the association of BMI with cognition and AD biomarkers varies across different cognitive status; 2) *APOE* ε4 and Aβ status might modify the relationship between BMI and AD biomarkers; 3) BMI may influence AD biomarkers and cognition through some intermediate variables; 4) FHS score without BMI (referred to as FHS1 score) in combination with both BMI and *APOE* ε4 status could improve the predictive accuracy for AD biomarkers.

MATERIALS AND METHODS

Alzheimer's Disease Neuroimaging Initiative

The data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI cohort was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI was to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment could be integrated to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org.

Standard protocol approval, registration, and patient consent

The ADNI study was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all the participants or their authorized representatives in accordance with the Declaration of Helsinki. The authors acquired consent from the ADNI Data Sharing and Publications Committee for data use and publication.

Participants' inclusion and exclusion criteria

The detailed enrollment procedure and inclusion criteria for the various diagnostic categories in the ADNI cohort have been described previously [18]. In the present study, all participants had neuroimaging data, CSF biomarkers data, neuropsychological data, blood pressure data, and laboratory examination data at baseline and were followed up at 1-year and 2-year intervals after enrollment.

Participants with normal cognition (Clinical Dementia Rating [CDR] global score = 0) were included in the CN group. Participants with MCI (CDR global score = 0.5) and mild dementia (CDR global score = 1) were included in the CI group.

Additionally, we also required that participants with CN were in relatively good health, which means no significant white matter lesions or only mild white matter lesions, to represent the general population to some extent. Therefore, CN participants with a high white matter hyperintensities (WMH) burden were excluded. These individuals, who may have cerebral small vessel disease, do not strictly fall under the category of healthy participants. WMH volume (adjusted total Intracranial volume values) greater than 0.00321 was regarded as a high WMH burden [19]. Considering the relatively small number of participants with underweight (BMI < 18.5 kg/m^2) and grade 3 obesity (BMI ≥ 40 kg/m^2), and the association of grade 3 obesity with increased mortality risk [20], we excluded participants with underweight and grade 3 obesity. According to the World Health Organization (WHO) criteria, participants were divided into three groups, normal weight (18.5 ≤ BMI<25 kg/m^2), overweight (25 ≤ BMI <30 kg/m^2), and obesity (30 ≤ BMI<40 kg/m^2).

Neuropsychological assessments

The neuropsychological assessments were performed by certified raters using standardized ADNI protocols (http://www.adni-info.org). Multiple scales were employed to assess cognitive functions, including the 13-item AD Assessment Scale-cognitive subscale (ADAS-cog 13), CDR, Mini-Mental State Examination (MMSE), ADNI memory composite score (ADNI-MEM) [21], and ADNI executive function score (ADNI-EF) [22]. The neuropsychological assessment data were obtained from the ADNI file ("MMSE.csv", "CDR.csv", "ADAS_ADNIGO23.csv", "UWNPSYCHSUM.csv"). Cognitive decline was defined as the

conversion of individuals with CN to MCI/dementia, and the conversion of individuals with MCI to dementia at the 2-year follow-up.

Neuroimaging data

MR examinations were performed according to the ADNI MRI scanning protocol (http://www.adni-info.org). All study participants who had a baseline brain MRI examination including T1-weighted, T2-weighted, and T2 fluid-attenuated inversion recovery sequences were included in the ADNI database. Four brain tissue (gray matter, white matter, CSF, and WMH) segmentation methods have been described previously, a thorough description can be found in the ADNI reference documentation "Four Tissue Segmentation in ADNI II". The HV and WMH volume data was obtained from the ADNI file ("ADNI_UCD_WMH.csv").

The detailed protocols for PET image acquisition have been outlined in previous studies [23]. This study used the following neuroimaging data extracted from the ADNI file ("ADNIMERGE.csv"): 1) average florbetapir (AV45) Standardized Uptake Value Ratio (SUVR) of the frontal cortex, parietal cortex, anterior cingulate cortex, and precuneus relative to the cerebellum; 2) average fluoro-2-deoxyglucose SUVR of bilateral angular gyrus, posterior cingular and inferior temporalgyrus. The threshold value for AV45 PET SUVR is 1.11 [24].

CSF data

The approach for CSF sample determination has been previously published, and the cutoff values for CSF biomarkers were defined as follows: $A\beta_{42}$, 980 pg/mL; p-tau181, 21.8 pg/mL; total tau, 245 pg/mL; p-tau181/$A\beta_{42}$, 0.021 [25]. In the present study, the Aβ and tau pathology (AT) classification was defined based on CSF $A\beta_{42}$ and p-tau181 levels. The CSF data was obtained from the ADNI file ("UPENNBIOMK_MASTER.csv", UPENNBIOMK9 batch).

Other assessments and data collection

Laboratory examination data was obtained from the ADNI file ("LABTESTS.csv"). APOE ε4 carrier status information was determined from the ADNI file ("APOERES.csv"). Participants with at least one copy of the *APOE* ε4 allele were considered as *APOE* ε4 carriers. The following data were collected from the clinical evaluation file ("ADNIMERGE.csv", "RECMHIST.csv", "VITALS.csv"): education years, current smoking, BMI (weight [kilograms]/height [meters] squared), use of antidementia and antihypertensive drugs, VRFs (hypertension and diabetes mellitus), systolic blood pressure (SBP), and diastolic blood pressure (DBP). We calculated the FHS score, which was a weighted sum of age, gender, SBP, antihypertensive medication use, diabetes mellitus status, current smoking, and BMI [13]. In addition, we calculated the FHS score without considering the weight of BMI, denoted as the FHS1 score.

Statistical analysis

The Shapiro-Wilk test was used for evaluating data distribution types. MMSE scores were z-transformed, and $A\beta_{42}$ and p-tau181 levels were log-transformed before conducting regression analysis. Student's t-test and one-way ANOVA with a Bonferroni correction for multiple comparisons were used to compare different groups in terms of normally distributed data. The chi-square test was used to compare the categorical variables, and the Kruskal-Wallis test was used to compare non-normally distributed continuous variables.

Cross-sectional analysis: 1) To assess the association of BMI and FHS1 score with AD biomarkers (including $A\beta_{42}$, p-tau181, p-tau181/$A\beta_{42}$ ratio, and HV), cognitive performance (including MMSE score, memory, and executive function), and outcome variables (including WMH burden, PET-defined Aβ status, p-tau181/$A\beta_{42}$ ratio abnormal, CSF biomarker defined AT classification status, and whether cognitive decline), linear and logistic regression analyses were conducted, with BMI and FHS1 (or FHS) score serving as predictor variables. Multivariate linear or logistic regression analyses were adjusted for *APOE* ε4 status, and in the model with cognitive scores as the outcome variable, additional adjustments were made for educational years and the use of anti-dementia medications. Likelihood ratio tests were used to compare the performance of different models. Variance inflation factors were calculated to test the collinearity assumption, which was not violated. 2) To examine the potential interaction effects of BMI and *APOE* ε4 status (or Aβ status) on the outcome variables, linear regression analyses were performed by including the interaction term of BMI x ε4 status (or Aβ status). 3) To assess the mediating effects of intermediate variables on the relationship

between BMI and AD biomarkers as well as cognition, mediation analyses were conducted. 4) To evaluate whether the performance of the combination model FHS1 + BMI+ε4 was superior to the models that used only the FHS score or FHS1 score in predicting AT classification status, Receiver Operating Characteristic (ROC) curves were employed.

Longitudinal data analyses: Linear mixed-effects models were used to investigate the longitudinal association of BMI with AD biomarkers and cognition, as these models can handle unbalanced and missing data effectively [26]. Longitudinal analyses were based on up to 2 years of follow-up. Random effects included intercept and slope nested within participants. Fixed effects included the main effects of *APOE* ε4 (or Aβ positive) status, BMI, interaction terms of *APOE* ε4 (or Aβ positive) status x BMI, and interaction terms of *APOE* ε4 (or Aβ positive) status x BMI x time. Likelihood ratio tests revealed that the model with the three-way interaction performed better than the model without the three-way interaction.

Statistical significance thresholds were set as two-tailed p-value<0.05. All statistical analyses were performed in R (version 4.2.2).

RESULTS

Demographic and clinical characteristics

Supplementary Figure 1 illustrated the screening process for the participants. Altogether 84 CN participants and 330 CI participants (316 cases of MCI, 14 cases of mild AD) were included in this study. There were no statistically significant differences in the demographic characteristics and VRFs between the CI and CN groups. Compared with the CN group, the CI group exhibited a higher rate of *APOE* ε4 carriers, lower $A\beta_{42}$ levels, higher p-tau181 levels, lower HV, and poorer cognitive performance (Table 1). Additionally, compared to participants with normal weight and overweight, those with obesity were found to have higher DBP (Supplementary Table 1).

The relationship between BMI and cognition, AD biomarkers, and clinical outcomes in different cognitive status

As shown in Table 2, in the analysis involving CI participants, multivariate linear regression revealed BMI was associated with MMSE score ($\beta = 0.03$, $p = 0.009$), HV ($\beta = 0.05$, $p < 0.001$), $A\beta_{42}$ ($\beta = 0.006$, $p = 0.029$), p-tau181/$A\beta_{42}$ ratio ($\beta = -0.001$, $p = 0.011$), and p-tau181 levels with a borderline significance ($p = 0.077$). Although no association was found between BMI and memory composite score, when BMI was categorized (normal weight, overweight, obesity), there was an association between obesity and higher memory composite score (Supplementary Table 2, $p = 0.037$). In the analysis comprising CN participants, multivariate linear regression revealed that BMI was associated with memory composite score ($\beta = -0.04$, $p = 0.038$), Aβ42 ($\beta = 0.016$, $p = 0.011$), p-tau181 ($\beta = 0.012$, $p = 0.014$), and MMSE score with a borderline significant ($\beta = -0.02$, $p = 0.076$). However, no significant association was found between BMI and p-tau181/$A\beta_{42}$ ratio ($p = 0.422$). When BMI was categorized, there was an association between obesity and lower memory composite scores (Supplementary Table 2, $p = 0.041$).

As depicted in Fig. 1, in the analysis involving CI participants, multivariate logistic regression revealed a higher BMI was associated with lower odds of AT classification positive status (CSF biomarker defined Aβ and p-tau181 positive, odds ratio [OR] 0.93, 95% confidence interval [CI] 0.87 to 0.99, $p = 0.03$), p-tau181/$A\beta_{42}$ ratio abnormal (OR 0.92, 95%CI 0.86 to 0.98, $p = 0.014$), cognitive decline (OR 0.89, 95%CI 0.82 to 0.97, $p = 0.012$), and Aβ positive status (PET-defined) with a borderline significance ($p = 0.061$). In the analysis comprising CN participants, there was no significant association between BMI and outcome variables.

The effect of BMI on MMSE score and HV in different APOE ε4 and Aβ status

In the CI group, *APOE* ε4 carriers with a higher BMI exhibited higher baseline HV, 2-year HV, and 2-year MMSE score. Non-carriers showed no significant association between BMI and HV or MMSE score. There was a significant difference in the association of BMI with baseline HV, 2-year HV, and 2-year MMSE score between *APOE* ε4 carriers and non-carriers (Fig. 2, $p < 0.05$). Similarly, Aβ positive individuals with a higher BMI exhibited higher baseline HV, 2-year HV, and 2-year MMSE score. Aβ negative individuals showed no significant association between BMI and HV or MMSE score. There was a significant difference in the association of BMI with baseline HV and 2-year HV between Aβ positive and Aβ negative individuals ($p < 0.05$).

We further investigated the effect of BMI on HV and MMSE score in different *APOE* ε4 status and Aβ status (ε4-β-, ε4+β-, ε4-β+, ε4+β+) in the CI group.

Table 1
Baseline characteristics of different cognitive groups

Indicators	CI ($n = 330$)	CN ($n = 84$)	p
Population characteristics			
Age	71.8 (7.28)	72.1 (5.67)	0.64
Gender (Female)	143 (43.3%)	38 (45.2%)	0.849
Education (y)	16 [14;18]	16 [15;19]	0.209
BMI (kg/m^2)	27.0 (3.91)	27.5 (3.66)	0.239
SBP (mmHg)	132 (16.5)	133 (15.5)	0.502
DBP (mmHg)	73.2 (9.57)	73.3 (9.47)	0.929
Vascular risk factors			
Hypertension	137 (41.5%)	33 (39.3%)	0.805
Diabetes mellitus	41 (12.4%)	9 (10.7%)	0.809
FHS score	16 [14;19]	17 [15;19]	0.285
FHS1 score	16 [14;19]	16 [14;18]	0.469
Accessory examination			
$A\beta_{42}$ (pg/mL)	871 [653;1364]	1618 [981;2011]	<0.001
p-tau181 (pg/mL)	24.4 [17.8;33.6]	18.8 [14.8;24.4]	<0.001
Hippocampus volume (ml)	6.29 [5.70;6.94]	6.68 [6.10;7.05]	0.002
WMH volume (ml)	3.64 [1.58;8.42]	1.89 [1.29;2.70]	<0.001
Total brain volume (ml)	1401 (138)	1392 (136)	0.569
APOE ε4 carrier	171 (51.8%)	20 (23.8%)	<0.001
Cognitive function			
MMSE	28 [26;29]	30 [29;30]	<0.001
CDRSB	1.5 [1;2]	0 [0;0]	<0.001
ADAS-cog 13	15 [10;20]	8 [5;12]	<0.001
ADNI-Mem	0.23 (0.72)	1.20 (0.62)	<0.001
ADNI-EF	0.32 (0.89)	1.18 (0.86)	<0.001

Data were presented as mean ± SD, median (interquartile range), or count (percentage). CN, cognitively normal; CI, cognitive impairment; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FHS score, Framingham Heart risk score; FHS1 score, FHS score did not include body mass index; WMH, white matter hyperintensities; MMSE, Mini-Mental State Examination; CDRSB, Clinical Dementia Rating Scale Sum of Boxes; ADAS-cog 13, Alzheimer's Disease Assessment Scale-cognitive subscale 13 item; ADNI-Mem, memory composite score; ADNI-EF, executive function score.

Table 2
Body mass index predicts Alzheimer's disease biomarkers and cognition

Variables	CI ($n = 330$)		CN ($n = 84$)	
Biomarkers	β (95% CI)	p	β (95% CI)	p
Hippocampal volume	0.05 (0.02, 0.07)	<0.001	0.03 (-0.02, 0.08)	0.216
$A\beta_{42}$	0.006 (0.001, 0.012)	0.029	0.016 (0.004, 0.029)	0.011
p-tau181	-0.005 (-0.01, 0.001)	0.077	0.012 (0.003, 0.022)	0.014
p-tau181/$A\beta_{42}$	–0.001 (–0.0017, –0.0002)	0.011	–0.0003 (–0.001,0.001)	0.422
Cognition				
MMSE	0.03 (0.01, 0.05)	0.009	-0.02 (–0.05, 0.002)	0.076
ADNI-MEM	0.01 (–0.01, 0.03)	0.26	-0.04 (–0.07, –0.002)	0.038
ADNI_EF	0.10 (–0.01, 0.03)	0.41	-0.01 (–0.06,0.04)	0.754

CN, cognitively normal; CI, cognitive impairment; FHS score, Framingham risk score; FHS1 score, Framingham risk score did not include body mass index; BMI, body mass index; MMSE, Mini-Mental State Examination; ADNI-MEM, ADNI memory composite score; ADNI-EF, executive function score. MMSE score has been z-transformed. Multivariate linear regression was constructed with BMI and FHS1 score as predictors, adjusting for *APOE* ε4 status.

We found that the effect of BMI on the baseline and 2-year HV, as well as the 2-year MMSE score, differed significantly between ε4+β+and ε4-β- individuals. Additionally, the effect of BMI on HV differed significantly between ε4+β+individuals and both ε4+β- and ε4-β+individuals (Supplementary Figure 2).

However, in the CN group, we did not observe any significant differences in the effect of BMI on HV or MMSE score between *APOE* ε4 carriers and non-carriers, or between Aβ positive and Aβ negative individuals (Supplementary Figure 3).

To validate the different effects of BMI on MMSE score and HV under different APOE ε4 and Aβ status, we performed a longitudinal data analysis. The data from participants in the CI group were analyzed using linear mixed-effects models at baseline,

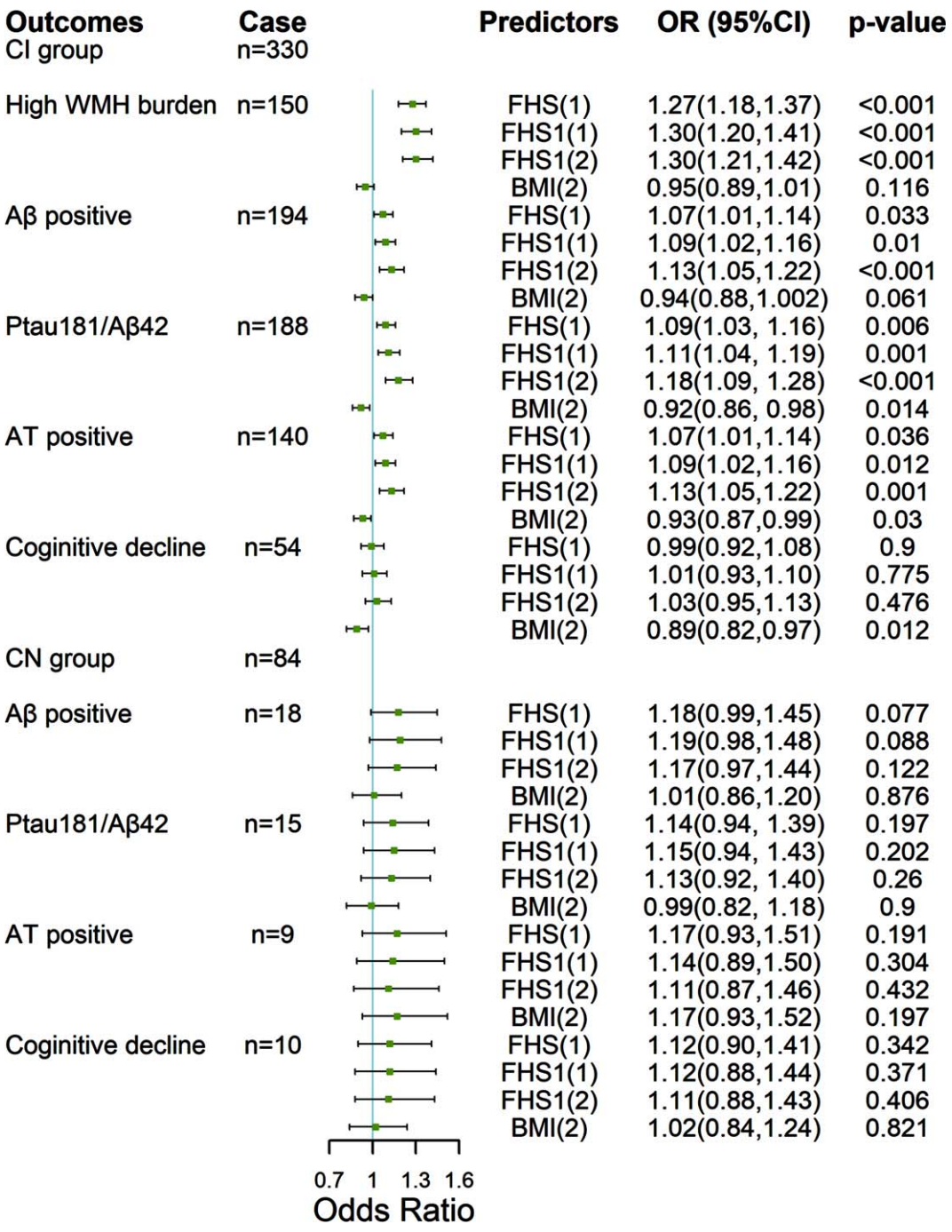

Fig. 1. Analysis of outcome variables across different groups. CN, cognitively normal; CI, cognitive impairment; FHS1 score, Framingham risk score did not include body mass index; BMI, body mass index. (1) represents univariate logistic regression, and (2) represents multivariate logistic regression. Multivariate linear regressions predict variables including FHS1 score, BMI, and *APOE* ε4 status. The coding for the AT classification was as follows: CSF $A\beta_{42}$ (+) and p-tau181 (+) were coded as 1, while others were coded as 0.

1-year follow-up, and 2-year follow-up (Table 3). The interaction effect of BMI and *APOE* ε4 status (or Aβ status) was positively associated with the HV ($p < 0.001$). The interaction effect of BMI x *APOE* ε4 status x time was positively associated with the MMSE score ($p = 0.009$).

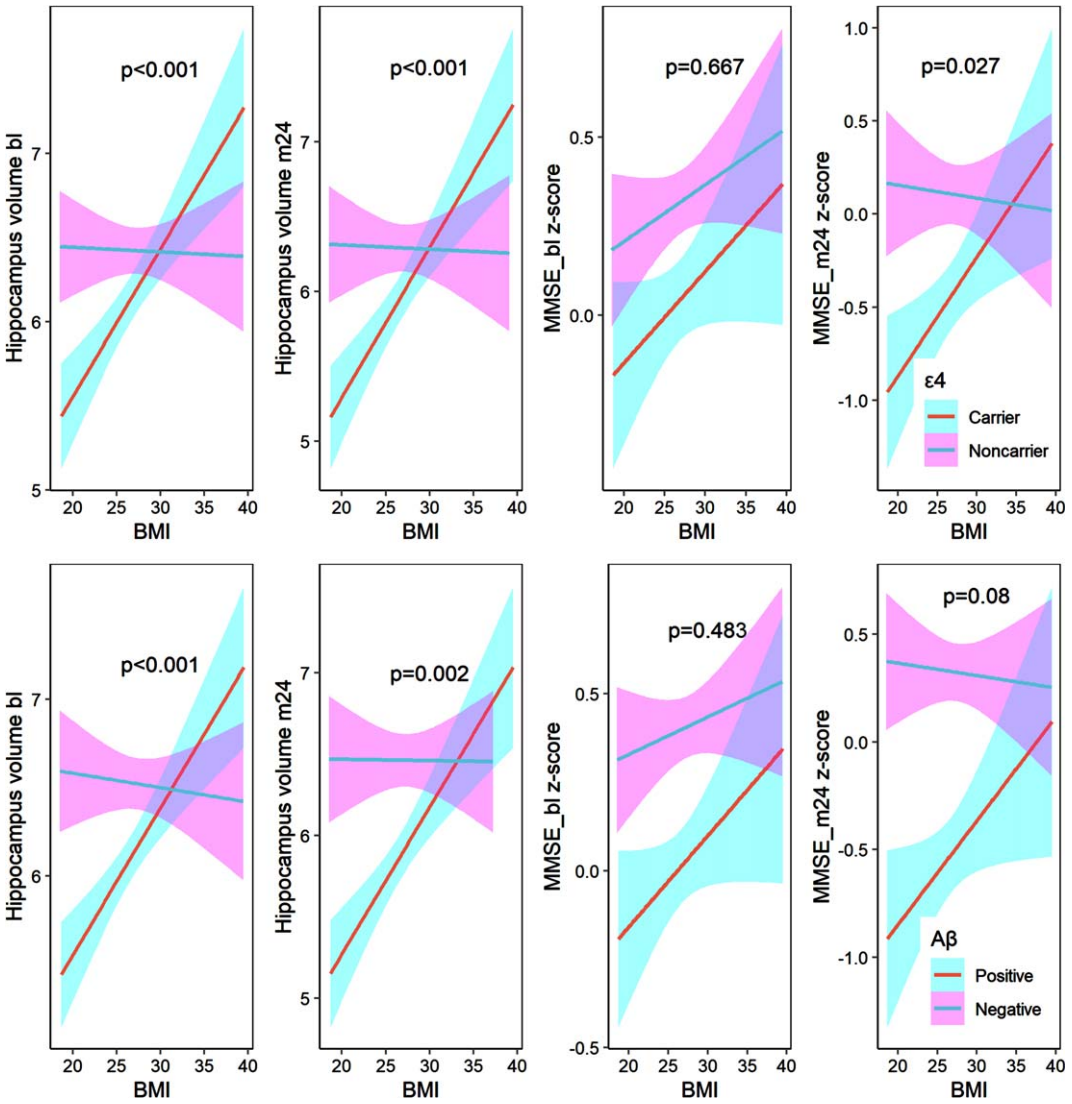

Fig. 2. The effect of body mass index on hippocampal volume and MMSE score in the cognitive impairment group. MMSE score has been z-transformed. The definition of Aβ positive was based on the Aβ PET. The linear models were adjusted for the FHS1 score.

DBP and HV mediated the effect of BMI on the MMSE score

Considering that individuals with obesity had higher DBP at baseline, mediation analysis was conducted to explore the relationship between DBP and baseline HV (Fig. 3). In the CI group, it was shown that the impact of BMI on HV was partially mediated by DBP (mediated proportion = 14.7%). In the CN group, the mediated effect of DBP on the relationship between BMI and HV was insignificant. Mediation analysis was further employed to investigate the mediating effect of the baseline HV on the relationship between BMI and the baseline MMSE score among different cognition groups. It was revealed that the effect of BMI on the MMSE score was mediated through HV (mediated proportion = 33.2%) in the CI group. While in the CN group, it was found that the mediating effect of HV was insignificant.

FHS1 score combined with BMI and APOE ε4 status to predict cognition, AD biomarkers, and outcome variables

Univariate/multivariate linear and logistic regression analyses were conducted to evaluate the relationship between the FHS1 score and cognition, AD biomarkers, and outcome variables (Fig. 1,

Table 3
Linear mixed-effects model predicts hippocampus volume and MMSE score

Predictors	Hippocampus volume		MMSE z-score	
	Estimate	*p*	Estimate	*p*
Fixed effects: covariates				
Aβ status	–2.63	<0.001	–0.55	0.319
BMI	0.001	0.966	0.015	0.315
APOE ε4	–0.08	0.476	–0.126	0.144
FHS1 score	–0.04	0.009	–0.023	0.038
Aβ status:BMI	0.09	**<0.001**	0.011	0.581
Aβ status:BMI:time	–0.001	0.626	0.022	0.096
Fixed effects: covariates				
APOE ε4	–2.408	<0.001	–0.035	0.949
BMI	0.006	0.728	0.022	0.113
Aβ status	–0.162	0.141	–0.256	0.006
FHS1 score	–0.04	0.004	–0.024	0.032
APOE ε4:BMI	0.082	**<0.001**	–0.003	0.859
APOE ε4:BMI:time	0.005	0.055	0.035	**0.009**

MMSE, Mini-Mental State Examination; FHS1 score, Framingham risk score did not include body mass index; BMI, body mass index. The linear mixed-effects model with hippocampus volume as the outcome variable was constructed using BMI x Aβ status (or *APOE* status) x time as the variable of interest and adjusting for FHS1 score and APOE status (or Aβ status). The linear mixed-effects model with MMSE score as the outcome variable was constructed using BMI x Aβ status (or *APOE* status) x time as the variable of interest and adjusting for FHS1 score, *APOE* ε4 status (or Aβ status), and the use of anti-dementia medications.

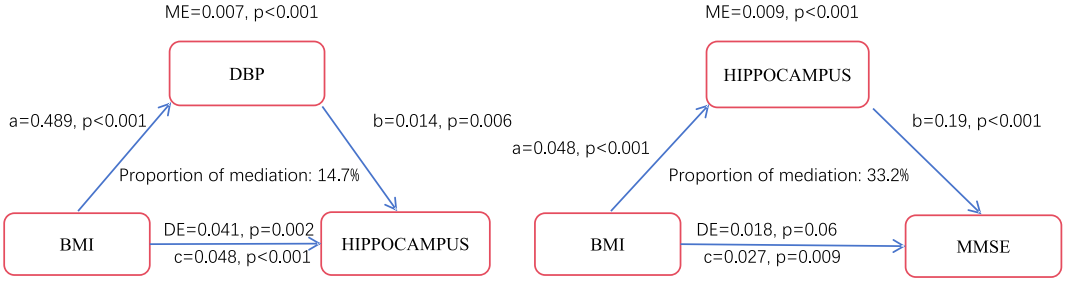

Fig. 3. Mediation models of the cognitive impairment group. ME, mediation effect; DE, direct effect. A, effect of BMI on the mediator variable; b, Effect of the mediator variable on the outcome variable; c, total effect. The mediation analysis models were adjusted for FHS1 score and *APOE* ε4 status.

Table 4). The likelihood ratio test indicated that the inclusion of BMI and *APOE* ε4 in the multivariate linear or logistic regression model enhanced its goodness of fit compared to the univariate linear or logistic regression model that used only the FHS score or FHS1 score as a predictor.

Regardless of whether in the CI or CN group, the results of the multiple linear regression analysis consistently showed a negative association between the FHS1 score and cognition (all $p<0.05$). In the analysis involving CI participants, FHS1 score was associated with HV ($\beta=-0.05, p<0.001$), $A\beta_{42}$ ($\beta=-0.007$, $p=0.014$), p-tau181 ($\beta=0.009$, $p=0.006$), and p-tau181/$A\beta_{42}$ ratio ($\beta=0.0009$, $p=0.024$); multivariate logistic regression revealed FHS1 score was associated with higher odds of WMH burden (OR 1.30, 95%CI 1.21 to 1.42, $p<0.001$), Aβ positive (OR 1.13, 95% CI 1.05 to 1.22, $p<0.001$), and AT positive (OR 1.13, 95%CI 1.05 to 1.12, $p=0.001$). ROC curves also revealed that the combination of FHS1 score, BMI, and *APOE* ε4 status (Fig. 4, Area Under Curve of ROC 0.776, 95% CI 0.725-0.828, compared to FHS and FHS1, $p<0.001$) significantly improved the accuracy of predicting AT positive compared to using only the FHS score (Area Under Curve of ROC 0.575, 95% CI 0.513-0.638) and FHS1 score (Area Under Curve of ROC 0.585, 95% CI 0.523-0.647). In the analysis comprising CN participants, linear or logistic regression showed that the association between FHS1

Table 4
Using FHS score to predict Alzheimer's disease biomarkers and cognition

Variables	CI ($n = 330$)		CN ($n = 84$)	
Hippocampal volume	β (95% CI)	*p*	β (95% CI)	*p*
FHS (1)	-0.03 (-0.06, -0.002)	0.039	-0.02 (-0.08, 0.04)	0.48
FHS1 (1)	-0.04 (-0.07, -0.01)	0.005	-0.03 (-0.09, 0.03)	0.345
FHS1 (2)	-0.05 (-0.08, -0.02)	<0.001	-0.03 (-0.09, 0.03)	0.292
$A\beta_{42}$				
FHS (1)	-0.005 (-0.011,0.002)	0.187	-0.001 (-0.017, 0.015)	0.886
FHS1 (1)	-0.006 (-0.013, 0.001)	0.079	-0.005 (-0.022, 0.011)	0.523
FHS1 (2)	-0.007 (-0.014, -0.002)	0.014	-0.007 (-0.022, 0.009)	0.415
p-tau181				
FHS (1)	0.006 (-0.003,0.012)	0.062	0.011 (-0.0001,0.023)	0.051
FHS1 (1)	0.007 (0.001, 0.014)	0.029	0.009 (-0.004, 0.021)	0.159
FHS1 (2)	0.009 (0.003, 0.015)	0.006	0.007 (-0.005, 0.019)	0.261
p-tau181/$A\beta_{42}$				
FHS (1)	0.0005 (-0.0004,0.0013)	0.286	0.0007 (-0.0003,0.002)	0.155
FHS1 (1)	0.0007 (-0.0002,0.0016)	0.125	0.0008 (-0.0002, 0.002)	0.125
FHS1 (2)	0.0009 (0.0001, 0.002)	0.024	0.0008 (-0.0002, 0.002)	0.127
MMSE				
FHS (1)	-0.01 (-0.04, 0.01)	0.236	-0.04 (-0.07, -0.01)	0.003
FHS1 (1)	-0.02 (-0.05, 0.002)	0.068	-0.04 (-0.07, -0.01)	0.009
FHS1 (2)	-0.02 (-0.05, -0.001)	0.041	-0.04 (-0.07, -0.01)	0.022
ADNI-MEM				
FHS (1)	-0.03 (-0.05, -0.01)	0.004	-0.06 (-0.10, -0.02)	0.005
FHS1 (1)	-0.04 (-0.06, -0.02)	<0.001	-0.06 (-0.10, -0.01)	0.015
FHS1 (2)	-0.04 (-0.06, -0.02)	<0.001	-0.06 (-0.10, -0.01)	0.014
ADNI-EF				
FHS (1)	-0.07 (-0.09, -0.04)	<0.001	-0.09 (-0.15, -0.03)	0.003
FHS1 (1)	-0.07 (-0.10, -0.04)	<0.001	-0.10 (-0.16, -0.04)	0.002
FHS1 (2)	-0.07 (-0.10, -0.05)	<0.001	-0.10 (-0.17, -0.04)	0.002

CN, cognitively normal; CI, cognitive impairment; FHS score, Framingham risk score; FHS1 score, Framingham risk score did not include body mass index; BMI, body mass index; ADNI-MEM, ADNI memory composite score; ADNI-EF, executive function score. $A\beta_{42}$ and p-tau181 have been log10 converted. (1) represents univariate linear regression, and (2) represents multivariate linear regression. Multivariate linear regression predicts variables including FHS1 score, BMI, and *APOE* ε4 status.

score, AD biomarkers, and outcome variables was insignificant.

DISCUSSION

In the present study, we investigated the relationship between late-life BMI and cognition as well as AD biomarkers across different cognitive status. We found that 1) in CI participants, a higher BMI was associated with better cognition, higher HV, and lower odds of AT positive, whereas, in CN participants, a higher BMI was found to be associated with higher p-tau181 levels and poorer memory performance; 2) in CI participants, the association between BMI and AD biomarkers was particularly prominent in those who were *APOE* ε4 carriers and Aβ positive; 3) DBP mediated the relationship between BMI and HV in CI participants; 4) FHS1 score (FHS score without consideration of BMI weight) combined with BMI and *APOE* ε4 status improved the predictive ability for AD biomarkers and clinical outcomes.

The association of BMI with cognition and AD biomarkers varied across different cognitive status

We found that the relationship between BMI and cognition as well as AD biomarkers varied depending on cognitive status. In the CI group, higher BMI was associated with better global cognition (MMSE score) and lower risk of cognitive decline. Some previous studies also indicated a link between higher BMI and a lower risk of cognitive deterioration in MCI individuals [27]. We also found that higher BMI was associated with higher HV, which aligned with a study conducted by Grundman et al. They found that BMI was positively associated with medial temporal lobe volume in AD patients [6]. Moreover, we found that higher BMI was associated with higher $A\beta_{42}$ levels, lower p-tau181/$A\beta_{42}$ ratio, and lower odds of AT positive status, which was consistent with some previous studies. Mathys et al. reported that BMI was positively associated with $A\beta_{42}$ levels and negatively

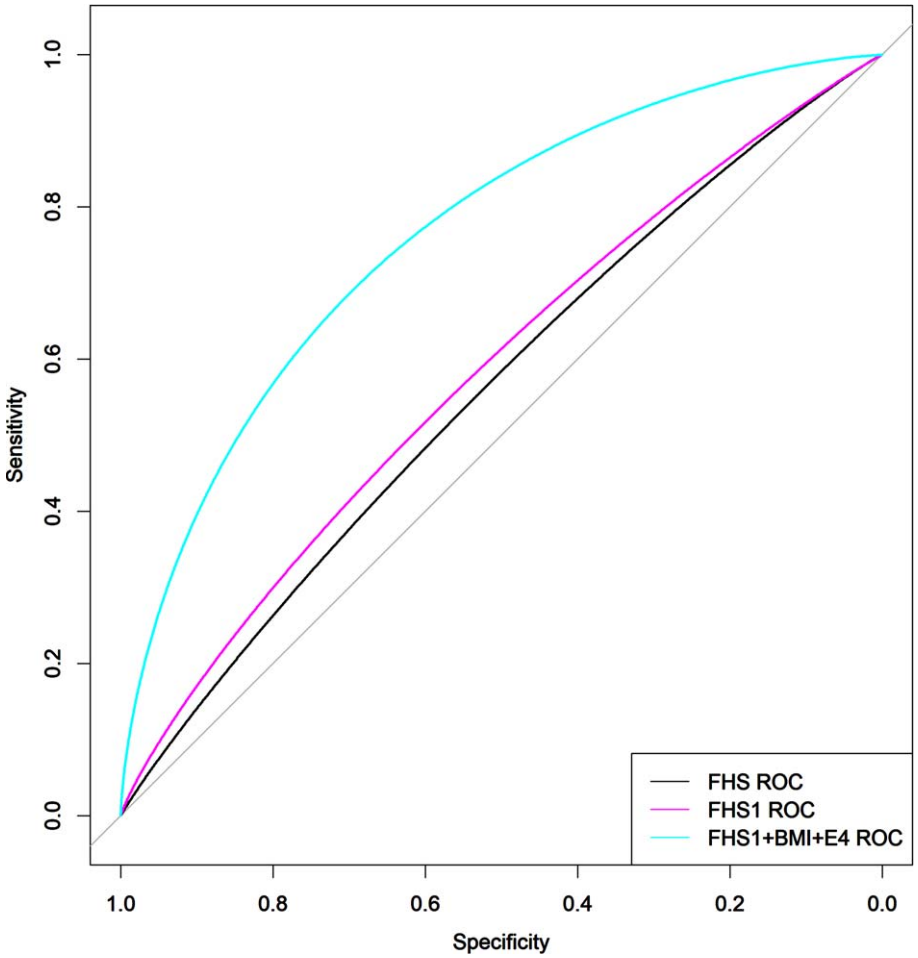

Fig. 4. Receiver Operating Characteristic curves for predicting AT classification positive. FHS score, Framingham risk score; FHS1 score, Framingham risk score did not include body mass index; BMI, body mass index. The performance of the combination model FHS1 + BMI+ε4 in predicting AT classification positive was better than ($p < 0.001$) the models that used only FHS score or FHS1 score.

associated with p-tau181 levels in participants with CI [28]. Thus, it appears that in individuals with CI, a higher BMI was associated with better cognition and milder AD pathological changes.

In the CN group, we observed that higher BMI was associated with poorer memory, especially in individuals with obesity. Our result was consistent with the findings of Masouleh et al., who also found that higher BMI might affect the memory of cognitively healthy older individuals [29]. In our study, we found no association between BMI and HV in individuals with CN. Whereas Hayes et al. found a negative correlation between BMI and HV in CN individuals at genetic risk for AD ($n = 126$) [9]. The lack of association may be due to the strict definition of normal individuals and the relatively small sample size of the CN group in our study. A noteworthy observation is the positive association between BMI and p-tau181 levels among CN participants, which was consistent with some previous studies. An autopsy study investigated the neuropathological alteration in obese patients and non-obese controls (none of the cognitive impairments) and reported increased AD pathology in obese patients, including tau pathology [30]. Some studies have indicated higher BMI is associated with an increased risk of obstructive sleep apnea [31] and arterial stiffness [32]. Meanwhile, obstructive sleep apnea and elevated arterial stiffness are also associated with increased tau burden in cognitively intact individuals [33, 34]. Therefore, a higher BMI may be associated with elevated tau levels in CN individuals. Given that tau pathology is closely related to neuronal injury and cognition [35], the hippocampus is one of the primary regions where tau neurofibril-

lary tangles accumulate [36] and are closely related to memory function [37], our results may help to explain the association between higher BMI and poorer memory performance in CN individuals. Although there was an association between higher BMI and higher $A\beta_{42}$ levels, we did not find a significant association between BMI and p-tau181/$A\beta_{42}$ ratio, and an increased risk of Aβ positive status as defined by PET. To further clarify the relationship between BMI and both Aβ and tau pathology in CN individuals, additional research is necessary.

In summary, our results indicated that the relationship between BMI and AD biomarkers as well as cognition varies across different cognitive status.

APOE ε4 carriers and Aβ status may modify the relationship between BMI and HV as well as cognition

Both cross-sectional and longitudinal data analyses indicated that the relationship between BMI and HV as well as cognition exhibited variations depending on *APOE* ε4 status. Especially in CI participants with *APOE* ε4 + Aβ+status, BMI demonstrated a more prominent association with HV compared to another status (ε4 + Aβ-, ε4-Aβ+, ε4-Aβ-). Only a limited number of studies have examined the impact of BMI on AD patients with different *APOE* ε4 status, with Blautzik et al. being one of them. Blautzik et al. observed that in individuals with *APOE* ε4 carriers and Aβ positive status, BMI was inversely associated with cortical Aβ burden and recent cognitive decline [16]. However, they did not conduct further analysis of the results in different cognitive groups. Our study provided a comprehensive analysis across different cognitive status. Uncertainty surrounds the mechanisms by which BMI impacts AD in *APOE* ε4 carriers. The *TOMM40-APOE* variants may potentially be associated with this relationship [38]. The *TOMM40-APOE* variants are known to be associated with both AD risk and body weight. In the elderly, rs429358 *APOE* variant (coding ε4) and rs2075650 (a genetic risk factor for AD) *TOMM40* variant are associated with a decrease in BMI. The rs429358 *APOE* variant and rs2075650 *TOMM40* variant are often in linkage disequilibrium and have the potential to increase both the risk of BMI decline and AD pathology, which could result in a parallel decline of BMI and the progression of AD, including hippocampal atrophy and cognitive decline. In individuals with CI, the presence of *APOE* ε4 carriers may further exacerbate disease progression compared to non-carriers [39]. As a result, in the CI groups, we observed a more pronounced positive association between BMI and both HV and cognitive performance in individuals who were *APOE* ε4 carriers compared to non-carriers.

Likewise, the association between BMI and HV displayed variations depending on the Aβ status, but the mechanism is still unclear. Blautzik et al. thought that in individuals with *APOE* ε4 carriers when the Aβ levels exceed a certain threshold, it might cause a decrease in BMI through leptin [16]. Buchman et al. thought that the decline in BMI may reflect the pathologic processes of AD [40]. We hypothesize that a higher BMI may mitigate some of the negative effects of Aβ-induced BMI decrease, like weakness. Meanwhile, AD patients with a higher BMI may indicate that they are in the early stage of the AD [41]. Therefore, their cognitive impairments and biomarker abnormalities are relatively mild. The inverse association mentioned above may result in a beneficial effect of higher BMI on AD.

Possible protective mechanisms of BMI against AD

Obesity can increase the risk of hypertension [42], leading to an increase in DBP [43]. In this study, we observed that participants with obesity had higher DBP compared to those with normal weight and overweight. Previous research has reported an association between decreased DBP and increased risk of AD in the elderly. One possible mechanism is that an increase in DBP provides sufficient cerebral perfusion to prevent cerebral hypoperfusion [44]. Moreover, Ngwa et al. discovered a correlation between higher DBP and a larger HV in early MCI participants [45]. Based on the above evidence, we conducted the mediation analyses and found that DBP mediated the association between BMI and hippocampal volume as well as cognition. In other words, higher BMI was associated with higher DBP, while higher DBP had a protective effect on HV and cognitive function. Therefore, BMI showed a positive association with HV and cognition. However, we have only confirmed the association between higher BMI and larger HV in individuals with CI. We have not yet demonstrated an association between higher BMI and lower HV in the cognitively intact population. Therefore, we did not conduct a mediation analysis in the CN group. Our findings suggest that higher BMI is linked to higher DBP, which in turn impacts hippocampal volume and cognitive function.

Other studies suggest that BMI may protect cognition through various mechanisms [46, 47]. BMI was positively associated with glucose metabolism in AD-vulnerable regions, like the anterior cingulate cortex [46]. The functional connectivity of the default mode network may also serve as an underlying mechanism through which higher BMI confers protective effects on cognition in late life [47]. Nevertheless, the mechanisms of late-life BMI in AD may be complex and await further research.

FHS1 score combined with BMI and APOE ε4 status improved the predicting ability for AD markers

Lane et al. found that the FHS score was not associated with Aβ pathology [12]. Considering the complex association between BMI and AD in the elderly population, we did not include BMI weighted score in the calculation of the FHS score. Then, we found that the predictive value of the FHS1 score combining BMI and *APOE* ε4 status was more predictive than the FHS score. Our study uncovered significant associations between a higher FHS1 score and several factors, including poorer cognition, lower $A\beta_{42}$ levels, higher p-tau181 levels, higher WMH burden, lower HV, and poorer cognition. In the future, when applying VRFs scoring for dementia screening in the elderly population, it should be considered to combine BMI (as an independent factor) and *APOE* ε4 status to improve the accuracy of dementia screening.

Strengths and limitations

Our study provided a comprehensive explanation of the association between BMI and both cognition and AD biomarkers in different cognitive status and explored potential underlying mechanisms. We excluded CN participants with a high WMH burden, which may be cerebral small vessel disease. Therefore, the definition of CN in our study was relatively strict, which has not been considered in some previous studies. Furthermore, we did not exclude Aβ negative individuals. This could contribute to the clinical applicability of our findings, as obtaining Aβ data in a clinical setting is not easy.

However, some limitations need to be pointed out. Firstly, the data utilized for analysis were retrospectively collected from the ADNI database, which may introduce some biases. Secondly, due to rigorous inclusion criteria, the number of CN participants was relatively small, which may have obscured associations between BMI and AD markers in the CN population. Thirdly, we faced challenges in further clarifying the relationship between BMI changes and AD markers as well as cognition due to a higher number of missing values for weight and height during follow-up in the ADNI database. However, previous studies have shown a clear association between a decrease in BMI and an increase in AD risk [41].

Conclusion

In conclusion, our findings suggest that the association of BMI with cognition and AD biomarkers varies across different cognitive groups. In particular, a lower BMI was associated with worse cognition, higher Aβ burden, and lower HV in individuals with CI. Clinical practice should strengthen the monitoring and management of BMI in AD patients. For the general population, it is necessary to maintain a BMI not too high ($<30\,kg/m^2$). Additionally, the value of BMI and *APOE* ε4 status should be considered in the cognitive screening process for the elderly population in the future.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available in the ADNI data repository, http://adni.loni.usc.edu/data-samples/access-data/. The data used in the study are available from the corresponding authors on reasonable request.

SUPPLEMENTARY MATERIAL

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