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지도교수 이동영

이 논문을 의학박사 학위논문으로 제출함

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Midlife lifestyle activities moderate APOE ε4 effect on *in vivo* Alzheimer's disease pathologies

By

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A Thesis submitted to the Department of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Medicine (Psychiatry) at Seoul National University College of Medicine

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Abstract

Midlife lifestyle activities moderate APOE ε4 effect on *in vivo* Alzheimer's disease pathologies

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Introduction: This study aimed to investigate whether midlife cognitive activity and physical activity moderate the relationship between apolipoprotein E ε4 (APOE4) and *in vivo* Alzheimer's disease (AD) pathologies.

Methods: In total, 287 non-demented older adults (mean age 72 years) from the Korean Brain Aging Study for the Early diagnosis and prediction of Alzheimer's disease cohort were included. Participants underwent a comprehensive clinical assessment

including the evaluation for midlife CA and physical activity, [^{11}C]-Pittsburgh Compound B positron emission tomography (PET), [^{18}F]-fluorodeoxyglucose PET, structural MRI, and APOE genotyping. We used linear regression and regression-based mediated-moderation models for statistical analyses.

Results: Neither midlife cognitive activity nor physical activity moderated the effect of APOE4 on β-amyloid (Aβ) retention itself. Midlife cognitive activity significantly moderated the effect of APOE4 on hippocampal volume: APOE4 carriers had smaller hippocampal volume than non-carriers at relatively high cognitive activity state, but not at relatively low cognitive activity condition. Midlife physical activity significantly moderated the effect of Aβ retention, which was closely related to APOE4, on AD-signature region cerebral glucose metabolism (AD-CM): Higher Aβ accumulation was associated with lower AD-CM in relatively low physical activity condition, whereas no such association was observed in relatively high physical activity state.

Conclusions: The findings suggest that high midlife cognitive activity may accelerate hippocampal atrophy induced by APOE4, whereas high midlife physical activity may delay AD-related cerebral hypometabolism by weakening the influence of APOE4-

associated Aβ retention.

Keywords: Alzheimer's disease; APOE ε4; β-amyloid; Neurodegeneration; Midlife; Physical activity; Cognitive activity

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List of Abbreviations

AAL: Autonomic Anatomic Labeling

Aβ: Beta-amyloid

AD: Alzheimer's disease

AD-CM: AD-signature region cerebral glucose metabolism

APOE: Apolipoprotein E

AD: Alzheimer's disease Dementia

CA: Cognitive Activity

CDR: Clinical Dementia Rating

CERAD-K: Consortium to Establish a Registry for Alzheimer's disease

CN: Cognitively Normal

FDG: ^{18}F-deoxyglucose

FLAIR: fluid-attenuated inversion recovery

HVa: Adjusted Hippocampal Volume

HVt: Total Hippocampal Volume

KBASE: Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease

ICV: Intracranical Volume

MCI: Mild Cognitive Impairment

MET: Metabolic equivalent

MNI: Montreal Neurological Institute

MRI: Magnetic Resonance Imaging

PC-PRC: Posterior Cingulate-Precuneus

PET: Positron Emission Tomography

PiB: Pittsburgh Compound B

ROI: Region-of-Interest

SBP: Systolic Blood Pressure

SPM: Statistical Parametric Mapping

SUVR: Standard Uptake Value Ratio

VRF: Vascular Risk Factor

VRS: Vascular Risk Score

I. Introduction

The apolipoprotein ε4 (APOE4) is the most well-evidenced risk gene for Alzheimer's disease (AD) (1) and is related to in vivo AD pathologies such as β-amyloid (Aβ) accumulation (2), reduced hippocampal volume (3), and decreased AD-signature region cerebral glucose metabolism (AD-CM) (4, 5). APOE4 has complex effects on AD pathophysiology through both Aβ-mediated pathway (i.e., indirect effect of APOE4 on hippocampal volume or AD-CM reduction via Aβ accumulation) and Aβ-independent pathways (i.e., direct effect of APOE4 on hippocampal volume or AD-CM reduction not mediated by Aβ accumulation) (6).

While APOE4 is a non-modifiable genetic risk factor, modifiable factors such as cognitive activity and physical activity have been associated with a decreased risk of cognitive decline (7) and AD dementia (8-10). However, studies on the in vivo neuropathological mechanisms underlying the association between cognitive activity or physical activity and AD-related cognitive decline have produced controversial findings (11-23). Such modifiable lifestyle activities may change the AD pathophysiological processes associated with

APOE4. However, their moderation for the influence of APOE4 on AD pathologies remains poorly understood (10, 11, 19).

Some previous studies have adopted current cognitive activity or physical activity to investigate the relationship between lifestyle activities and in vivo AD pathologies (12, 14, 16, 17, 19). However, as AD pathology, Aβ deposition in particular, precedes the clinical symptom onset of dementia by 10–15 years(24), current activity itself could be affected by pre-existing AD pathology (i.e., reverse causation) (25, 26). In contrast, midlife cognitive and physical activities are less likely to be affected by AD pathology. Moreover, many previous studies indicated that such midlife activities are related with a decreased risk of late-life cognitive decline (9, 27, 28) and AD dementia (8, 10, 29, 30).

Therefore, we aimed to investigate whether midlife cognitive activity and physical activity can moderate the effect of APOE4 on *in vivo* AD pathologies measured by neuroimaging modalities.

II. Materials and Methods

1. Subjects

The present study included 287 non-demented older adults [215 cognitively normal (CN), 72 mild cognitive impairment (MCI)] between 55 and 90 years of age who participated in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer s disease (KBASE), an ongoing prospective cohort study initiated in 2014 (31). The CN group consisted of participants with a Clinical Dementia Rating (CDR) (32) score of 0. All individuals with MCI met the core clinical criteria for MCI diagnosis recommended by the National Institute of Aging and Alzheimer's Association guidelines (33), which are as follows: 1) memory complaints confirmed by an informant; 2) objective memory impairments, 3) preserved global cognitive function; 4) independence in functional activities; and 5) no dementia. Regarding Criterion 2, the age-, education-, and sex-adjusted z-scores for at least one of four episodic memory tests was < -1.0. The four memory tests were the Word List Memory, Word List Recall, Word

List Recognition, and Constructional Recall tests, which are included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery (34). All MCI individuals had a CDR score of 0.5. The exclusion criteria were as follows: 1) presence of a major psychiatric illness, including alcohol-related disorders; 2) significant neurological or medical conditions or comorbidities that could affect mental function; 3) contraindications for an MRI scan (e.g., pacemaker or claustrophobia); 4) illiteracy; 5) the presence of significant visual/hearing difficulties and/or severe communication or behavioral problems that would make clinical examinations or brain scans difficult; 6) taking an investigational drug; and, 7) pregnant or breastfeeding. All the participants received comprehensive neuropsychological and clinical evaluation including midlife cognitive activity and physical activity according to the KBASE assessment protocol (31). More detailed information on the KBASE study methodology including the enrollment and assessment of participants was described previously (31).

The Institutional Review Board of Seoul National University Hospital (C-1401-027-547) and Seoul Metropolitan Government-Seoul National University Boramae Medical center (26-2015-60) in

South Korea approved the present study and all volunteers provided written informed consent prior to participation.

2. Assessment of midlife cognitive and physical activities

2.1. Cognitive activity

The cognitive activity of each subject was assessed using a 39 item expanded version (35) of a previously reported 25-item autobiographical self-report questionnaire (12, 36). This questionnaire has sufficient internal consistency and temporal stability (35, 36). Participants were asked to report how often they engaged in common cognitively demanding activities with few barriers to participation, such as reading newspapers, magazines, or books; visiting a museum or library; attending a concert, play or musical and writing letters or a diary, at 5 age epochs : 6,12,18, and 40 years and the current age. Responses for each item were made using a 5-point frequency scale: 5, every day or almost every day; 4, several times a week; 3, several times a month; 2, several times a year; and 1, once a year or less. Among the 39 items, 9 items were

for current age (i.e., late-life) cognitive activity and 9 items are for midlife (40 years of age) cognitive activity. The item scores for current age and midlife were averaged to yield current- and midlife cognitive activity value, respectively.

2.2. Physical activity

Midlife physical activity (age 40-55 years) was assessed using the interviewer-administered Lifetime Total Physical Activity Questionnaire, a tool with demonstrated reliability (37, 38) and validity (39). This questionnaire assesses occupational, household, and leisure activities separately throughout a respondent s lifetime. The frequency and duration of these activities were assessed by recording the number of years, months per year, weeks per month, days per week and hours per day that each activity was performed. The intensity of activity was estimated by the participant as sedentary, light, moderate or heavy. A metabolic equivalent (MET) value was assigned to each activity based on the *Compendium of Physical Activities* (40). A subset of 135 subjects in this study had actigraphy during 8 consecutive days. There were positive correlation between current physical activity (occupational, household and leisure activities) and activity variables measured by

actigraphy [r = 0.293, p = 0.001 for mesor (overall average level of activity), r = 0.303, p < 0.001 for amplitude (peak to nadir difference)]. The index of midlife- and current physical activity was the average MET-hr./week spent on leisure activity at the ages of between 40-55 years old and over the past 3 years each. We selected leisure activities, but not occupational or household activities because we wanted to include only a modifiable factor that could be controlled. Most previous studies about the influence of physical activity on AD or dementia risk have focused only on leisure time physical activity (8, 30, 41).

3. Assessment of AD Neuroimaging biomarkers

3.1. Measurement of cerebral Aβ accumulation

All subjects underwent simultaneous three-dimensional (3D) PiB-PET and T1-weighted MRI using a 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington DC, USA) according to the manufacturer's approved guidelines. After 40 min from intravenous administration of 555 MBq of 11C-PiB (range, 450-610 MBq), the PiB-PET image data were collected in list mode (5 min x 6 frames).

All PiB-PET images were processed with routine corrections for uniformity, UTE-based attenuation, and decay corrections, and reconstructed into a 256 x 256 image matrix using iterative methods (6 iterations with 21 subsets). T1-weighted 3D MR images were acquired in the sagittal orientation with following parameters; repetition time = 1670 ms, echo time = 1.89 ms, field of view 250 mm, 256 X 256 matrix with 1.0 mm slice thickness. The image preprocessing were performed using Statistical Parametric Mapping 12 (Wellcome Department of Cognitive Neurology, London, UK;http://www.fil.ion.ucl.ac.uk/spm) and Individual Brain Atlases using Statistical Parametric Mapping software (IBASPM;http://www.thomaskoenig.ch/Lester/ibaspm.htm). First, static PiB-PET images were co-registered to individual T1-weighted MR images and then transformation parameters for spatial normalization of individual T1-weighted MR images to a standard Montreal Neurological Institute (MNI) template were calculated. The inverse transformation parameters were used to transform coordinates from the automatic anatomic labeling (AAL) 116 atlas (42) into an individual space for each subject (a resampling voxel size = 1 x 0.98 x 0.98 mm), and the non-gray matter portions of the atlas were individually masked using the cerebral gray matter

segment image from each subject. Cerebellar gray matter was used as the reference region and mean [^{11}C]-PiB uptake value were extracted from the all cerebellar lobular regions except for the vermis from a probabilistic cerebellar atlas (Institute of Cognitive Neuroscience, UCL; Cognitive Neuroscience Laboratory, Royal Holloway).

The AAL algorithm (42) and a region combining method (43) were applied to determine regions of interest (ROIs) to characterize the [^{11}C]-PiB level in the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions. The standardized uptake value ratio (SUVR) values for each ROI were calculated by dividing the mean value for all voxels within each ROI by the mean cerebellar gray matter uptake value in the same image. A global cortical ROI consisting of the 4 ROIs was also defined, and a global Aβ retention value was calculated by dividing the mean PiB uptake value for all voxels of the global cortical ROIs by the mean cerebellar gray matter uptake value (43). The global Aβ retention values had skewed distribution and were log transformed in the analysis.

3.2. Hippocampal volume measurement

All T1-weighted images were acquired in the sagittal orientation

using the abovementioned 3.0T PET-MR machine. All MR images were automatically segmented using FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu/) with manual correction of minor segmentation errors. An adjusted hippocampal volume (HVa) was calculated as the unstandardized residual from the linear regression of total hippocampal volume (HVt) versus the total intracranial volume (ICV) of reference group (the young CN group of the study cohort) (44). HVa indicates the volume deviated from the expected HVt according to the ICV in young CN subjects.

3.3. Measurement of AD-signature cerebral glucose metabolism

All subjects also underwent FDG-PET imaging using the same PET-MR machine as described previously. The participants fasted for at least 6 hours and rested in a waiting room for 40 minutes prior to the scans after intravenous administration of 0.1 mCi/Kg of [^{18}F]-FDG radioligands. The PET data collected in list mode (5 minutes x 4 frames) were processed for routine corrections such as uniformity, UTE-based attenuation, and decay corrections. After inspecting the data for any significant head movements, we reconstructed them into a 20-minute summed image using iterative methods (6 iterations

with 21 subsets). The following image processing steps were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014a (Mathworks, Natick, MA, USA). First, static FDG-PET images were co-registered to individual T1 structural images, and transformation parameters for the spatial normalization of individual T1 images to a standard MNI template were calculated and used to spatially normalize the PET images to the MNI template. After smoothing the spatially normalized FDG-PET images with a 12-mm Gaussian filter, intensity normalization was performed using the pons as the reference region. AD-signature FDG ROIs, such as the angular gyri, posterior cingulate cortex, and inferior temporal gyri, which are sensitive to the changes associated with AD (45) were determined. AD-CM was defined as a voxel-weighted mean SUVR extracted from the AD-signature FDG ROIs.

4. Assessment of potential confounders

Lifestyle activities and AD neuroimaging biomarkers may be influenced by various other conditions. Therefore, all participants were systematically evaluated about potential confounders such as vascular risk factors, occupational complexity and APOE genotyping.

Vascular risk factors (VRFs) such as hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, transient ischemic attack, and stroke were assessed based on either a documented medical history of disease or treatment with medication. A VRF score (VRS) was calculated for the number of VRFs observed, and reported as a percentage(46). Information about occupation was obtained from self-report by the participants and confirmed by reliable informants. With regard to occupational complexity, we considered only the longest-held occupation and classified into 4 levels based on the skill levels described in International Standard Classification of Occupations(47). Occupations at skill level 1 typically involve simple and routine physical or manual tasks (i.e., office cleaners, freight handlers or garden laborers). Occupations at skill level 2 typically involve the performance of tasks, such as operating machinery and electronic equipment; driving vehicles; maintenance and repair of electrical and mechanical equipment; and manipulation, ordering and storage of information (i.e., butchers, bus drivers or secretaries). Occupations classified at skill level 3 typically involve the performance of complex technical and practical tasks that require complex problem solving, reasoning, and decision making in a specialized field (i.e., shop managers, medical laboratory technicians

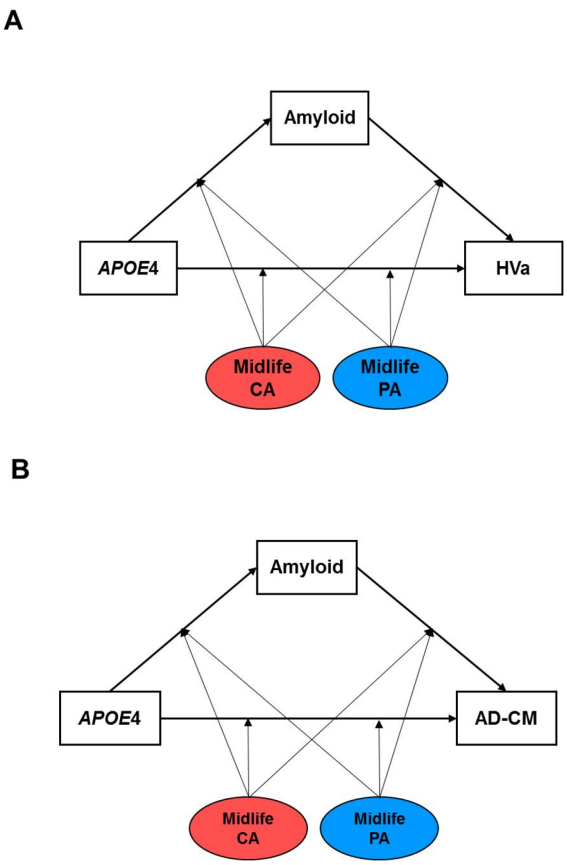
or diagnostic medical radiographers). Occupations classified at skill level 4 typically involve the performance of tasks that require complex problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialized field (i.e., sales and marketing managers, civil engineers or secondary school teachers). Blood samples were obtained via venipuncture and DNA was extracted from whole blood. APOE genotyping was performed as described in previous study (48). If an individual has at least one APOE4 allele, we defined it as an APOE4 carrier.

5. Statistical analysis

First, multiple linear regression analyses were conducted to examine the simple associations between midlife cognitive activity (or physical activity) and AD biomarkers using IBM SPSS Statistics software 23 (IBM Corp., Armonk, NY, USA). Then, we tested models including both Aβ-mediated- and Aβ-independent pathways of APOE4 effects using the Process Macro program(49) to investigate systematically the effects of APOE4 on AD biomarkers and moderation by midlife cognitive activity or physical activity (Figure 1). Inference was determined by 95% bias-corrected bootstrap

confidence intervals from 10,000 bootstrap samples. An effect was considered significant if the 95% confidence interval did not include zero. Three models were tested, with stepwise control of the potential confounders that could affect the association among APOE, midlife lifestyle activities and AD neuroimaging biomarkers. The first model (Model 1) included age, sex, educational year, and clinical diagnosis (CN vs. MCI) as covariates; the second model (Model 2) included the covariates in the first model plus occupational complexity and VRS; and the third model (Model 3) included the covariates in the second model plus current cognitive activity and physical activity. The $p-$value < 0.05 was considered significant.

Figure 1. The hypothetical moderated mediation model to analyze the associations of APOE4 with Aβ retention and (A) HVa or (B) AD-CM, and the moderation effect of cognitive and physical activity on the associations. The sequence of Alzheimer's disease (AD) pathologies are based on hypothetical amyloid cascade model of AD pathophysiology (50, 51)



Abbreviation: APOE4: APOE ε4; CA: cognitive activity; PA: physical activity; HVa: adjusted hippocampal volume; AD-CM: AD-signature region cerebral glucose metabolism

III. RESULTS

1. Participant characteristics

The characteristics of the subjects are shown in Table 1. Of the 287 study participants, 66 (23.0%) were APOE4 carriers. There were no differences between APOE4 carriers and non-carriers regarding age, sex, education, or midlife cognitive activity or physical activity. The proportion of MCI subjects was higher in the APOE4 carrier than in the non-carrier group. APOE4 carriers also had higher global Aβ accumulation, smaller HVa, and lower AD-CM than those of non-carriers.

Table 1. Patient characteristics in the overall sample and in the strata by APOE4 status (N = 287)

	All participants (N=287)	APOE4 non-carrier (n = 221)	APOE4 carrier (n = 66)	p-value[a]
Demographics				
Age (yr.)	71.91 ± 6.64	71.50 ± 6.83	73.23 ± 5.83	0.064
Sex (F %)	158 (55.05%)	120 (54.30%)	38 (57.58%)	0.742
Educational year (yr.)	11.19 ± 4.81	11.36 ± 4.92	10.70 ± 4.44	0.329
MCI, no. (%)	72 (25.09%)	44 (19.91%)	28 (42.42%)	< 0.001
Lifestyle enrichment variables				
Midlife physical activity (MET-hr./week)	17.04 ± 33.00	18.48 ± 36.05	12.35 ± 19.48	0.074
Midlife cognitive activity, score	2.30 ± 0.80	2.31 ± 0.81	2.26 ± 0.78	0.630
AD biomarkers				
Global β-amyloid burden (SUVR)[b]	0.24 ± 0.24	0.18 ± 0.20	0.41 ± 0.29	<0.001
HVa (mm^3)	−1143.81 ± 1011.63	−1006.85 ± 936.01	−1621.28 ± 1123.20	<0.001
AD-CM (SUVR)	1.38 ± 0.13	1.39 ± 0.12	1.34 ± 0.14	0.004

Note: Values are n (%) or mean (SD). [a] Comparison between APOE4 carriers and non-carriers by t-test for continuous variables and chi-square test for categorical variables. [b] coded as ln(global β-amyloid burden)

Abbreviations: APOE4: apolipoprotein ε4; MCI; mild cognitive impairment, SUVR: standardized uptake value ratio; HVa: adjusted

hippocampal volume; AD−CM: AD−signature region cerebral glucose metabolism

2. Simple associations of APOE4, cognitive activity and physical activity with AD biomarkers

Linear regression analyses showed that APOE4 positivity was significantly associated with increased global Aβ retention, decreased HVa, and decreased AD-CM (Table 2). In contrast, neither midlife cognitive activity nor physical activity was related to any of the AD neuroimaging biomarkers.

Table 2. Association of APOE4 and midlife activities with AD biomarkers (N = 287)

	Amyloid[a]					HVa					AD-CM				
	B	***SE***	***β***	***t***	***p*** [b]	***B***	***SE***	***β***	***t***	***p*** [c]	***B***	***SE***	***β***	***t***	***p*** [c]
APOE4	0.175	0.029	0.303	6.099	<0.001	-340.045	113.776	-0.141	-2.989	0.003	-0.049	0.019	-0.148	-2.567	0.011
CA	0.022	0.020	0.072	1.080	0.281	93.335	77.388	0.075	1.206	0.229	0.006	0.013	0.036	0.468	0.640
PA	0.001	0.001	-0.020	-0.389	0.698	0.151	1.581	0.005	0.095	0.924	0.001	0.001	0.044	0.737	0.462

Note: [a] coded as ln(global β-amyloid burden). [b] by multiple linear regression analysis controlling for age, sex, educational year and clinical diagnosis as covariates. [c] by multiple linear regression analysis controlling for age, sex, educational year, APOE4 status and clinical diagnosis as covariates.

Abbreviations: HVa: adjusted hippocampal volume; AD-CM: AD-signature region cerebral glucose metabolism; APOE4: apolipoprotein ε4; CA: cognitive activity; PA: physical activity.

3. Moderation of midlife lifestyle activities for the associations of APOE4 with Aβ retention and HVa

When a model including the moderating effect of midlife cognitive and physical activity for the association between APOE4, Aβ retention, and HVa (Figure 1A) was analyzed, midlife cognitive activity significantly moderated the Aβ-independent effect of APOE4 on HVa (Table 3 and Figure 2A). For the purpose of demonstration, the association between APOE4 carrier status and HVa was plotted for each of high and low midlife cognitive activity state (Figure 3A). At relatively high cognitive activity (1SD above mean) condition, APOE4 carriers had significantly smaller HVa than non-carriers [B (SE) = −561.576 (193.159), t = −2.907, p = 0.004], whereas no such difference was found APOE4 carriers and non-carriers at relatively low cognitive activity (1 SD below mean) condition [B (SE) = 13.707 (173.037), t = 0.079, p = 0.937] (Figure 3A). In contrast, midlife cognitive activity moderated neither the APOE4 effect on Aβ retention itself nor the Aβ-mediated effect of APOE4 on HVa (Table 3 and Figure 2A). In contrast to midlife cognitive activity, midlife physical activity did not show any moderating effect on the influence of APOE4 on Aβ retention and

HVa (Table3 and Figure 2A). Even after VRS, occupational complexity (Model 2), current cognitive and physical activity (Model 3) were controlled in the model as additional covariates, the results were unchanged (Table 4).

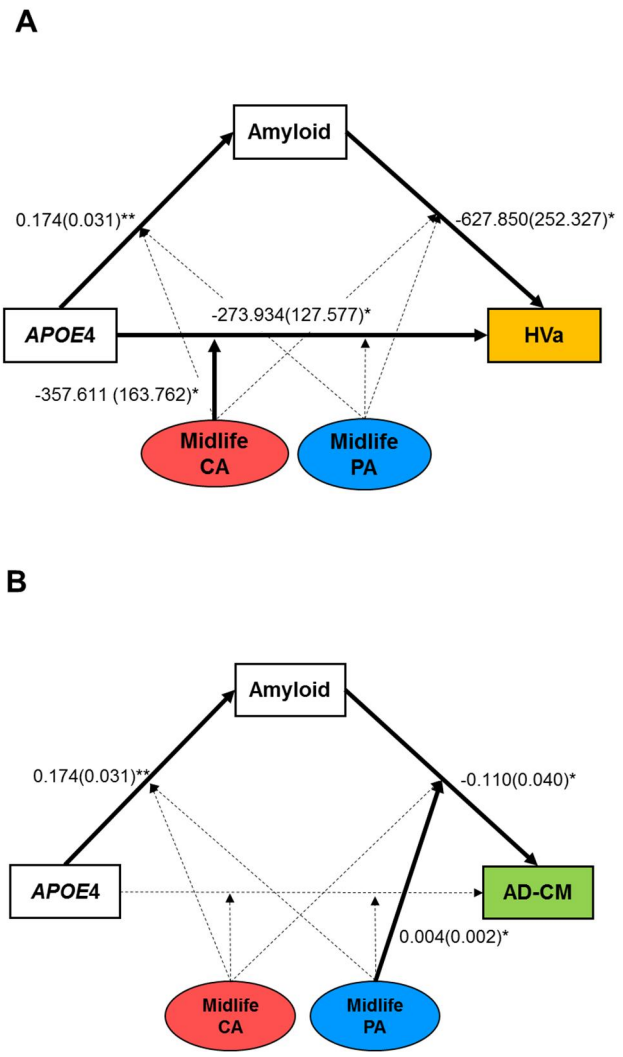
Table 3. Moderation of midlife activities for the association of APOE4 with Aβ retention and HVa: Results from moderated mediation analysis based on PROCESS (N = 287)

	Amyloid[a]				HVa			
	B	***SE***	***t***	***p*** [b]	***B***	***SE***	***t***	***p*** [b]
APOE4	0.174	0.031	5.656	< 0.001	-273.934	127.577	-2.147	0.033
CA	0.024	0.020	1.168	0.244	112.472	77.641	1.449	0.149
PA	-0.001	0.001	-0.561	0.575	-1.107	1.941	-0.570	0.569
APOE4 x CA	0.030	0.038	0.798	0.425	-357.611	163.762	-2.184	0.030
APOE4 x PA	0.001	0.002	0.402	0.688	-0.857	6.813	-0.126	0.900
Amyloid[a]					-627.850	252.327	-2.488	0.014
Amyloid[a] x CA					177.416	272.268	0.652	0.515
Amyloid[a] x PA					-3.862	13.225	-0.292	0.771

Note: [a] coded as ln(global β−amyloid burden). [b] adjusted for age, sex, educational year and clinical diagnosis

Abbreviations: HVa: adjusted hippocampal volume; APOE4: apolipoprotein ε 4; CA: cognitive activity; PA: physical activity.

Figure 2. Results from moderated mediation model analyses for the associations of APOE4 with Aβ retention and (A) HVa or (B) AD-CM, and the moderation effect of midlife cognitive and physical activity for the associations.



Note: Values are standardized regression coefficients (standard error) for the associations or moderation effect with statistical significance. Bold lines also indicate significant association or moderation effect. * $p < 0.05$,

** $p < 0.005$.

Abbreviations: APOE4: apolipoprotein ε4; CA: cognitive activity; PA: physical activity; HVa: adjusted hippocampal volume; AD-CM: AD-signature region cerebral glucose metabolism

Table 4. Moderation of midlife activities for the association of APOE4 with Aβ retention and HVa additionally adjusted for potential confounders: Results from moderated mediation analysis based on PROCESS (N = 287)

	Amyloid[a]					HVa				
	B	***SE***	***t***	***p*** [b]	***p*** [c]	***B***	***SE***	***t***	***p*** [b]	***p*** [c]
APOE4	0.176	0.031	5.735	<0.001	<0.001	-270.229	128.225	-2.107	0.036	0.033
CA	0.019	0.021	0.908	0.365	0.241	116.012	79.177	1.465	0.144	0.267
PA	-0.001	0.001	-0.569	0.57	0.496	-1.057	1.949	-0.542	0.588	0.627
APOE4 x CA	0.029	0.038	0.770	0.442	0.422	-363.787	164.568	-2.211	0.028	0.029
APOE4 x PA	0.001	0.002	0.519	0.605	0.506	-0.420	6.869	-0.061	0.951	0.911
Amyloid[a]						-638.513	254.586	-2.508	0.013	0.015
Amyloid[a] x CA						190.813	273.985	0.696	0.487	0.514
Amyloid[a] x PA						-4.166	13.287	-0.314	0.754	0.746

Note: [a] coded as ln(global β-amyloid burden). [b] Model 2: adjusted for age, sex, educational year, clinical diagnosis, occupational complexity and VRS; [c] Model 3: model 2 + current CA and current PA. Abbreviations: HVa: adjusted hippocampal volume; APOE4: apolipoprotein ε4; CA: cognitive activity; PA: physical activity; VRS: Vascular risk score.

4. Moderation of midlife lifestyle activities for the association of APOE4 with Aβ retention and AD-CM

While midlife cognitive activity did not have any moderation effect for the association between APOE4, Aβ retention and AD-CM, midlife physical activity significantly moderated the effect of Aβ retention on AD-CM (Table 5 and Figure 2B), suggesting the effect of global Aβ retention, which is closely related to APOE4, on AD-CM can be changed by midlife physical activity level. For the purpose of demonstration, the association between global Aβ retention and AD-CM was plotted for each of high and low midlife physical activity state (Figure 3B). At relatively low physical activity (1SD below mean) condition, higher global Aβ retention was significantly associated with lower AD-CM [B (SE) = −16.205 (0.179), t = −4.271, $p < 0.001$], whereas no such association was observed in relatively high physical activity (1 SD above mean) condition [B (SE) = 0.023(0.089), t = 0.264, $p = 0.791$] (Figure 3B). In contrast, midlife physical activity moderated neither the effect of APOE4 on Aβ retention nor the Aβ-independent effect of APOE4 on AD-CM (Table 5 and Figure 2B). Even after VRS, occupational complexity (Model 2), current cognitive and physical activity (Model 3) were controlled in the model as additional

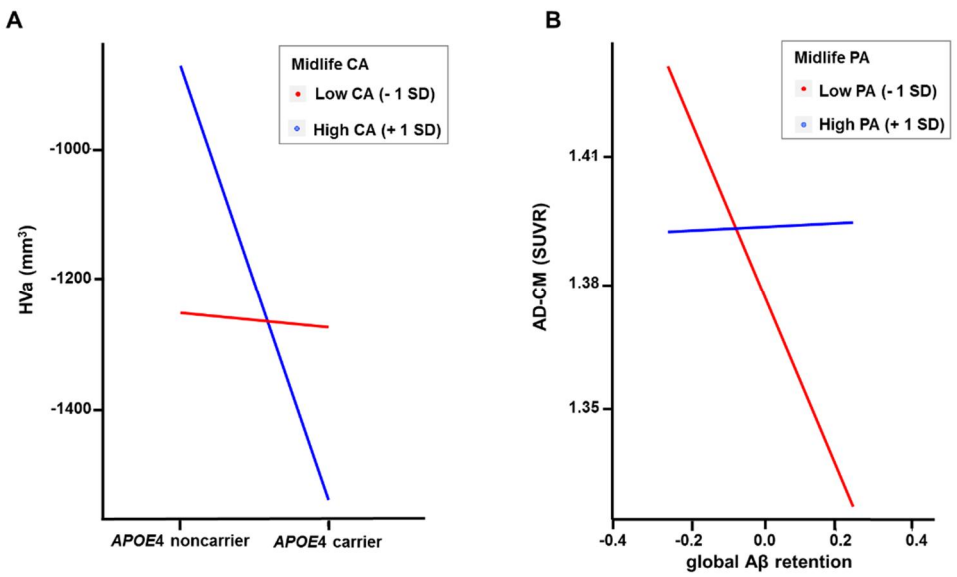
covariates, the results were similar (Table 6).

Table 5. Moderation of midlife activities for the association of APOE4 with Aβ retention and AD−CM: Results from moderated mediation analysis based on PROCESS (N = 287)

	Amyloid[a]				AD-CM			
	B	***SE***	***t***	***p*** [b]	***B***	***SE***	***t***	***p*** [b]
APOE4	0.174	0.031	5.656	< 0.001	-0.022	0.020	-1.090	0.277
CA	0.024	0.020	1.168	0.244	0.010	0.012	0.811	0.418
PA	-0.001	0.001	-0.561	0.575	0.001	0.001	0.850	0.396
APOE4 x CA	0.030	0.038	0.798	0.425	-0.042	0.026	-1.623	0.106
APOE4 x PA	0.001	0.002	0.402	0.688	-0.001	0.001	-1.257	0.210
Amyloid[a]					-0.110	0.040	-2.738	0.007
Amyloid[a] x CA					-0.021	0.043	-0.476	0.635
Amyloid[a] x PA					0.004	0.002	2.030	0.043

Note: [a] coded as ln(global β−amyloid burden). [b] adjusted for age, sex, educational year and clinical diagnosis
Abbreviations: AD−CM: AD−signature region cerebral glucose metabolism; APOE4: apolipoprotein ε 4; CA: cognitive activity; PA: physical activity.

Figure 3. Plots to demonstrate the moderation effect of (A) midlife cognitive activity on the relationship between APOE4 and HVa and (B) midlife physical activity on the relationship between Aβ retention and AD−CM.



Note: [a] coded as ln(global β−amyloid burden)

Abbreviations: APOE4: apolipoprotein ε4; CA: cognitive activity; PA: physical activity; HVa: adjusted hippocampal volume; AD−CM: AD−signature region cerebral glucose metabolism; − 1 SD: 1 standard deviation below mean value; +1 SD: 1 SD above mean value

Table 6. Moderation of midlife activities for the association of APOE4 with Aβ retention and AD−CM additionally adjusted for potential confounders: Results from moderated mediation analysis based on PROCESS (N = 287)

	Amyloid[a]					AD-CM				
	B	***SE***	***t***	***p*** [b]	***p*** [c]	***B***	***SE***	***t***	***p*** [b]	***p*** [c]
APOE4	0.176	0.031	5.735	< 0.001	< 0.001	-0.018	0.02	-0.892	0.373	0.375
CA	0.019	0.021	0.908	0.365	0.241	0.006	0.012	0.459	0.646	0.757
PA	-0.001	0.001	-0.569	0.57	0.496	0.001	0.001	0.894	0.372	0.529
APOE4 x CA	0.029	0.038	0.770	0.442	0.422	-0.046	0.026	-1.804	0.072	0.079
APOE4 x PA	0.001	0.002	0.519	0.605	0.506	-0.001	0.001	-1.100	0.272	0.311
Amyloid[a]						-0.125	0.039	-3.159	0.002	0.002
Amyloid[a] x CA						-0.012	0.042	-0.273	0.785	0.833
Amyloid[a] x PA						0.004	0.002	2.126	0.034	0.043

Note: [a] coded as ln(global β−amyloid burden), [b] Model 2: adjusted for age, sex, educational year, clinical diagnosis, occupational complexity and VRS, [c] Model 3: model 2 + current CA and current PA. Abbreviations: AD−CM: AD−signature region cerebral glucose metabolism; APOE4: apolipoprotein ε4; CA: cognitive activity; PA: physical activity; VRS: Vascular risk score.

IV. Discussion

We observed that APOE4 was strongly associated with increased global Aβ accumulation and reduced HVa and AD-CM, whereas neither midlife cognitive activity nor physical activity was related with any of the AD biomarkers in bivariate association analysis. In terms of the moderating effects of midlife lifestyle activities, midlife cognitive activity moderated the Aβ-independent influence of APOE4 on HVa, and midlife physical activity moderated the Aβ-mediated influence of APOE4 on AD-CM, while neither activity moderated the APOE4 effects on Aβ accumulation.

1. Association between APOE4, CA, and PA with AD biomarkers

Consistent with previous reports (2-5), APOE4 status was strongly associated with Aβ accumulation and the neurodegeneration biomarkers in our study.

In contrast, neither midlife cognitive activity nor physical activity were related to any of the AD neuroimaging biomarkers in bivariate

analysis. Many studies investigating the association between cognitive activity or physical activity and AD biomarkers have reported inconsistent findings (11–23). Among them, only a few have focused on the effect of midlife activities (13, 21, 23) and have shown no direct association between midlife cognitive activity or physical activity and AD biomarkers, which was similar to our findings. Such a null association with Aβ accumulation and AD-related neurodegeneration biomarkers appears discordant with the finding that midlife lifestyle activities are associated with a decreased risk of late-life cognitive decline (7) or AD dementia (8, 9). Such a discrepancy was also observed in prior studies (22, 52). A report based on the Harvard Aging Brain Study demonstrated that a history of greater cognitive activity is correlated with better cognitive performance, but not with Aβ accumulation, glucose metabolism, or hippocampal volume in CN older adults (22). A neuropathological study also showed that greater past cognitive activity is related to slower late-life cognitive decline, independently of AD neuropatholgies (52). Taken together, a change in AD pathology itself is not likely to be the direct substrate underlying the effect of past lifestyle activities on cognitive benefit.

2. Moderation of midlife cognitive activity or physical activity for APOE4 effects on Aβ deposition

In our study, neither midlife cognitive activity nor physical activity moderated the APOE4 effect on Aβ deposition itself. However, two previous studies reported a significant interaction effect between lifestyle activities and APOE4 on Aβ accumulation (11, 19). They showed a beneficial effect of cognitive activity (19) or physical activity (11) on Aβ accumulation only in APOE4 carriers. This discrepancy might be attributed to different study methods and sample characteristics. We focused specifically on midlife activities to reduce the possibility of reverse causation (25), whereas other studies adopted lifetime or recent 10 year lifestyle activities including current ones, which could be affected by underlying pathophysiological processes. In addition, the educational levels of their subjects (mean educational years : 16.86 (19) and 16.23 (11)) were higher than those of our study (11.19 years. Another study (23) detected an inverse association between midlife cognitive activity and Aβ accumulation in APOE4 carriers only in the high education group ($\geq$14 years), but not in the low education group (<14 years). Also, midlife cognitive activity level of our study (mean = 2.30)

somewhat lower than that of other study (mean = 3.64) using same cognitive activity questionnaire (19).

3. Moderation of midlife cognitive activity for APOE4 effects on HVa

Midlife cognitive activity moderated the Aβ-independent influence of APOE4 on HVa. More specifically, the direct negative effect of APOE4 on HVa was more evident in individuals with higher midlife cognitive activity than in those with a lower midlife cognitive activity. According to the APOE4 antagonistic pleiotropy hypothesis, APOE4 differentially impacts across different life stages. APOE4 offers cognitive benefits during early adulthood at the expense of more-rapid decline in cognitive function with aging (53). Young CN individuals with APOE4 have elevated resting-state activity in the default mode network including the hippocampus compared to those without APOE4 (54). APOE4 carriers in midlife have more strongly activated memory-related brain regions including the hippocampus to maintain the same level of performance than non-carriers, but this neural compensatory recruitment begins to decline by midlife (53, 55). Such increased activity in the memory-related brain regions is

also known to be related with atrophy of the medial temporal lobe including the hippocampus (56). Taken together, our results indicate that excessive midlife cognitive activity in APOE4 carriers may accelerate hippocampal atrophy by imposing hyperactivation of the related brain regions.

4. Moderation of midlife physical activity for APOE4 effects on AD-CM

While midlife physical activity did not moderate the Aβ-independent influence of APOE4 on AD-CM, it moderated the indirect pathway from APOE4 to AD-CM via Aβ accumulation. More specifically, Aβ accumulation, which is closely linked to APOE4, was associated with decreased AD-CM in individuals with a lower level of midlife physical activity, whereas such an inverse correlation between Aβ accumulation and AD-CM was not significant in those with a higher level of physical activity.

There are several possible pathways linking active physical activity and preserved AD-CM. First, physical activity has been suggested to increase cognitive or brain reserve through

angiogenesis, increased cerebral blood flow and enhanced synaptic plasticity (57, 58). Individuals with a greater reserve through active physical activity can tolerate a greater burden of cerebral Aβ accumulation and do not show reduced AD-CM as shown in the inactive physical activity group. Second, Aβ shares a consensus amino acid sequence with insulin and Aβ directly binds to the insulin receptor leading to increased insulin-resistance (59). Increased insulin-resistance is associated with reduced AD-CM (60). As active physical activity decreases insulin-resistance (61), it could prevent the reduction of AD-CM by Aβ. Finally, active physical activity also lowers chronic inflammation (58). Increased cerebral Aβ accumulation induces neuro-inflammation which can reduce AD-CM (62). Consistent with our result, a 21-year longitudinal follow up study reported that midlife physical activity is inversely associated with a late-life risk of AD dementia only among APOE4 carriers (8). Given the strong association between APOE4 and Aβ accumulation (2), our findings suggest that higher midlife physical activity decreases APOE4-related AD risk by weakening the influence of Aβ accumulation on further hypometabolism or neurodegeneration.

One of the key strengths of this study is the statistical approach using models including both the Aβ-mediated pathway and Aβ-independent pathway of APOE4 influence. This approach made it possible to clarify the complex associations and interactions between APOE, midlife lifestyle factors, and AD biomarkers. Our findings, based on such complex models, may explain why studies about the effects of lifestyle activities on AD biomarkers have resulted in inconsistent findings. The relatively large sample size, particularly of the CN group, is another strong point of this study. Third, controlling for potential confounding factors, such as occupational complexity, educational level, age, sex, vascular risk factors and current lifestyle activities permitted a clear explanation of the association among APOE, midlife lifestyle factors and AD biomarkers. Nevertheless, some limitations should also be mentioned. Because this was not a longitudinal study, we could not confirm causality for the observed associations. To overcome such a limitation in the study design, we used midlife cognitive activity and physical activity instead of current activities. Nevertheless, further long-term follow up studies are needed to clarify the causal aspects. Although the cognitive activity and physical activity questionnaires used in the present study were reliable and well-validated, they are based on self-reports and might

be biased due to recall problems. To minimize such recall bias, we only included non-demented subjects. Although MCI individuals have some memory problems, their problems are confined to recent memory, not remote memory (63). The proportion of individuals with insufficient PA, which is defined as adults not meeting the WHO recommendations (64) on PA for health, in this study (9.5%) was lower than that of general populations (35.4%) in Korea (65). This might be attributed to the fact that the present study excluded the patients with a history of stroke, severe vascular lesions on MRI or dementia, whose midlife PA is likely to be low (66, 67).

In conclusion, the current study was the first attempt to elucidate the moderating effect of modifiable midlife lifestyle factors on the influence of APOE4 on *in vivo* AD pathologies. Our findings suggest that high midlife cognitive activity may accelerate hippocampal atrophy induced by APOE4. In contrast, active midlife physical activity may delay AD-signature regional brain hypometabolism by weakening the influence of APOE4-associated Aβ accumulation. Overall, the information obtained in this study will be helpful to select preventive midlife lifestyle activities to reduce the negative influence of the genetic risk for AD.

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요약(국문초록)

서론: 본 연구에서는 중년기의 인지활동과 신체 활동이 알츠하이머병의 위험요인으로 알려진 APOE4 와 알츠하이머병 이미징 바이오마커간의 관계를 조절하는지 알아보고자 하였다. 이에 비치매노년군을 대상으로 APOE4 와 대뇌 베타 아밀로이드와 신경퇴행 바이오마커인 대뇌 포도당대사, 해마 부피의 관계를 중년기의 인지활동 및 신체활동이 어떻게 조절하는지 탐색하고자 하였다.

방법: 287명의 비치매 노년기 대상자들이 본 연구에 포함되었다. 각 대상자들은 포괄적 임상 및 신경심리평가 및 APOE 유전자형 검사를 시행하였고, [^{11}C]-PiB PET을 이용하여 대뇌 베타 아밀로이드 단백질 침착도를 측정하였고, FDG-PET을 이용하여 대뇌 포도당대사를 뇌 MRI를 이용하여 해마부피를 측정하였다.

결과: 중년기의 인지활동이나 신체활동은 APOE4의 대뇌 베타 아밀로이드 침착에 미치는 영향을 조절하지는 않았다. 중년기의 인지활동은 APOE4가 해마 부피에 미치는 영향을 유의하게 조절하는 것으로 나타났는데, 중년기의 인지활동이 높을 때에는 APOE4 보유군이 미보유군보다 해마부피가 유의하게 적었으나, 중년기의 인지활동이 낮을 때에는 이런 차이가 나타나지 않았다. 중년기의 신체활동은 APOE4와 밀접한 관련이 있는 대뇌 아밀로이드 침착이 대뇌 포도당 대사에 미치는

영향을 유의하게 조절하는 것으로 나타났다. 중년기의 신체활동이 낮을 때에는 대뇌 아밀로이드 침착이 높을 수록 유의하게 대뇌 포도당 대사가 낮게 나타났으나, 신체활동이 높을 때에는 이런 관계가 유의미하게 관찰되지 않았다.

결론: 본 연구 결과, 중년기의 높은 인지활동은 APOE4유전자에 의한 해마 부피 감소를 더 가중시키는 것으로 나타났으나, 중년기의 높은 신체활동은 APOE4와 관련된 대뇌 아밀로이드 침착의 대뇌 포도당 대사에 대한 영향을 약화시킴으로써, 알츠하이머-관련 신경퇴행을 지연시킬 수 있음을 시사한다.

주요어: 알츠하이머병; 아포지단백질; 아밀로이드; 신경퇴행; 중년기; 인지활동, 신체활동

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