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APOE gene region methylation is associated with cognitive performance in middle-aged urban adults

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ABSTRACT

Apolipoprotein (*APOE*) ε4 allele is a strong risk factor for Alzheimer's disease (AD) and cognitive decline. Epigenetic modifications such as DNA methylation (DNAm) play a central role in cognition. This study sought to identify DNAm sites in the APOE genomic region associated with cognitive performance in a racially diverse middle-aged cohort (n = 411). Cognitive performance was measured by 11 standard neuropsychological tests. Two CpG sites were associated with the Card Rotation and Benton Visual Retention cognitive tests. The methylation level of the CpG site cg00397545 was associated with Card Rotation Test score ($p = 0.000177$) and a novel CpG site cg10178308 was associated with Benton Visual Retention Test score ($p = 0.000084$). Significant associations were observed among the dietary inflammatory index, which reflects the inflammatory potential of the diet, cognitive performance and the methylation level of several CpG sites. Our results indicate that DNAm in the *APOE* genomic area is correlated with cognitive performance and may presage cognitive decline.

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1. Introduction

Apolipoprotein E (*APOE*) plays a central role in lipid and cholesterol metabolism in the central nervous system (CNS) (Mahley 2016). More specifically, *APOE* mediates the lipoprotein pathway that regulates cholesterol recycling and redistribution for cellular repair and maintenance (Boyles et al., 1990). In humans, the brain is the most cholesterol rich organ and synthesizes its own cholesterol. In the brain, APOE protein is mainly produced by astrocytes and is abundantly expressed in neurons and microglia under stress or injury conditions (Fernandez et al., 2019).

The human *APOE* gene has 3 common alleles (ε2, ε3, and ε4), coding functionally distinct *APOE* isoforms. The ε4 allele is associated with increased risk of developing Alzheimer's disease (AD) (Corder et al., 1993; Okuizumi et al., 1994). The *APOE* ε4 allele is the main genetic risk factor for sporadically occurring AD as well as the earlier stages of mild cognitive impairment (MCI) (Kryscio et al., 2006). While *APOE* ε4 allele carriers have an increased risk, ε2 allele carriers are protected from dementia (Farrer et al., 1997). The *APOE* ε4 allele is also associated with greater cognitive decline in non–demented individuals (Bretsky et al., 2003). Additionally, the *APOE* ε4 allele moderates the effects of known risk factors of cognitive decline including sex, age, hypertension, diabetes, and smoking status (Farrer et al., 1997; Carmelli et al., 1999; Dufouil et al., 2000; de Frias et al., 2014; Andrews et al., 2015; Riedel et al., 2016). Furthermore, single nucleotide polymorphisms in the *APOE* linkage disequilibrium (LD) locus including *TOMM40, NECTIN2,* and *APOC1* are associated with cognitive performance (Bartres-Faz et al., 2001; Takei et al., 2009; Cervantes et al., 2011; Zhou et al., 2014).

Genomic variations, epigenetic modifications including histone modifications, DNA methylation (DNAm) and non–coding RNA (ncRNA) have been associated with many diseases. Epigenetic changes link altered gene expression with environmental factors such as exercise and diet. DNAm is the addition of a methyl group to the C-5 position of the cytosine pyrimidine ring. DNAm in the promotor region of genes can perturb transcription factor binding and suppress gene expression (Landgrave-Gomez et al., 2015). One

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study found that DNAm in the *APOE* gene had significant interindividual epigenetic variability in post-mortem brains, which may contribute to AD predisposition (Wang et al., 2008). Several previous studies have examined the association between APOE DNAm and participants with diagnosed AD or mild cognitive impairment (Karlsson et al., 2018; Shao et al., 2018; Mancera-Paez et al., 2019). Two studies have evaluated the relationship of APOE DNAm and cognitive functions in cognitively healthy participants. One found DNAm in the APOE gene region was inversely associated with delayed recall during normal cognitive aging among 289 elderly African Americans with mean age 67 years (Liu et al., 2018). The other study observed no association between general cognitive ability and APOE DNAm in a large European based cohort (Mur et al., 2020). Most studies have focused on elderly AD patients and had relatively small sample sizes. The association between DNAm in the *APOE* genomic region and cognitive function in a middle-aged community-dwelling diverse cohort remains elusive.

Many studies have suggested that neuroinflammation plays an important role in AD pathogenesis (Morales et al., 2014; Heneka et al., 2015). Diet has been shown to be able to modulate systemic inflammation and neuroinflammation (Galland 2010; Tran et al., 2016). Accumulating evidence has suggested that dietary factors which can modulate inflammation may affect the progression of AD (Szczechowiak et al., 2019). The Dietary inflammatory index (DII) was developed to be a sensitive measurement to identify the inflammatory potential of the diet with a higher score indicating greater proinflammatory potential (Shivappa et al., 2014). Recently, a study has shown higher DII scores were associated with an increase in the risk for dementia incidence (Charisis et al., 2021). It is established that DNAm plays a pivotal role in the pathogenesis of cognitive decline, but little is known about the association between DII and DNAm. In this study, we aim to explore the association among DII, DNAm, and cognitive performance in a community-dwelling middle-aged cohort.

Here, we characterized DNAm across 4 genes in the *APOE* genomic region (*APOE, TOMM40, NECTIN2,* and *APOC1*) in blood samples collected from 411 middle-aged, community dwelling, AAs and whites, cognitively intact participants in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) cohort. Linear regression models were used to evaluate associations between DNAm and cognitive test scores adjusting for possible covariates. We tested for interactions among sex, age, race and *APOE* allele status and whether *APOE* gene region DNAm differences are associated with cognitive function. Our study on the DNAm of *APOE* region in a diverse middle-aged cohort may facilitate the development of new clinical biomarkers before the onset of dementia.

2. Material and methods

2.1. Study sample

The participants in this study were from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) cohort of the National Institute on Aging Intramural Research Program, National Institutes of Health (NIH) (Evans et al., 2010). HANDLS was initiated in 2004 and is an interdisciplinary, community-based prospective longitudinal study of AAs and whites based in Baltimore, Maryland. The HANDLS participants were drawn from 13 Baltimore neighborhoods (groups of contiguous census tracts) and were between the ages of 30–64 years at baseline. Poverty status was defined as above or below the 125% of the 2004 US federal poverty guidelines. Baseline data were collected through home visits and examination on the medical research vehicles (MRV). The participants were administered physical examination, medical history inquiries, cognitive testing, dietary recall interviews and other assessments. Details on the study design and protocols have been described elsewhere (Evans et al., 2010). HANDLS was approved by the Institutional Review Board of National Institutes of Health. All participants provided written informed consent. The sample in this study consists of 411 participants with mean age 49 years and balanced by sex, race, and poverty status (Table 1, Fig. S1).

Table 1
Descriptive statistics of participants by *APOE* allele carrier status.

Variables	Total	*APOE* ε4+	*APOE* ε4-
Number of Participants	411	134	277
Age (y) (mean [sd])	48.7 (8.67)	48.6 (9.05)	48.9 (8.16)
Sex (N [%])			
Male	209 (50.9%)	65 (48.5%)	144 (52.0%)
Female	202 (49.1%)	69 (51.5%)	133 (48.0%)
Race (N [%])			
White	199 (48.4%)	47 (35.1%)	152 (54.9%)
AfrAm	212 (51.6%)	87 (64.9%)	125 (45.1%)
Poverty Status (N [%])			
Above	204 (49.6%)	69 (51.5%)	135 (48.7%)
Below	207 (50.4%)	65 (48.5%)	142 (51.3%)
Smoking Status (N [%])			
Yes	183 (47.3%)	59 (44.7%)	124 (44.8%)
NO	204 (52.7%)	65 (49.2%)	139 (50.2%)
Diabetes (N [%])			
Yes	48 (12.7%)	17 (12.9%)	31 (11.2%)
NO	329 (87.3%)	104 (78.8%)	225 (81.2%)
CVD (N [%])			
Yes	154 (43.9%)	47 (35.6%)	107 (38.6%)
NO	197 (56.1%)	59 (44.7%)	138 (49.8%)
WRAT score (mean [sd])	42.40 (7.56)	43.02 (7.72)	41.49 (6.73)
BVRT score (mean [sd])	6.80 (4.31)	6.24 (4.29)	7.75 (4.27)
CRD score (mean [sd])	37.90 (17.32)	38.82 (17.64)	34.89 (16.98)

Four hundred and eleven of the 464 participants have *APOE* allele genotypes. Key: AfrAm, African American; CVD, cardiovascular disease; WRAT, wide range achievement test; BVRT, Benton visual retention test; CRD, card rotation test; sd, standard deviation.

2.2. Cognitive function measures

HANDLS participants were administered a battery of standard cognitive tests capturing different cognitive domains. The cognitive battery included: Mini-Mental State Examination total score (global mental status); California Verbal Learning Test, List A (verbal learning) and delayed free recall (verbal memory); Benton Visual Retention Test (visuospatial ability), total errors; Card Rotation Test (visuospatial ability); Digit Span Forward and Backward, total correct (attention, executive function and/or working memory); Animal Fluency Test (language and/or verbal fluency), total words minus intrusions and/or perseverations; Brief Test of Attention, total correct trials of 10; Trail-Making Test, part A (attention) and part B (executive function), number of seconds to completion; and the Clock-Drawing Test command total score (0–10) (visuo-constructional). For most of the cognitive tests, higher test scores indicate better cognitive performance, except for the Benton Visual Retention Test, which measures the total number of errors, and Trail-Making Test which record overall completion time.

2.3. DNA methylation measures

DNAm in peripheral white blood cell samples was profiled using the Illumina Human MethylationEPIC BeadChip as described previously (Tajuddin et al., 2019). Briefly, low quality samples, and probes with low detection rates were excluded. Unrelated participants were selected to reduce the potential influence of shared genetics on the findings. We restricted the analysis to

69 CpGs located on chromosome 19 between 44,846,297 and 44,919,346 bp, which corresponded to the genomic region encompassing the *PVRL2-TOMM40-APOE-APOC1* (UCSC GRCh38/hg19 genome build). For each CpG site, the methylation level used for analysis was defined as the β-value, adjusted for batch effects, and white blood cell proportions. The proportion of each white blood cell type was estimated using Houseman's method (Houseman et al., 2012). β-value outliers were excluded. We used annotation from Illumina MethylationEPIC product files to determine whether each CpG site was in a promoter region or gene body. DNAm levels were measured from blood samples collected during the MRV examinations for 411 unrelated participants. None of the participants has been diagnosed with dementia by a physician.

2.4. APOE *genotyping*

To evaluate the potential confounding effect of *APOE* genotype, we assessed the *APOE* genotype of our participants (N = 411) (Fig. S1). Based on the identity of the nucleotides at SNP positions rs429358 (*APOE*-C112R) and rs7412 (*APOE*-R158C), participants with the $\varepsilon 3/\varepsilon 4$ and $\varepsilon 4/\varepsilon 4$ haplotypes were classified as $\varepsilon 4$ carriers and the others as non–$\varepsilon 4$ carriers. Taqman Assays (Applied Biosystems Assay-On-Demand part numbers C__3084793_20 and C__904973_10) were utilized to genotype these SNPs on a 7900HT Sequence Detection System (Applied Biosystems). Absolute quantification was performed on ThermoHybaidPCR cycler blocks using the following conditions across 4 stages. Stage 1: consisted of 1 cycle at 50 °C for a total of 2 minutes. Stage 2: consisted of 1 cycle at 95 °C for a total of 10 minutes. Stage 3: consisted of 40 cycles at 95 °C, each for a period of 15 s. Stage 4: consisted of 1 cycle at 60 °C for a total of 1 minute. PCR plates were held at 4 °C until returning to the 7900HT Sequence Detection System to perform an allelic discrimination (Federoff et al., 2012).

2.5. Covariates

Covariates were selected based on reported influence on cognitive performance from prior research. Specifically, sex, race, age, poverty status, body mass index, hypertension, smoking status, diabetes mellitus, cardiovascular disease status, *APOE* allele status, and literacy level were chosen as the covariates (Deary et al., 2002; Scarmeas et al., 2006; Anstey et al., 2007; van den Berg et al., 2009; Carlsson 2010; Prickett et al., 2015). Body mass index (BMI, kg/m^2) was calculated from measured weight and height. Hypertension was defined as either an average of 2 measurements of systolic blood pressure (SBP) $\geq$140 mm Hg or diastolic blood pressure (DBP) $\geq$90 mm Hg, current use prescribed antihypertensive medication, or self-reported diagnosis of hypertension. Smoking status was self-reported as part of the MRV exam. Diabetes mellitus was defined as fasting plasma glucose concentration $\geq$126 mg/dL (7.0 mmol/L), self-reported diabetes diagnosis, or current use of prescribed hypoglycemic agents. A "CVD" covariate was created for cardiovascular disease status of the participants, which was defined as having a self-reported history of hypertension, stroke, coronary artery disease, or blood clot. The Wide Range Achievement Test (WRAT-3) was administered as a measurement of literacy and is used here as an evaluation of an individual's reading comprehension (Wilkinson 1993).

2.6. Dietary inflammatory index (DII) measures

The 24-hour dietary recall was used to collect food and beverage intakes of the HANDLS cohort. Data were collected through the computerized Automated Multiple-Pass Method (AMPM) established by the United States Department of Agriculture (USDA) (Moshfegh et al., 2008). The Dietary Inflammatory Index (DII) for HANDLS participants was calculated based on the 24-hour dietary recall data. The DII, developed by Shivappa and colleagues (Shivappa et al., 2014), consists of 45 dietary factors including a variety of macronutrients, micronutrients, vitamins, minerals, flavonoids, spices, and herbs. For this study, 35 of 45 food parameters were available for the calculation of the DII. These dietary intakes included alcohol, vitamin B_{12}, vitamin B_6, carotene, caffeine, carbohydrates, cholesterol, energy, total fat, fiber, folate, iron, magnesium, mono-unsaturated fatty acid, niacin, omega_3 fatty acids, omega_6 fatty acids, protein, poly-unsaturated fatty acid, riboflavin, saturated fatty acids, selenium, thiamin, vitamin A, vitamin C, vitamin D, vitamin E, zinc, tea, flavan-3-ols, flavones, flavones, flavanones, anthocyanidins, isoflavones. DII was calculated for the subset of participants (N = 363) with dietary data.

2.7. Statistical analysis

All statistical analyses were performed in RStudio version 1.3.1093 (R version 4.0.3) (R Core Team, 2020). For the analyses exploring effects of DNAm levels, linear regression models were used. The primary analysis was conducted in the full model with all covariates ($N = 411$). Linear regression was used to test for association between the methylation level of each CpG site and each cognitive measure, adjusting for all covariates stated above. For multiple comparisons, the threshold for statistical significance was Bonferroni-corrected for each CpG ($p < 0.0007$). Delta R^2 was calculated comparing the model of interest with the same model excluding the predictor variable. Interaction terms among age and *APOE* status were first tested in the model but no significant terms were found (data not shown). Therefore, these interaction terms were omitted from the final model.

3. Results

3.1. Description of study participant characteristics

Study participant characteristics are shown in Table 1 across *APOE* genotype groups. The age of the 411 participants ranged from 30.2 to 65.2 years with mean age of 48.7 years and standard deviation of 8.64. Other variables known to influence cognitive performance are listed in the table including smoking, diabetes, cardiovascular disease (CVD) status and the WRAT-3 which captures literacy level. Overall, 67.4% of the participants are *non–APOE4* carriers and 33.6% of participants carry at least 1 *APOE4* allele. No significant differences were found in sex, age, poverty, smoking, CVD status and WRAT-3 between the *APOE4* carrier group and *non–APOE4* carrier group. However, *APOE4* carriers were significantly more prevalent among AAs (64.9%) compared to whites (35.1%) in our cohort. We examined the correlation among all the covariates. We found that smoking was more prevalent in men than women. However, the proportion of cardiovascular diseases were higher among women than men.

3.2. APOE *methylation and cognitive function*

We examined the association between cognitive tests scores and DNAm levels of CpGs in the *APOE* genomic area in 411 participants. Two significant associations were discovered in the full model after correcting 69 CpGs for multiple testing (Fig. 1, Table 2). One CpG cg00397545 located in the promotor region of *APOC1* was significantly associated with the Card Rotation Test score ($p = 0.000177$), which captures visuospatial ability, and has

Table 2
Linear regression analyses between cognitive test scores and CpG methylation levels in *APOE* genomic region.

Cognitive Test	Associated CpGs	Gene	*p*-value	β-value	ΔR^2	PreviousLiterature
Card Rotation Test	cg00397545	*APOC1*	0.000177	-0.69	0.04	Associate with CSF Aβ42 in AD patients (Shao et al., 2018)
Benton Visual Retention Test	cg10178308	*NECTIN2*	0.000084	-0.14	0.04	Novel

Shao, Y., M. Shaw, K. Todd, M. Khrestian, G. D'Aleo, P. J. Barnard, J. Zahratka, J. Pillai, C. E. Yu, C. D. Keene, J. B. Leverenz and L. M. Bekris (2018). "DNA methylation of TOMM40-APOE-APOC2 in Alzheimer's disease." J Hum Genet 63(4): 459-471.

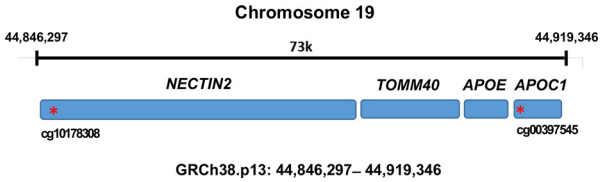

Fig. 1. Schematic for *APOE* genomic area Genomic region of *NECTIN2-TOMM40-APOE-APOC2* locus on chromosome 19 Key: *NECTIN2*: Nectin Cell Adhesion Molecule 2; *TOMM40*: Translocase of Outer Mitochondrial Membrane 40; *APOC1*: Apolipoprotein C1 CpG sites marked with an asterisk (*) are in promoter regions (within 1.5 kb before the transcription start site of the gene).

Table 3
Association of cognitive test scores with age and *APOE4* status.

	Age		*APOE4*	
	Estimate	*p*-value	Estimate	*p*-value
Basic Model (N = 411)				
Benton Visual Retention Test	0.1217	<0.0001	1.4462	0.009
Card Rotation Test	-0.5487	<0.0001	-3.2295	0.1
Full Model (N = 411)				
Benton Visual Retention Test	0.1167	0.0004	0.9963	0.08
Card Rotation Test	-0.4894	<0.0001	-0.8898	0.65

Full model is adjusted by sex, race, age, poverty status, body mass index, smoking status, diabetes mellitus, cardiovascular disease status, *APOE4* allele status, and WRAT score.

been reported be associated with cerebrospinal fluid amyloid β-peptide 42 (Aβ42) in AD patients (Shao et al., 2018). Another CpG cg10178308 in the promotor region of *NECTIN2* was significantly associated with Benton Visual Retention Test score ($p = 0.000084$), which captures visual recall ability, and has not been reported before. The methylation level of the 2 significant CpGs were not correlated with each other. No significant interactions were found between CpGs and covariates.

3.3. Age and APOE genotypes on cognitive performance

For middle-aged adults, when the development of dementia may be at its early stage, the APOE genotype effect on cognitive functioning remains unclear (Sager et al., 2005; O'Dwyer et al., 2012; Patel et al., 2013; Zimmermann et al., 2019). In this middle-aged cohort, age was strongly associated with performance on the Benton Visual Retention Test, and Card Rotation Test (Table 3). We found the *APOE* $\varepsilon 4$ allele was associated with worse performance on Benton Visual Retention Test ($p = 0.009$) (Fig. 2, Table 3). However, the effect of *APOE* genotype was reduced to a trend-level association ($p = 0.08$) after adjusting for covariates.

3.4. Association between DNA methylation and APOE genotype

DNA methylation, as one of the major epigenetic mechanisms, is regulated by DNA methyltransferases (Dnmts). Mutations in DNMT1 are associated with a form of neurodegenerative disease (Klein et al., 2011), suggesting that alterations in DNAm may play a crucial role in the pathogenesis of cognitive decline. Since little is known about the relationship between DNAm, *APOE* and cognition, we chose to examine DNAm in the genomic region of *APOE*. In our cohort, significant associations between *APOE* carrier status and DNAm level at 2 CpG sites were found after correcting for multiple testing in the full model with all available covariates. The 2 CpGs, cg07773593 ($p = 0.0004$) and cg13880303 ($p = 3.2 \times 10^{-8}$), were located closely to the promotor region of the *APOC1* gene. Their methylation levels were strongly correlated with each other (r = 0.69) and the methylation level of both CpGs in *APOE4* carriers were significantly reduced than non–*APOE4* carriers.

3.5. Association among dietary inflammatory index, cognitive performance, and CpGs in APOE region

We discovered that the Benton Visual Retention Test score was significantly associated with cg10178308, which is located in the promotor region of the *NECTIN2* gene. *NECTIN2* functions in immune modulation and is expressed in neurons (Samanta et al., 2012). Since inflammation plays a role in cognitive decline (Kravitz et al., 2009; Bettcher et al., 2012), we wanted to examine the influence of inflammation on cognitive performance in our cohort. To test this, we investigated the inflammatory potential of the diet of our participants as there is evidence that diet component such as saturated fat promoted neuroinflammation (Milanski et al., 2009). We evaluated the association between DII score and cognitive test scores in our cohort using the full model (N = 363). We observed significant associations between DII and Benton Visual Retention Test ($p < 0.001$), Card Rotation Test ($p = 0.036$), Mini-Mental State Examination ($p < 0.001$) and Animal Fluency Test ($p = 0.015$). We then examined the association between DII and the CpGs in the *APOE* genomic area using the full model and found that only 1 CpG cg10178308 passed multi-testing correction ($p = 0.003$).

4. Discussion

We examined the relationship between the DNAm level, *APOE* carrier status and cognitive performance in a cross-sectional analysis of participants from age 30 to 65. Our study utilized a middle-aged cohort with both African Americans and Whites and identified a novel and a previously reported CpG site that were associated with either the Card Rotation Test (cg00397545) or the Benton Visual Retention Test (cg10178308) after Bonferroni correction for multiple testing (Table 2). However, we did not correct cognitive tests for multiple comparisons. Thus, the chance of Type I error remains a concern. We found significant associations between *APOE* carrier status and DNAm level at 2 *APOE* gene region CpGs (cg07773593 and cg13880303, located close to the promotor region of the *APOC1* gene) after correcting 69 CpGs for multiple testing. We also observed a negative association between

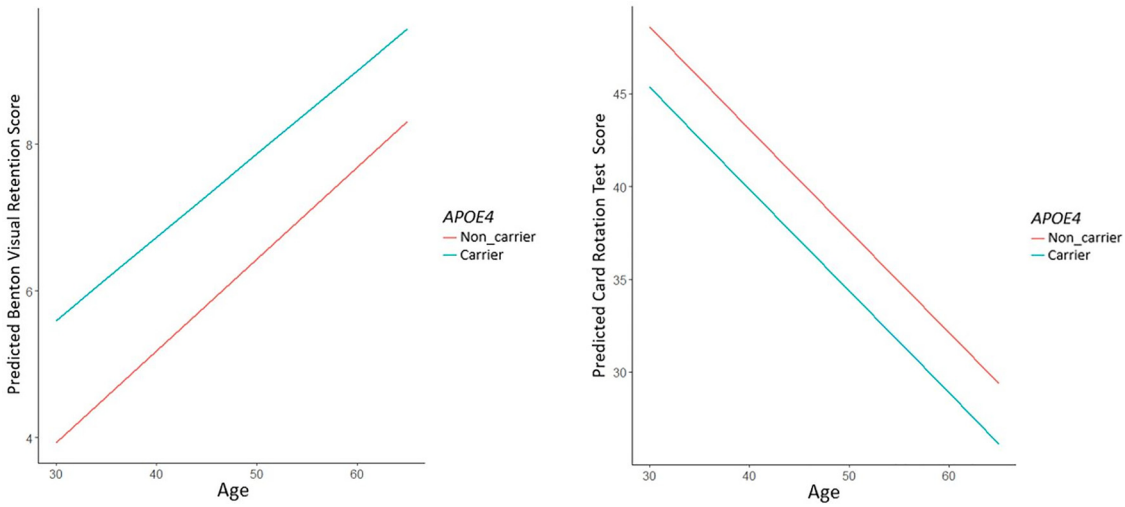

Fig. 2. Relationship between age and cognition test scores of (A) Benton visual retention test and (B) Card rotation test based on *APOE4* allele carrier status in an unadjusted model.

cognition and DII score, and another positive association between DII and the DNAm level of CpG cg10178308.

We identified a novel CpG, cg10178308 associated with the Benton Visual Retention Test score ($p = 0.000084$). Cg10178308 is located in the promotor region of Nectin Cell Adhesion Molecule 2 (*NECTIN2)* gene, which encodes a plasma membrane glycoprotein involved in adherens junctions as well as a modulator of T-cell signaling (Martinez and Spear 2001; Yu et al., 2009). *NECTIN2* binding to CD226 and stimulates T-cell proliferation and cytokine production, including IL2, IL5, IL10, IL13, and Interferon γ. However, NECTIN2 binding with PVR Related Immunoglobulin Domain Containing Gene (PVRIG) inhibits T-cell proliferation (Tahara-Hanaoka et al., 2004; Zhu et al., 2016). SNPs in the *NECTIN2* gene are associated with AD or cognitive impairment independent of *APOE* $\varepsilon 4$ carrier status (Takei et al., 2009; Cruz-Sanabria et al., 2021; Zhou et al., 2019). A recent study discovered that another CpG site, cg11670000, in *NECTIN2* was associated with the Rey Auditory Verbal Learning test (RAVLT) delayed recall instrument, which evaluates verbal learning, and memory (Liu et al., 2018). The Benton Visual Retention Test is a widely used test of visual memory and visual construction (Sivan 1992), and the Benton Visual Retention Test of visual memory is highly sensitive to early dementia. One study discovered that more errors on the Benton Visual Retention Test was associated with an elevated risk of AD up to 15 years later compared to participants with fewer errors (Kawas et al., 2003). The Benton Visual Retention Test score can be influenced by individual differences including age, socioeconomic status, and educational attainment (Strauss et al., 2006). In our study, we adjusted our model with participants' age, literacy level and other covariates and found an inverse association between Benton Visual Retention Test score and DNAm of cg10178308 in a middle-aged cohort (average 49 years old).

Further, we identified that DNAm of the CpG site cg00397545 was associated with the Card Rotation Test score. This cg00397545 site has been reported to be associated with cerebrospinal fluid amyloid β-peptide 42 ($A\beta_{42}$) in AD patients (Shao et al., 2018). Cg00397545 is located in the promoter region of the *APOC1* gene, which encodes apolipoprotein C1. APOC1 is mainly involved in lipoprotein metabolism and inhibits the APOE mediated uptake of very low density lipoprotein (Fuior and Gafencu 2019). Many studies have shown the *APOC1* gene is a genetic risk factor for AD, in association with *APOE* allele status (Poduslo et al., 1998; Ki et al., 2002; Tycko et al., 2004; Lucatelli et al., 2011). In mice, overexpression or knock out of human *APOC1* resulted in impaired memory and learning functions (Berbée et al., 2011). Additionally, apolipoprotein C1 suppressed pro-inflammatory cytokine secretion from glial cells, which is dependent on *APOE* genotype in humans (Cudaback et al., 2012). The Card Rotation Test is used to evaluate visuospatial ability, particularly spatial rotational ability. One study found that the Card Rotation Test showed the earliest change in rates of cognitive decline among 11 cognitive measurements in preclinical AD, suggesting its utility for early cognitive decline detection (Williams et al., 2020).

The neurodegenerative process can be caused by neuroinflammation due to the activation of immune cells that produce a large quantity of proinflammatory cytokines, which can cause damage to neurons (Fuhrmann et al., 2010). An increased level of proinflammatory cytokines was found in the brain and CSF of people with dementia, suggesting the role of microglia in the pathology of dementia (Domingues et al., 2017). Furthermore, markers of neuroinflammation colocalize with amyloid plaque and neurofibrillary tangles, which are the hallmarks of AD and cognitive decline (Kuo et al., 2005). Another study suggested participants that have high inflammatory concentrations at baseline may have an increased risk of developing dementia after about 2 decades of follow up (Schmidt et al., 2002). The Dietary Inflammatory Index (DII) was developed to assess the inflammatory potential of nutrients and foods in the context of a dietary pattern (Shivappa et al., 2014). DII has been shown to have significant positive associations with blood inflammatory markers including Interleukin 6 (IL-6), IL-7, C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) in diverse populations (Shivappa et al., 2015; Tabung et al., 2015; Cervo et al., 2020). Two studies have found significant association or predictive value of DII score with modified Mini-Mental State Examination score in older women and older Korean populations (Hayden et al., 2017; Shin et al., 2018). Another study discovered a significant relationship between DII score and Animal Fluency Test score in older participants from the U.S. (Frith et al., 2018). In our study, we replicated the findings of association among DII score, Animal Fluency Test score and Mini-Mental State Examination score, while we found additional association including Benton Visual Retention Test, Card Rotation Test, and Digit Span Forward and Backward Tests.

Our study has several strengths. We are among the first to assess the relationship between cognitive performance and *APOE* methylation in a diverse, urban sample of middle-aged men, and women. In addition, the DNAm profile of the *APOE* genomic area was characterized using high-density Methylation EPIC BeadChip, which has more CpG candidate sites compared to the previous Illumina HumanMethylation450 array. Moreover, a battery of 11 cognitive tests were performed to capture multiple domains of cognitive functions. To the best of our knowledge, this is the first study to characterize the relation between DII and DNAm. This study also has several limitations. First, only cross-sectional analysis of association between DNAm and cognitive performance has been conducted. Further longitudinal studies are necessary to infer causality and to characterize how DNAm and cognitive performance evolve with time. Moreover, we are not able to verify the correlation between blood DNAm with brain DNAm patterns as well as the relationship between DII with neuroinflammatory content. Blood DNAm in the APOE genomic area has modest correlation with brain DNAm (Hannon et al., 2015; Braun et al., 2019). Consequently, our findings based on blood DNAm may not reflect possible pathologic developments in the brain.

In conclusion, we identified 2 CpG sites in the *APOE* genomic area significantly associated with Benton Visual Retention Test, and Card Rotation Test in a diverse middle-aged urban-dwelling cohort. Cross-sectional analysis discovered that the cognitive performance of participants differed by the DNAm level of the significant CpGs. We showed DII exhibits strong associations with cognitive performance and the DNAm of cg10178308. Future work may explore the relationship between DNAm and cognitive performance in a longitudinal cohort to further strengthen our understanding of its evolvement as aging progresses.

Disclosure statement

The authors report no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.03.010.

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Figure S1. Flowchart of participants selected for this study