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Testing influences of *APOE* and *BDNF* genes and heart failure on cognitive function

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ABSTRACT

Background: Apolipoprotein E (*APOE*) ε2, ε4 and brain-derived neurotrophic factor (*BDNF*) Val66Met alleles have been associated with cognition. Associations of these alleles with cognition in heart failure (HF) and influences of HF across the cognitive spectrum (i.e., cognitively normal to Alzheimer's dementia [AD]) remain unexplored.
Objectives: To investigate influences of *APOE* ε2, ε4, *BDNF* Met and HF on cognition among participants across the cognitive spectrum.
Methods: Genetic association study using national databases ($N = 7{,}166$).
Results: *APOE* ε2 frequencies were similar across the cognitive spectrum among participants with HF. *APOE* ε4 frequency was lower among participants with HF and AD than non-HF participants with AD. *BDNF* Met frequencies did not differ across the spectrum. HF was associated with worse attention and language. In the HF subsample, ε4 was associated with worse memory.
Conclusion: Associations between *APOE* and cognition may differ in HF but need to be tested in a larger sample.

Introduction

Heart failure (HF) is a highly prevalent life-threatening condition affecting over 6.5 million adults in the U.S.[1] In past studies, 23–50% of patients with HF had cognitive dysfunction[2-4] in the domains of memory, attention, and executive function.[2-6] Cognitive dysfunction was an independent predictor of 12-month mortality in HF.[2,3] The etiology of cognitive dysfunction in HF has most often been attributed to decreased cerebral blood flow and increased cerebral microemboli.[4-9] Structural and functional alterations in the brain were detected among patients with HF.[10-13] The areas of impacted by HF were included prefrontal cortex, hippocampus, and anterior cingulate cortex which are consistent with the deficits in memory, attention, and executive function found among patients with HF.[10-13]

Risk factors associated with cognitive dysfunction in HF were HF symptom severity (e.g., left ventricular ejection fraction, New York Heart Association Class), comorbid medical conditions (e.g., depression, diabetes), and older age.[4,5,14-18] Although these factors have been supported as predictors of cognitive dysfunction, they do not fully account for the variability of cognitive dysfunction found among patients with HF. Other factors, particularly genes known to increase or decrease the risk of cognitive dysfunction in other groups such as apolipoprotein E (*APOE*), may improve understanding and prediction of cognitive dysfunction among these vulnerable patients with HF. However, few studies have been conducted that include genes known to increase or decrease risk of cognitive impairment in HF.[19,20]

To date, genomics researchers have identified genetic biomarkers for cognitive dysfunction including the risk for developing Alzheimer's dementia (AD).[21,22] Apolipoprotein E (*APOE*) ε4 allele is associated with increased risk of developing AD[23-26] and MCI.[27,28]

Abbreviations: AD, Alzheimer's dementia; *APOE*, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; CN, cognitively normal; HF, heart failure; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center

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The results of a meta-analysis showed that people who carried one copy of ε4 (ε3/ε4 heterozygotes) had 4.3 times greater odds of developing late-onset AD compared with people who had *APOE* ε3/ε3 genotype among people with reported White race.[29] A longitudinal study among 607 elderly adults (93% White race) from the Religious Order Study in the U.S. showed that the people who carried at least one *APOE* ε4 had 1.4-fold increased risk of developing MCI.[28] The frequency of having at least one *APOE* ε4 allele is 33% in the general U.S. population but increases to 58% in the U.S. older adult population with AD (> 60 years).[24] The frequency of *APOE* ε4 varies widely by ancestry, ranging from 8% to 41%.[30,31] For example, in a literature review study investigating *APOE* allele distributions in the world, the frequency of *APOE* ε4 was 15% in White race and 25% in African American race.[30,31]

In contrast to *APOE* ε4, the presence of the *APOE* ε2 allele appears to have a protective effect on cognitive function and may delay the development of AD.[23,26,32] The results of a meta-analysis showed that people who had one copy of ε2 (ε2/ε3 heterozygotes) were less likely to develop late-onset AD (OR = 0.6) compared with people who had *APOE* ε3/ε3 genotype among people with reported White.[29] In a study among 115 people with autopsy-confirmed late-onset AD and 243 control participants without AD, *APOE* ε2/ε3 was the least frequent genotype (1% of the AD and 16% of the controls) and having one ε2 allele was protective from developing AD (OR = 0.25).[32] The estimated prevalence of *APOE* ε2 allele is 14% in the U.S. population, but it is only about 4% in the AD population among adults over 60 years old.[24] The frequency of *APOE* ε2 varies by ancestry, ranging from 0% in Native American people to 14.5% in Papuans people.[29-31]

Another possible genetic biomarker of cognitive dysfunction is brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism. *BDNF* is associated with the promotion of survival and growth of neurons.[33] The *BDNF* Met allele (rs6265) has been associated with poor memory and learning among healthy individuals, older adults who reported race as White, patients with bipolar disease and schizophrenia, and persons with preclinical AD.[34-36] However, the results of research on these associations are mixed. In a study using Alzheimer's Disease Neuroimaging Initiative (ADNI) data, no significant differences were found in hippocampal volumes and memory function between people with and without Met allele.[37] Another study conducted in Scotland ($N = 904$) found that people with Met/Met genotype had better cognition than those with Val/Met and Val/Val genotypes.[38] The frequency of *BDNF* Met allele varies across different populations, ranging from 0% to 72%.[39] For instance, frequencies are very low among people from Sub-Saharan Africa (e.g., Mbuti Pygmies, Yoruba) and people who are American Indians (e.g., Piacoco, Karitiana) but high among Asian populations (e.g., Chinese, Japanese).[39] In a U.S. sample of healthy adults ($N = 133$) the frequency of *BDNF* Met allele was 32%.[33]

Despite the advances in genomics research related to cognitive dysfunction, two studies have been reported in the HF literature in which the allelic frequencies were studied of *APOE* ε4 and ε2, and *BDNF* Val66Met. In a small sample of 29 patients with HF (76% White), 24% had at least one *APOE* ε4 allele,[19] 21% had one *APOE* ε2 allele,[19] and 32% had at least one *BDNF* Met allele.[40] In a sample of 62 patients with HF in Netherlands, 33% had at least one *APOE* ε4 allele and having ε4 allele was associated with poorer cognitive function as measured by a neuropsychological battery examining 5 cognitive domains of memory, executive function, visuospatial function, language, and mental speed/attention.[20] In summary, little is known about *APOE* ε2 and *BDNF* Met alleles in relation to cognitive dysfunction in HF. The frequencies of *APOE* ε4 allele were different between the two HF study samples. Presence of ε4 allele may have the same negative influences in cognition in HF. However, the small sample sizes of these studies limit the conclusions that can be drawn and our understanding of the genetic risk factors for cognitive dysfunction in patients with HF.

Another limitation of past research about HF and cognitive dysfunction is the exclusion of HF patients with known MCI and AD[2,20,40,41] which may have led to an incomplete understanding of cognitive dysfunction in HF. For example, the genomic biomarkers associated with cognitive dysfunction may be uncovered only in part by excluding patients with MCI and AD who had more serious cognitive dysfunction. Another limitation to be considered is lack of reference groups of AD and MCI without HF to compare cognitive dysfunction. Previous studies in HF, healthy adults without HF and without AD or MCI were recruited as a reference group to compare cognitive dysfunction.[4,15,20] Although AD people without HF would be a good reference group in the other end of cognitive spectrum, people with AD or MCI but without HF may not have been designed as reference groups in HF studies. These limitations are missed opportunities to better understand cognitive dysfunction in HF and learn from genomics developments in AD research.

To address these limitations, this study was conducted to investigate influences of HF and genetic factors (i.e., *APOE* ε2 and ε4, and *BDNF* Met) on cognitive function among adults with and without HF and with and without symptomatic cognitive impairment (i.e., MCI and AD). The specific aims were to**:** 1) compare differences in the frequencies of *APOE* ε2 and ε4 and *BDNF* Met alleles among six groups of participants with and without HF who have normal cognition, MCI, or AD; 2) evaluate the relationships between HF and cognitive function (i.e., memory, attention, executive function, and language) after controlling for *APOE* ε2 and ε4, *BDNF* Met, and covariates (i.e., age, gender, education, comorbidities); and 3) examine the association between *APOE* ε2 and ε4 and *BDNF* Met and cognitive function in the HF subsample.

Methods

This study was a genetic association study using secondary data analysis.

Source data

Baseline cognitive and *APOE* genotype data were obtained from the National Alzheimer's Coordinating Center (NACC) database[42,43] and *BDNF* Val66Met genotype data were retrieved from Alzheimer's Disease Genetic Consortium database in September 2017. All participants in the database were included if they had documented history of HF (either yes or no), clinical diagnosis of cognitively normal (CN), MCI or AD, available neuropsychological tests, and genetic information. A total of 7328 participants' data were identified. Data from participants with reported White race were included. Data from participants with reported non-White race were not included because the sample size was small and would not be informative for analyses because of differences in genetic population structure.[30,31,39] The final sample consisted of 7166 participants.

History of HF was obtained from the NACC Uniform Data Set.[42,43] HF diagnosis was self-reported. Age, years of education, and gender were included to describe the sample and adjust performance on neuropsychological tests. Comorbidities (e.g., depression, stroke, transient ischemic attack, atrial fibrillation) were included as possible covariates.

Clinical diagnosis of cognitive impairment (i.e., CN, MCI, and AD) and neuropsychological test scores were retrieved from the NACC Uniform Data Set.[42] The following cognitive domains and measures were included in the analyses: verbal memory as measured by Logical Memory Test delayed recall; attention as measured by Digit Span Forward and Trail Making Test A; executive function as measured by Trail Making B and Digit Symbol Test; and language as measured by Category Fluency Test (Animals and Vegetables) and Boston Naming Test. The domains were chosen because they are the most common deficits among those with HF.[2-6]

Age, education, and gender-corrected z scores of neuropsychological tests were used as measures of cognitive function in the analysis. Higher *z* scores indicate better cognitive function. For each cognitive domain score, composite *z* scores were calculated by averaging the *z* scores when there were two and more tests used to examine one cognitive domain.

Statistical analysis

Descriptive statistics (e.g., frequencies and percentages for nominal; mean and standard deviation for quantitative variables) and logistic regression analyses were used to describe the sample and study variables and compare HF and non-HF groups.

For aim 1, absolute and relative frequencies of the alleles (*APOE* ε2 and ε4 and *BDNF* Met) were calculated[60] among the six groups of participants with and without HF who have normal cognition, MCI, and AD. Pearson's chi-squared tests were computed to make comparisons of the categorical variables. Bonferroni correction was applied for pairwise comparisons, resulting in different statistically significant thresholds for different analyses as referenced in the results section. Post hoc analysis of *BDNF* Met allelic frequencies was completed after controlling for the presence of depression, which has shown relationships with *BDNF* genotypes in the literature.[44,45]

The analysis for aim 2, investigating the relationship between HF and cognitive function, was completed using simultaneous multiple linear regressions controlling for *APOE* ε2 and ε4 and *BDNF* Met carrier status in the full sample. Comorbid conditions of atrial fibrillation, depression, and stroke or transient ischemic attack were included as covariates.

The analysis for aim 3, investigating the relationships between the genetic factors (i.e., *APOE* ε2, ε4, and *BDNF* Met) and cognitive function in HF, was completed using simultaneous multiple linear regressions (see Aim 2 analysis) in the HF subsample. Analyses were completed using SAS version 9.4. The significance level was set at $p < 0.05$.

Results

Data from 7166 participants were included in this study. Of these participants, 174 (2.4%) had HF. Participants' characteristics are presented in Table 1. Compared with participants without HF, those with HF were older ($p < 0.0001$) and had fewer years of education ($p < 0.0001$), lower diastolic blood pressure ($p < 0.0001$), and more comorbid conditions ($p = 0.003 \sim <0.0001$). HF and non-HF participants also differed in terms of their level of cognitive impairment (i.e., CN, MCI, and AD) ($p = 0.0191$). Specifically, compared to non-HF participants, participants with HF were more likely to have cognitive impairment; they were almost twice as likely to have MCI (OR = 1.82; 95% CI = 1.14 – 2.91) and 1.39 times more likely to have AD (OR = 1.39, 95% CI = 1.01 - 1.93).

Aim 1. Frequencies of APOE *ε2, ε4, and* BDNF *Met alleles*

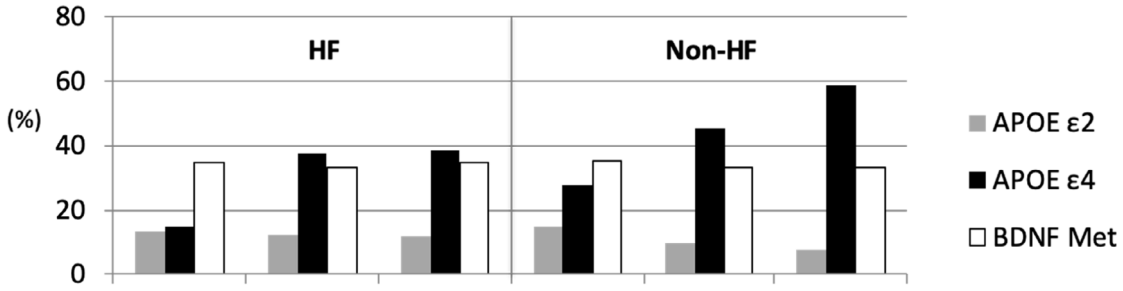
The frequencies of the three alleles across our six comparison groups determined by presence or absence of HF and cognitive impairment (CN, MCI and AD) are shown in Fig. 1. The percent of participants having at least one *APOE* ε2 allele ranged from 7.8% to 14.9%. The frequencies differed across the groups ($x^2 = 79.12$, $p = <0.0001$). The Bonferroni-corrected significance threshold for between group comparisons for these analyses was $p < 0.0033$. Among non-HF participants, the frequency of *APOE* ε2 was significantly higher in the CN group compared with the MCI group (14.9% vs. 9.6%, $x^2 = 13.02$, $p = 0.0003$) and AD group (14.9% vs. 7.8%, $x^2 = 74.65$, $p = < 0.0001$). However, HF participants had similar ε2 frequencies regardless of cognitive impairment status (13.3% in CN group vs. 12.5% in MCI group, $p = 0.9162$; 13.3% in CN group vs. 12.0% in AD group, $p = 0.8061$).

The frequencies of *APOE* ε4 ranged from 14.7% to 58.8% (Fig. 1). Compared with non-HF participants with AD, HF participants with AD had a significantly lower ε4 frequency (58.8% vs. 38.7%, respectively; $x^2 = 12.12$, $p = 0.0005$). There was no statistically significant difference in ε4 frequencies between MCI and CN participants with and without HF (HF with MCI = 37.5% vs. non-HF with MCI = 45.5%, $x^2 = 0.59$, $p = 0.4419$; HF with CN = 14.7% vs. non-HF with CN = 27.8%, $x^2 = 6.32$, $p = 0.0119$) at the *p* value of 0.0033 with the Bonferroni correction.

Although the frequency of ε4 allele appeared higher among HF participants with MCI compared with HF participants with CN, it was not statistically significant ($x^2 = 5.88$, $p = 0.0153$) at the p value of 0.0033. Among non-HF participants with MCI, ε4 frequency was significantly higher than the ε4 frequency among non-HF participants with CN. In both the HF and non-HF groups higher ε4 frequencies were reported among participants with AD than among those who are CN.

Table 1
Participant Characteristics at Baseline (N=7,166)

Characteristics mean ± SD or n (%)	HF (n = 174)	Non-HF (n = 6,992)	t or x^2	p
Age, years	83.7 ± 8.65	74.6 ± 9.05	-13.19	<0.0001
Gender				
Women	103 (59.2)	4,024 (57.6)	0.1879	0.6647
Men	71 (40.8)	3,022 (42.3)		
Education, years	14.1 ± 3.55	15.7 ± 2.94	5.64	<0.0001
Diastolic blood pressure, mmHg	69.1 ± 9.81	73.8 ± 10.35	5.64	<0.0001
Systolic blood pressure, mmHg	131.8 ± 19.08	133.6 ± 18.45	1.18	0.2388
Comorbid conditions				
Depression	35 (20.1)	886 (12.7)	8.3979	0.0030
Atrial fibrillation	80 (46.8)	503 (7.2)	343.5089	<0.0001
Stroke	26 (14.9)	249 (3.6)	59.2958	<0.0001
Transient ischemic attack	29 (16.7)	331 (4.8)	50.0848	<0.0001
Medications				
Currently take medications	165 (96.5)	6,373 (91.6)	5.2473	0.0220
Level of cognitive impairment				
Normal cognition	75 (43.1)	3,692 (52.8)	7.9189	0.0191
Mild cognitive impairment	24 (13.8)	649 (9.3)		
Alzheimer's dementia	75 (43.1)	2,651 (37.9)		
Mini-Mental Status Exam	24.7 ± 6.69	26.1 ± 5.52	2.66	0.0086



Allele n (%)	HF with CN (n=75)	HF with MCI (n=24)	HF with AD (n=75)	Non-HF with CN (n=3,692)	Non-HF with MCI (n=649)	Non-HF with AD (n=2,651)	X^2 p
APOE ε2	10 (13.3%)	3 (12.5%)	9 (12.0%)	550 (14.9%)	62 (9.6%)	206 (7.8%)	79.12 <0.0001
APOE ε4	11 (14.7%)	9 (37.5%)	29 (38.7%)	1,025 (27.8%)	295 (45.5%)	1,558 (58.8%)	641.29 <0.0001
BDNF Met	26 (34.7%)	8 (33.3%)	26 (34.7%)	1,294 (35.1%)	215 (33.1%)	880 (33.2%)	2.72 0.7423

Fig. 1. Frequencies of *APOE* ε2, ε4, and *BDNF* Metamong 6 groups of participants with and without HF and with and without cognitive impairment ($N = 7166$).

BDNF Met frequencies were similar across all groups, ranging from 33.1% to 35.1% ($x^2 = 2.72$, $p = 0.7423$). Post hoc analysis showed no statistically significant difference across the groups after controlling for depression.

Aim 2. Relationships between HF and cognitive function in the pooled sample

The cognitive function among participants with and without HF and with and without cognitive impairment is presented in Table 2. In multiple linear regressions ($N = 7166$), having history of HF was predictive of worse performance on cognitive function in the domains of attention ($\beta = -0.24$, $p = 0.0378$) and language ($\beta = -0.25$, $p = 0.0238$) after controlling for age, gender, education, history of atrial fibrillation, stroke or transient ischemic attack, depression, and genetic factors (i.e., *APOE* ε2, ε4, and *BDNF* Met) (Table 3). In our post hoc analysis, HF remained predictive of worse cognitive function, even after controlling for the clinical diagnosis of cognitive impairment (i.e., MCI and AD) on attention ($\beta = -0.21$, $p = 0.0305$) and language ($\beta = -0.19$, $p = 0.0191$). In addition, HF was predictive of worse executive function ($\beta = -0.28$, $p = 0.0063$), but not verbal memory ($\beta = 0.10$, $p = 0.2297$).

The presence of *APOE* ε2 was predictive of better cognitive function, while the presence of *APOE* ε4 was predictive of worse cognitive function in all domains of verbal memory, attention, executive function, and language in the pooled sample (Table 3). The presence of BNDF Met was not predictive of cognitive function.

Aim 3. Relationships between genetic factors and cognitive function in HF

In the HF subsample ($n = 174$), the presence of *APOE* ε4 predicted worse verbal memory ($\beta = -0.56$, $p = 0.0324$), but did not predict attention ($p = 0.5332$), executive function ($p = 0.0770$), or language ($p = 0.0872$) (Table 4) after controlling for age, gender, education, history of atrial fibrillation, stroke or transient ischemic attack, and depression. The presence of *APOE* ε2 and *BDNF* Met were not predictive of cognitive function among participants with HF.

Table 2
Cognitive function among 6 groups of participants with and without HF and with and without cognitive impairment (N=7,166)

Neuropsychological test raw scores, mean ± SD	HF with CN (n=75)	HF with MCI (n=24)	HF With AD (n=75)	Non-HF With CN (n=3,692)	Non-HF With MCI (n=659)	Non-HF With AD (n=2,651)	p
Mini-Mental Status Exam	28.6 ± 1.73	27.2 ± 2.06	19.5 ± 7.62	29.1 ± 1.19	27.4 ± 2.21	21.4 ± 6.57	<0.0001
Logical Memory, Delayed recall	11.8 ± 4.22	7.0 ± 5.42	3.3 ± 4.27	12.8 ± 4.10	7.2 ± 5.32	2.5 ± 3.66	<0.0001
Digit Span Forward	6.6 ± 1.05	6.6 ± 1.20	6.0 ± 1.26	6.8 ± 1.05	6.5 ± 1.12	6.1 ± 1.31	<0.0001
Trail Making A	46.5 ± 18.90	61.8 ± 31.66	69.2 ± 36.10	32.9 ± 13.85	42.3 ± 20.02	62.7 ± 37.80	<0.0001
Trail Making B	117.8 ± 47.44	166.5 ± 87.48	220.3 ± 86.39	84.1 ± 42.00	128.2 ± 68.78	187.5 ± 90.16	<0.0001
Digit Symbol	37.8 ± 10.95	30.8 ± 13.95	27.8 ± 12.22	48.4 ± 11.71	38.3 ± 11.31	29.1 ± 14.22	<0.0001
Category fluency – Animals	18.3 ± 4.07	15.1 ± 4.55	9.6 ± 5.22	21.0 ± 5.45	16.3 ± 5.25	11.6 ± 5.51	<0.0001
Category fluency – Vegetables	12.3 ± 3.02	10.6 ± 4.17	6.7 ± 3.79	15.0 ± 4.25	11.2 ± 3.93	7.5 ± 4.22	<0.0001
Boston Naming	26.4 ± 2.67	23.7 ± 6.46	20.0 ± 6.84	27.7 ± 2.36	25.6 ± 3.76	21.1 ± 7.04	<0.0001
z-scores for each cognitive domain							
Verbal memory	0.20 ± 1.05	-0.72 ± 1.39	-1.66 ± 1.10	0.16 ± 1.01	-0.65 ± 1.37	-1.86 ± 0.94	<0.0001
Attention	-0.11 ± 0.79	-1.25 ± 1.14	-1.65 ± 1.37	0.15 ± 0.66	-0.65 ± 0.93	-1.50 ± 1.52	<0.0001
Executive function	-0.17 ± 0.90	-2.60 ± 1.45	-3.45 ± 1.29	0.18 ± 0.76	-1.96 ± 1.17	-2.97 ± 1.52	<0.0001
Language	-0.04 ± 0.56	-1.00 ± 1.14	-2.00 ± 1.15	0.17 ± 0.67	-0.65 ± 0.85	-1.74 ± 1.29	<0.0001

Table 3
Multiple linear regressions to examine influences of HF on cognitive function (N = 7,166)

Predictor variables	Neuropsychological tests, β							
	Logical Memory, Delayed recall	Digit Span Forward	Trail Making A	Trail Making B	Digit Symbol	Category Fluency - Animals	Category Fluency - Vegetables	Boston Naming
Intercept	-0.31***	0.09***	-0.63***	-0.43***	-0.79***	-0.43***	-0.37***	-0.25***
HF	0.06	-0.02	-0.55**	-0.35*	-0.31	-0.24*	-0.30**	-0.27
Atrial fibrillation	-0.14*	0.10*	-0.26*	-0.28**	-0.30*	-0.15*	-0.09	-0.09
Stroke/ transient ischemic attack	-0.20**	-0.16**	-0.81***	-0.68***	-0.75***	-0.43***	-0.40***	-0.23**
Depression	-0.26***	-0.07	-0.59***	-0.63***	-0.72***	-0.36***	-0.29***	-0.33***
APOE ε2	0.26***	0.04	0.29***	0.17*	0.33***	0.18***	0.16**	0.22***
APOE ε4	-0.72***	-0.07**	-0.83***	-0.84***	-0.96***	-0.53***	-0.51***	-0.39***
BDNF Met	0.00	-0.03	0.01	-0.00	0.01	-0.01	0.00	0.02

Predictor variables	Cognitive domains, β			
	Verbal memory	Attention	Executive Function	Language
Intercept	-0.31***	-0.25***	-0.53***	-0.34***
HF	0.06	-0.24*	-0.31	-0.25*
Atrial fibrillation	-0.14*	-0.08	-0.27**	-0.11
Stroke/ transient ischemic attack	-0.20**	-0.46***	-0.71***	-0.35***
Depression	-0.26***	-0.32***	-0.67***	-0.32***
APOE ε2	0.26***	0.17***	0.20**	0.19***
APOE ε4	-0.72***	-0.44***	-0.88***	-0.47***
BDNF Met	0.00	-0.01	0.00	0.00

Note: * p < .05, ** p < .01, *** p < .001

Discussion

In this study, the frequencies of *APOE* ε2, ε4, and *BDNF* Met were first investigated using data from national repositories and well-characterized groups with and without HF and with and without cognitive impairment. Two different trends in *APOE* ε2 frequencies were found for non-HF and HF participants. Specifically, non-HF participants with CN had a higher frequency of ε2 than did those with MCI and AD, which is consistent with the previously reported protective effect of ε2 on cognition.[23,26,32] However, HF participants with MCI or AD in this study had similar ε2 frequencies with HF participants with CN. One possible explanation for this observation may be the known effect of ε2 on increasing the number of atherogenic lipoproteins and accelerating atherogenesis in atherosclerosis.[46,47] This suggests that ε2 may be associated with developing more cardiovascular diseases and subsequent cognitive dysfunction.

Interestingly, *APOE* ε4 frequency was distinctly lower among HF participants with AD (38.7%) than non-HF participants with AD (58.8%) in this study. In addition, HF participants with MCI and AD had similar frequencies of *APOE* ε4 (37.5% and 38.7%, respectively) unlike the significantly different frequencies between non-HF participants with MCI and AD. In previous studies, ε4 frequencies among patients with HF who did not have diagnosis of AD or MCI were 24% and 33%.[19,20] However, in this study, only 14.7% of the HF participants with normal cognition had ε4 allele. Based on the results, it appears that irrespective of their *APOE* ε4 and ε2 carrier status, participants

Table 4
Multiple linear regressions to examine influences of the genetic factors on cognitive function in HF subsample (n = 174).

Predictor variables	Neuropsychological tests, β							
	Logical Memory, Delayed recall	Digit Span Forward	Trail Making A	Trail Making B	Digit Symbol	Category Fluency - Animals	Category Fluency - Vegetables	Boston Naming
Intercept	-0.62**	0.11	-1.67**	-0.76*	-1.23***	-0.69**	-0.86***	-0.59
Atrial fibrillation	0.07	0.06	0.13	-0.34	-0.42	-0.16	0.09	-0.14
Stroke/ transient ischemic attack	0.59*	-0.14	-0.31	-0.47	-0.21	-0.06	-0.22	0.07
Depression	-0.10	0.06	-0.84	-0.47	-0.65	-0.20	-0.17	0.10
APOE ε2	-0.03	-0.54*	0.67	-0.21	-0.02	-0.34	-0.40	0.17
APOE ε4	-0.56*	-0.20	-0.13	-0.76	-0.61	-0.61*	-0.36	-0.58
BDNF Met	0.06	0.19	0.05	-0.13	-0.03	-0.01	0.23	-0.05

Predictor variables	Cognitive domains, β			
	Verbal memory	Attention	Executive Function	Language
Intercept	-0.62**	-0.67**	-0.87**	-0.71***
Atrial fibrillation	0.07	0.08	-0.26	-0.07
Stroke/ transient ischemic attack	0.59*	-0.13	-0.52	-0.10
Depression	-0.10	-0.54	-0.52	-0.08
APOE ε2	-0.03	0.03	-0.21	-0.23
APOE ε4	-0.56*	-0.16	-0.69	-0.42
BDNF Met	0.06	0.02	-0.15	0.09

Note: * p < .05, ** p < .01, *** p < .001
ε2 on Digit Span Forward, p = 0.036; ε4 on Logical Memory Delayed Recall, p = 0.032; ε4 on Category Fluency Animals, p = 0.020; ε4 on Verbal memory, p = 0.032.

with HF in this sample were more likely to have AD than those without HF. However, these results need to be confirmed in a larger study with more diverse sample.

In our comprehensive national data across the full cognitive spectrum (i.e., CN, MCI, and AD), the presence of HF was predictive of worse cognitive function after controlling for age, education, gender, comorbid conditions, and genetic factors (i.e., *APOE* ε4 and ε2 and *BDNF* Met). The specific domains affected were attention and language. Interestingly, however, verbal memory and executive function were not associated with the presence of HF in this pooled sample. This result somewhat contradicts previous literature that reported verbal memory was one of the most commonly impaired cognitive domains in HF.[4,41] The difference in our findings may be due to the small HF sample and the disproportionate distribution of CN, MCI, and AD in this national database.

HF is a serious chronic condition that frequently occurs with the other serious conditions such as atrial fibrillation, stroke, and depression. For example, atrial fibrillation and HF often co-exist as shown that 57% of HF patients had atrial fibrillation and 37% of patients with atrial fibrillation had HF from Framingham study.[48] HF commonly coexists with stroke, especially among older adults.[49] Patients with HF had increased risks of developing both ischemic and hemorrhagic stroke in a 30-year follow-up study using Danish population-based medical registries.[50] Depression is a common comorbid condition present over 20% of patients with HF[51,52] and the prevalence increases up to 42% in advanced HF.[52] Each of these serious conditions is associated with decreased cognitive function. In the current study, these conditions were significant explanatory variables of cognitive function as well. In future studies, investigators need to consider the interaction of these comorbid conditions and their combined influence on cognitive function and interventions to minimize patients' risk of poor cognition.

Although the influences of *APOE* ε2 and ε4 in the pooled sample were consistent with previous literature,[21-23,26,32] in this HF subsample the analysis did not align with the previous literature. First, in this study *APOE* ε2 was predictive of better cognitive function in the pooled sample of 7166. However, among the 174 participants with HF, ε2 was not predictive of better cognitive function. This may be because *APOE* ε2 has been known to influence vascular atherosclerotic changes that might lead to cognitive dysfunction.[46,47] Due to the low frequency of *APOE* ε2 in the HF subsample, however, this conclusion should be interpreted with caution.

Second, participants who had at least one ε4 allele performed worse on the cognitive domains of memory, attention, executive function, and language in the pooled sample of this study. In our HF subsample, however, HF participants who had at least one ε4 allele had worse memory, but no statistically significant worse cognitive function of attention, executive function, and language. This might suggest a more direct impact of *APOE* ε4 on memory function among participants with HF. These findings, however, should be interpreted with caution due to the limitations of relying on a single memory measure (i.e., Logical Memory Delayed Recall), the small sample size of HF participants, and the AD-focused cohort in which these relationships were studied.

BDNF Met frequencies were similar across the participants with and without HF and with and without cognitive impairment (i.e., AD and MCI). In addition, presence of Met allele was not predictive of cognitive function in the pooled sample as well as in the HF subsample. The preexisting literature is not in agreement regarding the relationship between *BDNF* Met and cognitive function.[53] Prior work reports that Met allele was associated with poor episodic memory and abnormal activation of the hippocampal area among healthy adults and adults with schizophrenia, but was not associated with other cognitive domains (e.g., semantic and working memory, executive function).[33,54] However, in recent meta-analytic studies, no association was found between *BDNF* Val66Met and cognitive function among healthy adults[55] and patients with neuropsychiatric conditions.[56] The inconsistencies may stem from the fact that *BDNF* is one of the most widely spread neurotrophins in the brain. Hence, the many factors that could influence its effect need to be considered (e.g., race, age, gender, ethnicity, environmental factors, gene-gene interactions).[57] Furthermore, some evidence indicates that the *BDNF* Met allele is associated with worse cognitive changes (i.e., perceptual speed) over 13 years of follow-up among healthy older adults[58,59] and more memory decline over three years in the prodromal AD stages.[35] This highlights the need for longitudinal studies of the relationship between presence of *BDNF* Met allele and cognitive function among patients with HF.

The study results are limited by the use of self-reported race data and the inclusion of participants with White race only. Although there is a high concordance between self-reported race and genetically-determined race (over 90%),[60] it is possible that the results may be less accurate compared to those obtained by analyzing the allele frequencies according to genetically-determined ancestry. The limited focus on participants with White race also prevents generalization to other races.

In conclusion, despite these limitations, this study found that the frequencies of *APOE* ε2 and ε4 were different between participants with HF and without HF. *APOE* ε2 and *BDNF* Met were not associated with cognitive function in HF. The presence of HF was associated with worse cognitive performance in attention and language after adjusting for *APOE* ε2, ε4, age, education, gender, and comorbidities in this sample.

Among participants with HF, *APOE* ε4 was associated with worse memory. The underlying mechanisms of poor cognitive function and any genetic contributions in HF may need more in-depth examination including effects of the common and major comorbid conditions (e.g., atrial fibrillation, stroke, and depression) on cognition among patients with HF. Clinicians need to assess patients with HF for atrial fibrillation, stroke, and depression and their combined influence on cognition. Prospective longitudinal studies with larger HF samples that have a well-defined ancestry are needed to elucidate mechanisms of cognitive dysfunction that may have treatment implications.

Declaration of Competing Interest

None.

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