

## Coronary artery disease and plasma apolipoprotein E4 in mild cognitive impairment

Majid Barekatin<sup>(1)</sup>, Faezeh Zahedian<sup>(2)</sup>, Hedyeh Askarpour<sup>(2)</sup>, Mohammad Reza Maracy<sup>(3)</sup>,  
Mohammad Hashemi-Jazi<sup>(4)</sup>, Mohammad Reza Aghaye-Ghazvini<sup>(5)</sup>

### Original Article

#### Abstract

**BACKGROUND:** Atherosclerosis and apolipoprotein E4 (APOE4) are known risks for Dementia. We sought to evaluate the relationship between coronary atherosclerosis and APOE4 with mild cognitive impairment (MCI).

**METHODS:** In a case-control study, subjects with age more than 60 years and recent coronary angiography were evaluated by mini-mental state examination and neuropsychiatry unit cognitive assessment tool (NUCOG) to find the patients with MCI (n = 40) and the controls with normal cognition (n = 40). Coronary angiography records were re-assessed to find the severity of coronary artery disease by the Gensini scores. Plasma levels of APOE4 were measured.

**RESULTS:** There were no-significant difference between the 2 groups regarding the plasma APOE4 levels (P = 0.706) and the Gensini scores (P = 0.236). Associations between the Gensini scores and the NUCOG scores in the MCI group (r = -0.196, P = 0.225) and the control group (r = 0.189, P = 0.243) were not significant. However, the interaction effect between the Gensini and the NUCOG scores based on allocation to the control or the patient groups showed statistically significant difference ( $F_{(1,67)} = 4.84$ , P = 0.031).

**CONCLUSION:** Although atherosclerosis has been considered as known risk factor for dementia and MCI, this study could not reveal that coronary atherosclerosis-related to declining in cognitive functioning. There was no significant association between plasma APOE4 levels and MCI.

**Keywords:** Mild Cognitive Impairment, Coronary Artery, Angiography, Apolipoprotein E4

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#### Introduction

World population is growing older. In the United States, the proportion of the population over 65 years has increased from 3.1% in 1900 to 13.2% by 2010.<sup>1</sup> The same trend has been observed other developed and in developing countries. In Iran, more than 5 million people are over 60 years, which is 7.26% of the population. It is estimated that more than 10% of the population will be in old age by 2030.<sup>2</sup>

Dementia is one of the most common health problems in the elderly population with estimation of 5-8% prevalence rate in people 65-70-year-old. This rate doubles every 5 years by aging.<sup>3</sup> It is defined as a

progressive impairment of cognitive function including difficulties with memory, language, visuospatial skills, praxis, attention, and executive functioning. The deficits would result in significant impairment in personal, social, or occupational functioning.<sup>3</sup> Neuropathological cascades leading to dementia starts decades before the clinical manifestations. Therefore, there is a prolonged transitional time with gradual cognitive decline between the normal state and overt dementia. This period has been named "mild cognitive impairment" (MCI).<sup>3,4</sup>

MCI is characterized by cognitive deterioration that is confirmed by family members and proved in

1- Associate Professor, Psychosomatic Research Center AND Department of Psychiatry, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

2- Resident, Department of Psychiatry, Isfahan University of Medical Sciences, Isfahan, Iran

3- Associate Professor, Department of Epidemiology and Biostatistics AND Behavioral Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

4- Associate Professor, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Department of Cardiology, Isfahan University of Medical Sciences, Isfahan, Iran

5- Isfahan Center of Health Research, Isfahan, Iran

Correspondence to: Majid Barekatin, Email: barekatin@med.mui.ac.ir

neuropsychological tests without influence on activities of daily living, MCI is sub-classified into two forms: amnesic MCI (a-MCI), which includes predominant memory deficit and non-amnesic MCI (na-MCI), which is characterized by deficit in cognitive domains other than memory such as language, visuospatial skills, and executive functioning.<sup>3</sup> MCI affects 12-18% of individuals over 65 years. It will progress to dementia in 10-15% of cases within a year, and this number is increasing each year.<sup>3,5</sup> MCI has an increasing rate by aging.<sup>3</sup> Lower education is another risk factor for MCI.<sup>6</sup> Late-life depression is also hypothesized to increase the risk for cognitive impairment.<sup>3</sup> The other frequently proposed risk factor is lower brain reserve. The concept of brain reserve indicates to the effects of brain size and neuron density, which means higher brain reserve may lead to protection against clinical manifestations of MCI despite the presence of neurodegeneration and vice versa.<sup>3</sup> Apolipoprotein E4 (APOE4) polymorphism in some, but not all, studies was found as a risk factor.<sup>7-9</sup> Similarly, vascular risk factors such as hypertension, diabetes, and hyperlipidemia have been reported as possible risk factors for MCI.<sup>10,11</sup> Cross-sectional studies revealed association between MCI and vascular diseases such as stroke, transient ischemic attack, cerebral hemorrhage, and peripheral artery disease.<sup>6</sup>

Ischemic heart diseases (IHD) are among the prevalent illnesses in the elderly population. Currently, the prevalence of IHD is about 21.10% for men and 10.60% for women at age of 60-79 years in the United States.<sup>12</sup> In one study in Iran, the prevalence of coronary artery disease (CAD) was reported 37.50% for women and 22.20% for men up to age 35 years that increased with aging.<sup>13</sup> Some researches have reported a relation between IHD and MCI. In one study, about 37-45% of candidates for coronary artery bypass graft had MCI.<sup>14</sup> In neuroimaging and post-mortem studies of patients who had history of CAD, despite absence of clinical dementia, degenerative changes and amyloid plaques were found in their brains.<sup>15,16</sup> Increased prevalence of silent myocardial infarction was reported in Alzheimer's disease and, to a lesser extent, in MCI.<sup>17</sup> Lima et al. reported that atherosclerosis extent in CAD is associated with severity of cognitive decline.<sup>18</sup> According to the study by Siuda et al., in MCI group with vascular risk factors more intensive dysfunction in learning ability, short-term memory, delayed recall and operational memory were found.<sup>4</sup> In most of

these studies, however, IHD were only diagnosed based on the clinical criteria and objective results of coronary angiography were not considered.<sup>14,18</sup>

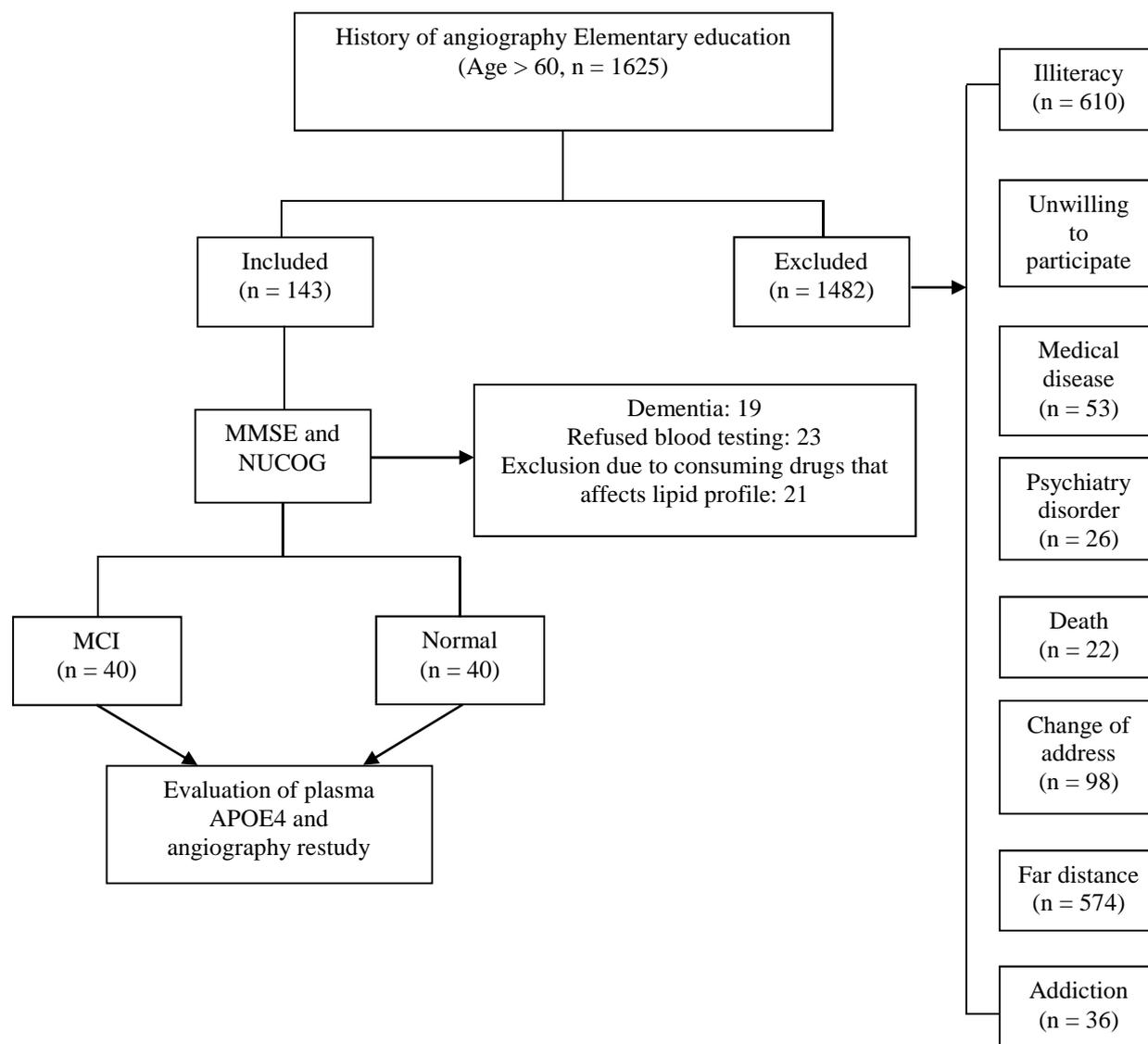
Diagnosis of MCI has been mainly based on clinical manifestations and neuropsychological evaluations.<sup>3</sup> Many research groups are working on MCI biomarkers for early diagnosis, faster treatment, better prevention, rising prognosis, and planning of rehabilitation programs.<sup>4</sup> Of these biomarkers, neuroimaging parameters, biochemical measures, and genetic markers have repeatedly been used.<sup>15,19,20</sup>

Parameters that indicate to vascular or endothelial health and atherosclerosis may also be considered as cognitive function biomarkers and may point to possibility of MCI.<sup>21</sup> In contrast to use of coronary angiography as an objective, reliable, and valid method for estimation of atherosclerosis in IHD,<sup>22</sup> measurement of cerebral atherosclerosis by cerebral angiography, especially in small sized arteries has not been possible. Coronary angiography parameters involve severity and location of stenosis and efficiency of collateral arteries in the heart.<sup>23</sup> Despite invasiveness, it is a routine procedure. About 1.5 million patients underwent coronary angiography in the United States in 2011 for precise diagnosis of CAD.<sup>22</sup>

In this study, we evaluated the relation of plasma APOE4 level and coronary angiography parameters with cognitive performance in different domains in MCI patients and control individuals. We sought to find if coronary angiography findings could use as an indirect index for possible MCI.

## Materials and Methods

This case-control study included subjects above 60 years with elementary or higher education. Subjects should undergo coronary angiography in the recent year. They were selected from patients who admitted to cardiac catheterization units of Sina and Nour Hospitals, Isfahan, Iran, from March 2012 to October 2012. The study design was scientifically and ethically discussed and approved by the deputy of research and technology, Isfahan University of Medical Sciences, Isfahan, Iran. Subjects with a history of major psychiatric disorders, substance misuse, head trauma, serious medical disease, and dementia were excluded. A total of 1625 subjects were screened based on inclusion and exclusion criteria to select 40 cases and 40 controls (Figure 1). The study process was explained for all subjects and written informed consent was obtained.



**Figure 1.** The flow chart of the study

MMSE: Mini-mental state examination; NUCOG: Neuropsychiatry unit cognitive assessment tool; MCI: Mild cognitive impairment

Subjects underwent neuropsychiatric interview considering Peterson's criteria for MCI.<sup>3</sup> Mini-mental state examination (MMSE) scores from 21 to 26 were utilized for validation of MCI diagnosis. Subjects, with MMSE scores more than 26, were considered normal controls.<sup>24</sup>

We used neuropsychiatry unit cognitive assessment tool (NUCOG) to confirm the diagnosis of MCI and as a dependent variable. The NUCOG provided five distinct cognitive domains including attention, memory, executive function, language, and visuoconstruction.<sup>25</sup> The NUCOG scores more than 86.5, between 75 and 86.5, and lower than 75 were considered normal cognitive state, MCI, and dementia respectively in Iranian population.<sup>26</sup>

In both groups, coronary angiography records

were re-assessed by an expert cardiologist (MH). The Gensini score was used as valid and reliable indicator for coronary arteries atherosclerosis. It was calculated by the multiplying severity of stenosis by the segment location by collateral adjustment factor. Increase in the Gensini score means more severity of coronary artery atherosclerosis.<sup>23</sup>

History of cigarette smoking, hyperlipidemia, diabetes, hypertension, and familial history of Alzheimer's disease were asked. General health questioner was administered for all participants. In physical examination, blood pressure, pulse rate, height, and weight were recorded, and body mass index was calculated. Plasma triglycerides, total cholesterol, fasting blood glucose, and creatinine were measured. Plasma APOE4 level was evaluated by

enzyme-linked immunosorbent assay plate rever kit.<sup>27</sup>

Independent t-test and Chi-square test were used to compare baseline variables. Pearson correlation test was used to find the associations. Analysis of covariance and multivariate analysis of covariance were used to find the effect of Gensini scores and plasma APOE4 level on cognitive state scores. Statistical significance was set at  $P < 0.050$ .

## Results

This study included 40 subjects with MCI (33 men and 7 women) as patient group and 40 subjects with normal cognitive state (29 men and 11 women) as a control group.

Baseline characteristics of subjects were summarized in table 1.

The Gensini scores, plasma APOE4 levels, and NUCOG scores were demonstrated in table 2. There were no significant difference between the two groups regarding the plasma APOE4 levels ( $P = 0.706$ ) and the Gensini scores ( $P = 0.236$ ). Relationships between plasma APOE4 levels and the NUCOG scores in the MCI group ( $r = 0.114$ ,  $P = 0.483$ ) and the control group ( $r = 0.127$ ,  $P = 0.435$ ) were not significant. Association

between plasma APOE4 levels and the Gensini scores in the MCI group ( $r = -0.110$ ,  $P = 0.500$ ) and the control group ( $r = 0.014$ ,  $P = 0.933$ ) were not significant.

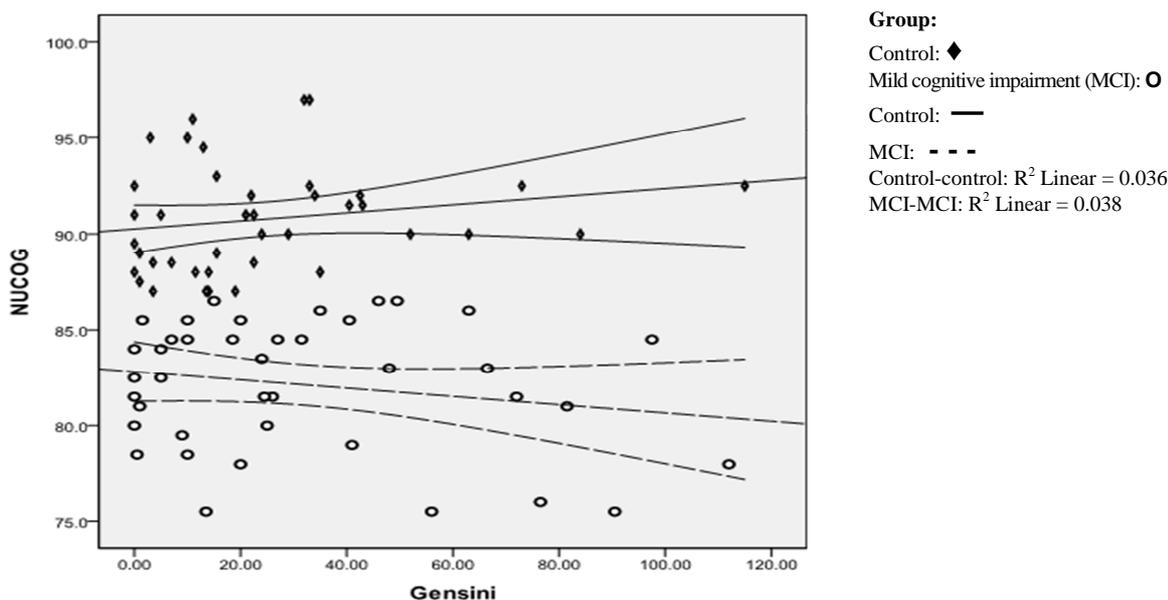
Increasing Gensini scores accompanied with decreasing NUCOG scores in the MCI group. However, it was not significant ( $r = -0.196$ ,  $P = 0.225$ ). In the control group, the increasing Gensini scores jointed with increasing NUCOG scores but it was not significant ( $r = 0.189$ ,  $P = 0.243$ ). However, the interaction effect between the Gensini and the NUCOG scores based on the allocation to the control or the MCI groups showed statistically significant difference ( $F_{(1,67)} = 4.84$ ,  $P = 0.031$ ) (Figure 2). On the other hand, the interaction effect between the plasma APOE4 levels and the NUCOG scores based on the allocation to the control or the MCI groups did not show statistically significant relationship between the MCI and the control groups ( $F_{(1,67)} = 0.32$ ,  $P = 0.575$ ).

The scores of the NUCOG subscales in its five different cognitive domains were displayed in table 2. The relations between the Gensini scores and each of the five different cognitive domains are shown in table 3.

**Table 1.** Baseline characteristics and cardiovascular risk factors

Characteristic	MCI (n = 40)	Control (n = 40)	P
Age (year)	65.3 ± 4.1	65.7 ± 4.1	0.627
Education (year)	9.5 ± 3.8	10.2 ± 3.2	0.073
GHQ score	17.0 ± 7.8	18.4 ± 8.5	0.463
BMI (kg/m <sup>2</sup> )	25.8 ± 2.9	25.3 ± 2.2	0.428
SBP (mmHg)	127.8 ± 13.7	126.6 ± 12.8	0.675
DBP (mmHg)	78.7 ± 9.1	80.2 ± 7.7	0.422
Fasting glucose (mg/dl)	124.5 ± 44.6	121 ± 47.4	0.733
Total cholesterol (mg/dl)	163.9 ± 39.6	165.7 ± 50.6	0.858
Triglycerides (mg/dl)	158.5 ± 98.4	143.8 ± 89.1	0.488
Creatinine (mg/dl)	1.3 ± 0.3	1.3 ± 0.4	1.000
Sex			
Male [n (%)]	33 (82.5)	29 (72.5)	0.284
Female [n (%)]	7 (17.5)	11 (27.5)	
Smoker [n (%)]	6 (15.0)	11 (27.5)	0.172
Diabetes [n (%)]	16 (40.0)	15 (37.5)	0.818
Hypertension [n (%)]	22 (55.0)	16 (40.0)	0.179
Hyperlipidemia [n (%)]	16 (40.0)	20 (50.0)	0.369
Family history of dementia [n (%)]	7 (17.5)	6 (15.0)	0.762

Continuous variables are represented as mean ± SD and categorical variables as frequency (percentage) BMI: Body mass index GHQ: General health questioner; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation



**Figure 2.** Correlation between the Gensini and the Neuropsychiatry Unit Cognitive Assessment Tool Scores in the mild cognitive impairment and the control groups

**Table 2.** Neuropsychological performance, Gensini scores and apolipoprotein E4 levels in the mild cognitive impairment and the control groups

Characteristics	MCI (n = 40)	Control (n = 40)	P
Gensini scores	31.9 ± 30.4	24.5 ± 23	0.236
APOE4 level	36.1 ± 40.5	32.3 ± 48.2	0.706
NUCOG	82.1 ± 3.3	90.7 ± 2.7	< 0.001
Attention	13.6 ± 1.4	15.3 ± 1.6	< 0.001
Visuospatial	17.8 ± 1.5	19.2 ± 1	< 0.001
Memory	15.4 ± 1.9	18 ± 1.5	< 0.001
Executive function	16 ± 1.9	18.3 ± 1.4	< 0.001
Language	19.2 ± 0.7	19.7 ± 0.3	< 0.001

APOE4: Apolipoprotein E4; NUCOG: Neuropsychiatry unit cognitive assessment tool  
MCI: Mild cognitive impairment

**Table 3.** Correlation between Gensini scores and cognitive domains of Neuropsychiatry Unit Cognitive Assessment Tool in the mild cognitive impairment and the control groups

Cognitive domains	Correlation with Gensini scores in control group	Correlation with Gensini scores in MCI group
Attention	r = -0.090 P = 0.581	r = -0.228 P = 0.157
Visuospatial	r = -0.205 P = 0.204	r = -0.016 P = 0.923
Memory	r = 0.084 P = 0.608	r = 0.067 P = 0.681
Executive function	r = 0.233 P = 0.149	r = -0.176 P = 0.278
Language	r = -0.013 P = 0.936	r = -0.078 P = 0.633

MCI: Mild cognitive impairment

### Discussion

We investigated the association between plasma APOE4 levels in the MCI group and cognitively

normal controls. We could not find significant relationship between the plasma APOE4 levels and cognitive functioning in the MCI group ( $r = 0.114$ ,  $P = 0.483$ ) or the control group

( $r = 0.127$ ,  $P = 0.435$ ). APOE4 allele is a genetic biomarker for dementia, especially of Alzheimer type. However, the extent to which this allele also predicts the development of MCI is unclear.<sup>7</sup> Risacher et al. reported that MCI patients have significantly more APOE4 allele than control subjects (40.70% vs. 24.45%).<sup>8</sup> In the study by Robert et al., there was a significant association of APOE4 carrier status with a-MCI but not na-MCI.<sup>28</sup> In contrast, another study revealed that the frequency of the APOE4 genotype did not differ between individuals with MCI and cognitively normal subjects (12.90% vs. 18.40%).<sup>7</sup> It would be concluded that APOE4 allele may be a risk factor for a-MCI. However, if MCI is considered as a single entity, which contains both a-MCI and na-MCI, this conclusion may not be found. The MCI patients in this study included both types of a-MCI and na-MCI that resulted in decreased power to reveal correlation between APOE4 level and cognitive function.

There were no significant correlations between cognitive performance and other risk factors such as elevated Plasma cholesterol, diabetes, increased blood pressure, and smoking in our study. In some studies, vascular risk factors including elevated Plasma cholesterol in midlife, diabetes, increased diastolic blood pressure, smoking, brain infarcts, and white matter brain lesions, have been suggested as risk factors for MCI.<sup>10,29-31</sup> In contrast, other reports did not confirm the role of vascular risk factors for cognitive impairment in non-demented MCI subjects.<sup>12,32</sup>

We also could not find any significant association between the Gensini scores and cognitive functioning in the MCI group ( $r = -0.196$ ,  $P = 0.225$ ) and in the control group ( $r = 0.189$ ,  $P = 0.243$ ). However, the interaction effect between the Gensini and the NUCOG scores based on the allocation to the control or the MCI groups showed statistically significant difference ( $F_{(1,67)} = 4.84$ ,  $P = 0.031$ ) (Figure 2). There are expanding bodies of evidence pointing CAD up as a specific risk factor for cognitive decline. In the cardiovascular health study cohort, the incidence of dementia was higher in those with prevalent CAD.<sup>33</sup> Several studies have confirmed that CAD has been associated with cognitive impairment<sup>11,14,34,35</sup> reduced hippocampal volume,<sup>35</sup> and increased senile plaque formation in cortical areas of the brain.<sup>16</sup> In cross-sectional study of “age, gene, environment susceptibility-Reykjavik,” Vidal et al. evaluated the computed tomography-based coronary artery calcium (CAC) measures, a measure for estimation of severity of atherosclerosis

and scores on each cognitive domain. They found that lower scores on specific cognitive domains were strongly related to atherosclerotic burden, estimated by CAC load. However, adjustment for white matter lesions, silent brain infarctions, cerebral micro-bleeds, and brain volumes attenuated the observed association between CAC load and cognitive state, implicating other vascular mechanisms.<sup>36</sup> In a population-based study with 1969 subjects of 70-89 years old, there was a positive association between a history of angiographic coronary stenosis and na-MCI [odds ratio (OR) = 3.21].<sup>28</sup> Lima et al. reported that atherosclerosis extent in CAD is associated with cognitive decline but not correlated with APOE4 Polymorphism and its plasma level.<sup>18</sup> However, a few studies did not show the relation between IHD and cognitive impairment. In the study by Rafnsson et al., clinical diagnosis of IHD was neither related to initial cognitive performance nor cognitive decline after 4 years.<sup>37</sup> Similarly, another study found no association between MMSE scores and coronary artery events.<sup>38</sup> Individuals with constitutional tendency for MCI may be predisposed to lower cognitive functioning if confronted with CAD. This may not be the case for subjects who do not have MCI diathesis. Significant association between CAD and psychomotor speed and executive dysfunction was reported.<sup>28</sup> There was also evidence that na-MCI subtype was a more concomitant state with vascular risk factors.<sup>5</sup> In the study by Robert et al., CAD was identified as an independent risk factor for na-MCI, especially in women.<sup>10</sup> Interestingly, our study revealed that patients with higher Gensini scores in MCI group had more problems in executive functioning, although, this was not significant ( $P = 0.09$ ).

Our study had a few limitations. First, it was a cross-sectional study that limited power for recognizing the risk factors. Second, we did not consider MCI subtypes for better classification of symptoms. Third, we did not consider clinical symptoms of IHD. Fourth, all participants have been treated for IHD, hypertension, hyperlipidemia, and diabetes. These interventions could have positive and negative effects on cognitive performance.

## Conclusion

Although atherosclerosis has been considered as known risk factor for dementia and MCI, this study could not reveal that coronary atherosclerosis-related to declining in cognitive functioning. There was not

significant association between plasma APOE4 levels and MCI.

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### Conflict of Interests

Authors have no conflict of interests.

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