The Relationship between Metabolic Syndrome and Cognitive Function

Hye-Mi Oh, Se-Hong Kim, Sung-Goo Kang, Seo-Jin Park, Sang-Wook Song*

Department of Family Medicine, St. Vincent's Hospital, The Catholic University of Korea School of Medicine, Suwon, Korea

Background: Metabolic syndrome has been reported to have adverse effects on cognitive function, although the results are conflicting. The purpose of this study was to examine the relationship between metabolic syndrome and cognitive function in elderly Korean participants older than 60 years.

Methods: We examined elderly participants who visited the health promotion center in Gyeonggi-do province. We categorized the participants into two groups based on the presence of metabolic syndrome (48 participants in the metabolic syndrome group and 45 in the control group). Cognitive function was assessed in all participants using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K).

Results: Compared with those without metabolic syndrome, participants with metabolic syndrome had lower mean total CERAD-K scores (64.2 ± 11.1 vs. 69.8 ± 9.2, P = 0.010). In the comparison of CERAD-K items, significantly lower scores were observed in the verbal fluency test, the construction recall test, the word list learning test, and trail making B in the group with metabolic syndrome. After controlling age, sex, education, smoking, alcohol, physical activity and the Korean version of the Short Geriatric Depression Scale of Korean, multiple regression analysis showed that metabolic syndrome was independently associated with cognitive function (P = 0.014). Alcohol intake (P = 0.002) and education years (P = 0.001) were also contributing factors to cognitive function.

Conclusion: This study found a significant relationship between cognitive function and metabolic syndrome. It will be necessary to perform a prospective study to determine whether metabolic syndrome causes cognitive dysfunction or if the correction of metabolic syndrome can improve cognitive function.

Keywords: Metabolic Syndrome; Cognitive Function; CERAD-K

INTRODUCTION

The proportion of people aged 65 years and over in South Korea is expected to increase from 7.3 % in 2000 to 15.1% in 2020. Accordingly, the health problems of the elderly gain increasing importance in socio-economic terms.[1] Dementia is a socially important disease among the senile disorders because it has a high prevalence and deteriorates comprehensive cognitive functions, behaviors and mental functions, considerably inconveniencing vocational and social activities and significantly reducing the quality of life. As the geriatric population increases rapidly, the number of elderly people with dementia is also

expected to increase dramatically. In Korea, the incidence of dementia in 2008 was 8.68%, and the number of patients with dementia was estimated at 430,000. It is expected that the prevalence of dementia will increase continuously to an estimated 1,140,000 patients in 2030, with a two-fold increase per 20 years.[2] Hence, it is important to attempt to decrease the occurrence of dementia by determining and eliminating its risk factors as well as detecting and treating dementia early.

Many studies have reported relationships between dementia and vascular risk factors such as glucose intolerance, insulin resistance, central obesity, lipid abnormalities and hypertension.[3] Hypertension,[4,5] diabetes[6,7] and hyperlipidemia[8,9] play important roles in the pathogenesis of impaired cognitive function and are related to the increase of Alzheimer's disease as well as other types of dementia.[10] Metabolic syndrome is a cluster of cardiovascular risk factors, and its prevalence is increasing significantly in Korea. Although diagnostic criteria differ, metabolic syndrome is found in 32.6% of adults 30 years old or older according to the 2005 National Health and Nutrition Survey,[11] and a study on diabetes found the prevalence of metabolic syndrome to be 62.0%.[12]

With the drastic increase in the prevalence of metabolic syndrome around the world and in South Korea, studies are examining the relationship between metabolic syndrome and cognitive function. Yaffe et al.[13] reported a decrease in cognitive function with metabolic syndrome. However, previous studies are limited in that they have not measured cognitive function comprehensively. Most of previous studies have applied simple tests, such as the Mini-Mental State Examination (MMSE), to the evaluation of cognitive function and have not accurately assessed early dementia or mild cognitive disorder.[14,15] The MMSE is a simple method that is high in sensitivity and specificity, but it is limited in measuring cognitive function comprehensively. Therefore, it is recommended that cognitive tests for the elderly jointly use the comprehensive measurement tool.[16,17] In South Korea, Moon et al.[18] reported the relationship between metabolic syndrome and cognitive function in adults older than 50, but no study has examined this relationship among the elderly, who are in the high-risk of dementia and metabolic syndrome.

This study investigated the relationship between metabolic syndrome and cognitive function among elderly persons using the CERAD-K, a more precise evaluation method than MMSE.

METHODS

1. Subjects

The subjects were elderly people who had no difficulties in daily life and consented to participate in the study after receiving a sufficient explanation of its purposes and content. Participants included adults 60 years old and older who were screened at the health promotion center of a university hospital or who attended a health program at the Dongtan public health center from March 2010 through July 2010 in Gyeonggi-do province. Ninety five volunteers were recruited, and 2 were excluded due to cerebrovascular history. Thus, cognitive function tests were performed on 93 subjects. When a subject visited the hospital, an inquiry and history taking were conducted, which included information on age, gender, education, vocation, smoking, drinking, exercise and underlying disorders and cognitive functions; and a cognitive function test was performed. Smokers were classified into current smokers, past smokers who had not smoked in the past year, and non-smokers who had never smoked. Drinking frequency was divided into no drinking, drinking 6 or more times per week, 3−5 times per week, 1 or 2 times per week and less than once per week. Frequency of exercise for 30 minutes or more was categorized into 3 or more times a week, once or twice a week and hardly ever. Trained nurses measured participants' height, weight, waist circumference and blood pressure and conducted blood tests. Excluded from the study are those who had or were suspected of having dementia (based on the DSM-IV), had any problems in daily life, were unable to communicate or had cerebrovascular disease or cancer that might lower cognitive function.

2. Evaluation of Cognitive Function

Experienced doctors evaluated the subjects using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K).[19] The CERAD-K neuropsychological assessment battery (CERAD-K[N]) is a standardized evaluation tool for the early diagnosis of dementia. The test takes a short time, approximately 30−40 minutes, and is relatively easy to perform. Thus, it is very useful for the evaluation of elderly patients with dementia. The CERAD-K neuropsychological evaluation consists of nine neuropsychological subtests (verbal fluency test, modified Boston naming test, Korean version of

the mini-mental state examination [MMSE], word list memory, vonstruction praxis, word list delayed recall, word list recognition, construction recall, and trail making tests A and B). The total CERAD-K score was calculated by adding the scores on six tests: the verbal fluency test, modified Boston naming test, word list memory, construction praxis, word list delayed recall, and word list recognition. The maximum of total CERAD-K score was 100 points.[20,21]

Depression was evaluated using the Short Geriatric Depression Scale, Korean version (SGDS-K). The SGDS-K consists of 15 questions and has been shown to be a reliable and valid screening test for geriatric depression.[22] The optimal SGDS-K cutoff point for depression was defined as 8 points.

3. Metabolic Syndrome

Meeting the following 3 items or more was defined as metabolic syndrome on the basis of National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III).[23] Abdominal obesity was defined as the waist circumference of ≥ 90 cm (male) and ≥ 85 cm (female), which were recommended by the Korean Society for the Study of Obesity (KSSO)[24] in 2005: 1) waist circumference (WC) ≥ 90 cm for men or ≥ 85 cm for women; 2) TG levels ≥ 150 mg/dL; 3) HDL levels < 40 mg/dL for men or < 50 mg/dL for women; 4) systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic (DBP) ≥ 85 mm Hg, or the use of antihypertensive medication; and 5) fasting plasma glucose (FBS) ≥ 100 mg/dL, or the use of anti-diabetic medication or insulin.

4. Statistical Analyses

The data were analyzed using the SPSS ver. 13 (SPSS Inc., Chicago, IL, USA). The results are expressed as the mean ± SD. Chi-square test and independent samples test were used to investigate socio-demographic characteristics and biochemical tests according to metabolic syndrome. Each item of the CERAD-K test was assessed according to metabolic syndrome with a multivariate covariance analysis (MANCOVA) after adjustment for age, education, and alcohol consumption. A multiple regression analysis was conducted to determine cognitive function's association with age, gender, education, smoking, alcohol drinking, exercise, depression and metabolic syndrome. P-values of less than 0.05 were regarded as statistically significant.

RESULTS

1. Comparison of the General Characteristics and Biochemical Tests according to Metabolic Syndrome

Of the 93 subjects, 48 subjects (24 male, 21 female) had metabolic syndrome. The incidence was higher in female subjects than male (63.8% vs. 31.4%). Of the 48 subjects with metabolic syndrome, 20 (41.6%), 14 (29.1%), and 4 (8.3%) were taking anti-hypertensive drugs, lipid-lowering agents and oral hypoglycemic agents, respectively. There was no significant difference in age, education, smoking, drinking, exercise or depression between the group with metabolic syndrome and the control group, but women made up a significantly higher part of the group with metabolic syndrome. Compared to the control group, the group with metabolic syndrome showed a significantly higher average in body mass index, blood pressure, waist circumference and lipid concentration (Table 1).

2. Performance on the Cognitive Function Test according to the Presence of Metabolic Syndrome

The total CERAD-K score was 64.2 ± 11.1 in the group with metabolic syndrome, which was significantly lower compared to the value of 69.8 ± 9.2 in the control group. In the comparison of CERAD-K items, significantly lower scores were observed in the Verbal Fluency test, the Construction Recall test, the Word List Learning test, and Trail Making B in the group with metabolic syndrome. The MMSE-KC score was 26.0 ± 2.6 in the group with metabolic syndrome, which was significantly lower compared to 27.2 ± 2.0 in the control group (Table 2).

3. Relationships between Metabolic Syndrome and Cognitive Function

A regression analysis was conducted on age, gender, education, physical activity, smoking, drinking, depression and metabolic syndrome (Table 3). The presence of metabolic syndrome, alcohol consumption, and education were significantly associated with the total CERAD-K score (P < 0.05). However,

Table 1. General characteristics in the elderly with and without metabolic syndrome.

Characteristics	Without metabolic syndrome (n = 45)	Withmetabolic syndrome (n = 48)	P-value*
Age (y)	68.2 ± 4.4	69.3 ± 4.4	0.245
Sex			0.005
Male	24 (53.3)	11 (22.9)	
Female	21 (46.7)	37 (77.1)	
Body mass index (kg/m^2)	22.9 ± 2.7	26.3 ± 2.9	<0.001
Systolic blood press (mm Hg)	126.7 ± 12.6	132.8 ± 12.0	0.019
Diastolic blood press (mm Hg)	74.1 ± 7.9	79.8 ± 7.6	0.001
Waist (cm)	83.2 ± 8.1	94.8 ± 5.8	<0.001
Glucose (mg/dL)	95.2 ± 8.7	111.3 ± 24.5	<0.001
Triglyceride (mg/dL)	100.5 ± 43.9	147.8 ± 80.1	0.001
HDL-cholesterol (mg/dL)	54.9 ± 14.4	47.8 ± 10.2.	0.008
SGDS-K	4.1 ± 3.1	4.2 ± 3.5	0.890
Education (y)	6.2 ± 1.6	5.6 ± 2.2	0.099
Smoking			0.288
No smoking	31 (68.9)	40 (83.3)	
Ex-smoker	8 (17.8)	4 (8.3)	
Current smoker	6 (13.3)	4 (8.3)	
Drinking			0.988
No drinking	31 (68.9)	33 (68.7)	
Current	14 (31.1)	15 (31.3)	
Physical activity (times)			0.546
None	9 (20.0)	12 (25.0)	
1−2	15 (33.3)	11 (22.9)	
≥3	21 (46.7)	25 (52.1)	

Values are presented as mean ± SD or number (%).
HDL: high density lipoprotein, SGDS: Short Geriatric Depression Scale.
*P: by T-test for continuous variables and chi-square test for discrete variables.

the SGDS-K score had no association with the total CERAD-K score. In terms of education level, cognitive function scores were significantly higher among people with more than 7 years of education compared to those with 3 years or less. In a multiple regression analysis using metabolic risk factors (waist circumference, TG, HDL, blood pressure, FBS), glucose and systolic blood pressure levels affected the total CERAD-K score (R^2 = 29.4%, P < 0.05) (Table 4).

DISCUSSION

In this study, the prevalence of metabolic syndrome was 63.8% in women, which was significantly high compared to the prevalence in men (31.4%). This figure is close to the findings of a previous study of the total population (63.4% female, 34.1% male).[11] The cognitive function was significantly high in participants with 7 or more years of higher education compared to those with 3 or fewer years of education. This finding supports

Table 2. CERAD-K scores in study subjects.

Neuropsychological test		Without metabolic syndrome (n = 45)	With metabolic syndrome (n = 48)	P-value*
Language	Verbal fluency	14.5 ± 3.6	12.8 ± 3.6	0.038
	Modified Boston naming	11.9 ± 2.3	10.6 ± 2.6	0.179
General	MMSE-KC	27.2 ± 2.0	26.0 ± 2.6	0.003
Verbal memory	Word list learning	17.9 ± 3.8	17.0 ± 4.6	0.001
	Word list recall	6.0 ± 1.7	5.7 ± 1.9	0.153
	Word list recognition	9.3 ± 0.9	8.8 ± 1.3	0.573
Visual memory	Constructional praxis	10.1 ± 1.3	9.4 ± 1.5	0.459
	Constructional recall	7.6 ± 2.7	6.0 ± 6.0	0.008
Attention	Trail making A	77.8 ± 56.3	92.5 ± 45.2	0.119
Working memory	Trail making B	194.5 ± 87.6	250.7 ± 72.3	0.001
Total score		69.8 ± 9.2	64.2 ± 11.1	0.001

Values are presented as mean ± SD.

MMSE-KC: mini-mental status examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) assessment packet.

*P: by MANCOVA after adjustment for age, education, alcohol drinking.

Table 3. Multiple regression analysis demonstrating association between several factors and cognitive function.

Variable	β-estimated	SE	P-value*
Age (y)	−0.218	0.23	0.345
Female	2.19	3.03	0.471
Education (y)			
4−6	2.08	3.05	0.50
>7	10.11	2.96	0.001*
Smoking			
Current smoker	−4.69	3.88	0.230
Ex-smoker	−3.57	3.64	0.329
Alcohol			
Current drinker	6.94	2.22	0.002*
Physical activity (times)			
1−2	2.48	2.72	0.365
≥3	4.97	2.57	0.057
SGDS	−0.03	0.30	0.908
Metabolic syndrome	−5.07	2.01	0.014*

Coefficient of determination (R^2): 0.394, β-estimated: parameter estimate.

SE: standard error, SGDS: Short Geriatric Depression Scale.

*P: by multiple regression analysis models.

Table 4. Multiple regression analysis on the association of CERAD-K total score with metabolic risk factors (age, alcohol drinking and education level adjusted).

Variable	β-estimated	SE	P-value*
Waist (cm)	−0.063	0.116	0.526
Glucose (mg/dL)	−0.252	0.047	0.007
Triglyceride (mg/dL)	−0.174	0.014	0.064
HDL-C (mg/dL)	−0.032	0.079	0.737
Systolic blood press (mm Hg)	−0.236	0.078	0.024
Diastolic blood press (mm Hg)	−0.166	0.118	0.075

Coefficient of determination (R^2): 0.294, β-estimated: parameter estimate.

CERAD-K: Korean version of the Consortium to Establish a Registry for Alzheimer's Disease, SE: standard error, HDL: high density lipoprotein.

*P: by multiple regression analysis models.

the hypothesis that a higher education level delays the occurrence of dementia by supplementing cognition.[25] The cognitive function was significantly high in the drinking group compared to the non-drinking group. This finding is in contrast to the findings from previous studies that drinking increased the risk of dementia.[26] In terms of drinking frequency, 93.1% of participants

drank less twice. According to previous studies, a small amount of alcohol (i.e., 1−3 standard drinks or less a day) prevents the reduction of cognitive function, reduces the risk of dementia[27] and deters the progress of dementia in patients with mild cognitive disorder.[28] However, the present study is limited by not determining accurate amount and types of alcohol drinking. It seems necessary to analyze this relationship to cognitive function based on an accurate drinking history. Depression symptoms were serious in the Alzheimer-type dementia group compared to the control group.[29] Many studies report that depression is closely related to the lowering of cognitive function, but this study found no relationship between SGDS-K scores and cognitive function. Because the subjects had normal cognitive function with an MMSE score over 26 points and an SGDS-K score under 8 points, it seems that no depression symptoms were observed with regard to the changes in cognitive function. However, it will be necessary to conduct additional studies on elderly people in the future.

Recently, many studies have reported a relationship between metabolic syndrome and cognitive function. According to a prospective study of adults aged 70 years or older, cognitive function declined significantly in the group with metabolic syndrome.[13] In a 3.5-year prospective study of 2,097 patients 65 years or older with mild cognitive disorder, Solfrizzi et al.[30] reported a significant increase in the risk of progressing from mild cognitive disorder to dementia when accompanied by metabolic syndrome. Additionally, it is suggested that dementia increases with the increase in vascular risk factors, such as hypertension, diabetes, hyperlipidemia and smoking, in middle age.[31] Based on the mixture of cardiovascular risk factors, metabolic syndrome seems to be related to cognitive function. In South Korea, Moon et al.[18] reported that cognitive function decreased in adults with metabolic syndrome. However, the authors assessed cognitive function with the MMSE-K and did not perform a comprehensive and detailed analysis of cognitive function. In addition, depression symptoms were not considered. We assessed the relationship between metabolic syndrome and cognitive function in elderly Korean people using the CERAD tool. In this study, CERAD-K total scores were 64.2 ± 11.1 in the metabolic syndrome group and 69.8 ± 9.2 in the control group, which is consistent with previous findings on the total CERAD-K score in the Korean population.[21] Cognitive function decreased

in the metabolic syndrome group compared to the normal control group, especially on the verbal fluency test, construction recall test, word list learning test, trail making B, and the total CERAD-K score. This result might indicate the reduction of frontal lobe functions related to initial changes in dementia.

In this study, the presence of metabolic syndrome was significantly associated with cognitive function. Among the metabolic risk factors, fasting plasma glucose and triglyceride levels affected the CERAD-K total score. Many studies have examined the mechanism by which metabolic syndrome affects cognitive function. Insulin resistance and hyperinsulimenia in metabolic syndrome cause a decrease in glucose use and energy metabolism in the cerebral cortex than in other tissues.[32] Furthermore, in cases of hyperinsulimenia, insulysin, which decomposes the beta amyloid and plays an important role in Alzheimer's dementia, is better combined with insulin, thus depositing beta amyloids and increasing the phosphorylation of tau proteins.[33] Cholesterol, a main component of myelin and cell membrane, plays an important role in maintaining the functions of cerebral tissues. According to Eckert et al.,[34] there is a decrease in the membrane fluidity of the hippocampus as a memory center in Alzheimer's dementia, which may be related to cholesterol disorder. Beta amyloids destroy the cell membrane structure of cerebral tissue. A low cholesterol concentration causes a reduction in beta amyloid formation in hippocampus neurons, thus delaying the occurrence of Alzheimer's dementia.[34] Hypertriglyceridemia changes cerebral blood by increasing the viscosity of blood and lowers cognitive function by causing arteriosclerosis.[35] Hypertension is said to decrease the number of nicotinic receptors sensitive to acetylcholine and to cause cerebrovascular diseases, cerebral infarction and cerebral gray substances, arteriosclerosis and lower cognitive function.[36] A chronic high blood sugar level deters the synthesis and secretion of cerebral acetylcholine[37] and causes the loss of neurons in the cerebral cortex and the reduction of glucose levels in cells, leading to a decrease in cognitive function.[38]

Given the studies that suggest the high possibility that a decrease in cognitive function or mild cognitive function disorder will develop into dementia,[39] elderly individuals with metabolic syndrome have a lower cognitive function compared to the control group, and they are likely to develop dementia, although they do not currently suffer from dementia. Accordingly, the early

detection and correction of metabolic syndrome in adults is likely to decrease cardiovascular diseases and to reduce the decrease of cognitive function and the risk of dementia. Given that early detection and treatment are effective for senile dementia, it seems that the precise assessment of cognitive function will be helpful for metabolic syndrome patients.

Our study has the following limitations. First, the subjects of this study are individuals who participated in a health promotion program of a hospital. Thus it is necessary to be cautious in applying the study results to normal population groups. Second, there were more women in the group with metabolic syndrome than in the control group. However, this trend is similar to the gender distribution in the elderly Korean population. There were statistically significant relationships between metabolic syndrome and cognitive function even after adjusting for gender and education. Third, this was cross-sectional study to assess the relationship between metabolic syndrome and cognitive function, but it was difficult to evaluate causal relationships. However, this study is significant in that it analyzed the relationships between metabolic syndrome and cognitive function in elderly Korean individuals using the CERAD tool. It will be necessary to perform a prospective study to determine whether metabolic syndrome causes cognitive dysfunction or dementia and whether the correction of cardiovascular risk factors can improve cognitive function.

REFERENCES

1. The National Statistical Office. The elderly statistics in Korea. Daejeon: The National Statistical Office; 2009.

2. The Ministry of Health and Welfare. The estimation of dementia in Korea. Seoul: The Ministry of Health and Welfare; 2008.

3. Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63:1882-91.

4. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-8.

5. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21:49-55.

6. Akomolafe A, Beiser A, Meigs JB, Au R, Green RC, Farrer LA, et al. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. Arch Neurol 2006;63:1551-5.

7. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658-63.

8. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62:1556-60.

9. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol 2002;59:378-84.

10. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20:93-100.

11. The Ministry of Health and Welfare. The Third Korea National Health & Nutrition Examination Survey (KNHANES III), 2005. Seoul: The Ministry of Health and Welfare; 2006.

12. Moon MK, Cho YM, Jung HS, Kim KW, Park YJ, Jang HC, et al. The prevalence of metabolic syndrome and its relation with chronic complications in Korean type 2 diabetic patients. Korean J Lipidol 2003;13:382-91.

13. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292:2237-42.

14. Penninx BW, Nicklas BJ, Newman AB, Harris TB, Goodpaster BH, Satterfield S, et al. Metabolic syndrome and physical decline in older persons: results from the Health, Aging And Body Composition Study. J Gerontol A Biol Sci Med Sci 2009;64:96-102.

15. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, West N. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc 2007;55:758-62.

16. Mitchell AJ. A meta-analysis of the accuracy of the mini-

mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009;43:411-31.

17. Scazufca M, Almeida OP, Vallada HP, Tasse WA, Menezes PR. Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the Sao Paulo Ageing & Health Study. Eur Arch Psychiatry Clin Neurosci 2009;259:8-15.

18. Moon SH, Oh HJ, Kim SH, Lee HR, Lee DC, Shim JY. Relationship between the metabolic syndrome and cognitive function. J Korean Acad Fam Med 2006;27:463-70.

19. Lee JH, Lee KU, Lee DY, Kim KW, Jhoo JH, Kim JH, et al. Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): clinical and neuropsychological assessment batteries. J Gerontol B Psychol Sci Soc Sci 2002;57:P47-53.

20. Chandler MJ, Lacritz LH, Hynan LS, Barnard HD, Allen G, Deschner M, et al. A total score for the CERAD neuropsychological battery. Neurology 2005;65:102-6.

21. Seo EH, Lee DY, Lee JH, Choo IH, Kim JW, Kim SG, et al. Total scores of the CERAD neuropsychological assessment battery: validation for mild cognitive impairment and dementia patients with diverse etiologies. Am J Geriatr Psychiatry 2010;18:801-9.

22. Bae JN, Cho MJ. Development of the Korean version of the Geriatric Depression Scale and its short form among elderly psychiatric patients. J Psychosom Res 2004;57:297-305.

23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

24. Lee S, Park HS, Kim SM, Kwon HS, Kim DY, Kim DJ, et al. Cut-off points of waist circumference for defining abdominal obesity in the Korean population. Korean J Obes 2006;15:1-9.

25. Mortimer JA. Do psychosocial risk factors contribute to Alzheimer's disease? In: Henderson As, Henderson JH, editors. Etiology of dementia of Alzheimer's type. New York: John Wiley & Sons; 1998. p. 39-52.

26. Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr,

Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA 2003;289:1405-13.

27. Standridge JB, Zylstra RG, Adams SM. Alcohol consumption: an overview of benefits and risks. South Med J 2004;97:664-72.

28. Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Baldassarre G, et al. Alcohol consumption, mild cognitive impairment, and progression to dementia. Neurology 2007;68:1790-9.

29. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing 2008;37:505-12.

30. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, et al. Metabolic syndrome, mild cognitive impairment, and progression to dementia: the Italian Longitudinal Study on Aging. Neurobiol Aging 2011;32:1932-41.

31. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277-81.

32. Cunnane S, Nugent S, Roy M, Courchesne-Loyer A, Croteau E, Tremblay S, et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 2011;27:3-20.

33. Hoyer S. The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update. J Neural Transm 2002;109:341-60.

34. Eckert GP, Cairns NJ, Maras A, Gattaz WF, Müller WE. Cholesterol modulates the membrane-disordering effects of beta-amyloid peptides in the hippocampus: specific changes in Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:181-6.

35. Koenig W, Sund M, Ernst E, Mraz W, Hombach V, Keil U. Association between rheology and components of lipoproteins in human blood. Results from the MONICA project. Circulation 1992;85:2197-204.

36. Geerlings MI, Appelman AP, Vincken KL, Algra A, Witkamp TD, Mali WP, et al. Brain volumes and cerebrovascular lesions on MRI in patients with atherosclerotic disease: the SMART-MR study. Atherosclerosis 2010;210:130-6.

37. Balakrishnan S, Mathew J, Antony S, Paulose CS. Muscarinic M(1), M(3) receptors function in the brainstem of

streptozotocin induced diabetic rats: their role in insulin secretion from the pancreatic islets as a function of age. Eur J Pharmacol 2009;608:14-22.

38. Redish AD, Touretzky DS. Cognitive maps beyond the hippocampus. Hippocampus 1997;7:15-35.

39. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.