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Association Between Obesity Measures and Cognitive Function in Korean Older Adults

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Sung-il Cho

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Graduate School of Public Health
Seoul National University
Department of Public Health Science

Sujeong Han

Confirming the Ph.D. Dissertation written by
Sujeong Han
November 2022

Chair	Ho Kim
Vice Chair	Joohon Sung
Examiner	Jun-Young Lee
Examiner	Byung Yeon Yu
Examiner	Sung-il Cho

Abstract

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Sujeong Han

Department of Public Health Science

Graduate School of Public Health

Seoul National University

Introduction: Aging is inevitable, accompanied by reduced intellectual ability, decline in sensory functions, and reduced emotional responses. Several socio-demographic characteristics and health habits can affect cognitive decline. These included older age, lower income, poorer education, poor self-rated health, limitations on the activities of daily living and chronic illness etc. Also Cognitive impairment was also associated with visceral fat. Therefore, identifying factors that affect cognitive function decline is essential for the prevent cognitive decline

and creation of effective interventions. The objectives of the present study were to identify distinct trajectories of cognitive function using the GBTM method. And I found out what risk factors existed for each identified group, such as demographics characteristics, lifestyle, comorbidities, and economic conditions. Second, I investigated changes in visceral fat over time and their association with cognitive function accordingly by gender. Third, I aimed to evaluate whether visceral obesity causes Non Amnestic/Amnestic mild cognitive impairment. I also investigated the variables affecting the Non-Amnestic/Amnestic mild cognitive impairment.

Methods: First, I collected data from the Seoul National University Hospital Healthcare System Gangnam Center. First, 637 individuals (274 males and 363 females) aged over 40 were included who got health check-up in the Seoul National University Hospital Healthcare System Gangnam Center 2005 to 2020. A group-based trajectory model was utilized to determine the appropriate number of groups and also to observe changes in cognitive function. Following the trajectory analysis, a multinomial regression analysis was performed to examine the related risk factors of cognitive function that influenced each trajectory groups.

Second, 642 individuals (275 males and 367 females) were selected who underwent bioelectrical impedance analysis (BIA) for visceral fat area and the Consortium to Establish a Registry for Alzheimer's Disease-K (CERAD-K) test at the Seoul National University Hospital Healthcare System Gangnam Center 2005 to 2020. A linear mixed model (LMM) was used to assess the association between cognitive function and visceral fat area.

Third, among those who participated in the Seoul National University Hospital Healthcare System Gangnam Center from 2005 to 2020, 569 people (281 males, 288 females) were included in the analysis, excluding those already suffering from mental disorders such as mild cognitive impairment or dementia. Kaplan-Meier analysis and Cox Proportional Hazard regression analysis were conducted to determine the association between visceral obesity and Non Amnestic/Amnestic mild cognitive impairment.

Results: From the first study, the cognitive function trajectories among adults over 40 years of age were heterogeneous. I identified four trajectories: High (27.3%), medium (41.0%), low (22.7%), and rapid cognitive function decline (9.1%). Older age, male, low educational level,

bad dietary habits, diabetes mellitus, technical worker, and lower income increased the likelihood of a cognitive function decline. From the second study, an increased visceral fat area was associated with worse Word List Memory score (β:-0.15, CI: -0.29 to -0.01) and Word List Recall score (β:-0.16, CI: -0.24 to -0.09) in males. In females, an increased visceral fat area was associated with worse Boston naming test score (β: -0.15, CI: -0.23 to -0.06), MMSE-KC score (β:-0.26, CI: -0.40 to -0.12), Word List Memory score (β: -0.25, CI: -0.41 to -0.09), Constructional praxis score (β: -0.09 CI: -0.14 to -0.03), and sum of domains except MMSE-KC (β: -0.71, CI: -1.20 to -0.22). From the third study, the risk of Non-Amnestic mild cognitive impairment in the visceral obesity group was 1.43 higher (95% CI=1.10-1.86) than that in the non-visceral obesity group. The risk of Non-Amnestic mild cognitive impairment in age of 40-64 was 1.44 higher (HR, 95% CI=1.11-1.87) than in age of 65-84, lower education level was 1.32 higher (HR, 95% CI=1.04-1.67) than that in higher education level and in monthly household income under 10 million won was 1.29 higher (HR, 95% CI=1.02-1.63) than that in over 10 million won. Also, the risk of Non-Amnestic mild cognitive impairment in subjects with having hypertension was 1.31 higher (HR, 95% CI=1.06-1.63) than not suffering from hypertension.

Conclusion: Through this study, it was found that various patterns exist in the cognitive decline of individuals. In addition, factors affecting cognitive decline were also identified. Older age, low education level, bad dietary habits, low income, technical workers, comorbidities, and increase in visceral fat act as risk factors for cognitive function. In addition, visceral obesity increases the risk of developing mild cognitive impairment.

Cognitive reserve is the brain's ability to withstand damage and to recover when it is damaged. The cognitive decline can be prevented by maintaining high cognitive reserve of the brain through healthy habits such as smoking cessation, abstinence from alcohol, exercise, and good dietary habits or through various daily activities. In order to reduce risk factors affecting cognitive function through this study, it is necessary to encourage changes in lifestyles that individuals can make and social interventions are needed.

Keywords: Cognitive function, cognitive deficit, group-based trajectory model, visceral fat, older adults

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Chapter 1. Overall Introduction

1.1 Cognitive function decline and population of dementia

Cognitive functions include various mental processes such as comprehension, perception, decision-making, and memory. Cognitive function also plays an important role in social activities and daily life. For example, in a situation where we have to choose an object, we have to think about which one to choose and why we chose it, and at school, we can hear and identify our friend and have a conversation with them.

Cognitive function changes throughout life. Cognitive function improves from childhood to adolescence, with working memory and executive functioning peaking in the twenties or thirties. However, as we get older, various cognitive functions, including memory, attention, and executive ability, deteriorate, which makes it difficult to perform basic activities in daily life. There are stages when cognitive function declines, and the stage before dementia is called mild cognitive impairment. Dementia refers to damage to the brain to the extent that it is almost impossible to perform daily life due to impairment of cognitive function. Dementia is one of the leading causes of morbidity and mortality worldwide, which negatively affects families, communities and health care systems.

The World Health Organization (WHO) estimates that there are

10 million cases of dementia each year[1]. The combined cost of treatment for dementia by individuals and countries is equivalent to 1.1% of global GDP[2].

In global prevalence of dementia, Asia Pacific had the highest prevalence, followed by Europe, Australia and North America. The prevalence of dementia was highest in Japan (3,079 cases per 100,000 people), Italy (2,269 cases), Slovenia (1,963 cases), Monaco (1,962 cases) and Greece (1,874 cases) in that order. And South Asia and Africa had the lowest prevalence of dementia [Figure 1-1], [Table 1-1][3].

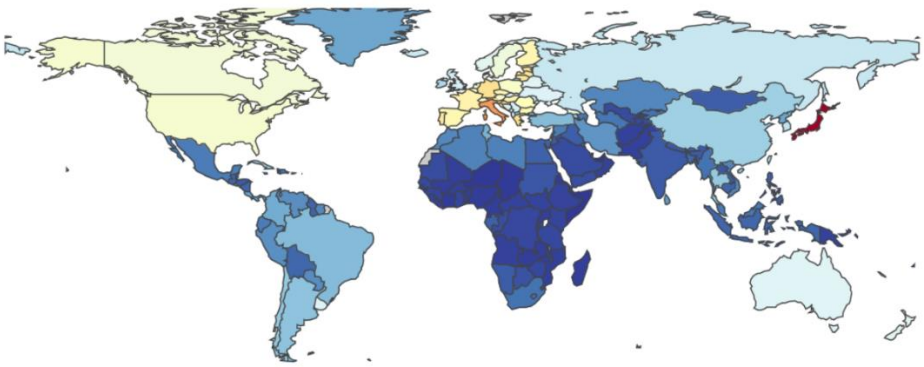

Figure 1-1 Prevalence rates per 100,000 population by country. Red, orange and yellow shades indicate higher prevalence (Source: Javaid, Syed Fahad, et al. "Epidemiology of Alzheimer's disease and other dementias: rising global burden and forecasted trends." F1000Research 10.425 (2021): 425, Global Burden of Disease, 2019)

Region	Prevalence (cases per 100,000 population)	The burden of human suffering (DALY per 100,000)	Total number of cases
Global average	667	327	51,624,000
Europe	1,443	689	12,251,000
Russia	1,150	515	1,686,000
Germany	1,864	836	1,582,000
Italy	2,270	1,110	1,369,000
France	1,698	881	1,124,000
United Kingdom	1,241	651	834,000
Asia	598	297	27,230,000
China	924	420	15,299,000
Japan	3,079	1,613	4,579,000
India	266	153	4,249,000
South Korea	1,119	537	685,000
Iran	559	271	542,000
Americas	938	439	9,474,000
United States	1,495	618	4,902,000
Canada	1,459	666	532,000
Mexico	430	272	537,000
Brazil	786	395	1,702,000
Argentina	839	393	378,000
Africa	197	108	2,591,000
South Africa	381	192	211,000
Nigeria	124	84	266,000
Egypt	299	137	295,000
Algeria	461	228	193,000
Morocco	485	240	174,000

Table 1-1 The dementia prevalence and the burden of human suffering (Source: Javaid, Syed Fahad, et al. "Epidemiology of Alzheimer's disease and other dementias: rising global burden and forecasted trends." F1000Research 10.425 (2021): 425.)

1.2 Cognitive reserve

The term "cognitive reserve" describes the brain's resistance to brain damage or sickness as well as its capacity to recover from it[4]. The concept and position of cognitive reserve is illustrated in [Figure 1-2].

In one previous study, an autopsy case was studied with Alzheimer's disease dementia patients and advanced Alzheimer's patients with normal cognitive abilities at the time of death[5]. The results of the study concluded that the higher the cognitive reserve, the greater the number of neurons, and thus the ability to maintain cognitive function even in the event of brain damage[6].

In other words, in comparison to a person with a lower brain reserve capacity, a person with a higher brain reserve capacity achieves this threshold for the onset of cognitive decline later in the illness course, or when more pathology has accumulated[7].

According to previous studies, sociodemographic factors such as education level[8], occupation[9], leisure activities and lifestyle[10] are associated with a lower risk of dementia. The study suggested that cognitive reserve is facilitated by the aforementioned sociodemographic factors [Figure 1-3].

It claims that parts of brain function and cognitive processing

abilities, such as cognitive reserve, are influenced by an individual's lifelong experiences, social influences, as well as their lifestyle[11].

Therefore, even those with the same degree of brain damage may have varying levels of cognitive reserve, which may affect how well they are able to preserve their cognitive functions even when dealing with a brain disease[7]. And factors that can increase cognitive reserve are most effective in preclinical and mild cognitive impair in Alzheimer's disease, indicating that the ability to cope with brain disease is highest in the early stages of the disease[12].

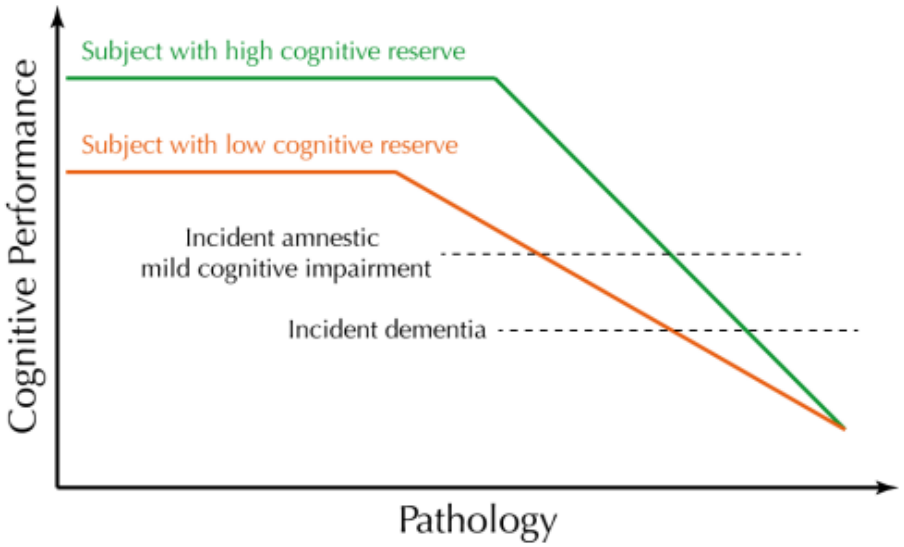

Figure 1-2 Illustration of how cognitive reserve may moderate the association between AD brain pathology and the clinical expression of cognitive symptoms (Source: Franzmeier, Nicolai. Neural mechanisms of cognitive reserve in Alzheimer's disease. Diss. lmu, 2017.)

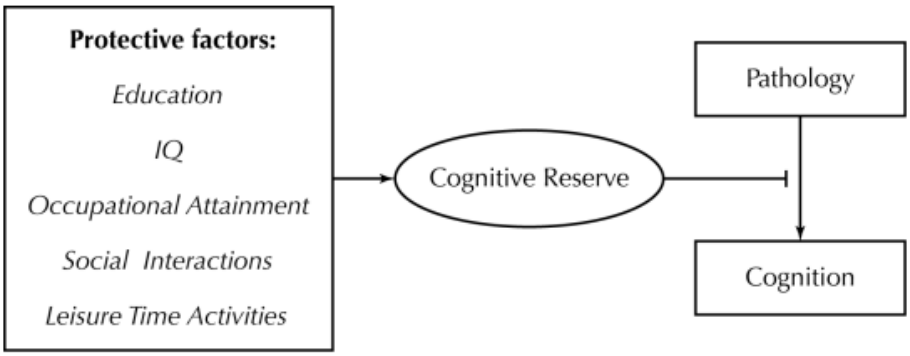

Figure 1-3 A working model on moderating effects of cognitive reserve on the association between brain pathology and cognitive performance (Source: Franzmeier, Nicolai. Neural mechanisms of cognitive reserve in Alzheimer's disease. Diss. lmu, 2017.)

1.3 Objective of the present study

It is a well-known fact that cognitive function declines with age. However, even if we look around, we can see that people who take good care of their health are less prone to diseases and live a long and healthy life.

As such, the rate or pattern of cognitive decline may vary from person to person. Some people may experience a sharp decline in cognitive function, and some may experience less cognitive decline as they age.

In the meantime, many previous studies have been able to identify factors that affect cognitive function. In this study, we will also identify factors that affect cognitive function, and in particular, we would like to examine the effects of visceral fat and obesity.

Therefore, the objectives of the present study were to 1) examine the changes in the trajectories of cognitive function and identify the risk factors that influence these changes, 2) to investigated changes in visceral fat over time and their association with cognitive function accordingly, by gender, 3) to evaluate whether visceral obesity causes Mild Cognitive Impairment.

1.4 Composition of the data

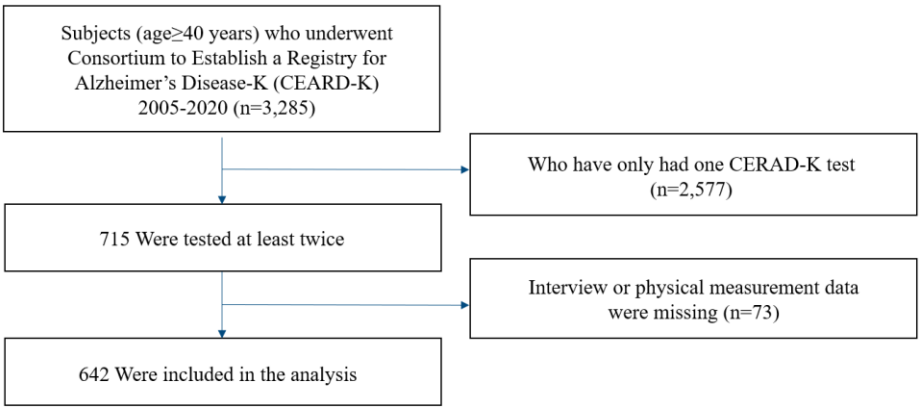

Figure 1-4 Flow chart of study population

I collected data from the Seoul National University Hospital Healthcare System Gangnam Center. Individuals visit the center voluntarily and received checkups to identify any health abnormalities rather than to investigate known clinical problems. At the center, the medical staff consider age and underlying diseases when deciding whether the check-up will include blood tests, tests of cognitive function (e.g., the CERAD-K), or physical measurements.

Some people do not return to the center for follow-up testing using the CERAD-K or physical measurements. This occurs when the health check-up does not include cognitive function tests or physical measurements, or when the results of these tests are within the normal

range. However, in cases where patients are at risk for cognitive decline, doctors recommend regular checkups that include the CERAD-K and physical measurements.

Not all subjects were followed from the same starting point for the same period of time. Subjects were tested again after as little as one year and as long as 13 years after the previous test. The highest number of repeated measurements was 11. The average follow-up period was 4.5 years, and the average number of repeat visits to undergo CERAD-K testing and physical measurements was 2.7. In total, 3,285 individuals underwent CERAD-K testing and physical measurements from 2005 to 2020. This includes individuals with and without repeat assessment of cognitive function and physical measurement. Because this study included a longitudinal study, I excluded those who measured cognitive function or body measurements only once.

To determine the demographic characteristics of 3,285 people, I used chi-square and t-tests for categorical and continuous variables, respectively. Demographic characteristics are presented as means, standard deviation or numbers (%). [Table 1-2] shows the characteristics of subjects. The 3,285 subjects included 1,397 males and 1,888 females. The mean age of males (61.83 years) was significantly higher than that

of females (60.44 years). The social characteristics showed significant differences between males and females in educational level (p<.0001), occupation (p<.0001), monthly household income (p<.0001), current smoking (p<.0001), alcohol consumption (p<.0001), exercise (p<.0001), dietary habits (p<.0001) and hypertension (p<.0001) and diabetes mellitus (p<.0001). The visceral fat area of males was significantly larger than that of females (109.50 vs. 87.76, p<.0001) [Table1-3]. [Table 1-3] include information on body measurement, cognitive function domain score for subjects.

Table 1-2. General characteristics of total population

Variables	Male (n=1,397)	Female (n=1,888)	Total (n=3,285)	P-value
Age, Mean (SD)	61.83 (10.00)	60.44 (9.73)	61.03 (9.87)	**<.0001**
Education				**<.0001**
Under high school	326 (23.34)	870 (46.08)	1,196 (36.41)	
Over high school	1,071 (76.66)	1,018 (53.92)	2,089 (63.59)	
Occupation				**<.0001**
Professional worker	914 (65.43)	220 (11.65)	1,134 (34.52)	
Technical worker	127 (9.09)	93 (4.93)	220 (6.70)	
No job	356 (25.48)	1,575 (83.42)	1,931 (58.78)	
Household income				**<.0001**
Under 5 million won	247 (17.68)	541 (27.22)	761 (23.17)	
5~10 million won	496 (35.50)	826 (43.75)	1,322 (40.24)	
Over 10 million won	654 (46.81)	548 (29.03)	1,202 (36.59)	
Current Smoking				**<.0001**
No	1,205 (86.26)	1,854 (98.20)	3,059 (93.12)	
Yes	192 (13.74)	34 (1.80)	226 (6.88)	
Alcohol consumption				**<.0001**
No	454 (32.50)	1,519 (80.46)	1,973 (60.06)	
Yes	943 (67.50)	369 (19.54)	1,312 (39.94)	
Exercise				**<.0001**
No	342 (24.48)	686 (36.33)	1,028 (31.29)	
Yes	1,055 (75.52)	1,202 (63.67)	2,257 (68.71)	
Dietary habits				**<.0001**
Bad dietary habits	1,001 (71.65)	1,040 (55.08)	2,041 (62.13)	
Good dietary habits	396 (28.35)	848 (44.92)	1,244 (37.87)	
Comorbidity				
Hypertension	570 (40.80)	615 (32.57)	1,185 (36.07)	**<.0001**
Diabetes mellitus	235 (16.82)	183 (9.69)	418 (12.72)	**<.0001**

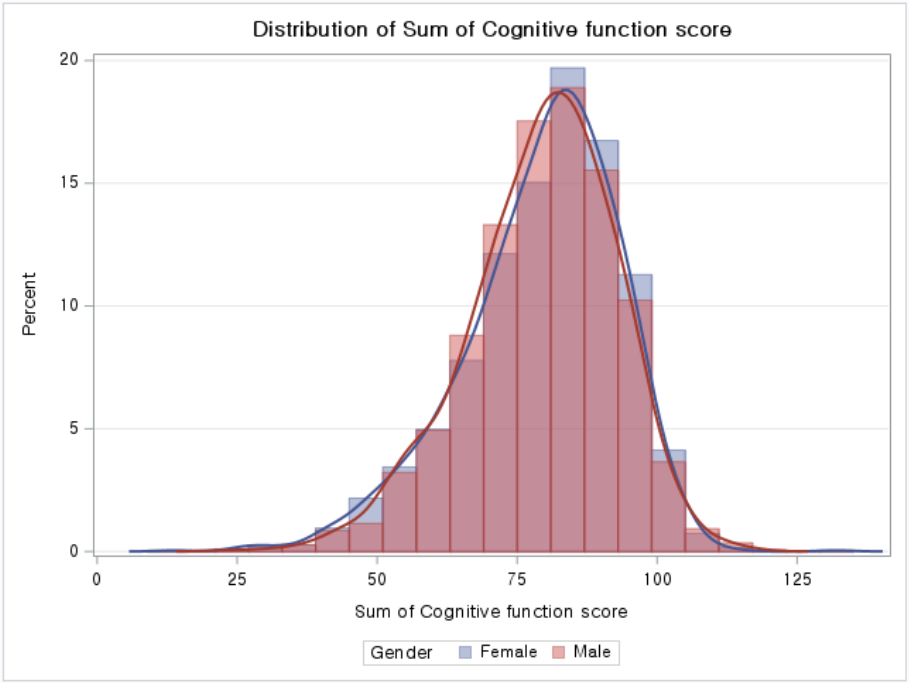

Figure 1-5 Distribution of cognitive function score

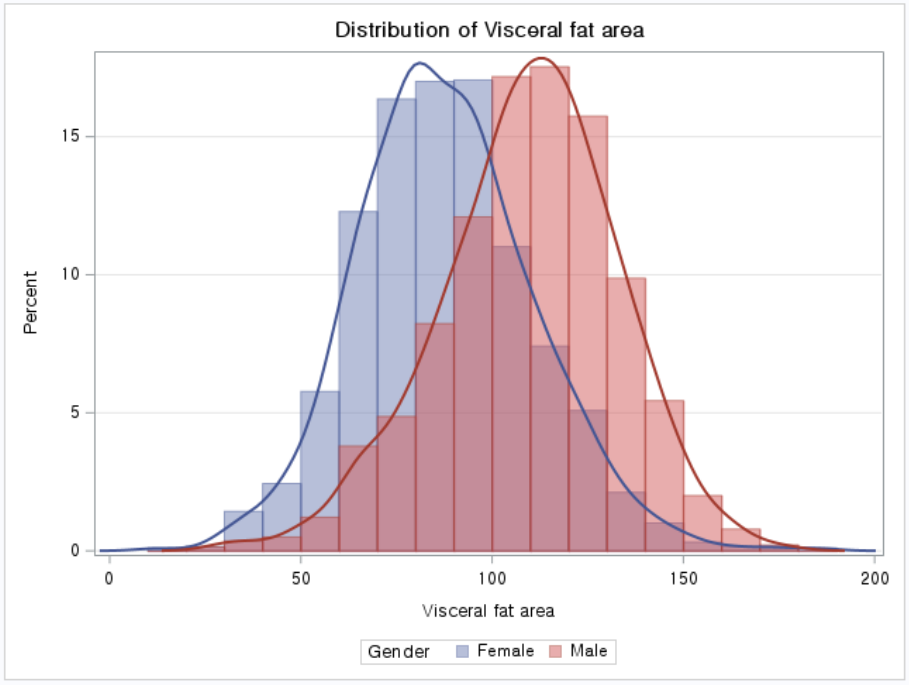

Figure 1-6 Distribution of visceral fat area

Table 1-3. Frequency of body measurement and cognitive function score of total population

Variables	Male (n=1,397)	Female (n=1,888)	Total (n=3,285)	P-value
Body measurement, Mean (SD)				
Systolic blood pressure	122.30 (14.82)	119.40 (16.86)	120.66 (16.08)	<.0001
Diastolic blood pressure	79.06 (10.44)	73.63 (10.91)	75.94 (11.04)	<.0001
Height	168.60 (5.77)	156.40 (5.40)	161.60 (8.23)	<.0001
Weight	69.09 (8.60)	56.41 (7.34)	61.81 (10.09)	<.0001
Body mass index	24.27 (2.50)	23.09 (2.91)	23.59 (2.80)	<.0001
Basal metabolic rate	1,505.90 (127.00)	1,205.80 (84.22)	1,333.63 (181.55)	<.0001
Percent body fat	23.60 (4.66)	30.90 (5.53)	27.79 (6.31)	<.0001
Protein	10.28 (1.15)	7.50 (0.76)	8.68 (1.67)	<.0001
Minerals	3.53 (0.36)	2.74 (0.25)	3.08 (0.50)	<.0001
Waist-hip ratio	0.91 (0.04)	0.89 (0.05)	0.90 (0.05)	<.0001
Waist circumference	88.56 (7.09)	83.97 (8.07)	85.93 (8.00)	<.0001
Muscle mass	29.45 (3.90)	20.29 (2.53)	24.20 (5.54)	<.0001
Body fat mass	16.48 (4.52)	17.69 (4.97)	17.18 (4.82)	<.0001
Visceral fat area	109.50 (23.30)	87.76 (23.04)	97.03 (25.53)	<.0001
Cognitive function domain				
Verbal Fluency	14.89 (4.81)	13.97 (4.58)	14.36 (4.70)	<.0001
Boston Naming Test	12.09 (2.14)	12.09 (2.27)	12.09 (2.22)	0.989
MMSE-KC	27.02 (2.51)	26.64 (3.11)	27.00 (2.87)	0.000
Word List Memory	17.87 (4.36)	19.06 (4.27)	15.56 (4.35)	<.0001
Constructional Praxis	10.70 (0.89)	10.46 (1.22)	10.56 (1.10)	<.0001
Word List Recall	6.37 (2.10)	6.76 (2.19)	6.59 (2.16)	<.0001
Word List Recognition	9.00 (1.53)	9.15 (1.49)	9.08 (1.51)	0.003
Constructional Recall	8.34 (2.81)	7.76 (3.05)	8.01 (2.96)	<.0001
Sum of domains except MMSE-KC	79.26 (13.27)	79.25 (13.93)	79.25 (13.66)	0.993

1.5 Methods for measuring cognitive function[13]

The test consists of 8 items.

1. Verbal Fluency: This test evaluates language, semantic memory, and vocal expression. The topic must provide as many examples of the category "animal" as they can in a minute.

2. Modified Korean version of the Boston Naming Test. This test is a test in which the subject looks at a picture made up of lines and says what it is. The top score is fifteen.

3. Mini-Mental State Examination is a well-known screening tool for the cognitive function that assesses memory, orientation, language, concentration, and constructional praxis. The test has a 30-point maximum score.

4. Word List Memory: This free-recall memory test evaluates a subject's capacity to learn new spoken material. The order in which the 10 words are presented varies from trial to trial. The participant is instructed to read each word out loud as it is provided. The individual is instructed to recollect as many items as they can in 90 seconds immediately after each trial. For the three trials, 30 correct answers are the maximum.

5. Constructional Praxis: This exercise evaluates constructional and visuospatial skills. The subject is given four line drawings of figures

ranging in complexity for copying, with two minutes allotted for each figure. For a drawing that is accurate in all four figures, the maximum score is 11.

6. Word List Recall: This test measures your capacity to recall the 10 words from the Word List Memory assignment after a brief pause. There is a 90-second maximum time limit and a 10 points maximum.

7. Word List Recognition: In the word list memory test, a mixture of 10 suggested words and 10 new words is presented and then instructed to select the previously presented word. It is possible to measure the episodic memory of the subject. The maximum score of this task is 10.

8. Constructional Recall: This task tests a person's memory for the four line drawings of the figures they saw in the Constructional Praxis test after a brief delay. A design that correctly depicts all four figures can get a maximum score of 11.

Chapter 2. Risk Factors for Various Cognitive Function Decline Trajectories in Adults Over 40 Years of Age

2.1 Introduction

Aging is inevitable, accompanied by reduced intellectual ability, decline in sensory functions, and reduced emotional responses[14]. The decline in intellectual ability begins with memory issues, and impairments of judgment and comprehension[15]. In most parts of the world, the prevalence of dementia in adults aged 60 and up is around 5–7%[16].

In 2018, it was estimated that 50 million people globally had dementia, with the number expected to triple by 2050[17]. Due to the fact that dementia is a prominent cause of mortality and is accompanied by expensive healthcare costs[18], preventative and interventional measures that reduce cognitive decline in older adults are essential.

Several socio-demographic characteristics and health habits can affect cognitive decline. These included older age, lower income[19] not cohabiting with a spouse[20], poorer education[21], rural residence[22], poor self-rated health[23], limitations on the activities of daily living[19] and chronic illness[24]. Current smokers[25] exhibited low cognitive functioning but normal alcohol consumers[26] and those who exercised[27] frequently maintained a healthy weight[19] and participated in social activities[28], exhibited high-level functioning[29]. In this regard, decline of cognitive

function affects people's general health as well as their mental health. Therefore, identifying factors that affect cognitive function decline is essential for the creation of effective interventions.

The trajectory analysis is intended to account for individual variability with respect to the average population trend. The trajectory is necessary in order to provide an intervention suitable for the group because the demographic characteristics or risk factors will be different for each group grouped with similar characteristics over time[30].

To implement the trajectory, a group-based trajectory mode (GBTM) is used. Group based trajectory model methods identify the individual characteristics of each study subject. And it is a method to show the progress pattern of how a specific variable changes with time and to classify it appropriately[31].

Among the studies related to mental illness, there are not many studies that have analyzed the trajectory of cognitive function, but there are many studies related to the trajectory of depression. In some psychiatric studies, there are studies that confirm the multiple change patterns of depression while reflecting the heterogeneity and dynamics of the group. Depression change does not appear as a single trajectory, but multiple trajectories exist. In addition, various patterns of change

were found to be diverse, such as a pattern of maintaining a low level of depression or a high level of depression, a pattern of decreasing the level of depression, and a pattern of increasing it[32–34].

Other previous study on the trajectory of depression, there was a high-risk group particularly vulnerable to depression among the elderly with disabilities, and risk factors affecting this group included social relationships and daily life performance. In that paper, it was revealed that the results can be used as evidence to prepare alternatives such as increasing opportunities to socialize with people and supporting assistive devices to improve daily life performance to prevent depression in the elderly[35]. As such, it is possible to devise an intervention method that can select and prevent high-risk groups through trajectory analysis.

Similarly, cognitive function may also appear in various ways, such as a pattern in which cognitive function is maintained high, a pattern in which the cognitive function is maintained at a moderate level, and a pattern in which cognitive function is rapidly decreased, depending on the person. Finding influencing factors for enhancing or sustaining cognitive function may be done by looking at the categorization of individuals' cognitive function trajectory. And ultimately, investigate effective strategies for improving mental health among older adults.

The aims of study were (1) to identify distinct trajectories of cognitive function using the GBTM method. And (2) to find out what risk factors exist for each identified group, such as demographics, lifestyle, comorbidities, and economic conditions.

2.2 Methods

2.2.1 Participants

Participants visited the Seoul National University Hospital Healthcare System Gangnam Center for health checkups that included the Consortium to Establish a Registry for Alzheimer's Disease-K (CERAD-K), medical interviews, blood tests, and physical measurements. In total, 3,992 individuals underwent CERAD-K testing and physical measurements from 2005 to 2020. This includes individuals with and without repeat assessment of cognitive function and physical measurement. For the longitudinal study, 637 remained and enrolled in the study, excluding participants without CERAD-K repeat tests, physical measurements, blood tests, or other measurements. The study was approved by the Institutional Review Boards of Seoul National University Hospital and Seoul National University Boramae Medical Center.

2.2.2 Study measures

2.2.2.1 Cognitive function

In this study, cognitive performance was defined as the CERAD-K score. I use seven subtests evaluating Verbal Fluency, Boston Naming,

Word List Memory, Word List Recall, Word List Recognition, Constructional Praxis and Constructional Recall. The Verbal Fluency test assesses verbal productivity, semantic memory and linguistic ability. For example, a subject is asked to name as many animals as possible in 1 min[36]. In the Boston Naming test, the subject looks at pictures and names the objects seen[13]. The Word List Memory requires immediate recollection. Participants read 10 common words every 2 seconds and immediately recall as many as they can over 90 seconds. After 15 min, the subject within 90 seconds recalls 10 words from the Word List Memory task in the Word List Recall Test, which assesses short-term memory. In the Word List Recognition test, the subject discriminates between 10 words used in the Word List Memory test and a new set of 10 words, this assesses recognition ability[37]. The Constructional Praxis assesses visual, spatial and constructional skills. Each subject is given four line drawings of increasing complexity. Each figure is studied for no more than 2 min. The Constructional Recall test assesses the capacity to recall figures presented in the Constructional Praxis test after a brief delay[13].

2.2.2.2 Independent variables

The independent variables were demographic, economic, lifestyle, and comorbidity variables. The demographic variables included age, gender and educational level (high school graduate or above). The economic variable was household income (monthly average less than or over 5 million won). Occupations were divided into professional and technical. The lifestyle variables included current smoking, current alcohol consumption, exercise (exercise regularly at least once a week or not) and dietary habits. If subjects eat three times a day, eat breakfast five times or more a week, have regular meal times, eat moderately and eat out once or twice a week, the subject's dietary habits are in the good category and If subjects skip a meal, eat fast, eat too much and eat out more than three times a week, subject’s dietary habits are classified as bad. The comorbidities included hypertension, diabetes mellitus, hyperlipidemia. Comorbidities were classified according to whether they were receiving treatment after diagnosis and whether they were currently taking medication. Obesity defined by the waist circumference is greater than 90cm in men and greater than 85cm in women.

2.2.3 Statistical analysis

Data analysis was divided into two parts: (1) Identification of cognitive function decline trajectories and (2) exploration of the associated risk factors.

In trajectory analysis, cognitive function was measured by CERAD-K total score. The STATA TRAJ program[38] employing the Nagin GBTM was used to identify trajectories of cognitive function decline. GBTM can discover diverse clusters within the sample population and develop trajectories based on their trends when using a single repeated measurement outcome. Based on their posterior probability, individuals are classified into the subcategories that are most likely[39]. This assumes that at least two significantly different change trajectories exist; the optimal trajectory number is found by calculating the Akaike information criterion(AIC)[40] and the Bayesian information criterion(BIC)[41,42]. The model for which AIC and BIC are closest to 0 is optimal[43,44]. Prior to calculation of the AIC and BIC, intercept, linear, quadratic, and cubic models are explored until a meaningful model is found for each trajectory.

Finally, a multinomial logistic regression analysis was conducted to explore associations among independent baseline variables.

Cognitive performance with multinomial logistic regression models adjusted for age, gender, education level, dietary habits, smoking, alcohol consumption and exercise. P-value of <0.05 was considered statistically significant. Analyses were performed using STATA MP version 16.

2.3 Results

2.3.1 Characteristics of the participants

The baseline demographic characteristics are summarized in [Table 2-1] Of all subjects, 274 (43.0%) were male and 363 (56.9%) female. A total of 339 (62.3%) were over high school graduates. Professional workers accounted for 223 (35.0%). A total of 521 (81.8%) had average monthly incomes over 5 million won. Totals of 601 (94.3%) and 427 (67.0%) did not smoke or drink alcohol respectively. Totals of 473 (74.2%) and 223 (35.0%) exercised and had good dietary habits respectively. In terms of comorbidities 270 (42.4%) suffered from hypertension, 90 (14.1%) diabetes mellitus, 158 (24.8%) hyperlipidemia and obesity 300 (47.1%). The demographic characteristics of trajectory group in [Table 2-2]. The baseline social characteristics differed significantly between the groups in age (P<.0001), educational level (P<.0001), dietary habits (P<.0001), exercise (P=0.02), household income (P<.0001), occupation (P=0.04), diabetes mellitus (P=0.01) and obesity (P = 0.01).

Table 2-1 General characteristics of study population

Variables at Baseline	N	%
Age, Mean(SD)	63.4(8.7)	
Gender		
Male	274	43.0
Female	363	56.9
Education		
Under high school graduate	238	37.3
Over high school graduate	339	62.3
Occupation		
Professional worker	223	35.0
Technical worker	414	65.0
Household income		
Under 5million won	116	18.2
Over 5million won	521	81.8
Current Smoking		
No	601	94.3
Yes	36	5.6
Current Alcohol consumption		
No	427	67.0
Yes	210	32.9
Exercise		
Never	164	25.7
Regularly at least once a week	473	74.2
Dietary habits		
Bad dietary habits	414	65.0
Good dietary habits	223	35.0
Comorbidity		
Hypertension	270	42.4
Diabetes mellitus	90	14.1
Hyperlipidemia	158	24.8
Obesity	300	47.1

2.3.2 Identification of the trajectories of cognitive function decline

To find an optimal model for the trajectories, the AICs and BICs of trajectory models featuring two to four groups were calculated; the latter model was optimal [Figure 2-1]. The cognitive function decline trajectories were (1) high cognitive function group, (2) medium cognitive function group, (3) low cognitive function group, and (4) rapid cognitive function decline group. The medium group was largest (41.0%), and the quadratic function yielded statistically significant data. This group maintained a CERAD-K score of 80 to 60. The second-largest group (27.3%) was and the quadratic function also yielded statistically significant data. This group maintained a CERAD-K score of 90 to late 70'. The third-largest group (22.7%) was statistically significant in the linear function. This group maintained a CERAD-K score in the range early 60' to late 50'. For the rapid cognitive function decline group (9.1%) was also statistically significant in the linear function. The CERAD-K score declined from 50 in to 10.

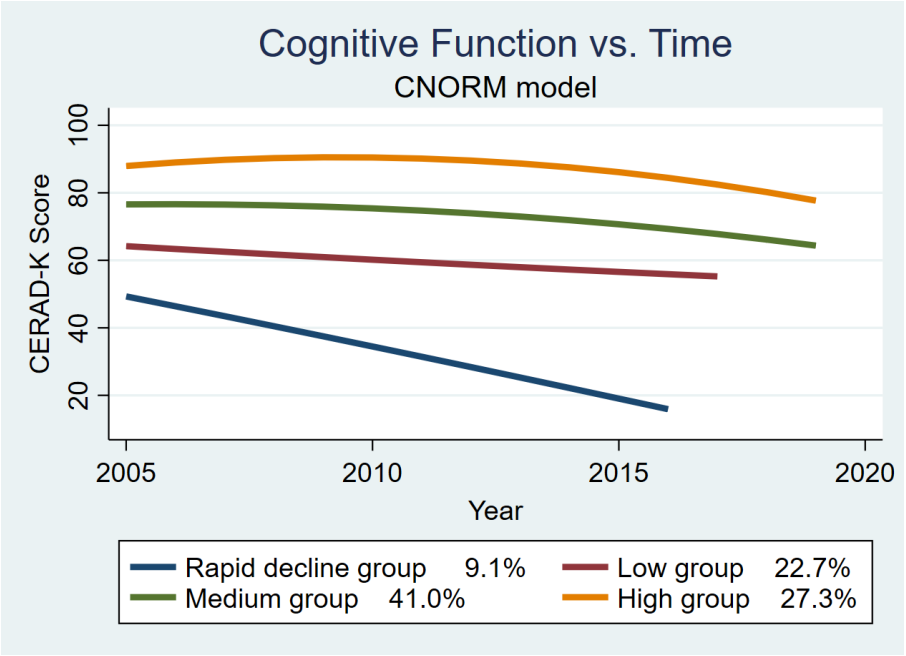

Figure 2-1 Identified trajectories of cognitvie function

Table 2-2 Demographic characteristics of cognitive function trajectory group

	Rapid Cognitive Function Decline Group		Low Cognitive Function Group		Medium Cognitive Function Group		High Cognitive Function Group		P-value
	N	%	N	%	N	%	N	%	
Age, Mean (SD)	71.87(9.47)		67.36(7.24)		63.05(7.73)		57.94(7.19)		
Gender									0.06
Male	19	33.93	61	43.88	131	48.16	63	37.06	
Female	37	66.07	78	56.12	141	51.84	107	62.94	
Education									
Under high school graduate	32	57.14	70	50.36	102	37.50	34	20.00	**<.0001**
Over high school graduate	24	42.86	69	49.64	170	62.50	136	80.00	
Dietary habits									
Bad dietary habits	23	41.07	82	58.99	180	66.18	129	75.88	**<.0001**
Good dietary habits	33	58.93	57	41.01	92	33.82	41	24.12	
Current Smoking									
No	54	96.43	133	95.68	257	94.49	157	92.35	0.53
Yes	2	3.57	6	4.32	15	5.51	13	7.65	
Alcohol consumption									
No	46	82.14	93	66.91	174	63.97	114	67.06	0.07
Yes	10	17.86	46	33.09	98	36.03	56	32.94	
Exercise									
Never	22	39.29	42	30.22	66	24.26	34	20.00	**0.02**
Regularly at least once a week	34	60.71	97	69.78	206	75.74	136	80.00	
Household income									**<.0001**
Under 5 million won	18	32.14	27	19.42	60	22.06	11	6.47	
Over 5 million won	38	67.86	112	80.58	206	75.74	159	93.53	
Occupation									
Professional worker	12	21.43	46	33.09	94	34.56	71	41.76	**0.04**
Technical worker	44	78.54	93	66.91	178	65.44	99	58.24	
Comorbidity									
Hypertension	19	33.93	64	46.04	121	44.49	66	38.82	0.29
Diabetes mellitus	14	25.00	24	17.27	37	13.60	14	8.24	**0.01**
Hyperlipidemia	9	16.07	35	25.18	72	26.47	42	24.71	0.44
Obesity	24	42.86	80	57.55	129	47.43	67	39.41	**0.01**

2.3.3 Factors affecting the trajectories

[Table 2-3] summarizes the results of multinomial logistic analysis using ‘high cognitive function group’ as the reference. The people who were older age (OR=1.27), bad dietary habits (OR=2.13), technical worker (OR=2.63), diabetes mellitus (OR=3.71) were more likely to be in the rapid cognitive function decline group than in the high cognitive function group. And the higher the education level (OR=0.12) and household income over 5 million won (OR=0.14) the lower the probability of belonging to rapid cognitive function decline group.

People in the low cognitive function group were more likely to be older age (OR=1.18), diabetes mellitus (OR=2.32), obesity (OR=2.08) than people in the high cognitive function. And the higher the education level (OR=0.15) and household income over 5 million won (OR=0.28) the lower the probability of belonging to low cognitive function group.

A comparison of the medium cognitive function group and high cognitive group revealed that older age (OR=1.09), male (OR=1.18), increased the likelihood of people in the medium cognitive group. And the higher the education level (OR=0.29) and household income over 5 million won (OR=0.24) the lower the probability of belonging to medium cognitive function group.

Table 2-3 Multinomial logistic regression of cognitive function decline

	Cognitive Function Trajectory Class (Ref: High Cognitive Function)								
	Rapid Cognitive Function Decline			Low Cognitive Function			Medium Cognitive Function		
Variables	**OR**	**CI**	**P-value**	**OR**	**CI**	**P-value**	**OR**	**CI**	**P-value**
Demographic variables									
Age (continuous variable)	**1.27***	1.21-1.34	<.0001	**1.18***	1.14-1.23	<.0001	**1.09***	1.06-1.12	<.0001
Male (ref: Female)	1.52	0.62-3.68	0.351	1.64	0.87-3.06	0.119	**1.18***	1.11-2.97	0.017
Over high school graduate (ref: under high school)	**0.12***	0.05-0.27	<.0001	**0.15***	0.08-0.27	<.0001	**0.29***	0.17-0.48	<.0001
Lifestyle related variables									
Bad dietary habits (ref: Good dietary habits)	**2.13***	1.01-4.48	0.045	1.40	0.79-2.45	0.240	1.34	0.83-2.14	0.221
Smoking (ref: No)	1.10	0.17-7.07	0.914	0.92	0.28-3.02	0.892	0.82	0.34-2.00	0.673
Alcohol consumption (ref: No)	0.73	0.28-1.93	0.534	1.54	0.82-2.89	0.177	1.38	0.83-2.28	0.203
Exercise regularly at least once a week (ref: Never)	0.64	0.29-1.41	0.273	0.71	0.39-1.30	0.278	0.83	0.50-1.38	0.485
Economic circumstances related variables									
Over 5 million won(ref: Under 5 million won)	**0.14***	0.06-0.33	<.0001	**0.28***	0.13-0.60	0.001	**0.24***	0.12-0.48	<.0001
Technical worker (ref: Professional worker)	**2.63***	1.29-5.33	0.007	1.45	0.90-2.31	0.118	1.35	0.91-2.01	0.128
Comorbidity related variables									
Hypertension (ref: No)	0.80	0.43-1.52	0.512	1.34	0.85-2.11	0.201	1.26	0.85-1.86	0.241
Diabetes mellitus (ref: No)	**3.71***	1.64-8.39	0.001	**2.32***	1.15-4.69	0.018	1.75	0.91-3.35	0.088
Hyperlipidemia (ref: No)	0.65	0.27-1.57	0.512	1.05	0.58-1.91	0.201	1.13	0.70-1.84	0.241
Obesity (ref: No)	1.15	0.62-2.12	0.648	**2.08***	1.21-3.28	0.001	1.38	0.94-2.04	0.099

2.4 Discussion

The purpose of this study was to look into various changes in cognitive function trajectories over time and to investigate what factors contributed to these changes by using GBTM. I found four distinct trajectories of change in cognitive function in adults over 40 years of age: High, medium, low, and rapid decline. Although cognitive decline is a natural phenomenon with age, the pattern of cognitive decline is different for each individual. Some people have a gradual decline in cognitive function, while others have a sharp decline in cognitive function.

Following the confirmation of the cognitive function trajectories, the relevant factors that influenced membership in each trajectory were identified. Older age, lower education level, bad dietary habits, comorbidities, a low household income and technical workers were more likely to indicate group of the low and rapid cognitive function decline. Such variables should be modified to prevent the risk of rapid cognitive function decline. Similar to the results of previous studies on Alzheimer's disease and dementia, my study found that cognitive function declines with age, with lower education and with lower household income[19,21]. Life competencies such as resilience, self-esteem, productive efficiency to risky and stressful circumstances are all acquired through higher

education[45]. Individuals with higher life competences are better able to avoid risk factors that may impair cognitive function and, on the other hand, engage in more cognitively demanding activities, which also help to maintain cognitive function in later life[46]. Furthermore, education enhances socioeconomic competencies, allowing access to additional resources such as increased earnings.

Noncommunicable diseases such as hypertension, diabetes mellitus, and obesity are associated with aging[47–49] and are caused by a lack of physical exercise[50,51]. Hypertension causes damage to the structure of cerebral blood vessels, increases atherosclerosis, and inhibits cerebrovascular regulating processes. These vascular abnormalities enhance the brain's sensitivity to ischemia injury, particularly in sensitive white matter regions crucial for cognitive function, and may contribute to the development of cognitive decline[52]. Diabetes mellitus is a metabolic disorder in which the body does not produce enough insulin or does not operate normally. Insulin is thought to have neuromodulatory properties that help synapses become more flexible. Insulin signaling dysfunction, chronic inflammation and hyperglycemia and increased oxidative stress all play important roles in the pathophysiology of Alzheimer's disease[53–55].

I also found associations between dietary habits and obesity and cognitive function. When body fat increases, harmful substances in visceral fat interfere with the action of insulin. Then, the reaction that allows the sugar component in the blood to be converted into an energy source and enter the cells becomes dull, resulting in insulin resistance, which makes it difficult for insulin to function properly. To compensate for the impaired insulin function, the brain induces more insulin to be secreted, resulting in hyperinsulinemia. Beta-amyloid, a commonly known substance associated with cognitive decline, is a surface protein of brain cells. When this protein is made in excess and accumulates in the brain, it causes damage to brain cells. Insulin interferes with the decomposition of beta-amyloid and, as a result, reduces brain perfusion, leading to cognitive decline[56]. This pathophysiologically explains the relationship between obesity and cognitive decline.

Dietary habits affect obesity. Irregular meals increase insulin secretion and fat synthesis by enhancing the activities of adipogenic enzymes[57]. Too many meals or difficulties in controlling intake enhance obesity. Skipping breakfast can trigger snacking and overeating at lunch or dinner. I noted frequent consumption of processed and fast foods; the higher these intakes, the higher the blood cholesterol and triglyceride

levels, triggering cardiovascular disease and obesity[58]. According to these findings, it's possible that controlling one's dietary habits and obesity is important factors in the prevention of cognitive function decline.

There are strengths in my research. Many previous studies used the MMSE to evaluate cognitive function; the MMSE evaluates orientation, memory, and calculation, recall, language, and spatial and temporal abilities over about 20 minutes[59]. The CERAD-K that I used evaluates Verbal Fluency, Boston Naming, MMSE, Word List Memory, Construction Praxis, Word List Recall, Word List Recognition, Constructional Recall and Trail Making Test A/B; the test requires over 1 hour[13]. CERAD-K has more questions and is more accurate than MMSE. The strengths of my study are that I tracked subjects for several years using the CERAD-K test, which is better than the MMSE.

No research has yet been conducted on whether the previously known factors influencing cognitive function also affect the trajectory of cognitive function change. And the fact that bad eating habits can affect cognitive function decline is a new point that can be suggested.

The limitations are that it is difficult to generalize my results this was a single Healthcare system Gangnam Center of Seoul National

University work. However, about 45,000 patients visit center annually; our results will be robust. Also, I did not assess social relationships such as meetings with close friends or social gatherings. In previous studies, meetings with close friends and family, and religious and club activities, improved mental health[60,61] because humans are constantly aware of the situation and keep thinking while understanding the other person's point of view while talking to the other person and anticipating how their actions will affect their future relationships.

Despite these limitations, I identified trajectories of cognitive decline in adults aged over 40 years and identified risk factors. My research results can be used to prevent cognitive decline with aging. In the future, it is important more specific programs such as dietary improvement and weight management can be prepared based on the research results.

In conclusion, I identified four distinct trajectories of cognitive decline in those aged over 40 years; the declines were associated with different demographic, lifestyle, and economic factors, as well as comorbidities. A younger age, a higher educational level, a professional worker, good dietary habits, no diabetes mellitus, and no obesity

improved cognitive function. The combination of these factors is a "cognitive reserve" that delays cognitive decline.

My findings highlight the need to prevent such decline. Identification of those at high risk followed by interventions that prevent decline are essential.

Chapter 3. Decrease in Cognitive Function Associated with Changes in Visceral fat area

3.1 Introduction

Excessive body fat causes diseases such as high blood pressure, type 2 diabetes, dyslipidemia, insulin resistance, cancer, and increases the medical and socioeconomic burden. It is also a risk factor for mortality[62,63].

The body fat distribution is more related to health risk than the body fat mass in obese people. In individuals with severe obesity, the incidence of metabolic-related abnormalities decrease as the amount of subcutaneous fat increases and that of visceral fat decreases[64,65]. Visceral fat, which is found in the mesentery and omentum around the abdominal viscera, differs from subcutaneous fat. Visceral and subcutaneous tissue have different fat cells, endocrine functions, lipolytic activities, and insulin and other hormone responses[66,67]. Visceral fat makes about 10-20% of total fat in male, compared to 5-8% in female. In both genders, the quantity of visceral fat increases with age[68]. If the accumulation of visceral fat is severe, the risk of cardiovascular disease and metabolic syndrome increases irrespective of body weight[69,70]. In addition, the amount of visceral fat rather than that of total body fat is linked to complications of obesity [71]. Therefore, accurate measurement of visceral fat mass is necessary.

Cognitive impairment is more common among individuals with a lot of visceral fat[72]. In Asia, there is a significant correlation between increased visceral fat and decreased cognitive performance[73]. When the amount of body fat increases, harmful substances therein interfere with the action of insulin, resulting in insulin resistance. To compensate for the impaired insulin function, the brain increases insulin secretion, resulting in hyperinsulinemia. Excess β-amyloid, a surface protein of brain cells, accumulates in the brain, damaging brain cells. Insulin interferes with the decomposition of β-amyloid, reducing brain perfusion and leading to cognitive decline[56].

Most prior studies using visceral fat as an independent variable were of cross-sectional design or used general cognitive function as the dependent variable. There are several domains of cognitive function, such as language, memory, and visuospatial ability. It is necessary to examine which domain is affected by the increase of visceral fat.

Cognitive ability differs according to gender. Females outperform males in memory, verbal learning tasks, and fine motor skills. Males outperform females in visuospatial tasks, visual memory and mathematical problem solving[74]. Therefore, I evaluated males and females separately.

I investigated changes in visceral fat over time and their association with cognitive function accordingly by gender. I identified gender differences in domains of cognitive function associated with amount of visceral fat. This longitudinal study was based on a sample of individuals undergoing repeated measurements of cognitive function and visceral fat in the course of periodic health checkups conducted over two or more years at the Seoul National University Hospital Healthcare System Gangnam Center.

3.2 Methods

3.2.1 Participants

I collected data from the Seoul National University Hospital Healthcare System Gangnam Center. Individuals visit the center voluntarily and received checkups to identify any health abnormalities rather than to investigate known clinical problems. At the center, the medical staff consider age and underlying diseases when deciding whether the check-up will include blood tests, tests of cognitive function (e.g., the CERAD-K), or physical measurements.

Some people do not return to the center for follow-up testing using the Consortium to Establish a Registry for Alzheimer's Disease-K (CERAD-K) or physical measurements. This occurs when the health check-up does not include cognitive function tests or physical measurements, or when the results of these tests are within the normal range. However, in cases where patients are at risk for cognitive decline, doctors recommend regular checkups that include the CERAD-K and physical measurements.

Not all subjects were followed from the same starting point for the same period of time. Subjects were tested again after as little as one year and as long as 13 years after the previous test. The highest number

of repeated measurements was 11. The average follow-up period was 4.5 years, and the average number of repeat visits to undergo CERAD-K testing and physical measurements was 2.7.

In total, 3,972 individuals underwent CERAD-K testing and physical measurements from 2005 to 2020. This includes individuals with and without repeat assessment of cognitive function and physical measurement. After excluding participants without repeat CERAD-K tests, physical measurements, blood tests, or other measures, 642 people remained and were enrolled in the study. The study was approved by the Institutional Review Boards of Seoul National University Hospital and Seoul National University Boramae Medical Center.

3.2.2 Variables

3.2.2.1 Independent variable

Bioelectrical impedance analysis (BIA) was conducted to measure visceral fat(cm^2), which is based on the differences in electrical conductivity among tissues[75,76]. It predicts body composition using differences in electrical conductivity according to the biological characteristics of tissues. Electrical conductivity is proportional to the amount of water and electrolyte, and decreases as the shape of the cell

approaches a circle. Adipose tissue is composed of circular cells and contains relatively little water compared to other tissues such as muscle, so the electrical conductivity decreases as the amount of fat increases. BIA automatically outputs the visceral fat area through a regression formula developed by BIA.

On the analyzer, participants wore light clothing and stood barefoot and removed all metal items.

3.2.2.2 Dependent variable

Cognitive performance was evaluated by calculating the CERAD-K score. I used the subtests evaluating Verbal Fluency, Boston Naming, the Mini-mental State Examination in the Korean version of the CERAD assessment packet (MMSE-KC), Word List Memory, Word List Recall, Word List Recognition, Constructional Praxis, and Constructional Recall.

The Verbal Fluency test evaluates executive function including flexible thinking, working memory, and self-control[77,78]. For example, a subject is asked to name as many animals as they can in a min[36]. In the Boston Naming test, asks the subject to name of the objects from images [13]. This test assesses language ability[79]. The MMSE-KC assesses

memory, orientation, constructional praxis and language skills[59]. The Word List Memory tests immediate recall. Participants read 10 common words every two seconds and immediately try to remember as many as they can in 90 seconds. The Constructional Praxis test assesses visuospatial, and constructional skills. Each subject is given four line-drawings of increasing complexity and study each for no more than 2 minutes. The Word List Recall assesses delayed recall. 15minutes after the Word List Memory, the subject within 90 seconds recalls 10 words from the Word List Memory test. In the Word List Recognition also test delayed recall[80(p)], the subject discriminate between 10 words used in the Word List Memory test and a new set of 10 words[37]. The Constructional Recall test assesses the capacity to recall figures presented in the Constructional Praxis test after a few-minute delay[13].

3.2.2.3 Demographic and behavioral covariates

Potential confounding variables including age, educational level, occupation, dietary habits, smoking, alcohol consumption, exercise and comorbidities were controlled. Education level was classified as high-school graduate or above. Monthly average household income was classified as under 5 million won, 5~10 million won, and over 10 million

won. Occupations were divided into professional, technical and no job. The lifestyle variables comprised current smoking, current alcohol consumption, exercise (exercise regularly at least once a week or not), and dietary habits. If a subject ate three times a day, ate breakfast five times or more a week, had regular mealtimes, ate moderately, and ate out once or twice a week, the subject had ‘good’ dietary habits. If a subject skipped a meal, ate quickly, ate too much, and ate out more than three times a week, they had ‘bad’ dietary habits. To assess comorbidities, I used questionnaires to collect information on hypertension and diabetes mellitus. Subjects who had been diagnosed with hypertension by a doctor or were currently taking anti-hypertensive medications were classified as having hypertension. Subjects who had been diagnosed with diabetes mellitus by a doctor or were currently taking medication for diabetes mellitus were considered to have diabetes mellitus.

3.2.3 Statistical analysis

The chi-squared test and t-test for categorical and continuous variables, respectively, were used to examine demographic features by gender. Demographic characteristics are presented as means, standard deviation or numbers (%). Statistical analysis was performed by gender.

The relationship between the two variables is shown by plotting cognitive function according to age, visceral fat according to age, cognitive function according to time, and visceral fat according to time. Locally weighted regression (LOESS or LOWESS) is a potent yet straightforward method to fit smoothing curves to data. The process is an expansion of traditional least-squares techniques[81].

If using LOESS to estimate a *Y* value when given *X*, points that are near *X* are given a large weight, whereas points that are far from *X* are given less weight. This is to compensate for possible distortion of least squares regression caused by outliers. The locally weighted regression formula is shown below and a weighted least squares regression model is fitted using the weight function[82].

$$\sum_{k=1}^{n} w_k(x_i)(y_k - \beta_0 - \beta_1 x_k - \cdots \beta_d x_k^d)^2 \ ^{82}$$

The dots represent cognitive function or area of visceral fat for individual subjects. These points incorporate all repeated measurements for each subject.

The association between cognitive function and visceral fat was assessed using a linear mixed model (LMM) to account for repeated observations of these variables during follow-up. Both the random intercept model and the random slope model were examined in the linear

mixed model. The formula for the random intercept and slope model is as follows:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})*\text{Time} + e_{ij}$$ [83]

$i = 1, 2, \ldots, 642$ (subjects) $\quad j = 1, 2, \ldots, 11$ (visits)

In the formula, Y_{ij} is response for individual i at time j, $(\beta_0 + b_{0i})$ is intercept for individual i, $(\beta_1 + b_{1i})$ is slope for individual i, e_{ij} and is random error. In this model, β_0 represents the average mean reaction across all people at time zero, and β_1 represents the average rate of change of the mean response over time across all individuals. The population-averaged response is described by β_0 and β_1, which are referred to as the fixed effects. Additionally, each random effect b_{0i} is the difference between the intercept for individual i and the population-averaged intercept β_0. And, each random effect b_{1i} is the difference between the slope for each individual i and the population-averaged slope β_1 [83].

In the LMM, visceral fat area was the independent variable and cognitive function test score was the dependent variable. The model was adjusted for age, educational level, occupation, income, current smoking, alcohol consumption, exercise, hypertension, diabetes mellitus, and dietary habits. The analysis was performed using SAS PROC MIXED

with a compound symmetry variance-covariance matrix. Parameter estimates with standard errors and 95% confidential intervals were reported, and p-values < 0.05 were considered indicative of statistical significance. Also, for the sensitivity analysis, a linear mixed model analysis was performed for those who did not receive the health examination more than twice, that is, those who received the health examination only once.

I conducted a causal mediation analysis (CAUSALMED procedure in SAS) to explore the mediating effects of cognitive function. Through the analysis, three estimates—the total impact (TE), natural direct effect (NDE), and natural indirect effect—were derived (NIE). When the mediator is fixed, the NDE is the result of a shift in the outcome based on exposure, and NIE is the sum of the NDE and NDE. Assuming that the exposure is constant, NIE is the result of a change in the outcome based on the mediator. The mediated percentage, which is the ratio of NIE to TE, was also obtained[84]. [Figure 3-5] shows a directed acyclic graph of this causal mediation analysis. In addition, the moderating effect was verified to see the effect of muscle mass between visceral fat and cognitive function. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

3.3 Results

[Figure 3-1~3-4] show the LOESS fitting results. All subjects with repeated measurements are included in the figure. This represents the raw data and shows age, year, and age trends for cognitive function and visceral fat area. The LOESS smoothing curves show that cognitive function tended to decrease with increasing age and year. The curve for visceral fat area shows that visceral fat tended to increase with age.

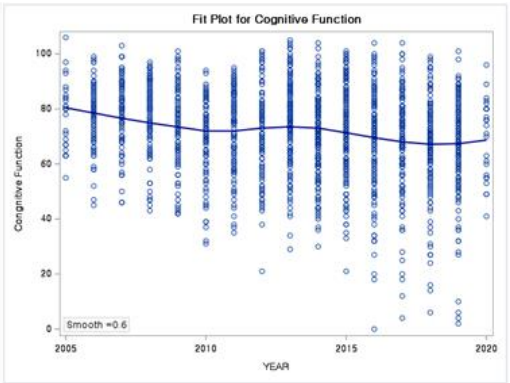

Figure 3-1 Correlation between year and cognitive function. Smoothing curve fitted by a LOESS

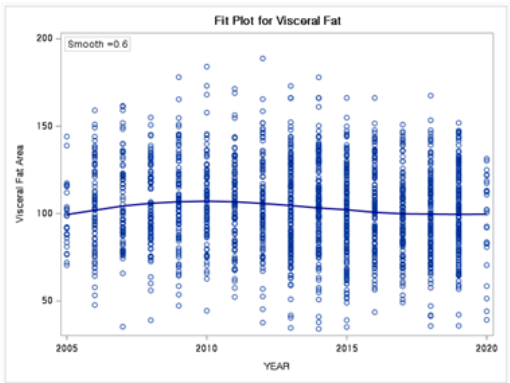

Figure 3-2 Correlation between year and visceral fat area. Smoothing curve fitted by a LOESS

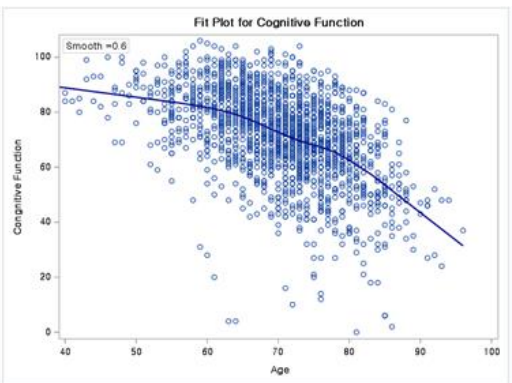

Figure 3-3 Correlation between age and cognitive function. Smoothing curve fitted by a LOESS

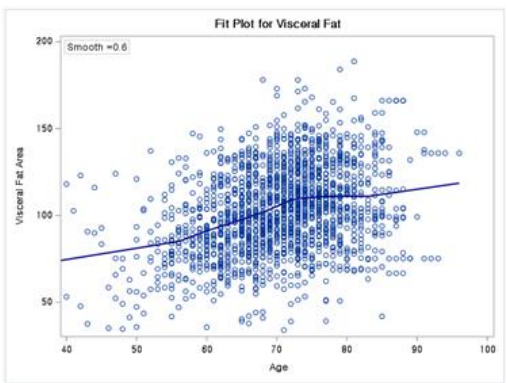

Figure 3-4 Correlation between age and visceral fat area. Smoothing curve fitted by a LOESS

[Table 3-1] shows the baseline characteristics of subjects with repeated measurements in the longitudinal data. The 642 subjects included 275 males and 367 females. The mean age of males (68.00 years) was significantly higher than that of females (66.05 years). The baseline social characteristics showed significant differences between males and females in educational level ($p<.0001$), occupation ($p<.0001$), monthly household income ($p<.0001$), current smoking ($p<.0001$), alcohol consumption ($p<.0001$), exercise ($p=0.005$), and dietary habits ($p=0.001$). The visceral fat area of males was significantly larger than that of females (115.50 vs. 91.39, $p<.0001$). [Table 3-2] presents the mean and standard deviation of the subjects' scores on their first and last CERAD-K tests score. On average, scores on last CERAD-K tests score was lower than scores on first cognitive function tests. [Table 3-3] shows the result of linear mixed model analysis using repeated measurements from longitudinal data considering both the random intercept and the random slope. [Supplementary Table 3-7] shows the results of the sensitivity analysis. The decline in cognitive function due to visceral fat was more severe in female than in male. This was similar to the results of those who received health checkups more than once.

It is possible to group which ability each domain of CERAD-K

evaluates among cognitive functions. Verbal fluency (J1) is executive ability, Boston naming test (J2) is language ability, and word list memory (J4) is immediate recall. Constructional praxis (J5) can evaluate visuospatial ability, word list recall (J6), word list recognition (J7), and constructional recall (J8) can evaluate delayed recall ability. The results of linear mixed model analysis by grouping each domain are shown in [Supplementary Tables 3-8].

Table 3-1 Baseline demographic characteristics of subjects

Variables	Male (n=275)	Female (n=367)	Total (n= 642)	P-value
Age, Mean (SD)	68.00 (8.64)	66.05 (8.60)	66.89 (8.66)	**0.005**
Education				**<.0001**
Under high school	56 (20.36)	182 (49.59)	238 (37.07)	
Over high school	219 (79.64)	185 (50.41)	404 (62.93)	
Occupation				**<.0001**
Professional worker	188 (68.36)	38 (10.35)	226 (35.20)	
Technical worker	25 (9.09)	15 (4.09)	40 (6.23)	
No job	62 (22.55)	314 (85.56)	376 (58.57)	
Household income				**<.0001**
Under 5 million won	39 (14.18)	80 (21.80)	119 (18.54)	
5~10 million won	85 (30.91)	185 (50.41)	270 (42.06)	
Over 10 million won	151 (54.91)	102 (27.79)	253 (39.41)	
Current Smoking				**<.0001**
No	242 (88.00)	363 (98.91)	605 (94.24)	
Yes	33 (12.00)	4 (1.09)	37 (5.76)	
Alcohol consumption				**<.0001**
No	115 (41.82)	312 (85.01)	427 (66.51)	
Yes	160 (58.18)	55 (14.99)	215 (33.49)	
Exercise				**0.005**
No	55 (20.00)	109 (29.70)	164 (25.55)	
Yes	220 (80.00)	258 (70.30)	478 (74.45)	
Dietary habits				**0.001**
Bad dietary habits	198 (72.00)	219 (59.67)	416 (64.95)	
Good dietary habits	77 (28.00)	148 (40.33)	225 (35.05)	
Comorbidity				
Hypertension	130 (47.27)	139 (37.87)	269 (41.90)	**0.017**
Diabetes mellitus	54 (19.64)	36 (9.81)	90 (14.02)	**0.000**
Visceral fat, Mean(SD)	115.50 (22.10)	91.39 (21.76)	101.70 (24.83)	**<.0001**
Sum of CERAD-K domains except MMSE	74.34 (12.60)	74.35 (14.21)	74.34 (13.54)	**0.994**

Table 3-2 Cognitive function domain score by gender

Cognitive Function	Male		Female	
	Baseline	Last follow-up	Baseline	Last follow-up
Verbal Fluency	13.63 (4.01)	13.83 (4.65)	12.86 (4.23)	13.13 (4.72)
Boston Naming Test	11.31 (2.25)	11.15 (2.47)	11.62 (2.50)	11.25 (2.86)
MMSE-KC	26.51 (2.66)	25.69 (3.42)	25.83 (3.34)	24.66 (4.73)
Word List Memory	16.76 (4.16)	16.20 (4.19)	17.88 (4.60)	17.25 (5.01)
Constructional Praxis	10.64 (0.95)	10.46 (1.07)	10.37 (1.28)	10.12 (1.80)
Word List Recall	5.65 (2.30)	5.27 (2.11)	6.01 (2.30)	5.64 (2.64)
Word List Recognition	8.48 (1.93)	8.43 (2.07)	8.75 (1.76)	8.39 (2.37)
Constructional Recall	7.80 (3.01)	7.00 (3.18)	6.83 (3.28)	6.34 (3.58)

Table 3-3 Association between domain-specific cognitive function and visceral fat area in a random intercept and random slope model

	Total				Male				Female			
Cognitive Function	**β**	**95% CI**		**P-value**	**β**	**95% CI**		**P-value**	**β**	**95% CI**		**P-value**
Verbal Fluency	**-0.13**	-0.24	-0.02	0.02	-0.07	-0.23	0.08	0.34	-0.16	-0.31	0.00	0.05
Boston Naming Test	**-0.11**	-0.17	-0.06	<.0001	-0.04	-0.11	0.03	0.31	**-0.15**	-0.23	-0.06	0.00
MMSE-KC	**-0.20**	-0.29	-0.11	<.0001	-0.06	-0.17	0.04	0.23	**-0.26**	-0.40	-0.12	0.00
Word List Memory	**-0.22**	-0.32	-0.11	<.0001	**-0.15**	-0.29	-0.01	0.03	**-0.25**	-0.41	-0.09	0.00
Constructional Praxis	**-0.07**	-0.10	-0.03	0.00	-0.03	-0.07	0.01	0.13	**-0.09**	-0.14	-0.03	0.00
Word List Recall	**-0.11**	-0.17	-0.06	<.0001	**-0.16**	-0.24	-0.09	<.0001	-0.05	-0.13	0.03	0.21
Word List Recognition	-0.05	-0.10	0.01	0.09	-0.01	-0.09	0.06	0.71	-0.04	-0.12	0.03	0.28
Constructional Recall	**-0.08**	-0.16	-0.00	0.04	-0.08	-0.19	0.04	0.18	-0.05	-0.16	0.07	0.42
Sum of domains except MMSE-KC	**-0.69**	-1.00	-0.37	<.0001	**-0.43**	-0.83	-0.04	0.03	**-0.71**	-1.20	-0.22	0.00

3.3.1 Results for all subjects

An increased visceral fat area was associated with a worse Verbal Fluency score (β: -0.13, CI: -0.24 to -0.02), Boston Naming Test score (β: -0.11, CI: -0.17 to -0.06), MMSE-KC (β: -0.20 CI: -0.29 to -0.11), Word List Memory (β: -0.22, CI: -0.32 to -0.11), Constructional Praxis (β: -0.07 CI: -0.10 to -0.03), Word List Recall (β: -0.11, CI: -0.17 to -0.06), Constructional Recall (β: -0.08, CI: -0.16 to -0.00) and sum of domains except MMSE-KC (β: -0.69 CI: -1.00 to -0.37) adjusting for age, gender, educational level, income, occupation, current smoking, alcohol consumption, exercise, dietary habits, hypertension and diabetes mellitus [Table 3-3].

3.3.2 Results for males

An increased visceral fat area was associated with worse Word List Memory score (β:-0.15, CI: -0.29 to -0.01), Word List Recall score (β: -0.16, CI: -0.24 to -0.09) and sum of domains except MMSE-KC (β: -0.43, CI: -0.83 to -0.04) adjusting for age, educational level, income, occupation, current smoking, alcohol consumption, exercise, dietary habits, hypertension and diabetes mellitus [Table 3-3]. No other

domain-specific cognitive function was associated with visceral fat area in males.

3.3.3 Results for females

An increased visceral fat area was associated with worse Boston Naming Test score (β: -0.15, CI: -0.23 to -0.06), MMSE-KC (β:-0.26, CI: -0.40 to -0.12), Word List Memory (β: -0.25, CI: -0.41 to -0.09), Constructional Praxis (β: -0.09 CI: -0.14 to -0.03), and sum of domains except MMSE-KC (β: -0.71, CI: -1.20 to -0.22) adjusting for age, educational level, income, occupation, current smoking, alcohol consumption, exercise, dietary habits, hypertension and diabetes mellitus [Table 3-3]. No other domain-specific cognitive function was associated with visceral fat area in females.

3.3.4 Mediating effects of muscle mass, protein, minerals and basal metabolic rate

Visceral fat area had significant effects on cognitive function (β= -0.08, 95% CI = -0.09 to -0.06), while muscle mass, protein, basal metabolic rate and minerals, mediated visceral fat area (Natural indirect

effect(NIE) of muscle mass β= 0.04, 95% CI =0.04 to 0.05; NIE of protein β= 0.04, 95% CI = 0.03 to 0.05; NIE of basal metabolic rate β= 0.04, 95% CI= 0.03 to 0.05 and NIE of minerals β= 0.04, 95% CI = 0.03 to 0.05). The Natural direct effect (NDE) of muscle mass, protein, metabolic rate and minerals were also significant (β= -0.12, 95% CI= -0.14 to -0.10, β= -0.12, 95% CI= -0.14 to -0.10, β= -0.12, 95% CI= -0.14 to -0.10, β= -0.11, 95% CI= -0.13 to -0.10). Percentage mediated represents the percentage of natural indirect effects to the total effect. About 59% of the effect of visceral fat is due to the mediation of muscle mass, about 55% is due to the amount of protein, about 56% is due to basal metabolic rate, and about 56% is due to minerals. It can be attributed to 52% [Table 3-4].

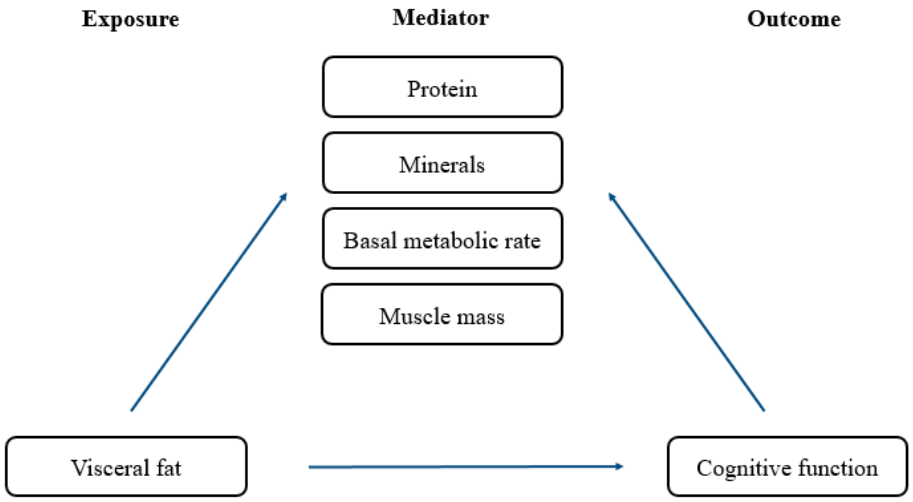

Figure 3-5 Directed acyclic graph for the mediation analysis

Table 3-4 The mediating effects of muscle mass, protein, basal metabolic rate, minerals between visceral fat area and cognitive function

	Association of visceral fat and cognitive function			
	β	**95% CI**		**P-value**
Mediation of muscle mass				
Total effect	**-0.08*** **	**-0.09-**	**-0.06**	**<.0001**
Natural indirect effect	**0.04*** **	**0.04**	**0.05**	**<.0001**
Natural direct effect	**-0.12*** **	**-0.14**	**-0.10**	**<.0001**
Percentage mediated, %	**58.95**			
Mediation of protein				
Total effect	**-0.08*** **	**-0.09**	**-0.06**	**<.0001**
Natural indirect effect	**0.04*** **	**0.03**	**0.05**	**<.0001**
Natural direct effect	**-0.12*** **	**-0.14**	**-0.10**	**<.0001**
Percentage mediated, %	**54.51**			
Mediation of basal metabolic rate				
Total effect	**-0.08*** **	**-0.09**	**-0.06**	**<.0001**
Natural indirect effect	**0.04*** **	**0.03**	**0.05**	**<.0001**
Natural direct effect	**-0.12*** **	**-0.14**	**-0.10**	**<.0001**
Percentage mediated, %	**55.56**			
Mediation of minerals				
Total effect	**-0.08*** **	**-0.09**	**-0.06**	**<.0001**
Natural indirect effect	**0.04*** **	**0.03**	**0.05**	**<.0001**
Natural direct effect	**-0.11*** **	**-0.13**	**-0.10**	**<.0001**
Percentage mediated, %	**52.06**			

Adjusted for gender, education, occupation, income, dietary habits, alcohol consumption, current smoking, exercise, hypertension, diabetes mellitus

*p<0.05, **p<0.01

3.3.5 Moderator effects of muscle mass

As a result of analysis to verify the control effect of muscle mass on the influence of visceral fat on cognitive function, the interaction term between visceral fat and muscle mass was statistically significant [Figure 3-6], [Table 3-5]. As the interaction term was significant, the moderating effect was explored using the 'specific value selection method' to explore the conditional effect of muscle mass [Table 3-6]. As a result of the analysis, the interaction term between visceral fat and muscle mass was found to be statistically significant.

When muscle mass is -1SD, cognitive function decreases by -0.23 for every 1 unit increase in visceral fat, and when muscle mass is average, cognitive function decreases by -0.18 for every 1 unit increase in visceral fat. For those with +1 SD of muscle mass, cognitive function decreased by -0.13 for every 1 unit increase in visceral fat. In other words, depending on the level of muscle mass, the effect of visceral fat on cognitive function is different.

Looking at the graph [Figure 3-7], in the case of a person with high muscle mass, cognitive function is as high as about 90 points when the amount of visceral fat is low, but cognitive function decreases to about 70 points when the amount of visceral fat is high. In addition, in

the case of a person with low muscle mass, the cognitive function is as high as about 88 points when the visceral fat is small, but the decrease in the slope is greater in the case of a large amount of visceral fat than in the case of a person with large muscle mass.

In the graph drawn as a result of using the Johnson-Neiman method for muscle mass, the Y-axis is the effect of muscle mass between visceral fat and cognitive function. As muscle mass increases, the effect of visceral fat on cognitive function increases, but it is not significant from muscle mass over 40 [Figure 3-8].

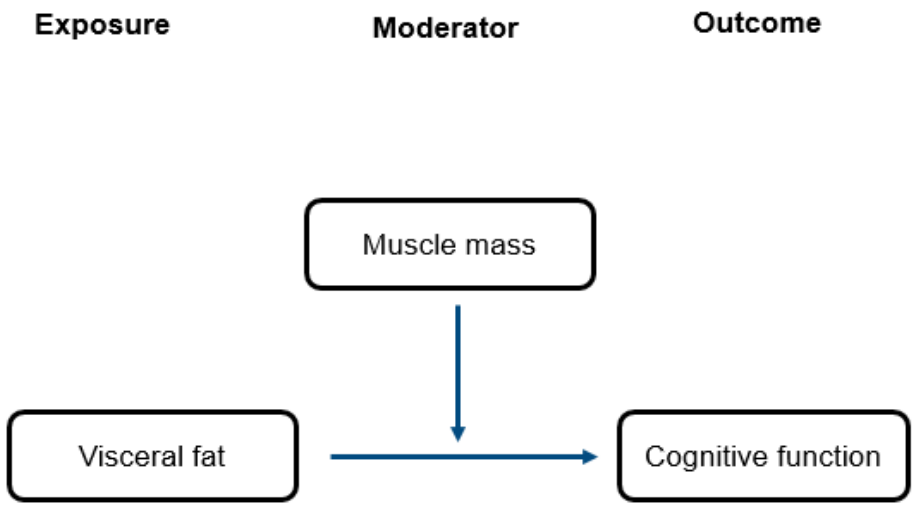

Figure 3-6 Moderate effect model

Table 3-5 Moderate effect by muscle mass on the association between visceral fat area and cognitive function

	β	SE	t	P-value	LLCI	ULCI
Visceral fat area	-0.400***	0.039	-10.279	0.000	-0.477	-0.324
Muscle mass	-0.245	0.169	-1.454	0.146	-0.575	0.085
Visceral fat area*Muscle mass	-0.009***	0.001	5.833	0.000	0.006	0.012

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

Table 3-6 Effects of visceral fat area on cognitive function according to muscle mass level

Muscle mass	β	se	t	P-value	LLCI	ULCI
18.653	-0.232***	0.014	-17.078	0.000	-0.259	-0.206
24.188	-0.182***	0.010	-17.449	0.000	-0.203	-0.162
29.724	-0.133***	0.013	-9.882	0.000	-0.156	-0.106

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

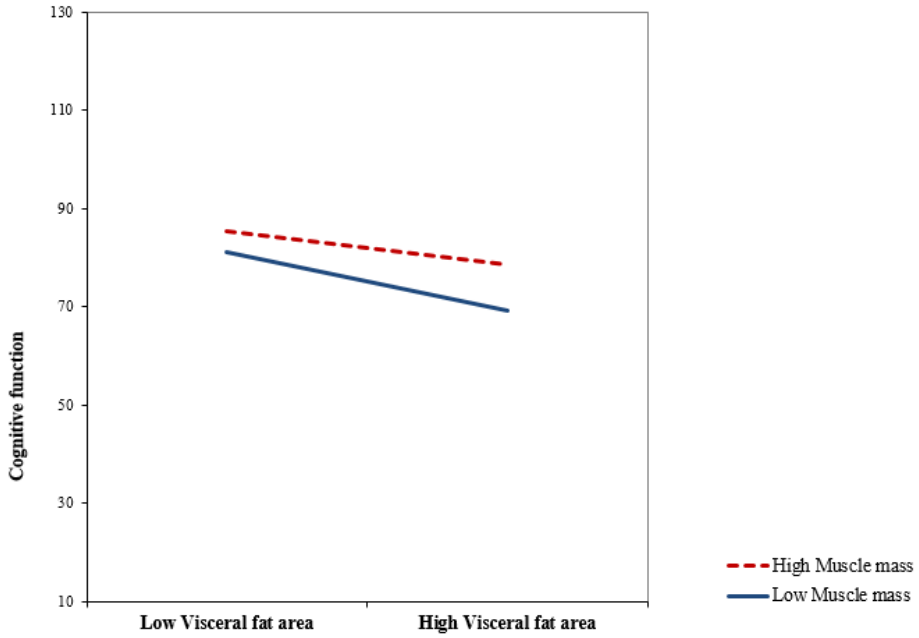

Figure 3-7 Moderation of the effect of visceral fat area on cognitive function at value of the moderator muscle mass

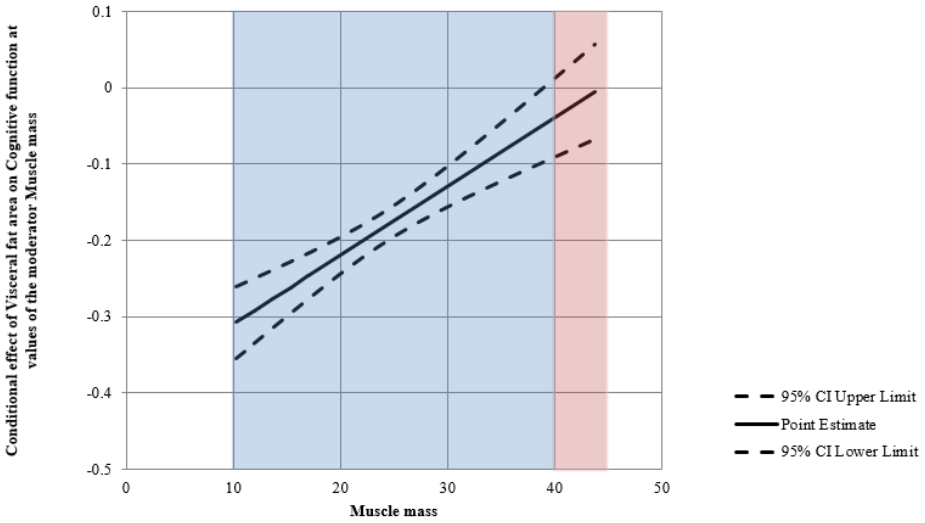

Figure 3-8 Conditional effect of visceral fat area on cognitive function at values of the moderator muscle mass

Supplementary Table 3-7 Sensitivity analysis: Association of domain-specific cognitive function with visceral fat area

Cognitive Function	Total (2,626)				Male (n=1,113)				Female (n=1,513)			
	β	95% CI		P-value	β	95% CI		P-value	β	95% CI		P-value
Verbal Fluency	**-0.14**	-0.23	-0.06	0.00	**-0.15**	-0.28	-0.02	0.02	-0.16	-0.27	-0.05	0.00
Boston Naming Test	**-0.06**	-0.09	-0.02	0.00	-0.03	-0.08	0.02	0.25	**-0.08**	-0.13	0.03	0.00
MMSE-KC	**-0.08**	-0.12	-0.03	0.00	-0.01	-0.07	0.05	0.67	**-0.12**	-0.19	-0.05	0.00
Word List Memory	-0.05	-0.12	0.02	0.14	0.09	-0.01	0.20	0.08	**-0.19**	-0.28	-0.10	<.0001
Constructional Praxis	**-0.02**	-0.04	-0.00	0.02	0.01	-0.01	0.03	0.48	**-0.04**	-0.07	-0.01	0.00
Word List Recall	-0.03	-0.07	0.00	0.07	0.04	-0.01	0.08	0.15	**-0.09**	-0.14	-0.04	0.00
Word List Recognition	-0.01	-0.03	0.01	0.37	0.02	-0.02	0.05	0.34	**-0.03**	-0.07	-0.00	0.04
Constructional Recall	**-0.09**	-0.14	-0.05	0.00	-0.02	-0.09	0.05	0.61	**-0.14**	-0.21	-0.07	<.0001
Sum of domains except MMSE-KC	**-0.41**	-0.62	-0.20	0.00	-0.04	-0.36	0.27	0.79	**-0.74**	-1.03	-0.44	<.0001

Supplementary Table 3-8 Association between domain-specific cognitive function group and visceral fat area in a random intercept and random slope model

	Total				Male				Female			
Cognitive Function	**β**	**95% CI**		**P-value**	**β**	**95% CI**		**P-value**	**β**	**95% CI**		**P-value**
Executive function	**-0.13**	-0.24	-0.02	0.02	-0.07	-0.23	0.08	0.34	-0.16	-0.31	0.00	0.05
Language ability	**-0.11**	-0.17	-0.07	<.0001	-0.04	-0.11	0.03	0.31	**-0.15**	-0.23	-0.06	0.00
Immediate recall	**-0.22**	-0.32	-0.11	<.0001	**-0.15**	-0.29	-0.01	0.03	**-0.25**	-0.41	-0.09	0.00
Visuospatial function	**-0.07**	-0.10	-0.03	0.00	-0.03	-0.07	0.01	0.13	**-0.09**	-0.14	-0.03	0.00
Delayed recall	**-0.07**	-0.11	-0.02	0.01	**-0.07**	-0.14	-0.01	0.03	-0.03	-0.10	0.04	0.35
Sum of domains	**-0.58**	-0.82	-0.34	<.0001	**-0.32**	-0.62	-0.02	0.04	**-0.66**	-1.05	-0.28	0.00

3.4 Discussion

This study found that an increase in visceral fat area over time was associated with decreased cognitive function. In males, Verbal Fluency and Word List Recall score were decreased as visceral fat area increased. In females, Verbal Fluency, Boston Naming Test, MMSE-KC, Word List Memory, Constructional Praxis score were decreased as visceral fat area increased. Among the CERAD-K test, Verbal Fluency, Boston Naming Test, Word List Memory, Word List Recall and Constructional Praxis assessed executive function, language ability, immediate recall, delayed recall, and visuospatial ability respectively.

According to the Japan study, in females aged 65 to 74 years, the WAIS-R Digit Span Forward test score (attention, working memory) increased as the waist circumference increased. The word list immediate recall test score (learning, acquisition) increased with waist circumference in males 65 to 74 years old. The WAIS-R Digit Span Forward and Backward test, which measures attention and working memory, and verbal fluency letter test showed declining scores in male aged 75 to 84 years, as waist circumference increased[85]. In that study, the effects of obesity and physical movement on cognitive function were explained. Physical exercise can improve learning, acquisition, memory,

attention, working memory, and executive function. Obese males aged 75 to 84 years have little physical activity, promoting cognitive decline. By contrast, obesity and cognitive function in females are influenced by estrogen. Estrogen enhances cognitive performance via estrogen receptors in the hippocampus, amygdala, and adipose tissue[86]. The risk of cognitive impairment decreases with increasing central fat mass and estradiol level[87,88]. Leptin, a hormone produced by adipocytes, may link obesity and cognitive function[89].

In most previous studies, obesity was measured by BMI (Body mass Index). A Korean study evaluated the relationship between BMI and cognitive function. In males aged 70 to 84 years, as BMI increased, word list memory, recall, and recognition improved[90]. A Swedish prospective study reported that a higher BMI was associated with an increased risk of Alzheimer disease[91]. However, BMI is not a reliable indicator of obesity in the older population because as people age, their muscle mass declines and their fat mass increases. Therefore, I use the BIA method to accurately measure visceral fat.

Similar to our study, there have been studies that have looked at the association between visceral fat and cognitive function, but there are some differences. One prior study measured visceral fat by MRI and

cognitive function by digital symbol substitution test. For every 1 standard deviation increase in body fat percentage, the cognitive function score decreased by 0.8. points[92]. Therefore, strategies to prevent or reduce obesity could preserve cognitive function. In that study, general cognitive function was analyzed using the Digital Symbol Substitution Test and the Montreal cognitive assessment; the individual domains of cognitive function—such as language, memory, and visuospatial cognitive ability—were not evaluated. Another study explored the relationship between visceral fat amount and five domains of executive function; obese subjects had impaired working memory. Obesity was inversely associated with the executive functions of monitoring and inhibition. Because this was a cross-sectional study, I was unable to establish causality. The subjects were volunteers from the community intending to participate in a weight loss intervention program based on the advantages of the Mediterranean diet. Therefore, they may have been more driven to lose weight than a typical member of the general population, possibly introducing bias[93].

In this study I found, executive function in males reduced as visceral fat area grew. Executive function, linguistic skills, memory, and visuospatial function declined in females as visceral fat area rose. The

reason is presumed as follows. In obese females, disturbance of the hypothalamic pituitary ovarian axis causes hormonal disturbances. Estrogen levels typically decrease during menopause[94]. In females, estrogen differentially mediates cognitive aspects in numerous brain regions and neural pathways. Thus, estrogen may have a selective rather than an overall effect on cognition. In general, females are better at verbal fluency, memory, and fine motor skills than males are at gross motor coordination. According to a previous study that administration of estrogen to postmenopausal women enhanced verbal fluency and memory, so it is likely to improve cognitive function[95]. In males, the activity of aromatase, which converts testosterone to estrogen, increases with age and with increasing fat mass, thereby increasing the estradiol level[96]. Estradiol improves verbal short-term memory and creative thinking in males. In males, divergent thinking, verbal fluency, and verbal flexibility were increased by estrogen compared to placebo[97]. In addition, the effect of muscle mass on the relationship between visceral fat and cognitive function was examined.

Even if there was a lot of visceral fat, it was found that the decrease in cognitive function was smaller in the case of a large amount of muscle than in the case of a small amount of muscle. This suggests

that muscle mass may have a protective effect on cognitive function as we age.

Unfortunately, I did not evaluate the levels of sex hormones, such as estradiol and testosterone, so further studies are needed. Also, this study had another limitation. BIA measures the body into five cylindrical columns. (left and right upper and lower extremities as well as torso). However, the data are affected by water intake and excretion, as well as temperature and humidity[98]. Nevertheless, BIA does not involve radiation exposure and is inexpensive than computed tomography (CT) and magnetic resonance imaging (MRI)[99].

Another limitation is that the study participants consist of individuals visiting the center voluntarily. The examination fee for follow-up appointments is paid by participants. The use of data from participants with follow-up appointments, suggesting health risks, may introduce selection bias.

On the contrary, this study has several strengths. The MMSE, used in most prior works, evaluates orientation, memory, and calculation, recall, language, and spatial and temporal abilities in about 20 min[59]. The CERAD-K, as used in this study, involves Verbal Fluency, Boston Naming, MMSE, Word List Memory, Construction Praxis, Word List

Recall, Word List Recognition, Constructional Recall, and Trail Making Test A/B; the test requires over 1 h[13]. Therefore, it is more specific and has the advantage of using a measuring tool in that it can see language ability, memory, executive function, and visuospatial function that cannot be seen in the existing cognitive function tests. Others have evaluated the correlation between general cognitive function and risk factors, but I investigated both general cognitive function and each domain thereof. Few studies have evaluated the link between visceral fat and cognitive function.

In conclusion, decreased cognitive function associated with increased visceral fat differed by gender in adults over 40 years old. The adverse effects of increased visceral fat on cognition were greater in females than in males. Therefore, prevention programs and interventions are needed.

Chapter 4. Visceral Obesity is Associated with an Increased Risk of Mild Cognitive Impairment

4.1 Introduction

Visceral body fat, sometimes known as "hidden" fat, is fat that is stored in the abdominal cavity and encircles the liver and intestines among other internal organs[100]. It accounts for around one-tenth of the body's total fat. In male, visceral fat contributes for 10–20% of total fat, while in female, it accounts for 5–8% of total fat. In both genders, the quantity of visceral fat increases with age[68]. If the accumulation of visceral fat is severe, the risk of cardiovascular disease and metabolic syndrome increases irrespective of body weight[69,70]. In addition, the amount of visceral fat rather than that of total body fat is linked to complications of obesity[101]. Therefore, accurate measurement of visceral fat mass is necessary.

A high Body Mass Index (BMI) is associated with the prevalence of Mild Cognitive Impairment. According to previous studies on the relationship between BMI and Mild Cognitive Impairment, Central obesity with high BMI could act as a risk factor for mild cognitive impairment and dementia[102]. Similarly, Cognitive impairment is more common among individuals with a lot of visceral fat[72]. According to a previous study in Asia, there is a significant correlation between increased visceral fat and decreased cognitive performance[73].

The basic definition of mild cognitive impairment is "a state in which cognitive decline is more severe than predicted, but not enough to be declared dementia." It is an intermediate stage between normalcy and dementia. Mild cognitive impairment is classified into amnestic MCI and non-amnestic according to the presence or absence of memory impairment. Amnestic MCI is more likely to progress to Alzheimer's disease, and non-amnestic MCI is more likely to progress to non-Alzheimer's dementia such as Lewy body dementia or frontotemporal lobe degeneration[103]. The distinction between Mild Cognitive Impairment and dementia is determined by whether the cognitive decline is severe enough to cause functional impairment. Mild cognitive impairment is clinically important in that it has a relatively high probability of progressing to dementia and can provide insight into dementia at an early stage of dementia. Dementia occurred in 1-2% of normal persons aged 65 years or older, whereas 10-15% of patients with Mild Cognitive Impairment developed dementia[104]. The incidence of Mild Cognitive Impairment is approximately 5.1-168 out of a population of 1,000, with large differences between studies. Although the prevalence also differs depending on the diagnostic criteria and the study subjects, the prevalence of Mild Cognitive Impairment among people

over 65 years of age is about 10-20%[105]. The prevalence of mild cognitive impairment is higher in those with low educational background, cognition of vascular risk such as hypertension, diabetes mellitus, apolipoprotein E4 genotype etc. In addition, it is higher in older male, and it is more likely to improve than in female[106–108].

The aim of this study was to evaluate whether visceral obesity causes mild cognitive impairment and to investigate the variables affecting mild cognitive impairment.

4.2 Methods

4.2.1 Participants

I analyzed data collected by the Gangnam Center of Seoul National University Hospital. Participants visited the center for health checkups, including medical interviews, blood tests, and anthropometric measurements. I enrolled those who visited at least once from 2005 to 2020. Of the 3,948 individuals who underwent Consortium to Establish a Registry for Alzheimer's Disease-K (CERAD-K) testing, 739 were tested at least twice. Excluding those with missing interview or anthropometric test data and those defined as dementia or mild cognitive impairment at baseline assessment, 569 patients were finally included in the analysis. The study was approved by the Institutional Review Boards of Seoul National University Hospital and Seoul National University Boramae Medical Center.

4.2.2 Variables

4.2.2.1 Independent variable

Bioelectrical Impedance Analysis (BIA) was conducted to measure visceral fat(cm^2), which is based on the difference in electrical conductivity among tissues[75,76]. On the analyzer, participants wore light

clothing and stood barefoot and removed all metal items. The definition of visceral obesity by visceral fat area was set as visceral fat area ≥ 100 cm^2 [109].

4.2.2.2 Dependent variable

In cognitive function testing, when there is objective evidence that one or more domains among memory, executive function, attention, language, or visuospatial skills are impaired, it is called Mild Cognitive Impairment[104]. The cognitive function test used in this study is the CERAD-K. In this study, according to the criteria of previous studies, one or more domains in CERAD-K below 1.5SD were defined as Mild Cognitive Impairment [104,110]. Among them, amnesia-MCI was defined as less than 1.5 SD on a delayed recall, word list learning task[111] and subject over this cut-off score as non-amnestic MCI.

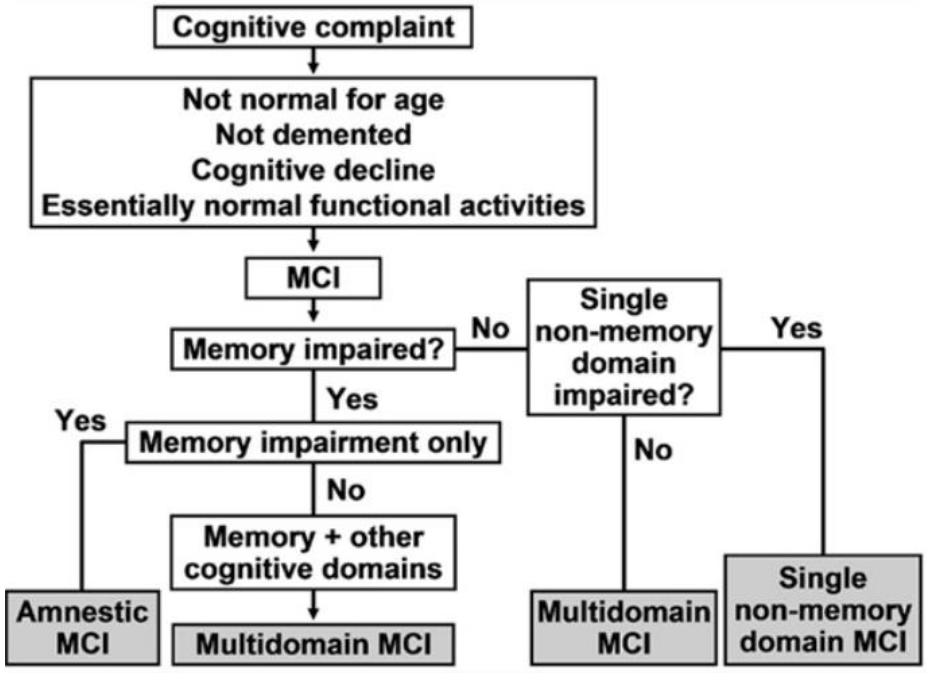

Figure 4-1 Flowchart showing pathway for diagnosis and subtypes of mild cognitive impairment (Source: Petersen, Ronald C. "Mild cognitive impairment." CONTINUUM: Lifelong Learning in Neurology 10.1 (2004): 9-28.)

4.2.2.3 Demographic and behavioral covariates

Potential confounding variables including age, educational level, occupation, monthly household income, dietary habits, smoking, alcohol consumption, exercise and comorbidities were controlled. Education level was classified as high-school graduate or above. Monthly average household income was classified as under 5 million won, 5~10 million won, and over 10 million won. Occupations were divided into professional, technical and no job. The lifestyle variables comprised current smoking, current alcohol consumption, exercise (exercise regularly at least once a week or not), and dietary habits. If a subject ate three times a day, ate breakfast five times or more a week, had regular mealtimes, ate moderately, and ate out once or twice a week, the subject had ‘good’ dietary habits. If a subject skipped a meal, ate quickly, ate too much, and ate out more than three times a week, they had ‘bad’ dietary habits. The comorbidities were hypertension, diabetes mellitus. Subjects who had been diagnosed with hypertension by a doctor or were currently taking anti-hypertensive medications were classified as having hypertension. Subjects who had been diagnosed with diabetes mellitus by a doctor or were currently taking

medication for diabetes mellitus were considered to have diabetes mellitus.

4.2.3 Statistical analysis

Frequency distribution analysis and chi-square tests were conducted to examine differences of distributions in general characteristics.

A Kaplan-Meier failure time plot was used to describe the occurrence of Mild Cognitive Impairment according to the visceral obesity, and the log-rank test was used to compare differences in the curves between two groups

A multivariate Cox proportional hazard model was used to examine the association between visceral obesity groups and Non-Amnestic mild cognitive impairment/ Amnestic mild cognitive impairment. Age, gender, educational level, occupation, monthly household income, dietary habits, smoking, alcohol consumption, exercise hypertension and diabetes mellitus were adjusted. Statistical significance was defined as a p-value of 0.05. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

4.3 Results

The demographic characteristics of the subjects are summarized in [Table 4-1]. The 569 subjects comprised 281 non-visceral obesity and 288 visceral obesity. The baseline social characteristics differed significantly between the visceral obesity and non-visceral obesity in age ($p<.0001$), gender ($p=0.12$), occupation ($p<.0001$), household income ($p=0.00$), current smoking ($p=0.03$), alcohol consumption ($p<.0001$), hypertension ($p<.0001$), and diabetes mellitus ($p=0.00$).

Table 4-1 Baseline characteristics of study population

Variables of Baseline	Total (n=569)	Non-Visceral obesity (n=281)	Visceral obesity (n=288)	p-value
Age, Mean (SD)	66.26 (8.30)	63.51 (8.13)	68.94 (7.56)	**<.0001**
Gender				**<.0001**
Male	253 (44.46)	55 (19.57)	198 (68.75)	
Female	316 (55.54)	226 (80..43)	90 (31.25)	
Education				0.12
Under High school	191 (33.57)	102 (36.30)	89 (30.90)	
Over High school	378 (66.43)	179 (63.70)	199 (69.10)	
Occupation				**<.0001**
Professional worker	210 (36.91)	58 (20.64)	152 (52.78)	
Technical worker	37 (6.50)	17 (6.05)	20 (6.94)	
No job	322 (56.69)	206 (73.31)	116 (40.28)	
Household income				**0.00**
5 million	96 (16.87)	56 (19.93)	40 (13.89)	
5~10 million won	230 (40.42)	127 (45.20)	103 (35.76)	
Over 10 million won	243 (42.71)	98 (34.88)	145 (50.35)	
Current smoking				**0.03**
No	534 (93.85)	271 (96.44)	263 (91.32)	
Yes	35 (6.15)	10 (3.56)	25 (8.68)	
Alcohol consumption				**<.0001**
No	368 (64.67)	210 (74.73)	158 (54.86)	
Yes	201 (35.33)	71 (25.27)	130 (45.14)	
Exercise				0.13
No	130 (22.85)	72 (25.62)	58 (20.14)	
Yes	439 (77.15)	209 (74.38)	230 (79.86)	
Comorbidity				
Hypertension	242 (42.53)	81 (28.83)	161 (55.90)	**<.0001**
Diabetes mellitus	76 (13.36)	21 (7.47)	55 (19.10)	**0.00**

4.3.1 Non-Amnestic mild cognitive impairment

The number of patients with non-amnestic mild cognitive impairment and the results of cox regression analysis are presented in [Table 4-2]. Cox regression analysis showed that the risk of Non-Amnestic mild cognitive impairment in the visceral obesity group was 1.43 higher (95% CI=1.10-1.86) than that in the non-visceral obesity group. The Cox regression adjusted for age, gender, educational level, occupation, household, current smoking, alcohol consumption, exercise, dietary habits, hypertension, and diabetes mellitus. The risk of Non-Amnestic mild cognitive impairment in age of 40-64 was 1.44 higher (HR, 95% CI=1.11-1.87) than in age of 65-84, lower education level was 1.32 higher (HR, 95% CI=1.04-1.67) than that in higher education level and in monthly household income under 10 million won was 1.29 higher (HR, 95% CI=1.02-1.63) than that in over 10 million won. Also, the risk of Non-Amnestic mild cognitive impairment in subjects with having hypertension was 1.31 higher (HR, 95% CI=1.06-1.63) than not suffering from hypertension.

The Kaplan-Meier survival curves for the risk of Non-Amnestic mild cognitive impairment differed significantly between the two groups, and the risk of Mild Cognitive Impairment was

significantly higher in the visceral obesity group than the non-visceral obesity group (Log-rank p=0.014). After 2 years, the probability of occurrence of Non-Amnesic MCI is about 50% or more, and after 5 years, the probability of occurrence of Non-Amnestic MCI exceeds 60% [Figure 4-1].

Table 4-2 Number of Non-Amnestic mild cognitive impairment and adjusted HRs from the Cox's proportional hazards model

	Non-Amnestic MCI		Adjusted HR (95% CI)	P-value
	N (%)	P-value		
Visceral obesity		0.03		
Yes	170 (54.57)		**1.43 (1.10-1.86)**	0.01
No	149 (45.43)		Reference	
Age		0.47		
40-64	92 (28.05)		**1.44 (1.11-1.87)**	0.01
65-84	236 (71.95)		Reference	
Gender		0.71		
Male	148 (45.12)		1.03 (0.77-1.38)	0.85
Female	180 (54.88)		Reference	
Education level		0.04		
Under high school	120 (35.59)		**1.32 (1.04-1.67)**	0.02
Over high school	208 (63.41)		Reference	
Occupation		0.37		
Professional worker	114 (34.76)		0.88 (0.70-1.11)	0.30
Technical worker	24 (7.32)		1.08 (0.71-1.65)	0.72
No job	190 (57.93)		Reference	
Household income		0.38		
Under 10 million won	193 (58.84)		**1.29 (1.02-1.63)**	0.03
Over 10 million won	135 (41.16)		Reference	
Lifestyle related variables				
Smoking (ref: Yes)	20 (6.10)	0.95	1.08 (0.67-1.74)	0.11
Alcohol consumption (ref: Yes)	120 (36.59)	0.46	1.03 (0.79-1.33)	0.85
Exercise (ref: Yes)	260 (79.27)	0.16	0.80 (0.61-1.05)	0.10
Comorbidity variables				
Hypertension (ref: No)	152 (46.34)	0.03	**1.31 (1.06-1.63)**	0.01
Diabetes mellitus (ref: Yes)	49 (14.94)	0.20	0.85 (0.62-1.16)	0.30

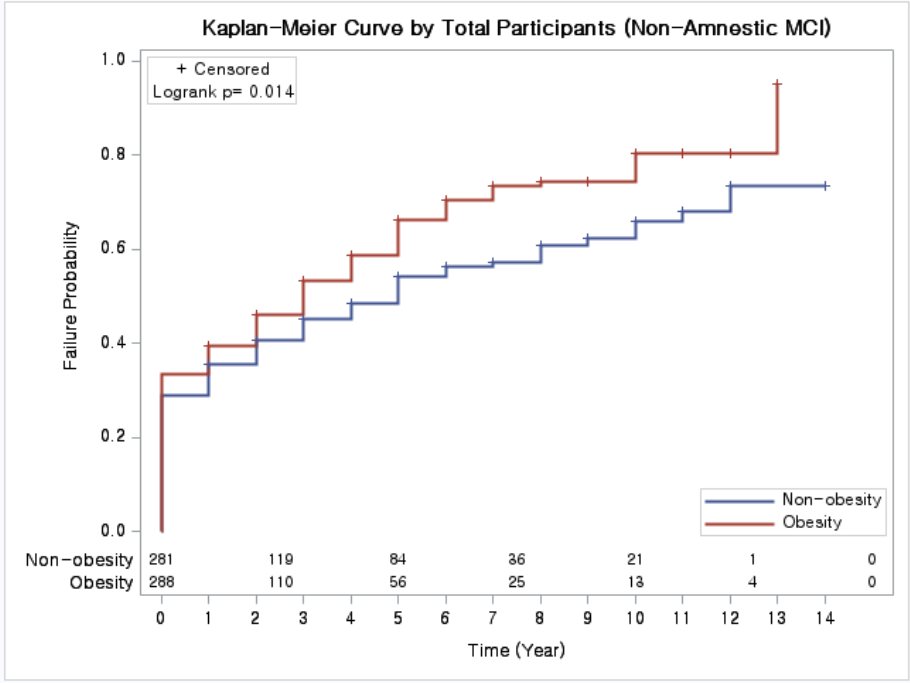

Figure 4-2 Non-Amnestic mild cognitive impairment survival curve between with and without visceral obesity

4.3.2 Amnestic mild cognitive impairment

The number of patients with amnestic mild cognitive impairment and the results of cox regression analysis are presented in [Table 4-3]. The risk of amnestic mild cognitive impairment in lower education level was 1.65 higher (HR, 95% CI=1.13-2.42) than that in higher education level and in monthly household income under 10 million won was 1.69 higher (HR, 95% CI=1.13-2.52) than that in over 10 million won.

The Kaplan-Meier survival curves for the risk of amnestic mild cognitive impairment not statistically significant between the two groups (Log-rank p=0.375) [Figure 4-2].

Table 4-3 Number of Amnestic mild cognitive impairment and adjusted HRs from the Cox's proportional hazards model

	Non-Amnestic MCI		Adjusted HR (95% CI)	P-value
	N (%)	P-value		
Visceral obesity		0.39		
Yes	67 (54.03)		1.12 (0.73-1.72)	0.60
No	57 (45.97)		Reference	
Age		0.15		
40-64	21 (16.94)		0.89 (0.54-1.46)	0.64
65-84	103 (83.06)		Reference	
Gender		0.56		
Male	58 (46.77)		1.19 (0.69-2.03)	0.53
Female	66 (63.23)		Reference	
Education level		0.04		
Under high school	50 (40.32)		**1.65 (1.13-2.42)**	0.01
Over high school	74 (59.68)		Reference	
Occupation		0.44		
Professional worker	51 (41.13)		1.31 (0.79-2.15)	0.30
Technical worker	6 (4.84)		0.63 (0.26-1.53)	0.31
No job	67 (54.03)		Reference	
Household income		0.04		
Under 10 million won	81 (65.32)		**1.69 (1.13-2.52)**	0.01
Over 10 million won	43 (34.68)		Reference	
Lifestyle related variables				
Smoking (ref: Yes)	9 (7.26)	0.56	0.89 (0.44-1.83)	0.76
Alcohol consumption (ref: Yes)	45 (36.29)	0.80	0.97 (0.63-1.49)	0.88
Exercise (ref: Yes)	92 (74.19)	0.37	1.18 (0.78-1.79)	0.43
Comorbidity variables				
Hypertension (ref: No)	49 (39.52)	0.44	1.27 (0.87-1.86)	0.21
Diabetes mellitus (ref: Yes)	22 (17.74)	0.10	0.75 (0.46-1.20)	0.23

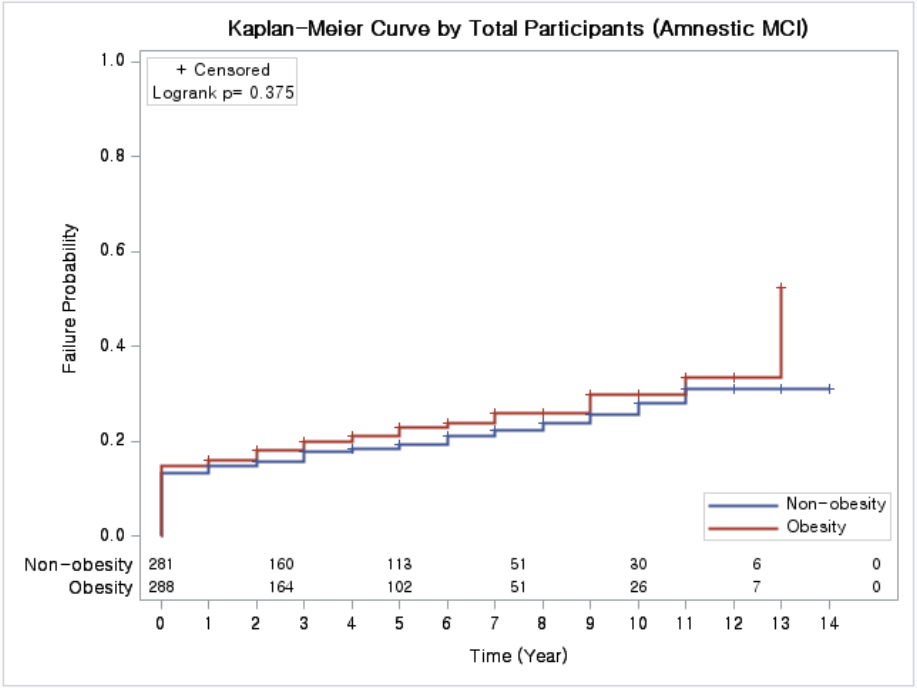

Figure 4-3 Amnestic mid cognitive impairment survival curve between with and without visceral obesity

4.4 Discussion

This study found a significant association between visceral obesity and increased Non-Amnestic mild cognitive impairment after adjusting for confounding factors. The risk of Non-Amnestic mild cognitive impairment was remained significantly higher in visceral obesity group compared to the non-visceral obesity group.

Aged 40-64, low education level, and lower monthly household income, hypertension were also found to be risk factors for Non-Amnestic mild cognitive impairment in the subjects. This is in line with the findings of previous studies suggesting that subjects with obesity have an increased Mild Cognitive Impairment.

In the Netherlands, a population study revealed that older persons with metabolic illnesses performed worse in the areas of executive function, executive function speed, and attention, but not memory[112]. The same research team published a study on non-demented people who were part of a memory clinic population. They demonstrated that metabolic illnesses were linked to worse performance on tests of executive function, attention, and speed, as well as visuoconstructive ability, but not overall cognitive function as measured by the MMSE[113]. In a population study of stroke-free people aged 60 or older, it was

discovered that people with many characteristics of metabolic diseases performed worse on visuospatial abilities, sustained attention, and motor speed of processing, than people with metabolic diseases[114]. In line with these previous studies, the results of our current study suggest that rather than memory function, attention may be impaired by diseases related to metabolism.

According to the results of a systematic review, obese persons have a larger chance of observing and Mild Cognitive Impairment and higher incidence of Mild Cognitive Impairment than people of normal weight[115]. In that study, BMI has been used to measure obesity. Mild Cognitive Impairment has been evaluated using the Addenbrooke's Cognitive Examination (ACE) and Mini-Mental State Examination (MMSE) recognized cut-off values. The prevalence of Mild Cognitive Impairment in the general population is about 6.0% and 9.6%[116,117]. Therefore, it is suggested that the frequency of Mild Cognitive Impairment is higher among obese individuals than it is in the general population. Additionally, stroke, depression[116], sleep issues[117], a history of head trauma, and poorer educational status[118] are other possible related factors for Mild Cognitive Impairment in the general population.

In another study, the risk of Mild Cognitive Impairment was

higher in people with high Lipid Accumulation Product (LAP) index, an indicator of visceral obesity, with type 2 diabetes mellitus[119]. The pathways implicated in cognitive impairment brought on by type 2 diabetes mellitus and visceral obesity may be connected as a potential basis for this connection. Insulin resistance causes tau hyperphosphorylation and amyloid-β protein buildup to rise, which impairs cognition [120,121]. Another mechanism mentioned in other papers is same as above, When the amount of body fat increases, harmful substances therein interfere with the action of insulin, resulting in insulin resistance. To compensate for the impaired insulin function, the brain increases insulin secretion, resulting in hyperinsulinemia. Excess β-amyloid, a surface protein of brain cells, accumulates in the brain, damaging brain cells. Insulin interferes with the decomposition of β-amyloid, reducing brain perfusion and leading to cognitive decline[56].

In a Japanese study, visceral fat had a negative effect on cognitive function[122]. The rationale stated in that paper is as follows. High levels of the 244 amino acid protein hormone adiponectin circulate and account for 0.01 percent of all the proteins in serum. Adiponectin is an adipokine that is abundantly generated and secreted by adipose tissues and is well known for its anti-diabetic, anti-inflammatory,

cardioprotective actions, and neuroprotective. Patients who are obese have lower serum and adiponectin levels. So, that study discovered a negative correlation between plasma adiponectin levels and Mild Cognitive Impairment. Given that the abdomen subcutaneous fat area and plasma adiponectin levels were inversely correlated, adiponectin levels that were elevated in response to a reduction in abdominal subcutaneous fat may have a compensating effect on dementia development. These results support their hypothesis that adiponectin might perhaps act as a protective factor in the development of early-stage cognitive impairment[122,123].

Our study has several strengths. Most of the previous studies dealing with fat and cognitive function used BMI and waist circumference. However, BMI is not a reliable indicator of obesity in the older population because of changes in body composition and an increase in abdominal obesity, BMI can understate body fat. On the other side, because of the reduced measured height, kyphosis, or contraction of the spine caused by scoliosis and spinal bone loss, may produce an overestimation of body fat in older adults[124]. And measuring waist circumference cannot differentiate between subcutaneous fat and visceral fat. Therefore, in this study, visceral fat was used to define

obesity. In order to measure visceral fat, I use the BIA method to accurately measure. Also, Mild cognitive impairment is defined as the presence of objectively demonstrable impairment in one or more of the following cognitive function domains; memory, executive function, attention, language, or visuospatial skills[104]. Since CERAD-K is a tool that can inspect each of these items, Mild Cognitive Impairment can be judged more accurately.

This study had limitation. First, in the previous study mentioned, sex hormones can influence obesity in cognitive function. Unfortunately, estradiol and testosterone levels were not included in our study, so further studies are needed. Second, BIA measures the body into five cylindrical columns. (left and right upper and lower extremities as well as torso). However, the data are easily affected by water intake and excretion, as well as temperature and humidity[98]. Nevertheless, BIA does not involve radiation exposure and is less expensive than computed tomography (CT) and magnetic resonance imaging (MRI)[99]. Third, when diagnosing mild cognitive impairment, there must be no impairment in activity of daily living (ADL) or instrumental ADL (IADL), and cognitive decline is intermediate between normal and mild Alzheimer's disease patients[125]. However, due to the limitations of the data, it was not

possible to know the daily living ability and tool daily living ability.

Nevertheless, this study is worthwhile. To overcome the limitations of many previous studies with cross-sectional studies, this study conducted a follow-up study with subjects. And it is reported that body fat distribution is more related to health risk than body fat mass in obese people[64]. Therefore, if the accumulation of visceral fat is severe, the risk of cardiovascular disease and metabolic syndrome increases regardless of body weight [69]. In addition, recently, it has been found that the amount of visceral fat rather than total body fat plays a more important role in the incidence of complications due to obesity[71]. Therefore, in this study, obesity was determined with visceral fat. To our knowledge, this is the first study to conduct a survival analysis between visceral obesity and Mild Cognitive Impairment. Based on the results of this study, early detection of Mild Cognitive Impairment in the general community's visceral obese population might be helpful to prevent further decline in cognitive function that eventually results in dementia in later life.

In conclusion, our findings suggest that visceral obesity was associated with a higher risk of Non-Amnestic mild cognitive impairment. Therefore, early detection of Non-Amnestic mild cognitive

impairment in obese individuals is crucial to prevent future cognitive decline.

Chapter 5. Overall discussion

This study identified patterns of cognitive decline and related risk factors for cognitive decline. And among the risk factors, in particular, the relationship between visceral fat and cognitive function was investigated. The first study determined the causal relationship between patterns of cognitive function decline and risk factors affecting the changes in the cognitive function decline. The second study investigated changes in visceral fat over time and their association with cognitive function accordingly by gender. The last study evaluated whether visceral obesity causes Non-Amnestic/ Amnestic mild cognitive impairment. Group-based trajectory model, linear mixed model and survival analysis were performed respectively.

As we get older, our memory and orientation decrease. Whether it is due to congenital reasons or environmental factors that an individual is in, there may be individual differences in the way the symptoms of the disease worsen or improve. The rate or pattern of cognitive decline may vary from person to person. Some people may experience a sharp decline in cognitive function, and some may experience less cognitive decline as they age. Therefore, it is important to find out which factors cause rapid decline in cognitive function and which factors act as protective factors for cognitive decline. The results were presented in Chapter 2; Older age,

lower education level, bad dietary habits, comorbidities, a low household income and technical workers were more likely to indicate group of the low and rapid cognitive function decline. Such variables should be modified to prevent the risk of rapid cognitive function decline. Conversely, a younger age, a higher educational level, a professional worker, good dietary habits, no diabetes mellitus, and no obesity improved cognitive function. Our findings highlight the need to prevent such decline. Identification of those at high risk followed by interventions that prevent decline are essential.

Excessive body fat causes diseases such as type 2 diabetes, dyslipidemia, insulin resistance, and increases the medical and socioeconomic burden. It is also a risk factor for mortality. As aging progresses, the amount of muscle decreases and the amount of visceral fat increases, increasing the likelihood of visceral obesity. If the accumulation of visceral fat is severe, the risk of cardiovascular disease and brain related disease increases regardless of body weight. The results were presented in Chapter 3; This study found that an increase in visceral fat area over time was associated with a decrease in cognitive function. In males, Word List Memory and Word List Recall score were decreased as visceral fat area increased. In females, Boston Naming Test, MMSE-

KC, Word List Memory, Constructional Praxis score were decreased as visceral fat area increased. Among the CERAD-K test, Verbal Fluency, Boston Naming Test, Word List Memory, Word List Recall and Constructional Praxis assessed executive function, language ability, immediate recall, delayed recall, and visuospatial ability respectively. So, in this study I found, immediate and delayed recall in males reduced as visceral fat area increased. Language ability, immediate memory, and visuospatial function declined in females as visceral fat area rose. The results of this study suggested that management for visceral fat reduction is necessary regardless of gender.

A high Body Mass Index (BMI) is associated with the prevalence of Mild Cognitive Impairment. According to previous studies on the relationship between BMI and Mild Cognitive Impairment, Central obesity with high BMI could act as a risk factor for mild cognitive impairment and dementia. Similarly, Cognitive impairment is more common among individuals with a lot of visceral fat. Mild cognitive impairment is clinically important in that it has a relatively high probability of progressing to dementia and can provide insight into dementia at an early stage of dementia.

The results were demonstrated in Chapter 4; This study found a

significant association between visceral obesity and increased Non-Amnestic mild cognitive impairment after adjusting for confounding factors. The risk of Non-Amnestic mild cognitive impairment was significantly higher compared to the non-visceral obesity group. Low education level, and lower monthly household income, hypertension were also found to be risk factors for Non-Amnestic mild cognitive impairment in the subjects. The study suggest that visceral obesity was associated with a higher risk of Non-Amnestic mild cognitive impairment. This necessitates consideration of the future risk of dementia in terms of visceral obesity after a diagnosis of mild cognitive impairment. Therefore, early detection of Non-Amnestic mild cognitive impairment in obese individuals is crucial to prevent future cognitive decline and to increase research on Non-Amnestic mild cognitive impairment in obese individuals in general.

In this study, similar to the results of previous studies on Alzheimer's disease and dementia, I found that cognitive function decreased with age, education level, and lower household income. This study suggests that eating habits can also affect cognitive function, and that visceral fat can affect each area of cognitive function, and that there were differences between male and female.

Dietary habits affect obesity. Irregular meals increase insulin secretion and fat synthesis by enhancing the activities of adipogenic enzymes. Too many meals or difficulties in controlling intake enhance obesity. Skipping breakfast can trigger snacking and overeating at lunch or dinner. I noted frequent consumption of processed and fast foods; the higher these intakes, the higher the blood cholesterol and triglyceride levels, triggering cardiovascular disease and obesity. According to these findings, it's possible that controlling one's dietary habits and obesity is important factors in the prevention of cognitive function decline.

Aging causes changes in the composition of the body. A decrease in muscle mass and an increase in fat mass are typical examples. In other words, it can be summarized as the conversion of muscle into fat. About 40% of the basal metabolic rate is consumed in the muscles, and when the muscle decreases, the basal metabolic rate also decreases. With age, fat accumulation and sarcopenia lead to metabolic disorders and risk of cerebrovascular disease, as well as death.

This study has several public health and policy implications. This study showed that cognitive function can decline in various patterns with age, and among the factors affecting cognitive function, the effect of visceral fat was shown for men and women separately.

In conclusion, this study tried to study the risk factors for cognitive decline due to aging and to elucidate the causal relationship between visceral fat and cognitive function using an epidemiological method. Group based trajectory model, linear mixed model, and survival methods were used to provide previously unknown information and to increase the utilization of longitudinal study data. The results of this study will serve as a basis for suggesting a healthy way to age at this point in time when the average life expectancy is increasing.

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국문초록

한국 성인에서의 비만지표와 인지기능 변화의 연관성 연구

서울대학교 보건대학원
보건학과 보건학전공
한수정

서론

노화는 지적 능력 저하, 감각 기능 저하, 정서적 반응 감소를 동반한다. 전 세계에서 60세 이상 성인의 치매 유병률은 약 5-7%이다. 2018년에는 전 세계적으로 5천만 명이 치매에 걸린 것으로 추산되었으며, 2050년에는 그 수가 3배로 증가할 것으로 예상된다. 치매는 사망률의 주요 원인이며 높은

의료 비용이 수반된다는 사실 때문에 인지기능을 감소시키는 예방 및 중재 조치가 필수적이다.

인지저하에는 여러 인구·사회학적 특성과 건강 습관이 영향을 미친다. 여기에는 나이, 소득, 교육수준, 직업 및 기저 질환 그리고 비만 등이 포함된다. 그러므로 인지 기능 저하에 영향을 미치는 요인을 알아내는 것은 인지기능 저하 예방을 위한 효과적인 중재를 만드는 데 필수적이다.

본 연구의 첫번째 목적은 집단중심추세모형을 사용하여 인지기능 감소의 궤적을 식별하고 식별된 각 그룹마다 어떠한 위험 요소가 존재하는지 알아보는 것이다. 두번째 목적은 시간에 따른 내장지방의 변화와 그에 따른 인지기능과의 연관성을 성별에 따라 조사하는 것이고, 마지막으로 내장 비만이 기억상실형/비기억상실형 경도인지장애를 유발하는지 여부를 평가하고, 이에 영향을 미치는 위험요인들을 살펴보는 것이다.

방법

연구 데이터는 서울대학교병원 강남검진센터 수검자들의 자료를 이용하였다. 첫번째 연구에서는 2005년부터 2020년까지 서울대학교병원 강남검진센터 방문하여 인지기능과 문진, 신체계측 검사를 받은 40세 이상 637명(남 274명, 여 363명)을 대상으로 하였다. 두번째 연구에서는 2005년부터 2020년까지 서울대학교병원 강남검진센터에서 생체전기저항 방식으로 내장지방 측정하고 CERAD-K 심리신경평가집으로 인지기능 검사를 받은 남성 275명, 여성 367명을 분석에 포

함하였다. 세번째 연구에서는 2005년부터 2020년까지 서울대학교병원 강남검진센터를 방문하여 생체전기저항 방식으로 내장지방 측정하고 CERAD-K 심리신경평가집으로 인지기능 검사를 받은 사람들 중에서 기존에 치매와 경도인지장애를 앓고 있는 사람들은 제외한 569명을 분석에 포함하였다. 첫번째 연구에서는 인지 저하의 궤적을 살펴보기 위해 집단중심추세모형을 이용하였다. 이어, 다양한 인지기능 궤적 그룹에 영향을 미치는 요인을 조사하기 위해 다항회귀분석을 수행하였다. 두번째 연구에서는 선형혼합모델을 사용하여 인지기능과 내장지방 간의 연관성을 남녀를 나누어 알아보았다. 세번째 연구에서는 내장비만과 기억상실형/비기억상실형 경도인지기능의 연관성을 알아보기 위해 카플란마이어 곡선과 콕스 비례위험모형을 이용하였다.

결과

첫 번째 연구에서 40세 이상 성인의 인지 기능 궤적은 다양하게 나타났다. 궤적은 높음(27.3%), 중간(41.0%), 낮음(22.7%), 빠른 인지 기능 저하(9.1%)의 4가지로 구분되었다. 나이가 많을수록, 남성, 교육수준이 낮을수록, 좋지 않은 식습관, 당뇨병, 기술직 종사자, 낮은 소득은 인지기능 저하의 가능성을 증가시켰다. 두 번째 연구에서는 남성의 경우 내장지방이 증가할수록 단어 목록 기억 점수 (β:-0.15, CI: -0.29~-0.01) 및 단어 목록 회상 점수 (β:-0.16, CI: -0.24~-0.09)가 감소되었다. 여성의 경우 내장 지방이 증가할수록 보스턴 이름

대기 점수 (β: -0.15, CI: -0.23~-0.06), 간이 정신상태 점수 (β:-0.26, CI: -0.40~-0.12), 단어 목록 기억 점수(β: -0.25, CI: -0.41~-0.09), 구성행동 점수(β: -0.09, CI: -0.14~-0.03), 간이 정신상태 검사를 제외한 도메인의 총합 점수(β: -0.71, CI: -1.20 ~ -0.22)가 감소되었다. 세 번째 연구에서는 내장 비만이 있는 경우 비기억상실형 경도 인지 장애의 발생 위험이 더 높았다 (Adjusted HR=1.44, 95% CI=1.11-1.87).

결론

본 연구를 통하여 인지기능 저하에는 다양이 패턴이 존재한다는 것을 알 수 있었다. 그리고 고령, 낮은 교육수준, 좋지 않은 식습관, 낮은 소득, 기술직 종사자, 기저 질환을 앓고 있는 경우, 내장지방의 증가는 인지기능에 위험요인으로 작용하였다. 뿐만 아니라 내장 비만은 경도인지장애 발병의 위험을 증가시킨다.

'인지예비능'은 우리의 뇌가 손상을 받을 때 그 피해를 견디며 회복할 수 있는 뇌의 능력이다. 금연, 금주, 운동과 같은 올바른 생활습관 및 좋은 식습관 등을 통해 뇌의 '인지예비능'을 높게 유지하면 인지기능이 감소되는 것을 예방할 수 있다. 본 연구 결과를 통해 인지기능에 영향을 미치는 위험요인들을 줄이기 위해 개인의 생활습관을 바꾸도록 독려하고 중재를 마련함으로서 '인지예비능'을 향상 시킬 수 있다.

주요어

노화, 인지기능, 인지저하, 경도인지장애, 치매, 내장지방, 내장비만, 집단중심추세모형

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