Master of Medicine

# The association between free testosterone level and cognition in elderly men and women : Korean Frailty and Aging Cohort Study

The Graduate School

of the University of Ulsan

Department of Medicine

Shin Who Park

# The association between free testosterone level and cognition in elderly men and women
## : Korean Frailty and Aging Cohort Study

Supervisor: Kyoung Hyo Choi

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Shin Who Park

Department of Medicine

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## : Korean Frailty and Aging Cohort Study

This certifies that the dissertation of Shin Who Park is approved.

Committee Chair: Dr. Won Kim _____

Committee Member: Dr. Kyoung Hyo Choi _____

Committee Member: Dr. Seung Hak Lee _____

Department of Medicine

Ulsan, Korea

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**ABSTRACT**

**Objective** To investigate the association between serum free testosterone level and cognitive function in Korean community-dwelling elderly men and women.

**Method** This is a cross-sectional study using the Korean Frailty and Aging Cohort Study database. A total of 2,851 patients were included in this study. Cognitive function was assessed by the Frontal Assessment Battery and the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet which includes Mini-Mental State Examination, Trail Making Test, Digit Span, and Word List Memory, Recall and Recognition. Univariate and multivariate logistic regression analyses were performed to investigate the association between free testosterone level and cognitive function.

**Results** Global cognition (OR, 1.362; 95% CI, 1.030-1.801, p-value for trend, 0.002), psychomotor speed (OR, 1.338; 95% CI, 1.002-1.787, p-value for trend, 0.046), executive function (OR, 1.390; 95% CI, 1.059-1.825, p-value for trend, 0.040) and verbal memory (OR, 1.518; 95% CI, 1.153-1.999, p-value for trend, 0.012) showed significant association and trend with free testosterone in women. On the other hand, I did not find significant

association or trend in men's cognition.

**Conclusion** There is a dose response relationship between FT and cognition function. Further investigations are needed to confirm the present findings.

**Keywords** cognition, cognitive dysfunction, testosterone, aged

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## INTRODUCTION

Testosterone has been thought to play a neuroprotective role in the brain[1-3]. Testosterone can pass through the blood–brain barrier and affect neuronal cells[4]. And it act via androgen receptors, which are present in neurons throughout the central nervous system[5, 6]. Eventually it has ability of neuroprotective antioxidant and anti-apoptotic potential[7-9]. In situations of testosterone deprivation, cognitive decline was aggravated via increasing oxidative stress, glial activity and apoptosis[10].

Serum testosterone levels decrease with age. Previous studies have shown a greater decrease in serum free testosterone (FT) levels compared to total testosterone (TT) levels[11, 12]. Serum FT is known as a biologically more active fraction of circulating testosterone[13]. It is thought that the decline of FT in the elderly may lead to a decrease in its neuroprotective function, leading to a decrease in cognitive function. In basic studies, there have been many positive evidences for the neuroprotective function of testosterone affecting the central nervous system. On the other hand, the evidences from observational and interventional studies in human were inconsistent and unclear[14-23]. Previous studies investigating testosterone levels in association with cognitive function have found a wide variety in the direction of results, ranging from positive, negative or no associations. In order to understand the relationship between human cognitive function and testosterone, it is necessary to consider the causes of inconsistent results in existing studies.

Testosterone is known to be an important hormone in women as well as men. With physiological actions mediated directly or via aromatization to estradiol throughout the body, testosterone is an essential hormone for women and affects women‘s central nervous system and cognitive function[24]. In women, relatively small differences in testosterone levels (in nmol/ L) could potentially lead to large differences in endogenous estradiol levels (in pmol/L)[25]. Despite the crucial role of testosterone and the high circulating concentrations of this hormone relative to estradiol in women, studies of its action and the effects of

testosterone deficiency and replacement in women are scarce[26]. It is thought that more study on association between women's cognition and testosterone is needed.

Most of the previous observational studies of cognitive function and testosterone had limitation that they conducted studies in small groups and researches on Asians are rare. In particular, there have been no large-scale cross sectional studies of Asian men and women. In addition, the wide age distribution of existing study made it difficult to show the characteristics of a particular age group, and few studies have measured the multi-domain of cognitive function. Furthermore, most previous studies have not considered the effect of physical function despite the fact that physical function is associated with cognitive function in elderly[27-29].

In this study, I conducted the cross-sectional study of the association between levels of endogenous FT and cognitive function in Korean men and women aged 70-84 using the Korean Frailty and Aging Cohort Study (KFACS) database, which is a nationwide multicenter large-scale cohort study. And I sought to determine which specific cognitive domains are associated with testosterone.

## METHODS

### *1. Data Sources and Study Population*

This is a cross-sectional study using the Korean Frailty and Aging Cohort Study (KFACS) database. The KFACS is a nationwide multicenter large-scale cohort study conducted in 10 centers in urban and rural regions throughout South Korea. The baseline survey was conducted in 2016-2017, and recruited sex- and age-stratified community-dwelling people aged 70-84 years. The purpose of KFACS was to identify risk factors and prevention of frailty for community-dwelling older adults. Details of the design of the KFACS have been presented elsewhere[30]. A total of 3,014 community-dwelling elderly completed baseline survey. Of them, 2,851 participants were identified after the exclusion of 147 people who had previous medical history of cerebrovascular diseases and 16 people who did not answer their cerebrovascular medical history. Finally, eligible participants (n=2710) were selected after the exclusion of those with missing data (n=141) (Figure 1).

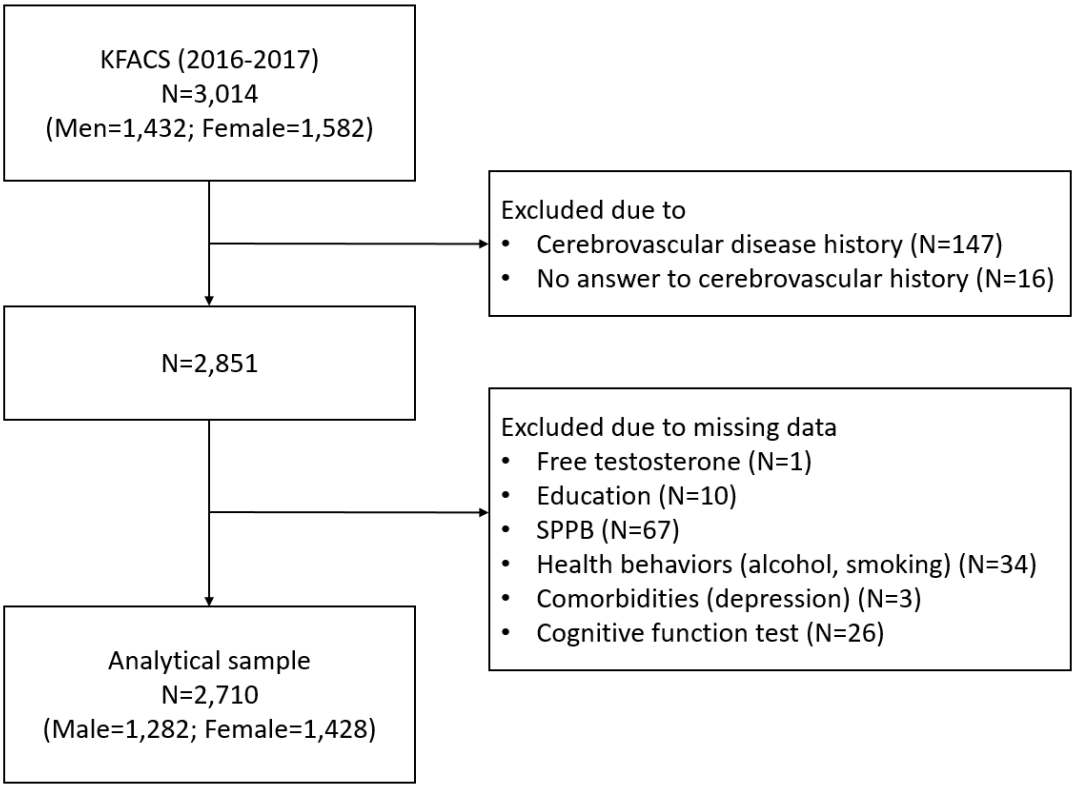


**Fig. 1. Flow chart of participant selection.**

KFACS, Korean Frailty and Aging Cohort Study; SPPB, Short Physical Performance Battery

### *2. Free Testosterone Measurement*

Blood samples were obtained in the morning after 8 hours of fasting to minimize circadian variation. And sera were stored at -80℃ until the time of analysis. Serum total testosterone, free testosterone (FT) and sex hormone-binding globulin levels were assayed with radioimmunoassay kits. Free testosterone was estimated using mass action equations as described by Vermeulen et al.[31].

### *3. Cognitive Function Assessment*

Cognitive function was assessed by the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K)[32, 33] and Frontal Assessment Battery (FAB)[34].

In this study, Mini-Mental State Examination in the CERAD-K (MMSE-KC) was used for global cognitive function assessment. The MMSE-KC differs from the original MMSE in 3 items: orientation, attention and calculation, and language. Considering the high illiteracy rate among elderly Korean people, 'reading and writing' was replaced with 'judgment' and the '100-7 calculation' was replaced with 'speaking backward'[35]. The highest score is 30 and a higher score indicates a higher level of cognitive function.

Word List Memory is a free-recall memory test that assesses the learning ability for new verbal information. Three trials of a 10-item word list are presented. Immediately following each trial, the subject is asked to recall as many items as possible. The maximum number of correct responses is 30 for the 3 trials. Word List Recall assesses the ability to delayed recall the 10 words given in the Word List Memory task after a delay of a few minutes. Word List Recognition evaluates the recognition of the target words presented in the Word List Memory task when presented among the 10 distractor words. Final score is calculated as the

total number of correct answers for both the 10 target words and the 10 distractor words minus 10. A score of zero is given if the result is less than zero, the maximum score of this task is 10[33].

Psychomotor speed and attention was assessed by Trail Making Test part A (TMT). The subject was asked to draw a line as rapidly as possible joining consecutive numbers (1-25). A maximum time of 360 sec is allowed[36, 37].

Digit Span (DS) test was used to test verbal episodic memory and working memory. Respondents were asked to recall numbers forward (range 3-9) and backward (range 2-8). The sum of points (28 points) that gave the correct answer by doing it twice in the same number of forwards and backwards (14 points each)[38].

FAB was conducted to assess the executive function affecting both cognitive and motor behavior. The maximum possible sum of the scores is 18[34]. Well-trained clinical research coordinators measured the cognitive function studies.

The lowest quartile group of the value measured by TMT, DS, Word List, and FAB, and less than 24 points in MMSE-KC were considered clinically relevant indication of cognitive impairment.

### *4. Physical Performance: Short Physical Performance Battery (SPPB)*

SPPB was conducted to measure the physical performance. It consisted of the chair stand test (4 points), balance test (4 points), and a 4 m gait speed test (4 points), with a total score of 12 points. In the chair stand test the participants were initially seated. On verbal command, they stood up then sat down five times. The time in seconds to complete the task was recorded using a stopwatch. Balance was measured in three tests, following an explanation. In the side-by-side stand test, feet were positioned together and balance was maintained for 10 s. In the semi-tandem stand test, each participant stood with a toe of the dominant foot touching the middle of the opposite foot for 10 s. In the tandem stand test, each participant

stood with the toe of the dominant foot touching the heel of opposite foot for 10 s. In the walking speed test, the four-m gait test was used. The average time of two trials of the walking speed test was recorded[39]. Less than 9 points of SPPB considered a poor physical function group[40].

### *5. Covariates*

Covariates were selected based on the possible mechanism of the effect on cognitive function. Demographic variables included age, sex, and duration of education. Age was categorized into three groups: 70–74, 75–79, and 80–84 years. Duration of education was categorized as junior high school graduate or below (0-9 years) and high school admission or above (>9years). Health behaviors included smoking status, alcohol consumption. Smoking status was divided into "current smoker" or "non- or ex-smoker". Alcohol consumption was divided into "drinking twice a month or more" or "once a month or less." Comorbidities included depressive disorder history diagnosed by physicians.

### *6. Statistical analysis*

Statistical analysis was performed using SPSS 21.0 (IBM Corporation, Chicago, IL, USA). The subjects' characteristics for men and women were compared by student's t-test for continuous variables and chi-squared tests for categorical variables. Logistic regression analysis was performed to investigate the association between serum FT level and each cognitive function domain, and p-value for trend. All logistic regression analyses were performed separately for each sex. Participants were placed into four different groups according to quartiles of FT level: G1, highest; G2, high; G3, low; G4, lowest. Different confounder adjustment models were constructed as follows: unadjusted univariate; model 1, adjusted by age group; model 2, adjusted by age group and education duration; and model 3, further adjusted by current smoker status, alcohol intake, depressive disorder history, and

SPPB. Odds ratios (ORs) were accordingly calculated with corresponding 95 % confidence intervals (CI) and p-values of $< 0.05$ were considered to be statistically significant.

## RESULTS

### *1. Clinical characteristics of the subjects*

The characteristics of the study subjects according to the sex are shown in Table 1. Of the 2,710 eligible subjects, 1,282 were men and 1,428 were women. The mean MMSE-KC score was 26.2±3.0 in men, and 25.1±3.4 in women. 14.7% of men (n=189) and 26.8% of women (n=382) scored less than 24. Serum free testosterone levels showed significant differences between sexes. Mean values of free testosterone levels were 9.42±3.37 pg/mL in men and 0.91±0.89 pg/mL in women. The mean education year was 10.53±4.68 in men, and 6.80±4.65 in women.

**Table 1. Characteristics of the study population**

| Characteristics | Men (N=1,282) | Women (N=1,428) | p-value |
|---|---|---|---|
| Age (years) | 76.3 ± 3.9 | 75.7 ± 3.9 | <0.001 |
| 70-74 | 478 (37.3) | 617 (43.2) | |
| 75-79 | 491 (38.3) | 510 (35.7) | |
| 80-84 | 313 (24.4) | 301 (21.1) | |
| Education (years) | 10.5 ± 4.7 | 6.8 ± 4.7 | <0.001 |
| ≤Junior high school | 586 (45.7) | 1066 (74.6) | |
| ≥High school | 696 (54.3) | 362 (25.4) | |
| SPPB (point) | 11.2 ± 1.2 | 10.6 ± 1.5 | <0.001 |
| <9 | 55 (4.3) | 141 (9.9) | |
| ≥9 | 1227 (95.7) | 1287 (90.1) | |
| Serum FT (pg/mL) | 9.42 ± 3.37 | 0.91 ± 0.89 | <0.001 |
| G1 | 13.60 ± 2.29 | 1.79 ± 1.34 | |
| G2 | 10.29 ± 0.57 | 0.99 ± 0.11 | |
| G3 | 8.35 ± 0.55 | 0.66 ± 0.09 | |
| G4 | 5.38 ± 1.80 | 0.21 ± 0.18 | |
| Current smoker | 149 (11.6) | 14 (1.0) | <0.001 |
| Depression | 21 (1.6) | 50 (3.5) | 0.002 |
| Alcohol consumption ≥2/month | 646 (50.4) | 167 (11.7) | <0.001 |
| MMSE-KC(point) | 26.2 ± 3.0 | 25.1 ± 3.4 | <0.001 |
| <24 | 189 (14.7) | 382 (26.8) | |
| ≥24 | 1093 (85.3) | 1046 (73.2) | |
| TMT(sec) | 65.51 ± 40.50 | 97.96 ± 71.94 | <0.001 |
| FAB (point) | 14.2 ± 2.7 | 12.9 ± 3.0 | <0.001 |
| DS (point) | 11.6 ± 3.7 | 9.8 ± 3.8 | <0.001 |
| Word List (point) | | | |
| Memory | 16.5 ± 4.0 | 17.1 ± 4.4 | 0.001 |
| Recall | 5.5 ± 2.0 | 5.6 ± 2.1 | 0.691 |
| Recognition | 8.6 ± 1.8 | 8.6 ± 1.8 | 0.896 |

Values are presented as the mean ± standard deviation or as a number (%).

p-values were obtained using the student t-test or chi-square test.

SPPB, Short Physical Performance Battery; FT, free testosterone; G, quartile group; MMSE-KC, Mini-Mental Status Examination in the Korean version of the CERAD Assessment Packet; TMT, Trail Making Test; FAB, Frontal Assessment Battery; DS, Digit Span.

### *2. Association between FT level and cognitive function*

In men, there was no significant association between FT level and low cognitive function (Table 2). On the other hand, in women, low FT level showed association with decreased cognitive function in most of domains. In univariate analysis, low FT level was associated with MMSE-KC (OR, 1.677; 95% CI, 1.294-2.173), TMT (OR, 1.706; 95% CI, 1.311-2.221), DS (OR, 1.387; 95% CI, 1.074-1.791), FAB (OR, 1.722; 95% CI, 1.336-2.221), Word List Memory (OR, 1.764; 95% CI, 1.361-2.285), and Word List Recall (OR, 1.472; 95% CI, 1.142-1.896). After adjusting for all potential confounding factors including age, duration of education, alcohol consumption, smoking, depression and SPPB (Model 3), these associations were constantly observed in MMSE-KC (OR, 1.362; 95% CI, 1.030-1.801), TMT (OR, 1.338; 95% CI, 1.002-1.787), FAB (OR, 1.390; 95% CI, 1.059-1.825), and Word List Memory (OR, 1.518; 95% CI, 1.153-1.999) (Table 3).

**Table 2. Odds ratio of low serum free testosterone level for low cognitive function in elderly men**

| | Univariate analysis | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| MMSE-KC | 0.980 | 0.686-1.400 | 0.849 | 0.590-1.223 | 0.849 | 0.582-1.237 | 0.854 | 0.583-1.252 |
| TMT | 1.059 | 0.793-1.415 | 0.894 | 0.663-1.206 | 0.891 | 0.651-1.219 | 0.892 | 0.649-1.226 |
| DS | 1.068 | 0.810-1.409 | 0.976 | 0.736-1.294 | 0.971 | 0.724-1.301 | 0.981 | 0.730-1.319 |
| FAB | 1.095 | 0.840-1.428 | 1.015 | 0.775-1.330 | 1.011 | 0.760-1.344 | 1.014 | 0.760-1.353 |
| Word List | | | | | | | | |
| Memory | 1.081 | 0.823-1.421 | 0.904 | 0.680-1.202 | 0.902 | 0.675-1.207 | 0.895 | 0.667-1.201 |
| Recall | 1.084 | 0.822-1.429 | 0.928 | 0.698-1.234 | 0.928 | 0.696-1.237 | 0.930 | 0.696-1.243 |
| Recognition | 1.226 | 0.942-1.595 | 1.131 | 0.865-1.477 | 1.130 | 0.864-1.478 | 1.149 | 0.876-1.507 |

The odds ratio of developing cognitive function decrease in the lowest free testosterone quartile group relative to the rest was analyzed by logistic regression analysis. Low cognitive function was defined as the lowest quartile in each cognitive domain or less than 24 points in MMSE-KC.

$^{*}p<0.05$

Model 1 was adjusted for age group.

Model 2 was adjusted for age group and education duration.

Model 3 was adjusted for age group, education duration, alcohol consumption, smoking, depression and SPPB.

OR, odds ratio; CI, confidence interval; MMSE-KC, Mini-Mental Status Examination in the Korean version of the CERAD Assessment Packet; TMT, Trail Making Test; FAB, Frontal Assessment Battery; DS, Digit Span; SPPB, Short Physical Performance Battery.

**Table 3. Odds ratio of low serum free testosterone level for low cognitive function in elderly women**

| | Univariate analysis | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| MMSE-KC | **1.677*** | **1.294-2.173** | **1.658*** | **1.272-2.162** | **1.391*** | **1.056-1.832** | **1.362*** | **1.030-1.801** |
| TMT | **1.706*** | **1.311-2.221** | **1.682*** | **1.279-2.211** | **1.393*** | **1.049-1.851** | **1.338*** | **1.002-1.787** |
| DS | **1.387*** | **1.074-1.791** | **1.360*** | **1.049-1.764** | 1.123 | 0.857-1.472 | 1.084 | 0.824-1.425 |
| FAB | **1.722*** | **1.336-2.221** | **1.698*** | **1.311-2.200** | **1.431*** | **1.093-1.873** | **1.390*** | **1.059-1.825** |
| Word List | | | | | | | | |
| Memory | **1.764*** | **1.361-2.285** | **1.743*** | **1.335-2.277** | **1.556*** | **1.185-2.043** | **1.518*** | **1.153-1.999** |
| Recall | **1.472*** | **1.142-1.896** | **1.453*** | **1.117-1.889** | **1.328*** | **1.017-1.734** | 1.295 | 0.989-1.695 |
| Recognition | 1.233 | 0.963-1.580 | 1.205 | 0.939-1.548 | 1.150 | 0.893-1.480 | 1.126 | 0.873-1.453 |

The odds ratio of developing cognitive function decrease in the lowest free testosterone quartile group relative to the rest was analyzed by logistic regression analysis. Low cognitive function was defined as the lowest quartile in each cognitive domain or less than 24 points in MMSE-KC.

*$p<0.05$

Model 1 was adjusted for age group.

Model 2 was adjusted for age group and education duration.

Model 3 was adjusted for age group, education duration, alcohol consumption, smoking, depression and SPPB.

OR, odds ratio; CI, confidence interval; MMSE-KC, Mini-Mental Status Examination in the Korean version of the CERAD Assessment Packet; TMT, Trail Making Test; FAB, Frontal Assessment Battery; DS, Digit Span; SPPB, Short Physical Performance Battery.

### *3. Association between FT quartile and the risk of low cognitive function*

In men, the analysis based on four categories revealed no significant FT level dependent association and no significant trend to cognitive function after adjusting for all potential confounding factors (Figure. 2). Contrarily, in women, the odds ratios of G2 (OR, 1.654; 95% CI, 1.125-2.431), G3 (OR, 1.569; 95% CI, 1.072-2.296), and G4 (OR, 1.898; 95% CI, 1.311-2.750) increased significantly compared to the highest FT level quartile group (G1) in MMSE. And in Word List Memory, the odds ratio of G4 increased significantly (OR, 1.631; 95% CI, 1.148-2.319) compared to the G1 (Figure. 3). The trend between the lower FT and the higher odds ratio of cognitive decline was significant in MMSE (p-value for trend, 0.002), TMT (p-value for trend, 0.046), FAB (p-value for trend, 0.040), Word List Memory (p-value for trend, 0.012), and Word List Recall (p-value for trend, 0.038) (Figure. 3). However, this trend was not observed in elderly men.

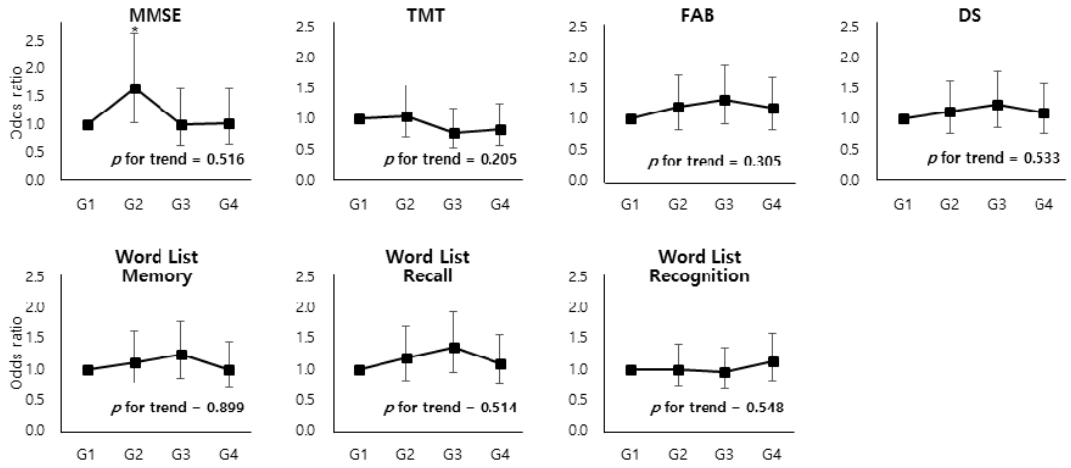


**Fig. 2. Odds ratio of each quartile of serum free testosterone level for decreased cognitive function in elderly men.**

The odds ratios of developing cognitive dysfunction in the respective quartile group relative to the 1st quartile group (G1) and p-value for trend were analyzed by logistic regression analysis. The quartile groups were numbered in descending order.

This model was adjusted for age group, education duration, alcohol consumption, smoking, depression and SPPB.

* p <0.05; Gn, nth quartile group of free testosterone level; MMSE, Mini-Mental Status Examination in the Korean version of the CERAD Assessment Packet; TMT, Trail Making Test; DS, Digit Span; FAB, Frontal Assessment Battery.

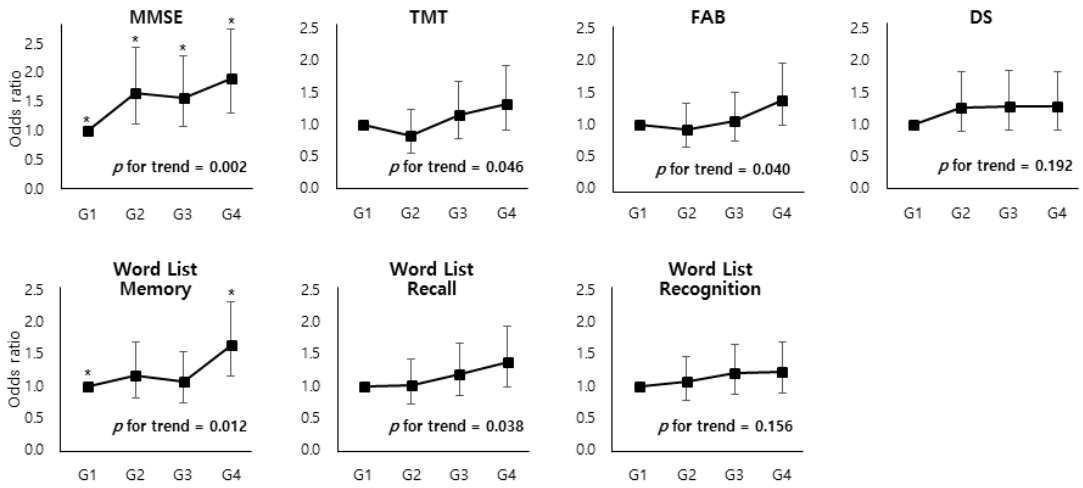


**Fig. 3. Odds ratio of each quartile of serum free testosterone level for decreased cognitive function in elderly women.**

The odds ratios of developing cognitive dysfunction in the respective quartile group relative to the 1st quartile group (G1) and p-value for trend were analyzed by logistic regression analysis. The quartile groups were numbered in descending order.

This model was adjusted for age group, education duration, alcohol consumption, smoking, depression and SPPB.

* p <0.05; Gn, nth quartile group of free testosterone level; MMSE, Mini-Mental Status Examination in the Korean version of the CERAD Assessment Packet; TMT, Trail Making Test; DS, Digit Span; FAB, Frontal Assessment Battery.

## DISCUSSION

I conducted the cross-sectional study of the association between levels of endogenous FT and cognitive function in Korean men and women aged 70-84. The results of the present study suggest sex differential associations of FT levels with cognitive function. In older men, there was no significant association between level of FT and cognitive function and there was no significant trend according to the FT quartiles either. This result is consistent with the findings of a previous study conducted by Zhao et al., which studied in Asian men and showed no association between cognition and testosterone[19]. On the other hand, many previous observational studies showed controversial results suggesting positive association[14, 17, 18, 56] and negative association[20, 21] in older men. In addition, previous interventional studies[57-59] and meta-analysis studies[60-62] have shown inconsistent results.

In older women, on the other hand, there were significant positive associations between FT levels and multi domains of cognitive function. Low FT level was associated with decreased cognitive function in the domains of global cognition, psychomotor speed, attention, executive function and verbal memory. And the association between FT quartiles and the risk of low cognitive function revealed significant FT level dependent association in global cognition (MMSE) and verbal memory (Word List Memory). In global cognition, the risk of impairment was significantly increased in high, low, and lowest FT quartiles compared to the highest FT quartile. In verbal memory, the risk of impairment was significantly increased in the lowest FT quartile compared to the highest FT quartile. Furthermore, significant trends showed not only in global cognition and verbal memory, but also in psychomotor speed (TMT), executive function (FAB), and delayed verbal memory (Word List Recall), suggesting that the lower the FT level, the greater the risk of cognitive decline. These associations and trends were particularly prominent in the global cognition, which revealed the strongest association with FT level among other domains. In previous studies on women,

cognitive function was associated with several domains such as verbal fluency[23], verbal learning and memory[22, 43], visuospatial ability[51, 52, 53], mathematical ability[15]. Considering the various results of previous studies, present study is considered to be consistent with them and represent comprehensively. However, as in men's studies, previous studies in women have not reached consensus.

Testosterone acts on the entire central nervous system via androgen receptors present in neurons[5, 6, 54]. Testosterone is known to have neuroprotective functions such as neuro-protective antioxidant, anti-apoptotic potential[7-9], and increase neuronal viability[55]. Roselli et al. reported the sex differences in neural responsiveness of the brain to androgen[66, 67]. In the same vein, findings of this study can be explained by sex specific influence on cognition. Apart from study of aforementioned studies, the regulation and expression of androgen receptors in both sexes' neural tissue demonstrated dose-response relationship with testosterone in a study by Lu et al.[68]. Considering the significant difference in serum FT levels between men and women (9.42±3.37 pg/mL vs. 0.91±0.89 pg/mL, respectively; $p<0.001$), I could hypothesize that there is a dose response relationship between testosterone and cognitive function, and neuroprotective function of the FT in the brain decreases when the level of FT is very low.

In previous studies, various methods of measuring testosterone have been used. This might be a potential reason for the discrepancies among the previous studies. Many of them have measured TT[22, 23] instead of FT. FT is bioactive form of testosterone and is considered to be the clinically important marker[31]. In elderly men, for example, FT level drops sharply due to increased sex hormone-binding globulin, but TT does not[69]. Furthermore, in some other studies, salivary hormonal samples[15, 70] or genetically predicted testosterone level[19] were used instead of measuring serum testosterone. This also could account for the inconsistent results of previous studies. Given the very low levels of FT in women and elderly men, it is important to maintain consistency of measurement methods. This is why serum FT was

measured in this study.

The results of present study were obtained by adjusting various variables that affect cognitive function, such as age, duration of education, alcohol consumption, smoking, depression and SPPB. Variables adjusted for previous studies varied in a wide range and it seemed lacking consensus on confounding factors on cognitive function. In this study, I tried to include various factors that influence cognitive function. Present study is valuable as the first study to adjust SPPB as a confounding factor to investigate the association between FT and cognitive function. Poor physical function linked to cognitive impairment in older individuals[27-29, 46-50]. Therefore, SPPB, a typical indicator of the elderly's physical function, was selected as a variable[39, 40]. None of the previous studies of the testosterone and cognition considered the effect of physical performance on cognitive function. Some studies adjusted body mass index (BMI) as a confounder[16, 21, 41], the relationship between BMI and cognitive function is unclear[42-45], however.

The major strength of this study is that it is the first study to analyze nationwide multicenter large-scale Asian cohort study to investigate the association between testosterone and cognitive function. Also, this study has the advantage of making various efforts to overcome the limitations of previous studies. I measured serum FT and investigated the association with multi domains of cognition. Additionally, a substantial range of covariates affecting cognitive function, including SPPB, were analyzed.

***Study Limitations***

Several limitations of my study deserve mention. Its cross-sectional design did not allow evidence of any cause–effect relationship between FT and cognitive function. I plan to conduct a follow-up longitudinal study in the near future. Since this study included only Asian older people, there may be limitations in its application to other ethnic groups.

## CONCLUSIONS

FT levels and global cognition, psychomotor speed, executive function and verbal memory had significant association in elderly women. And significant trends also existed, suggesting that the lower the FT level, the greater the risk of cognitive function decrease. On the other hand, in elderly men, there was no association between FT and cognition. Presumably, there is a dose response relationship between FT and multi domains of cognition. Future longitudinal and interventional studies are needed to confirm the present findings.

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## 노인에서 혈중 유리 테스토스테론과 인지기능 간의 연관성

**목적** 한국 노인들의 유리 테스토스테론 혈중 농도와 인지 기능의 연관성을 조사하고자 하였다.

**방법** 본 연구는한국 노인 노쇠 코호트 자료를 이용한 단면적 연구로 총 2851명의 환자가 포함되었다. 연구 대상자들의 유리 테스토스테론 혈중 농도를 측정하고 인지기능을 평가하였다. 인지기능은 신경심리평가 (Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet; CERAD-K)와 전두엽 기능검사 (Frontal Assessment Battery)를 사용하여 평가하였다. 유리 테스토스테론 혈중 농도와 인지 기능의 연관성을 조사하기 위해 단변량 및 다변량 로지스틱 회귀 분석을 시행하였다.

**결과** 여성에서 전반적 인지기능 (OR, 1.362; 95% CI, 1.030-1.801, p-value for trend, 0.002), 정신운동 속도(OR, 1.338; 95% CI, 1.002-1.787, p-value for trend, 0.046), 집행기능(OR, 1.390; 95% CI, 1.059-1.825, p-value for trend, 0.040), 언어적 기억력(OR, 1.518; 95% CI, 1.153-1.999, p-value for trend, 0.012) 영역에서 유리 테스토스테론 농도와 유의한 연관성이 있었다. 반면에 남성에서는 이러한 연관성이 관찰되지 않았다.

**결론** 유리 테스토스테론 혈중 농도와 인지기능 사이에는 용량 반응 관계가 있다고 생각된다. 보다 확실한 결론을 위해서는 향후 추가적인 연구가 필요하다.