Doctoral Dissertation

Testosterone supplementation effect on cognition in men

- A systematic meta-analysis -

Department of Medicine

Graduate School of Keimyung University

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1. Introduction

In resource-rich countries, the health of aging people has become a clinical issue in recent decades. Aging is an important risk factor for cognitive impairment which can lead to dementia (1), whose incidence during old age is associated with poor quality of life and mortality (2). As quality of life is important for continuing health during old age, preventing or improving cognitive impairment in this age group is vital.

Several studies have been conducted on the relationship between cognition and androgens. Old age is characterized by an increase in cognitive decline (3) and a gradual decrease in testosterone levels (4). Androgens are established promoters of neuron viability during neural development (5), and testosterone can modulate neuronal damage caused by oxidative stress (6) and reverse myelin damage in chronic demyelinated brain lesions (7). Moreover, there is evidence that the loss of testosterone in older men is associated with cognitive decline (8,9).

However, the results of randomized control trials and reviews on this issue are inconsistent (10-13). To clarify whether the loss of testosterone in older men is associated with cognitive decline, we conducted a systematic review of randomized control trials.

2. Materials and Methods

2.1. Data sources and keywords

A systematic literature survey was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (14). The PubMed, the Cochrane Library, and Embase databases were used to search for studies between December 2019 and March 2021. The search terms used were testosterone, androgen, hormone replacement therapy, cognitive function, and their synonyms.

2.2. Inclusion and exclusion criteria

The trials selected for this study met the following inclusion criteria: (1) study design: randomized controlled trials, including published or unpublished studies; (2) language: English; (3) in vivo studies; (4) participants: adult males (> 18 years) including healthy individuals and those comprising a clinical sample; (5) interventions: testosterone or testosterone analogs, regardless of the method of administration; (6) control: placebo; and (7) outcomes: global cognitive ability and any specific domains of cognition, including memory, attention, language, verbal fluency, visuospatial ability, and executive ability, which were measured using neuropsychological tests or other objective measurements. Patients without available data were excluded.

2.3. Study identification and data extraction

The literature search, study identification, and data extraction were performed between December 2019 and March 2021. In the cases of discrepancies, the disagreements were resolved through discussion with a third reviewer. Data were extracted by one reviewer using the prepared form and checked for accuracy by another reviewer. The extracted information from the eligible studies included the participants' characteristics, sample sizes, study designs, methodological information with regard the study quality, experimental and control interventions, durations, frequencies, and outcomes. Since, there are various types of outcomes for measuring cognitive function, we restricted these outcomes to 11 categories: cognitive speed, verbal memory functions (immediate), visual memory function (immediate), working memory, memory function (delayed), executive function, perception, cognitive inhibition, visual attention, auditory attention, and cognitive score. In addition, better execution time is demonstrated by a lower score. Therefore, we converted the data to a negative score to pool with other scores. All the selected trials were analyzed and classified using the Jadad score, when possible. Studies with a Jadad score ≥ 3 were graded as being of high quality.

2.4. Data analysis

The Review Manager software V.5.3, provided by the Cochrane Collaboration, was used for the statistical analysis, and statistical significance was defined as a two-sided p value of < 0.05. The pooled effect was calculated using the fixed-effect model if the data were available and no significant heterogeneity was detected.

Otherwise, a random-effects model was applied. We used the standardized mean difference (SMD) and its 95% confidence interval (CI) to measure the effect size of testosterone supplementation on cognitive function. Statistical heterogeneity among the included studies was assessed using a $\chi 2$ test and a Higgins I2 value, with I2 > 75% suggesting high statistical heterogeneity (15). Publication bias was assessed using funnel plots.

3. Results

3.1. Identification of studies included for analysis

After the removal of duplicates, we identified 4536 records and after screening the abstracts, there were 64 studies left in the review. Sixteen studies had no original data, and 11, seven, nine and five studies were excluded because they were observational studies, not randomized studies, using other treatment and studies among women, respectively. A total of 16 studies were included in the final meta-analysis (16-31). The study selection process is illustrated in Figure 1.

3.2. Characteristics of observational studies reviewed

The sample sizes of the selected studies varied from 11 to 493. Two studies had a sample size of > 100 (20,28). One study presented separate results for healthy men and men with Alzheimer's disease (26) and another study included separate results for older and younger males. The mean age of most of the studies was over 61 years, with only two studies including young participants (27,31). The characteristics of the included studies are listed in Table 1. Eleven of the 16 studies had a Jadad score ≥3 and were graded as high quality (Table 2).

3.3. Cognitive speed, verbal memory function (immediate), visual memory function (immediate)

Cognitive speed refers to the ability to process information quickly. Six studies provided results on cognitive speed. Computerized Simple Reaction Time, Trail Making Test Part A, and Digit Symbol Substitution outcomes were included as indicators of cognitive speed. There were no statistically significant differences after the pooled analysis (n = 392, SMD = -0.04, 95% CI -0.24 to 0.15, $p \geq 0.05$). Immediate verbal memory function refers to the memory of words and other abstractions involving language in short term. Ten studies were included for immediate verbal memory function. The verbal memory test, Buschke Selective Remining Test, Paragraph Recall test, Rey Auditory Verbal Learning Test, and Story Recall test were included as indicators of immediate verbal memory function. There were no statistically significant differences after the pooled analysis (n = 1044, SMD = 0.05, 95% CI -0.07 to 0.18, $p \geq 0.05$). Immediate visual memory function refers to our ability to preserve some characteristics of our senses that are related to visual experience in the short term. Eight studies were included for immediate visual memory function. Benton visual retention, visual spatial learning test, route test, visual reproduction test, Rey-Osterrieth Complex Figure Test, and Complex Figure Test were included as indicators of immediate visual memory function. There were no statistically significant differences after the pooled analysis (n =7 87, SMD =-0.01, 95% CI -0.15 to 0.13, $p \geq 0.05$; Figure 2).

3.4. Working memory function, memory function (delayed), executive function

Working memory refers to the ability to hold information temporarily in memory while performing other mental tasks on the information. Four studies were included

for working memory function. The digit span backward test, letter-number sequencing test, self-ordered pointing test, and subject-ordered pointing test were included as indicators of working memory function. There were no statistically significant differences after the pooled analysis (n = 125, SMD = -0.02, 95% CI -0.38 to 0.34, $p \geq 0.05$). Ten studies were included for delayed memory function. The Rey Auditory Verbal Learning Test - delayed recall trial, delayed Paragraph Recall, California Verbal Learning Test-long delay score, delayed visual spatial learning test, and delayed story recall test were included as indicators of delayed memory function. There were no statistically significant differences after the pooled analysis (n = 1081, SMD = -0.02, 95% CI -0.14 to 0.10, $p \geq 0.05$). Executive function refers to a set of cognitive processes and mental skills that help an individual plan, monitor, and successfully execute goals. There were 14 studies on executive function. Trail Making Test Part B, Complex Design Construction, Grooved Pegboard, Block Design Subtest, Visual-Motor Integration, Verbal fluency, and Controlled Oral Word Association Test were included as indicators of for executive function. There was a statistically significant difference after the pooled analysis (n = 1170, SMD = 0.01, 95% CI -0.10 to 0.13, $p \geq 0.05$; Figure 3).

3.5. Perception, cognitive inhibition, visual attention, cognitive status scores

Perception means organizing, identifying, and interpreting sensory information to represent and understand the presented information or environment. Three studies were included for perception. The Mental Rotation and Shepard Mental Rotation tests and the Figure Discrimination test were included as indicators of perception.

There were no statistically significant differences after the pooled analysis (n = 288, SMD = -0.11, 95% CI -0.34 to 0.12, $p \geq 0.05$). Cognitive inhibition refers to the blocking or modulation of information not relevant to the task or focus at hand. Two studies were included in the analysis of cognitive inhibition. The Stroop Test and Stroop Interference Test were used as indicators of cognitive inhibition. There were no statistically significant differences after the pooled analysis (n = 117, SMD = -0.13, 95% CI -0.49 to 0.23, $p \geq 0.05$). Visual attention refers to a set of cognitive tasks that select relevant information and filter out irrelevant information in a complex visual scene. Five studies focused on visual attention. Benton judgment of line orientation, judgment of line orientation test, and card rotation test were included as indicators of visual attention. There were no statistically significant differences after the pooled analysis (n = 840, SMD = -0.02, 95% CI -0.16 to 0.11, $p \geq 0.05$). There were four studies on cognitive scores. The Dementia Rating Scale, Folstein Mini Mental Status Examination, Mini Mental Status Examination, Global cognitive function, and Alzheimer's Disease Assessment Scale-Cognitive Subscale were used to assess the cognitive scores. There were no statistically significant differences after the pooled analysis (n = 595, SMD = -0.02, 95% CI -0.18 to 0.14, $p \geq 0.05$; Figure 4).

3.6. Sensitivity analysis

In two studies, the participants were young, while those in other studies were older. A sensitivity analysis was conducted to elucidate the effects of age. However, no significant differences were observed in the sensitivity analysis. Ten studies researched low testosterone or cognitively abnormal individuals. However, in the separated analysis, there were no significant differences between normal and

abnormal persons. Supplementation was administered using various methods in the studies. Seven studies used intramuscular injection, eight studies used topical agents, while only one study used oral supplementation. However, there was no significant differences in the outcomes achieved between the different methods through with the supplements were administered.

3.7. Heterogeneity

Heterogeneity was assessed visually using forest plots. There was moderate heterogeneity in working memory function (I2 = 59%) and in the cognitive scores (I2 = 37%). The other analysis showed no heterogeneity in this study.

3.8. Publication bias

A funnel plot was used to qualitatively assess publication bias. The funnel plot shown in Figure 5 represents executive function. The plot is symmetrical, without obvious evidence of asymmetry; therefore, there is no evidence of publication bias.

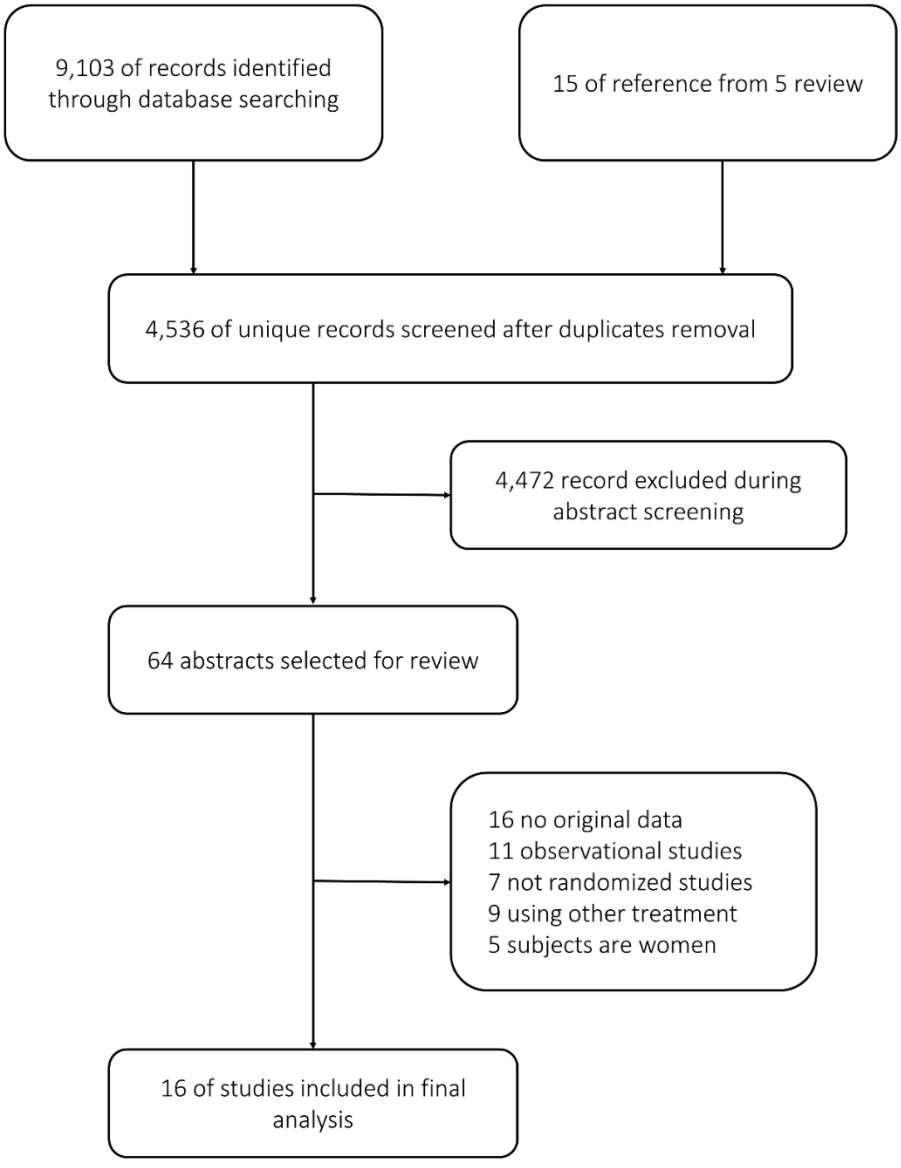

Figure 1. Flow chart summarizing identification of studies included for analysis.

Table 1A. Characteristics of Observational Studies Reviewed

Study identification	Country	Intervention	Subjects	Sample size	Mean age	Duration of follow up	Outcomes
Borst, 2014(16)	USA	Testosterone enanthate 125 mg/week, intramuscular injections	60 year or more, hypogonadal men	30	70 years	12 months	Trail making test, Benton Judgment of Line Orientation, Rey-Osterrieth Complex Figure Test, Draw from memory test
Cherrier, 2001(17)	USA	Testosterone enanthate 100 mg/week, intramuscular injections	Aged 50 to 80	25	68 years	6 weeks	Block Design, Story Recall, Route Test
Cherrier, 2005(18)	USA	Testosterone enanthate 100 mg/week, intramuscular injections	Aged 50 to 90	41	65 years	6 weeks	Route Test, Story Recall, Verbal fluency, Stroop Test, Self-Ordered Pointing Test
Cherrier, 2015(19)	USA	Testosterone gel 50 to 100 mg/day, topical	Aged 60 to 90, mild cognitive impairment	19	70 years	6 months	Rey Auditory Verbal Learning Test, Story Recall, Visual Spatial Learning Test, Letter-Number Sequencing, Computerized Simple Reaction Time, Route Test, Complex Design Construction, Verbal Fluency, Mental Rotation
Emmelot-Vonk, 2008(20)	Netherlands	Testosterone undecenoate, 160 mg/day, oral	Aged 60 to 80, testosterone level lower than 13.7 nmol/L	223	67 years	6 months	Benton Judgment of Line Orientation, Digit symbol substitution, Shepard Mental Rotation, Rey auditory verbal learning test, Trail Making Test
Huang, 2016(21)	USA	7.5 g/day of 1% testosterone gel, topical	Aged 60 or older, low-to-normal testosterone level	76	67 years	36 months	Complex Figure Test, Paragraph recall test, Buschke Selective Reminding Test, Verbal fluency test, Visual Spatial Learning Test, Stroop Interference Test, Trail Making Test
Janowsky, 1994(22)	USA	testosterone scrotal patch (Place & Nichols, 1991; Alza, Palo Alto, CA) 15 mg/day	Aged 60 to 75	56	67 years	3 months	Delayed Recall test, Visual Reproduction II test, Grooved Pegboard test, Trail Making Test, Block Design Test
Janowsky, 2000(23)	USA	Testosterone enanthate 150 mg/week, intramuscular injections	Aged 61 to 75	19	67 years	1 month	Stimuli and procedures for the working memory task
Kenny, 2002(24)	USA	Nonscrotal testosterone patch 5 mg/day	Aged 61 to 75, bioavailable testosterone levels below 128 ng/dl	44	75 years	12 months	Digit Span, Digit Symbol, Trail Making Test
Kenny, 2004(25)	USA	Testosterone enanthate 200 mg for every 3week, intramuscular injections	Early cognitive decline and bioavailable testosterone level below 128 ng/dl	11	80 years	12 weeks	Dementia Rating Scale score, Folstein MMSE score, Digit Span, Verbal Fluency, Clock Face Drawing, Clock Face Perception, Trail Making Test
Lu, 2006a(26)*	USA	Testosterone gel (Laboratoires Besins-Iscovesco, Paris, France) 75 mg/day, topical	Male patients with mild Alzheimer disease	18	69 years	24 weeks	Alzheimer's Disease Assessment Scale- Cognitive Subscale, California Verbal Learning Test, Block Design Subtest, Judgment of Line Orientation, Developmental Test of Visual Motor Integration
Lu, 2006b(26)*	USA	Testosterone gel (Laboratoires Besins-Iscovesco, Paris, France) 75 mg/day, topical	Healthy male volunteers	29	62 years	24 weeks	Alzheimer's Disease Assessment Scale- Cognitive Subscale, California Verbal Learning Test, Block Design Subtest, Judgment of Line Orientation, Developmental Test of Visual Motor Integration

Table 1B. Characteristics of Observational Studies Reviewed (continued)

Study identification	Country	Intervention	Subjects	Sample size	Mean age	Duration of follow up	Outcomes
O'Connor, 2001(27)	UK	Testosterone enanthate 200 mg/week, intramuscular injections	Healthy male volunteers	30	28 years	8 weeks	Block design test, Grooved Pegboard Test, Trail making test, Controlled Oral Word Association Test, Rey Auditory Verbal Learning Test
Resnick, 2017(28)	USA	Testosterone gel in a pump bottle (AndroGel, AbbVie), dose was adjusted.	65 years or older with low testosterone levels	493	72 years	12 months	Delayed paragraph recall, Benton Visual Retention Test, Card Rotation Test, Trail Making Test, Global cognitive function, Immediate paragraph recall
Vaughan, 2007(29)	USA	Testosterone enanthate 200 mg/week, intramuscular injections	Aged 60 or older, baseline testosterone below 350 ng/dL and no evidence of cognitive impairment	47	70 years	36 months	Benton Visual Retention test, Judgment of Line Orientation test, Digit Span, Trail Making Test, Selective Reminding test, Selective Reminding test
Wahjoepramono, 2016(30)	Indonesia	Testosterone cream 50 mg (AndroForte 5%) daily, topical	Aged 50 or older, presenting with subjective memory complaints	44	61 years	24 weeks (without crossover)	Mini Mental State Examination, Rey Auditory Verbal Learning Test
Young, 2010a(31)**	USA	Testosterone gel (Auxilium Pharmaceutical, Inc., Malvern, PA) 75 mg/day, GnRH agonist was added	Aged 60 to 80, healthy male	30	68 years	6 weeks	Trail Making Test, Subject-ordered Pointing, Verbal Fluency, Paragraph Recall, Mental Rotation, Figure Discrimination
Young, 2010b(31)**	USA	Testosterone gel (Auxilium Pharmaceutical, Inc., Malvern, PA) 100 mg/day, GnRH agonist was added	Aged 25 to 35, healthy male	16	29 years	6 weeks	Trail Making Test, Subject-ordered Pointing, Verbal Fluency, Paragraph Recall, Mental Rotation, Figure Discrimination

MMSE: Mini-Mental State Examination; UK: United Kingdom; USA: United States of America

*Lu et al.(26) presented a separate group of patients with mild AD and healthy controls, and the reference is thus represented with two different studies in the table.

**Young et al.(31) presented separated group on older and younger male and the reference is thus represented with two different studies in the table.

Table 2. Quality of Literature Included in The Meta-analysis (Jadad score)

Study identification	Randomization (2 points)	Double blinding (2 points)	Withdraw and dropout (1 point)	Total score (5 points)
Borst, 2014(16)	1	0	0	1
Cherrier, 2001(17)	1	1	1	3
Cherrier, 2005(18)	1	1	1	3
Cherrier, 2015(19)	1	2	1	4
Emmelot-Vonk, 2008(20)	2	2	1	5
Huang, 2016(21)	1	1	1	3
Janowsky, 1994(22)	1	1	0	2
Janowsky, 2000(23)	1	1	1	3
Kenny, 2002(24)	1	0	1	2
Kenny, 2004(25)	1	1	1	3
Lu, 2006(26)	1	1	1	3
O'Connor, 2001(27)	1	0	0	1
Resnick, 2017(28)	2	2	1	5
Vaughan, 2007(29)	2	0	1	3
Wahjoepramono, 2016(30)	1	1	1	3
Young, 2010(31)	1	1	0	2

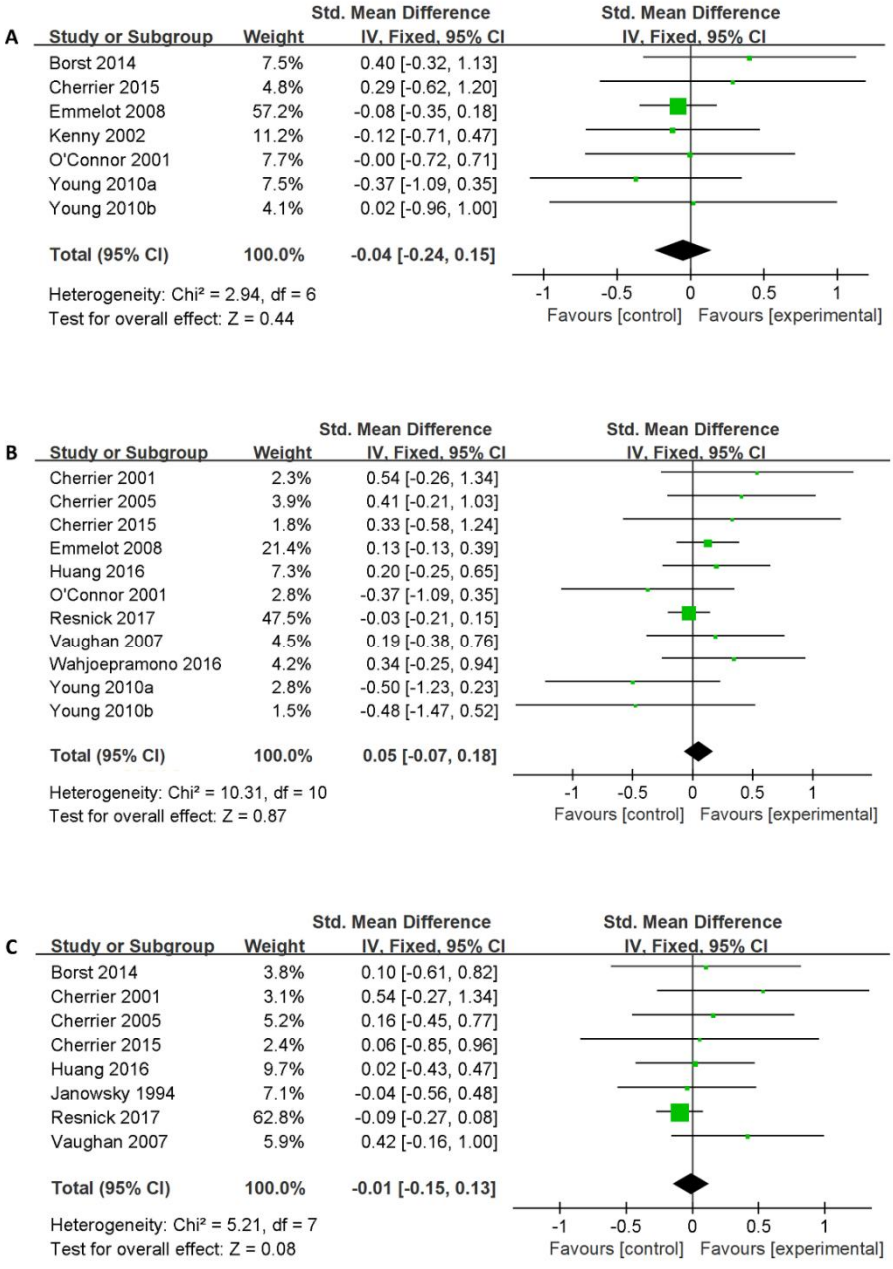

Figure 2. Forest plot for testosterone supplementation effect on cognitive speed(A), verbal memory function (immediate)(B), visual memory function (immediate)(C).

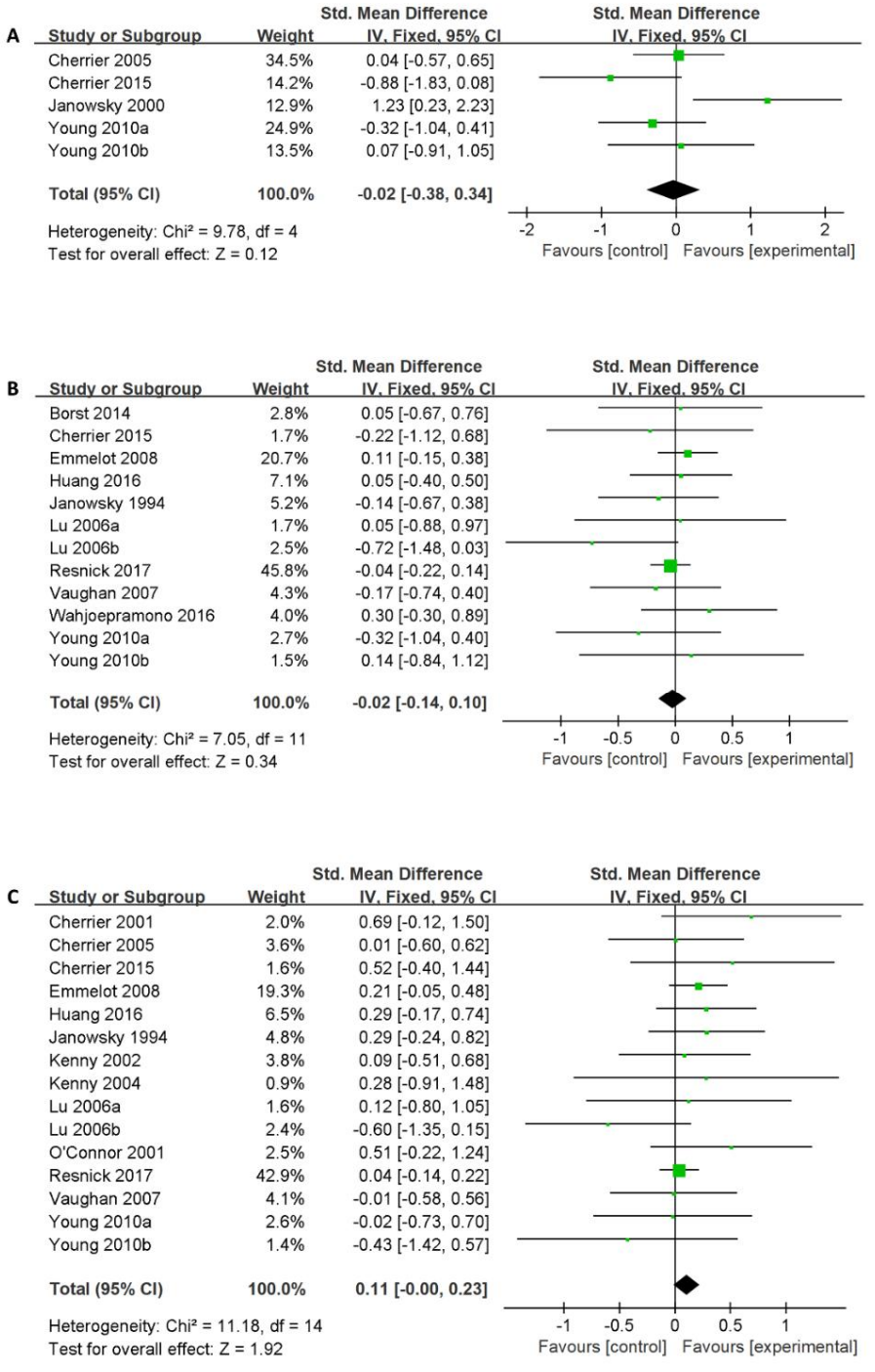

Figure 3. Forest plot for testosterone supplementation effect on working memory function(A), memory function (delayed)(B), executive function(C).

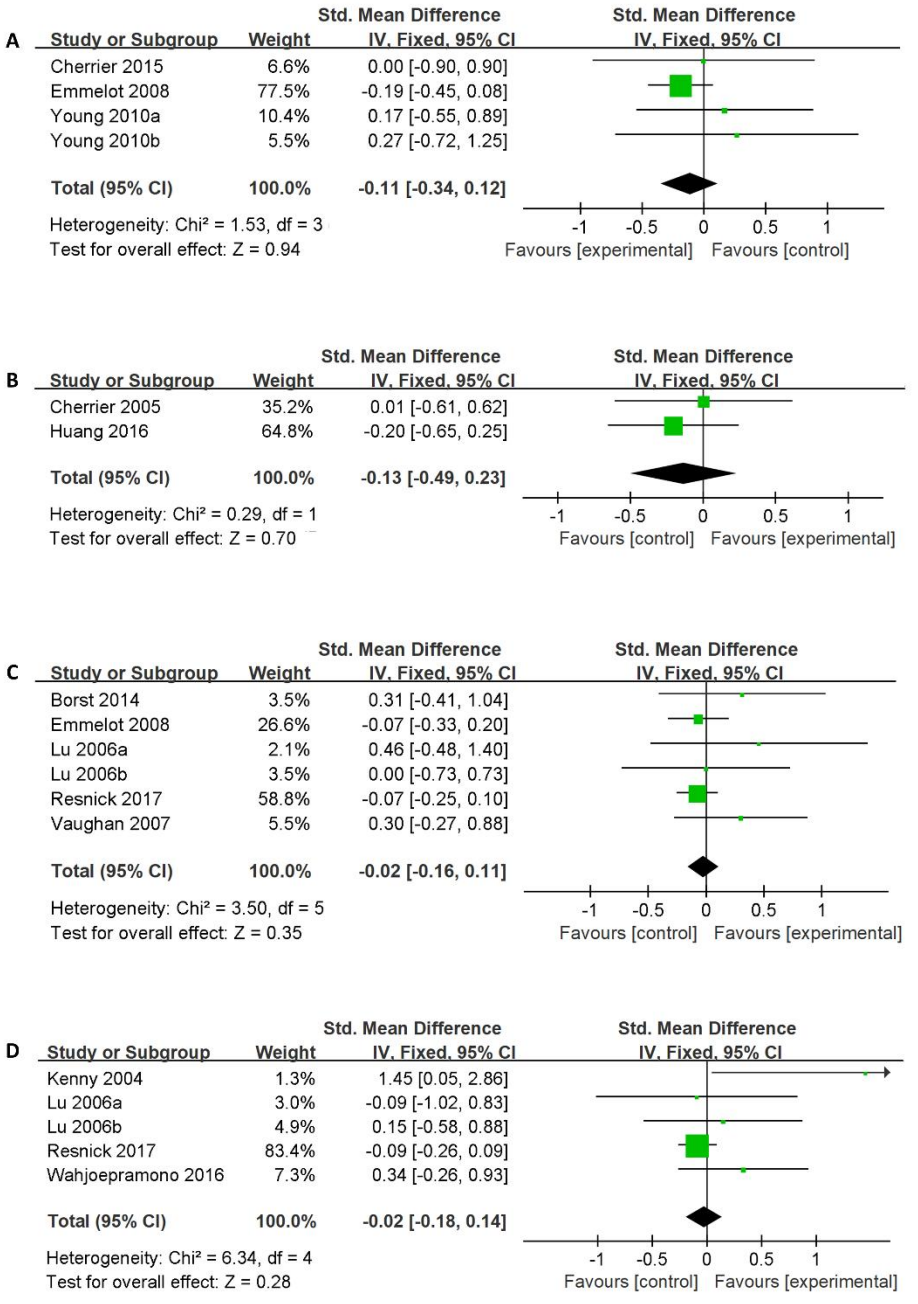

Figure 4. Forest plot for testosterone supplementation effect on perception(A), cognitive inhibition(B), visual attention(C), cognitive status scores(D).

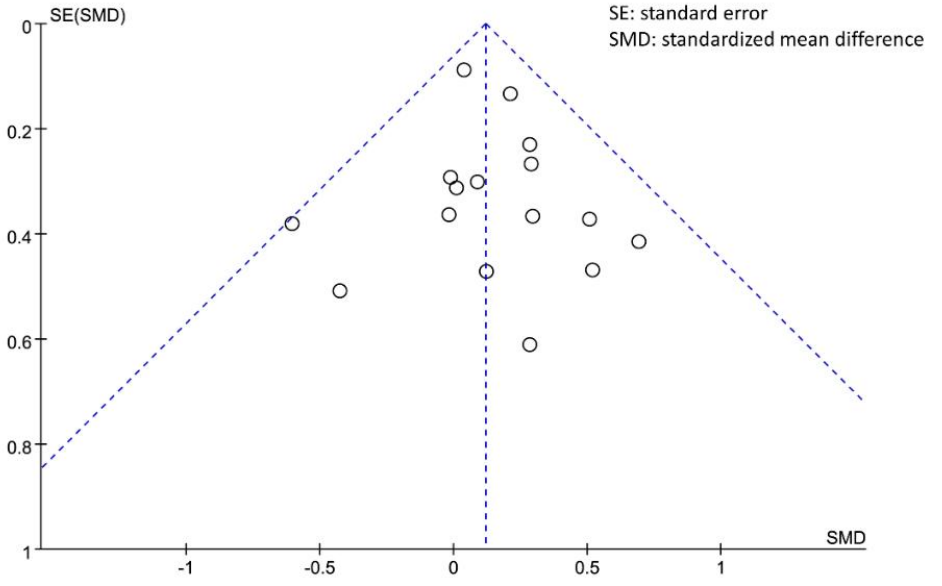

Figure 5. Funnel plot of publication bias analysis in executive function.

4. Discussion

This study aimed at determining whether testosterone was effective in improving cognitive function. Some studies have indicated that testosterone benefits cognitive function by modulating the neuronal damage caused by oxidative stress, stimulating the formation of new myelin, and reversing the myelin damage in chronic demyelinated brain lesions (6,7). However, other review studies have suggested that there may be little effect on cognition (10,13,32,33). Nevertheless, the evidence in these reviews is insufficient and it is also possible that no neuroprotective function was observed because the testosterone levels did not reach working concentrations *in vivo*.

While there were many outcomes related to cognitive functions in the selected studies, there were no common outcomes. Therefore, we classified the results into the following categories: cognitive speed, immediate verbal memory function, immediate visual memory function, working memory function, delayed memory function, executive function, perception, cognitive inhibition, visual attention, and cognitive status score. There was moderate heterogeneity in working memory function ($I^2 = 59\%$) and little heterogeneity in the cognitive status score ($I^2 = 37\%$), while the other categories of cognition showed no heterogeneity.

There were some limitations to our study. Only two studies had a sample sizes of > 100. Therefore, the effect size was not firm, and the deviations of each study were large. We included all the studies with male participants without any limitations; this may have led to a bias in the outcome. However, in the sensitivity analysis, we did not observe any effect of age or condition on each participant. In addition, there were few studies on long-term administration. There were only two small sized studies

with 36 months of follow-up. Therefore, it is possible that there was not enough time to evaluate the neuroprotective function of testosterone.

The strength of our study was that the numerous outcomes were subdivided and each outcome was calculated separately to minimize the bias. However, this may have resulted in a smaller sample size for each category. Moreover, the inclusion of more studies in the future may be unlikely to produce meaningful results. Compared to previous systematic reviews, the results of our study were different. According to Tan et al. the use of testosterone supplements improved executive function unlike the findings of our study(13). In addition, there were differences in the method of classification of the cognitive function domains. We classified the domains according to Lezak et al. (34) and there were also differences in the number of polled studies. Moreover, we found some handling errors in using the “lower is better” score in other reviews. However, this did not change the small effect size.

In conclusion, the findings of this study provided no evidence that androgens improved the cognitive function. Furthermore, we found limitations in other reviews that suggested that androgens could improve cognitive function. Summarizing the studies to date, the use of androgens for the purpose of preventing cognitive decline is not recommended.

5. Summary

Using a systematic meta-analysis, we determined whether androgen supplementation improves cognitive function. A systematic literature survey was conducted according to the PRISMA guidelines. The PubMed, the Cochrane Library, and Embase databases were searched. The literature search, study identification, and data extraction were performed between December 2019 and March 2021. There were no statistically significant differences in cognitive speed, immediate verbal memory function, immediate visual memory function, working memory function, delayed memory function, executive function, perception, cognitive inhibition, and cognitive status scores. The findings of this study indicated that supplementation with testosterone did not improve cognitive function in adult men. Therefore, using testosterone to improve cognitive function is not recommended. Further studies are needed to confirm the long-term effects of testosterone administration.

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Effect of Testosterone Supplementation on Cognition in Men

- A Systematic Meta-analysis -

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(Abstract)

Cognitive function in older individuals is an important issue in aging societies. There is evidence that testosterone and cognitive function are correlated; however, the clinical conclusions remain controversial. Therefore, using a systematic meta-analysis, we aimed to investigate whether androgen supplementation improves cognitive function.

A systematic literature survey was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. The PubMed, the Cochrane Library, and Embase databases were searched. The literature search, study identification, and data extraction were performed between December 2019 and March 2021.

A total of 16 studies were included in the meta-analysis. The sample sizes of the selected studies varied from 11 to 493. There were no statistically significant differences in cognitive speed, immediate verbal memory function, immediate visual memory

function, working memory function, delayed memory function, executive function, perception, cognitive inhibition, and cognitive status scores.

The findings of this study indicated that supplementation with testosterone did not improve cognitive function in adult men. Therefore, using testosterone to improve cognitive function is not recommended.

테스토스테론의 투여가 남성의 인지기능에 미치는 영향

– 메타분석 –

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(초록)

노년층에서의 인지 기능은 고령화 사회에서 매우 중요한 주제이다. 인지기능과 테스토스테론의 상관관계에 대해서는 이미 알려져 있으나 임상적인 효용성에 대해서는 아직 정립되어 있지 않다. 이에 본 연구에서는 체계적인 메타 분석을 이용하여 테스토스테론의 투여가 인기지능을 향상시키는 지 여부에 대해 확인하고자 한다.

체계적인 문헌조사는 체계적 고찰 및 메타분석의 가이드라인에 따라 수행하였다. 문헌 검색, 연구 식별 및 데이터 추출은 2019년 12월에서 2021년 3월 사이에 수행되었으며 PubMed, Cochrane Library 및 Embase의 데이터베이스를 이용하였다.

총 16개의 연구가 메타분석에 포함되었다. 인지 속도, 언어 기억 능력, 시각 기억 능력, 작업 기억 능력, 지연 기억 능력, 실행 기능, 지각, 인지 억제 및 인지 상태 점수 분야에서 통계학적인 유의성은 없었다.

이 연구에서는 테스토르테론의 투여가 남성의 인지기능을 개선한다는 통계학적인 근거는 없었다. 따라서 남성에서 인지기능 개선을 목적으로 테스토르테론을 사용하는 것은 권장하지 않는다.

□ Life History

Born in Ulsan, in 1980

BA from Keimyung University, Department of Medicine

MA in Medicine from the Graduate School of Keimyung University

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Clinical Instruction at Keimyung University Dongsan Hospital (present)

□ Papers & Books

The Relationship between History of Weight Change and Fatty Liver in Overweight or Obese Korean Adult Male, MA thesis, the Graduate School of Keimyung University. December 2010

The Risk Factors of Sexual Behaviour Among Middle School Students in South Korea, International Journal of Sexual Health. February 2018

Manifestations of Sasang Typology according to Common Chronic Diseases in Koreans, Evidence-Based Complementary and Alternative Medicine. 2018, Article ID 7378608

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