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Effect of Testosterone Supplementation on Cognition in Elderly Men: A Systematic Meta-Analysis

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Background: Cognitive function is an important issue in aging societies. Testosterone levels and cognitive function are known to be correlated; however, the clinical conclusions remain controversial. This study aimed to investigate whether testosterone supplementation improve cognitive function in adult men through a systematic meta-analysis.

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

Results: A total of 15 studies were included in the meta-analysis. The sample sizes of the selected studies varied from 11 to 493. There were no significant differences in cognitive speed (standardized mean difference [SMD]=−0.05; 95% confidence interval [CI], −0.26 to 0.16), immediate verbal memory function (SMD=0.07; 95% CI, −0.05 to 0.20), immediate visual memory function (SMD=−0.01; 95% CI, −0.15 to 0.13), working memory function (SMD=−0.04; 95% CI, −0.42 to 0.35), delayed memory function (SMD=−0.02; 95% CI, −0.14 to 0.10), executive function (SMD=0.03; 95% CI, −0.08 to 0.15), perception (SMD=−0.13; 95% CI, −0.37 to 0.11), cognitive inhibition (SMD=−0.13; 95% CI, −0.49 to 0.23), visual attention (SMD=−0.02; 95% CI, −0.16 to 0.11), and cognitive status scores (SMD=−0.02; 95% CI, −0.18 to 0.14).

Conclusion: The findings of this study indicate that there is a lack of evidence that testosterone administration has an effect on preventing cognitive decline. Therefore, testosterone use to prevent cognitive decline may not be recommended.

Key Words: Aging, Cognition, Hormone replacement therapy, Testosterone

INTRODUCTION

In resource-rich countries, the health of aging people has become a clinical issue in recent decades. Among the medical issues related to the elderly, one of the most important problem in quality of life is cognitive function. And it is aging that is a risk factor for cognitive impairment which can lead to dementia [1]. The incidence of mild cognitive impairment is reported by ranged 1.7 to 22.6% in older adults [2]. Preventing cognitive function decline is a very important medical task to maintain quality of life in old age. When cognitive function declines in the elderly, the radius of daily life narrows, and social activities are also reduced. In addition, the patient could be exposed to risks of various accidents, and dependency increases, making it difficult to live alone and increasing the possibility of developing dementia [3-5].

One of the candidates for preventing cognitive decline is an androgen. Several studies have reported the relationship

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between androgens and cognitive function. Testosterone can increase neuronal resilience and also can reduce beta-amyloid accumulation in Alzheimer's disease [6]. And testosterone can modulate neuronal damage caused by oxidative stress [7], reverse myelin damage in chronic demyelinated brain lesions [8] and delay neuronal apotosis [9]. Moreover, there is evidence that the loss of testosterone in older men is associated with cognitive decline [10].

However, the results of interventional studies and reviews on this issue are inconsistent [11-13]. Some meta-reviews unified cognitive function domains by random selection without subdividing them, and some reviews did not consider negative scores in variable calculation, which was at risk of error. So, we conducted a meta-analysis by subdividing the domain and accurately establishing a scoring system.

MATERIALS AND METHODS

1. Sources of data & keywords

This literature review was conducted by 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. Inclusion & exclusion criteria

The literature selected for this study satisfied the following criteria: (1) study design: randomized controlled trials; (2) language: English; (3) in vivo studies; (4) participants: adult males (≥60 years) including healthy individuals and those belonging to a clinical sample; (5) interventions: testosterone or testosterone analogs, regardless of the method of administration; (6) control: placebo; and (7) outcomes: cognitive function and any domains of cognition.

3. Study identification & data extraction

The information from the selected studies included participant characteristics, study designs, sample sizes, methodological information, interventions, durations, frequencies, and outcomes. Since there are various types of outcomes for measuring cognitive function, we restricted these outcomes to 11 categories suggested by Lezak et al. [15]: verbal memory functions (immediate), cognitive speed, auditory attention, visual memory function (immediate), memory function (delayed), working memory, executive function, cognitive inhibition, perception, visual 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 scored using the Jadad score. A Jadad score of 3 or higher was assumed to be a high-quality study.

4. Analysis of data

The Review Manager V.5.3, provided by the Cochrane Collaboration, was used for the systematic analysis. 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 was assessed using a Higgins I^2 value and a χ^2 test, with $I^2 > 75\%$ suggesting high heterogeneity [16]. Publication bias was assessed using funnel plots.

5. Clinical Research Ethics

This study was not reviewed by the Institutional Review Board because it is a study that examines the existing literature and does not use personal information.

RESULTS

1. Identification of studies included for analysis

After the removal of duplicates, we identified 4536 studies; after screening the abstracts, there were 64 studies for a detailed review. Forty-nine studies were excluded due to following reasons; they had no original data (n=16), were observational studies (n=11), not randomized studies (n=7), using other treatment (n=9), studies among women (n=5), and a study among young age (n=1). A total of 15 studies were included in the final meta-analysis [17-31]. The study selection process is illustrated in Figure 1.

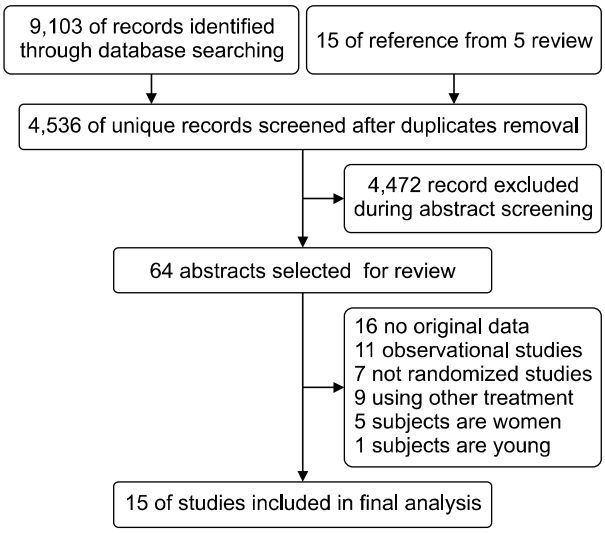

Figure 1. Flow chart summarizing identification of studies included for analysis.

2. Characteristics of the included studies

The sample sizes of the selected studies varied from 11 to 493. Two studies had a sample size of >100. One study presented separate results for healthy men and men with Alzheimer's disease [27] and another study included separate results for older and younger males [30]. The mean age of participants in all of the studies was over 61 years. The characteristics of the included studies are listed in Table 1. Eleven of the 15 studies had a Jadad score ≥3 and were graded as high quality (Table 2).

3. Effects on cognitive speed, immediate verbal memory function, and immediate visual memory function

Cognitive speed refers to the ability to process information quickly. Five studies provided results on effect of testosterone 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 significant differences between experimental and control groups after the pooled analysis (SMD=−0.05; 95% CI, −0.26 to 0.16; P=0.63). Immediate verbal memory function refers to the memory of words and other abstractions involving language in the short term. Nine 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 significant differences after the pooled analysis (SMD=0.07; 95% CI, −0.05 to 0.20; P=0.24). Immediate visual memory function refers to the 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 significant differences after the pooled analysis (SMD=−0.01; 95% CI, −0.15 to 0.13; P=0.93) (Figure 2).

4. Effects on working memory function, delayed memory function, and 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 significant differences between experimental and control groups after the pooled analysis (SMD=−0.04; 95% CI, −0.42 to 0.35; P=0.85). 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 significant differences after the pooled analysis (SMD=−0.02; 95% CI, −0.14 to 0.10; P=0.70). Executive function refers to a set of cognitive processes and mental skills that help an individual plan, monitor, and successfully execute goals. There were 13 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

Table 1. Characteristics of the included studies

Study Identification	Country	Intervention	Subjects	Sample size	Mean age	Duration of follow up	Outcomes
Borst, 2014 [17]	USA	Testosterone enanthate 125 mg/week, intramuscular injections	60-year-old, 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 [20]	USA	Testosterone enanthate 100 mg/week, intramuscular injections	Age 50 to 80 years	25	68 years	6 weeks	Block Design, Story Recall, Route Test
Cherrier, 2005 [19]	USA	Testosterone enanthate 100 mg/week, intramuscular injections	Age 50 to 90 years	41	65 years	6 weeks	Route Test, Story Recall, Verbal fluency, Stroop Test, Self-Ordered Pointing Test
Cherrier, 2015 [18]	USA	Testosterone gel 50 to 100 mg/day, topical	Age 60 to 90 years, 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 [21]	Netherlands	Testosterone undecenoate, 160 mg/day, oral	Age 60 to 80 years, 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 [22]	USA	7.5 g/day of 1% testosterone gel, topical	60-year-old, 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 [24]	USA	testosterone Scrotal Patch (Place & Nichols, 1991; Alza, Palo Alto, CA) 15 mg/day	Age 60 to 75 years	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	Age 61 to 75 years	19	67 years	1 month	Stimuli and procedures for the working memory task
Kenny, 2002 [25]	USA	Nonscrotal testosterone patch 5 mg/day	Age 61 to 75 years, bioavailable testosterone levels below 128 ng/dL	44	75 years	12 months	Digit Span, Digit Symbol, Trail Making Test
Kenny, 2004 [26]	USA	Testosterone enanthate 200 mg every 3 weeks, 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 [27]*	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

Table 1. Continued

Study Identification	Country	Intervention	Subjects	Sample size	Mean age	Duration of follow up	Outcomes
Lu, 2006b [27]*	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
Resnick, 2017 [28]	USA	Testosterone gel in a pump bottle (AndroGel, AbbVie), dose was adjusted	65-year-old, 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	60-year-old, 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	50-year-old, presenting with subjective memory complaints	44	61 years	24 weeks (without crossover)	Mini-Mental State Examination, Rey Auditory Verbal Learning Test
Young, 2010 [31]	USA	Testosterone gel (Auxilium Pharmaceutical, Inc., Malvern, PA) 75 mg/day, GnRH agonist was added	Age 60 to 80 years, healthy male	30	68 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. [27] presented separated group on mild Alzheimer's disease and healthy controls 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 [17]	1	0	0	1
Cherrier, 2001 [20]	1	1	1	3
Cherrier, 2005 [19]	1	1	1	3
Cherrier, 2015 [18]	1	2	1	4
Emmelot-Vonk, 2008 [21]	2	2	1	5
Huang, 2016 [22]	1	1	1	3
Janowsky, 1994 [24]	1	1	0	2
Janowsky, 2000 [23]	1	1	1	3
Kenny, 2002 [25]	1	0	1	2
Kenny, 2004 [26]	1	1	1	3
Lu, 2006 [27]	1	1	1	3
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

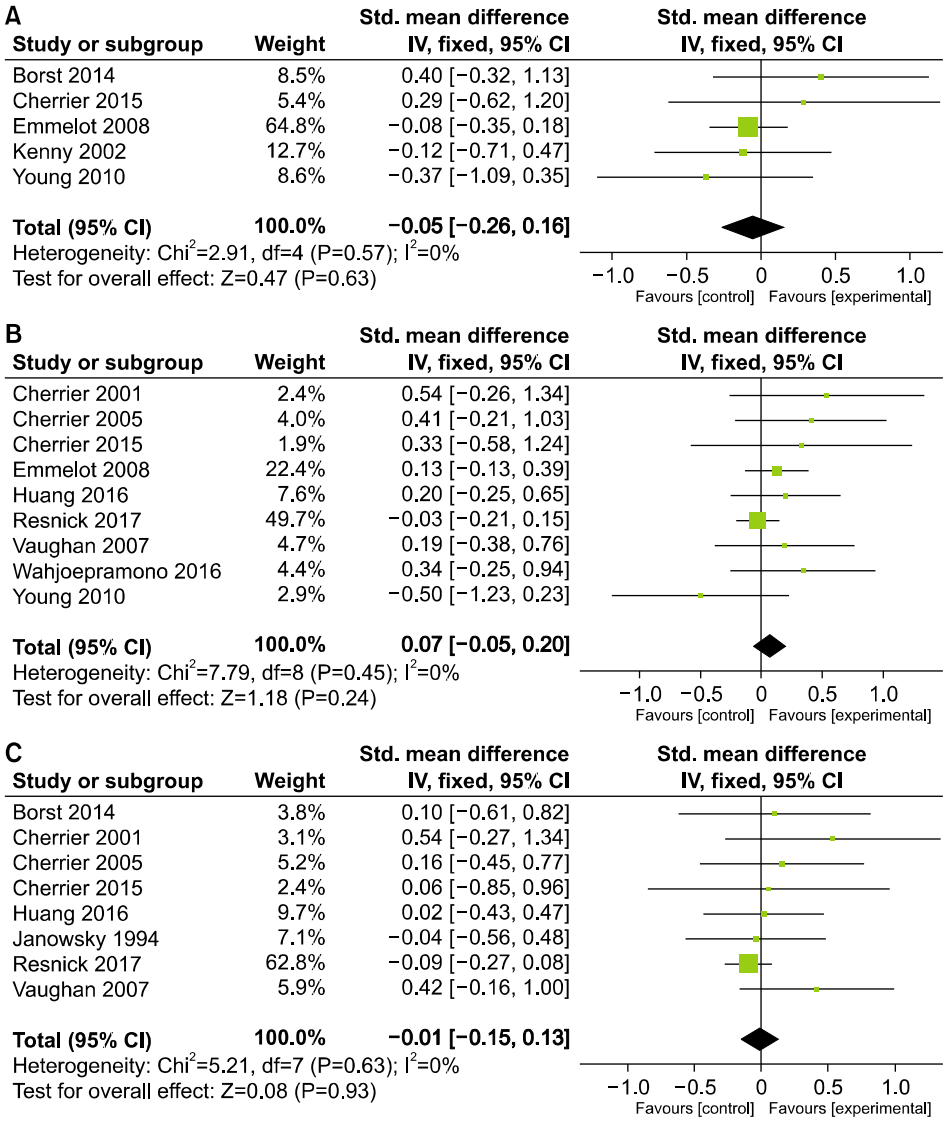

Figure 2. Forest plot for testosterone supplementation effect on (A) cognitive speed, (B, C) immediate verbal, visual function.

executive function. There was a significant difference after the pooled analysis (SMD=0.03, 95% CI −0.08 to 0.15, P=0.59) (Figure 3).

5. Effects on perception, cognitive inhibition, visual attention, and 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 significant differences after the pooled analysis (SMD=−0.13; 95% CI, −0.37 to 0.11; P=0.27). 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 significant differences after the pooled analysis (SMD=−0.13; 95% CI, −0.49 to 0.23; P=0.49). Visual attention refers to a set of cognitive tasks that are aimed at selecting relevant information and filtering 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 significant differences after the pooled

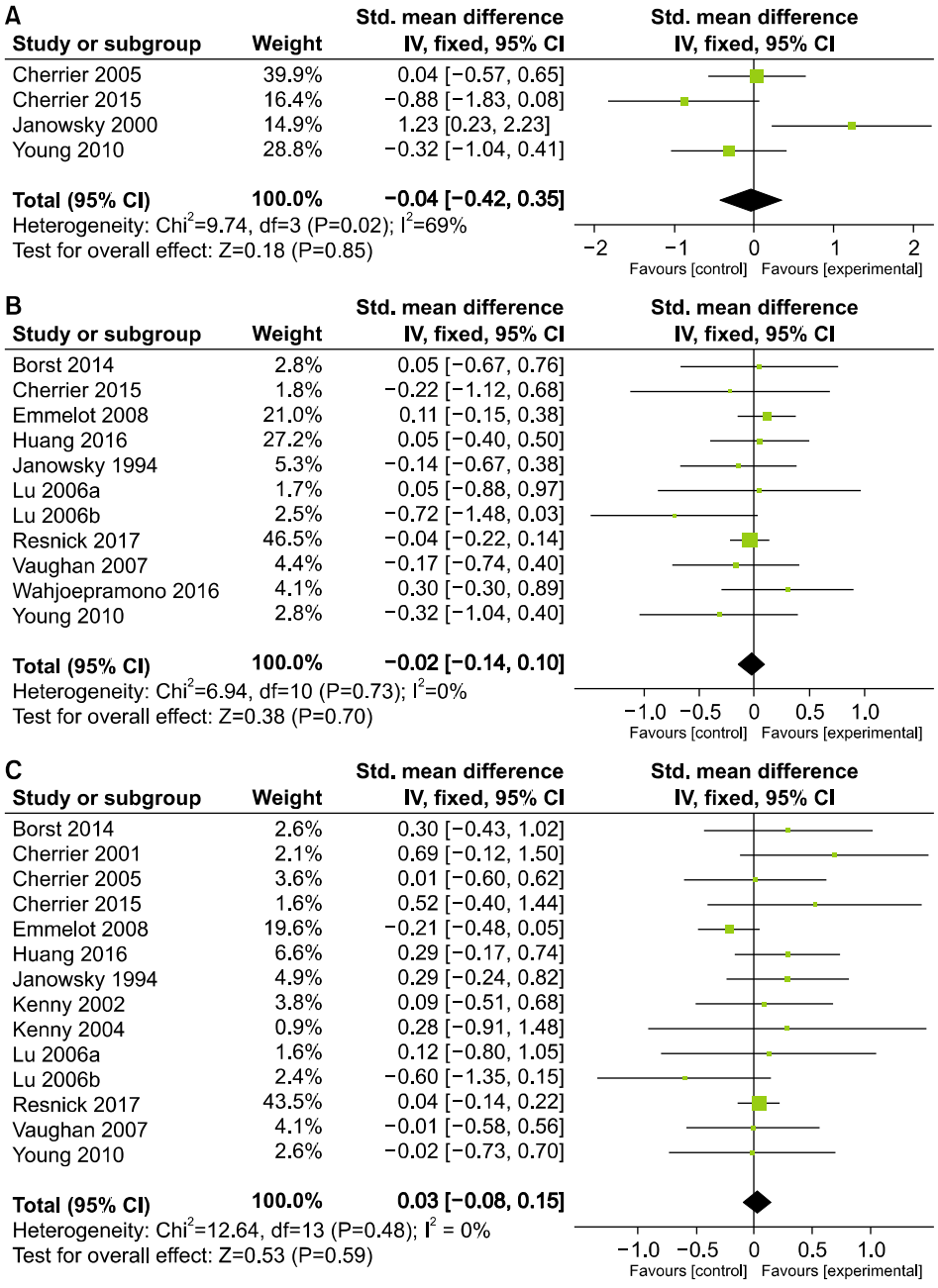

Figure 3. Forest plot for testosterone supplementation effect on (A) working memory function, (B) memory delay, (C) executive function.

analysis (SMD=−0.02; 95% CI, −0.16 to 0.11; P=0.73). 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 significant differences after the pooled analysis (SMD=−0.02; 95% CI, −0.18 to 0.14; P=0.78) (Figure 4).

6. Sensitivity analysis

Ten studies researched individuals with low testosterone or cognitive abnormality. However, in the separated analysis, there were no significant differences between normal group and morbid group. Supplementation of testosterone was administered via various routes in the studies. Seven studies used intramuscular injections, eight studies used topical agents, while only one study used oral supplementation. However, there were no significant differences in the outcomes achieved between the different routes of supplement administration.

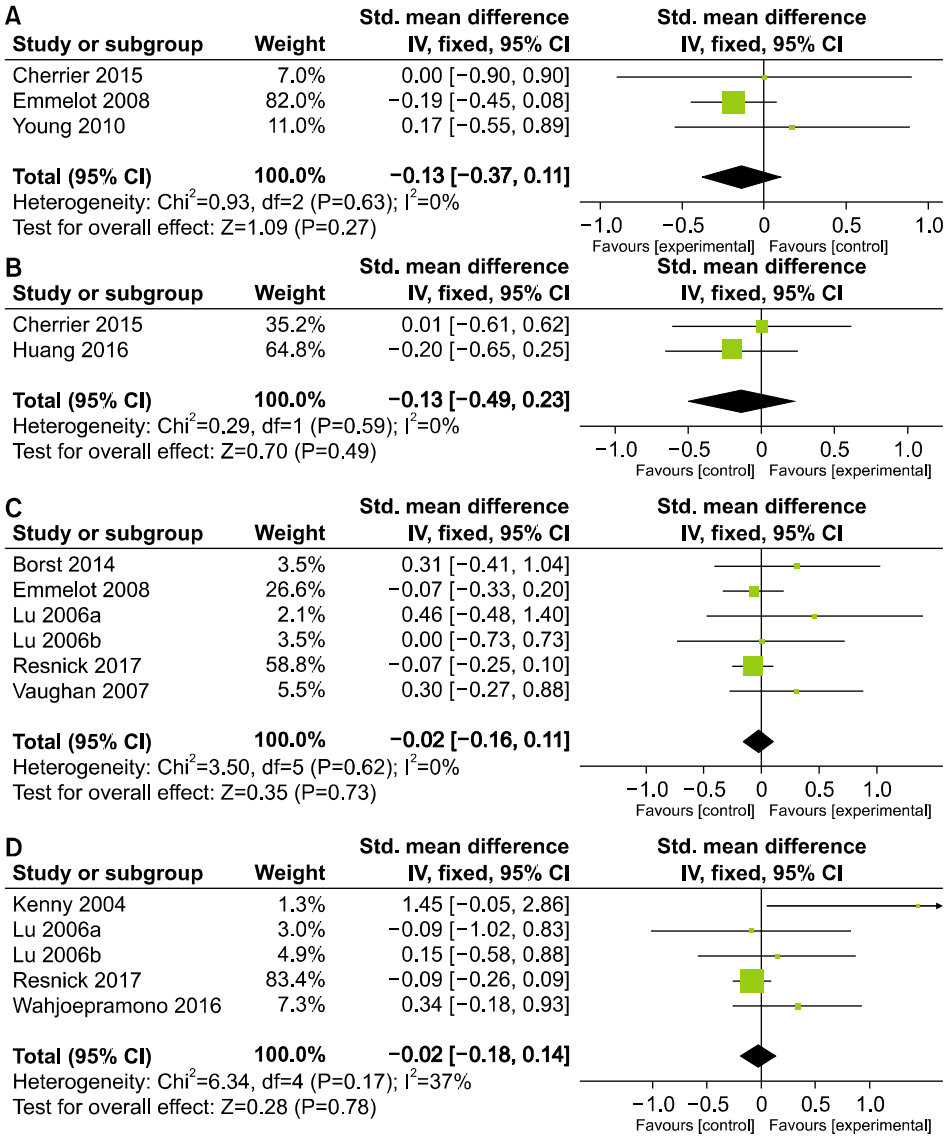

Figure 4. Forest plot for testosterone supplementation effect on (A) perception, (B) cognitive inhibition, (C) visual attention, (D) cognitive status score.

7. Heterogeneity

Heterogeneity was assessed visually using forest plots. There was moderate heterogeneity in working memory function (I^2=69%) and in the cognitive scores (I^2=37%). There was no heterogeneity in other variables.

8. Publication bias

Funnel plots were used to qualitatively assess publication bias. Figure 5 represents the funnel plot for executive function. The plot is symmetrical, without obvious evidence of asymmetry; therefore, there is no evidence of publication bias.

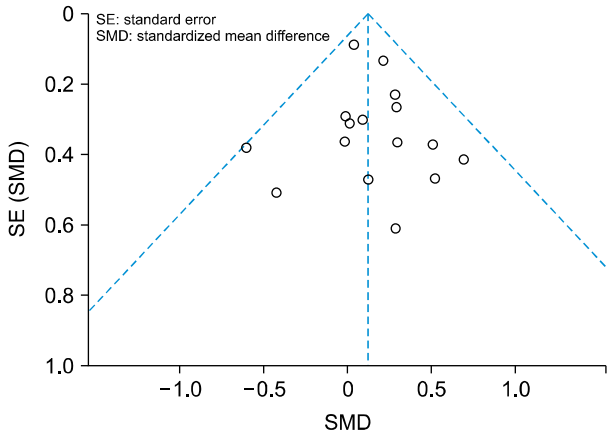

Figure 5. Funnel plot of publication bias analysis in executive function.

DISCUSSION

This study aimed to determine whether testosterone was effective in improving cognitive function. Previous laboratory 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 [7,8]. However, several reviews have suggested that the effect on cognition may be little [11,13,32,33]. Nevertheless, the evidence in these reviews is insufficient to draw a conclusion.

In our study, administration of testosterone did not improve any cognitive domain. Although the potential of testosterone to improve cognitive function has been confirmed by several laboratory studies, our meta-analysis of intervention studies has not shown any significant improvement in cognition. Some reviews said that there was an improvement in cognitive function in a specific domain, but this is the result of an error made in the process of combining the scores [13]. Based on the evidence so far, administration of testosterone has not significantly increased cognitive function, so administration of testosterone for the purpose of cognitive improvement is not recommended yet.

Our study had some limitations. Only two studies had sample sizes of >100. Therefore, the effect size was not firm, and the deviations of each study were large. However, in the sensitivity analysis, we did not observe any effect of condition on each participant. In addition, there were few studies on long-term supplement use; there were only two studies with 36-month follow up with small sample size. Therefore, it is possible that the time to evaluate the neuroprotective function of testosterone was insufficient. To solve this issue, large-scale, long-term interventional study is needed.

In conclusion, the findings of this study provided no evidence suggesting that androgens improved the cognitive function. Summarizing the studies to date, the use of androgens for the purpose of cognitive improvement is not recommended.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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