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EFFICACY OF TESTOSTERONE SUPPLEMENATION ON COGNITIVE FUNCTION: A META-ANALYSIS

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ABSTRACT

Previous randomized controlled trials (RCTs) have reported inconsistent findings regarding the efficacy of testosterone supplementation on cognitive function. We performed a meta-analysis of RCTs to investigate the efficacy of testosterone supplementation on cognitive function. We searched PubMed, EMBASE, Cochrane Library, and relevant bibliographies in August 2015, using common keywords related to testosterone supplementation and cognition. Out of 245 articles retrieved from databases, a total of 10 RCTs, which involved 554 participants (277 intervention and 277 placebo groups), were included in the final analysis. A fixed-effect meta-analysis of all 10 RCTs revealed that testosterone supplementation had no efficacy on cognitive functions such as spatial memory (standardized mean difference [SMD], -0.06, 95% confidence interval [CI], -0.24, 0.12), verbal memory (SMD, -0.07; 95% CI, -0.25, 0.11), visual memory (SMD, -0.08; 95% CI, -0.27, 0.12), working memory (SMD, -0.18; 95% CI, -0.44, 0.07), verbal ability (SMD, -0.16; 95% CI, -0.59, 0.27), cognitive processing speed (SMD, -0.06; 95% CI, -0.26, 0.14), and executive functioning (SMD, -0.04; 95% CI, -0.22, 0.15). Similarly, subgroup meta-analyses by testosterone levels of study participants showed that there was no significant difference in cognitive function between the two groups. The current meta-analysis of RCTs found that there is no sufficient clinical evidence to support the use of testosterone supplementation for the improvement on cognitive function.

INTRODUCTION

Aging in males is associated with a progressive decline in serum testosterone levels [1]. Also, it has been recognized that age-related decline in serum testosterone levels is associated with a progressive decline in cognitive abilities [2]. Additionally, low bioavailable testosterone levels are reported to be associated with a higher risk of cognitive disorders including Alzheimer's disease and mild cognitive impairment [3,4].

A review of observational studies published in 2011 indicated that there was a positive association between testosterone levels and cognitive function such as

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global cognition, memory, executive function, and spatial performance [5].

Results from cell culture and animal studies provide evidence that testosterone supplementation could have protective effects on brain function [5]. However, randomized controlled trials have reported inconsistent findings regarding the efficacy of testosterone supplementation on cognitive function. Several RCTs investigating the effects of testosterone supplementation in the elderly men reported beneficial effects on cognition [6-9, 11, 13].

In contrast, other studies found no evidence for its beneficial effects on cognition in healthy older men and older men with low-normal gonadal, hypogonadal status, or mild cognitive loss [10, 12, 14, 15]. Regarding the conflicting evidence on this topic, we investigated the efficacy of testosterone supplements on cognitive function such as spatial memory, verbal memory, visual memory, working memory, verbal ability, cognitive processing speed, and executive functioning by using a meta-analysis of RCTs. Additionally, subgroup meta-analyses were performed by testosterone levels of participants.

METHODS

Literature search

We searched PubMed, EMBASE, and the Cochrane Library in Aug 2015, using common keywords related to testosterone or androgen and cognitive function. The keywords were as follows: 'testosterone' or 'androgen' and 'cognitive function', 'cognitive decline', 'dementia', or 'Alzheimer's disease' and 'randomized controlled trials'. The bibliographies of relevant articles were also searched to locate additional studies. The main outcome measure were changes in scores (or time to be taken in tasks or procedures) for each cognitive function measurement.

Study Selection and data Acquisition

We included RCTs that met all of the following criteria: reported the efficacy of testosterone supplements for cognitive function and compared an intervention group with a placebo group; followed study participants for at least 1 month. From the studies selected for the final analysis, we retrieved the study name (with first author and year of publication), country, study design, study participants (number, mean age, and underlying conditions), duration of supplementation, contents of intervention and control, domains of cognitive function, and outcomes in each group.

Selection of relevant studies

Based on the pre-determined selection criteria, two of the authors independently selected all trials retrieved from the databases and bibliographies. Disagreements between evaluators were resolved by discussion.

Assessment of Methodological Quality

The methodological quality of the finally included trials was assessed based on the Jadad scale [16], which is the most widely used assessment tool. Its score ranges from zero (very poor) to five-point (rigorous). The 5-point quality scale consists of points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, additional 1 point), double-blind (described as double-blind, 1 point; use masking such as identical placebo, additional 1 point), and follow-up (state the numbers and reasons for withdrawal in each group; 1 point) in the report of each trial.

Main and subgroup analyses

The main analysis examined the efficacy of testosterone supplements on main domains of cognitive functions such as spatial memory, verbal memory, visual memory, working memory, verbal ability, cognitive processing speed, and executive functioning. Subgroup meta-analyses were also performed by testosterone levels of study participants (hypogonal or eugonadal).

Statistical Analysis

We investigated the efficacy of testosterone supplementation on cognitive function before and after supplementation compared with the placebo group. Because not all RCTs used the same measurement tools or scales for the assessment of cognitive function, we used standardized mean difference (SMD) as the main effect size to calculate the differences in each cognitive function between the supplementation and control groups. Before calculating SMD in the two groups, changes (mean ± standard deviation) in cognitive function in each group before and after intervention were calculated. SMD is a difference in means between the two groups divided by a pooled standard deviation (SD). SMD was calculated as follows:

$$SMD = (M_1 - M_2)/\text{a pooled SD}$$

Where M_1 is a mean of change in cognitive function of the testosterone supplementation group before and after intervention, M_2 is a mean of change in cognitive function of the placebo group before and after intervention, and a pooled SD is a pooled intervention specific standard deviation.

For the other cognitive functions excluding cognitive processing speed and executive functioning, if an SMD indicates a significant negative value (i.e., a 95 % confidence interval does not include zero), it means that the supplementation group has a more improvement

in cognitive function than the placebo group. In order to estimate heterogeneity across studies, we used Higgins I^2, which measures the percentage of total variation across studies. Negative values of I^2 are set at zero; I^2 ranges between 0 % (no observed heterogeneity) and 100 % (maximal heterogeneity). An I^2 value greater than 50 % is considered as having substantial heterogeneity [17]. The SMD with 95 % confidence intervals (CI) was calculated on the basis of either the fixed- or random-effects models. When substantial heterogeneity was not observed, the SMD calculated based on the fixed-effects model was reported. When substantial heterogeneity was observed, the SMD based on the random-effects model was reported. Stata SE version 12.1 software package (StataCorp, College Station, TX, USA) was used for statistical analysis.

RESULTS

Study selection

As shown in Figure 1, a total of 245 articles were identified after searching three databases, i.e. PubMed, EMBASE, and the Cochrane Library and hand-searching relevant bibliographies. After excluding 75 duplicated articles and 101 articles that did not satisfy the selection criteria, two authors of this study reviewed the full texts of 47 articles. Among those, 37 articles were excluded for the following reasons: supplements not relevant to this study subject (n = 15), not fulfilling inclusion criteria (n = 4), results not relevant to study (n = 2), letter or comment (n = 2), insufficient data (n = 14). A total of 10 trials (6-15) were included in the final analysis**.**

General characteristics of the included trials

The finally included 10 trials included a total of 554 participants with 277 intervention and 277 control groups, respectively. The mean age of the study participants ranged from 11.9 to 70.8. Table 1 shows the general characteristics of the included trials. The year of publication of the included trials ranged between 1994 and 2015. The countries where the studies were conducted were as follows: US (n = 8), UK (n = 1), and Netherlands (n = 1). The intervention periods ranged from 6 weeks to 36 months. The number of study participants ranged from 11 to 223 across trials.

Among the 10 trials, four were prevention trials in healthy elderly men and one for eugonadal young men, and the rest six RCTs were therapeutic ones for patients with Alzhemer's disease (AD), mild cognitive impairment (MCI), or in hypogonadal old men and Turner syndrome girls. Testosterone preparations used in each trial were as follows: testosterone Enanthate (100mg/week intramuscular [IM], 200mg/2weeks IM, 200mg/3weeks IM, or 80mg twice/day oral), testosterone scrotal patches (15mg/day), testosterone transdermal patches (5mg/day), testosterone gel (75mg/day, 50-100mg/day). The main domains of cognitive function were as follows: spatial memory, verbal memory, visual memory, working memory, verbal ability, cognitive processing speed (Trail Making Test A), and executive functioning (Trail Making Test B).

Methodological Quality

Table 2 shows the methodological quality of studies included in the final meta-analysis. Overall quality of the included studies was high: the quality scores ranged from 3 to 5. Four RCTs received a score of 5, four RCTs received a score of 4, and the remaining two RCTs received a score of 3.

Main analysis

Out of ten RCTs, six reported a significant improvement in several parts of cognitive domains in the testosterone supplementation group (6-9,11,13). The remaining four RCTs showed no significant effect (10,12, 14,15).

In the fixed-effect meta-analysis of all trials by domain of cognitive function such as spatial memory (standardized mean difference [SMD], -0.06, 95% confidence interval [CI], -0.24, 0.12), verbal memory (SMD, -0.07; 95% CI, -0.25, 0.11), visual memory (SMD, -0.08; 95% CI, -0.27, 0.12), working memory (SMD, -0.18; 95% CI, -0.44, 0.07), verbal ability (SMD, -0.16; 95% CI, -0.59, 0.27), cognitive processing speed (SMD, -0.06; 95% CI, -0.26, 0.14), and executive functioning (SMD, -0.04; 95% CI, -0.22, 0.15) (Figure 2).

Subgroup meta-analysis

As shown in Figures 3 and 4, there was no significant efficacy of testosterone supplementation on cognitive function in the subgroup meta-analysis by testosterone levels of study participants (eugonadal or hypogonadal).

Table 1. Characteristics of randomized controlled trials included in the final analysis (n = 10).

Source	Country	Study participants (age: years)	Duration	Intervention (dosage and route of administration) vs. control group	Main Outcomes		
					Domains of cognitive function	Mean±SD or Mean (SE) baseline/follow-up	
						Intervention group	Control group
1994 Janowsky et al.[6]	U.S.	56 Healthy older men (67.4, range 60-75)	3 months.	Testosterone scrotal patch (15mg/day, transdermal) vs. placebo	Spatial cognition (memory)	27.96±7.56/30.17±6.78	28.72±8.61/27.90±8.57
					Verbal memory (delayed recall)	9.19±2.47/10.85±2.70	9.21±3.14/11.21±2.23
					Visual memory (reproduction)	25.19±8.10/29.30±7.00	26.21±8.83/29.59±7.45
					Motor dexterity & speed	77.74±12.80/75.96±10.83	73.03±8.63/74.9±11.66
					Cognitive flexibility	79.7±29.97/72.11±19.17	87.86±32.99/78.83±26.71
2001 O'Connor et al.[7]	U.K.	29 Eugonadal young men (28.2, range 19-45)	8 weeks.	Testosterone Enanthate, intramuscular (100mg/week) vs. placebo	Visuospatial ability (memory)	39.62 (2.07)/39.71 (2.70)	40.40 (1.74)/44.07 (1.41)
					Verbal fluency (word)	39.5 (2.32)/47.57 (3.35)	36.40 (2.82)/41.67 (2.38)
					Verbal fluency (category)	20.29 (0.99)/20.79 (1.46)	21.87 (1.63)/22.00 (1.60)
					Cognitive flexibility	27.43 (2.54)/22.42 (1.89)	26.33 (1.45)/22.41 (1.37)
					Perceptual motor speed	57.79 (4.06)/45.71 (3.98)	58.33 (5.13)/49.93 (3.70)
					Motor dexterity & speed	45.64 (8.20)/59.00 (2.00)	58.60 (2.95)/58.13 (1.57)
					Verbal memory	52.64 (2.32)/56.43 (2.53)	56.33 (1.86)/59.47 (1.43)
2002 Kenny et al.[8]	U.S.	44 Older men (76±4, range 65-87)	1 year.	Testosterone patch (5mg/day, transdermal) vs. placebo	Working memory	11.4±2.6/11.5±2.5	11.8±1.8/12/4±1.9
					Digit symbol	42±8/46±9	43±8/47±7
					Cognitive flexibility (sec)	42±14/38±8	39±16/38±17
					Perceptual motor speed (sec)	104±39/87±29	95±30/90±38
2003 Ross et al.[9]	U.S.	51 Turner syndrome girls (range 10.0-14.9)	2 years.	Oxandrolone (0.06mg/kg/day, oral) vs. placebo	Working memory	-1.2±1.3/-0.3±1.4	-0.8±1.7/-1.0±1.5
					Spatial cognition	-2.82.4±/-2.6±2.9	-2.8±3.6/-2.8±3.1
					Executive function	0.5±1.3/0.9±1.5	0.5±1.2/1.0±1.3
					Verbal abilities	-0.1±1.6/-0.3±1.9	0.0±1.8/-0.3±1.7

2004 Kenny et al.[10]	U.S.	11 Hypogonadal older men with mild cognitive loss (80±5, range 73-87)	12 weeks	Testosterone Enanthate (200mg/3weeks, intramuscular) vs. placebo	Working memory		15.2±1.0/15.0±2.3	13.6±6.3/12.8±6.1
					Verbal abilities (fluency)		12.5±6.0/13.2±5.8	12.2±5.1/11.4±5.8
					Visuoconstruction & perception		3.8±0.4/3.8±0.4	3.0±1.7/3.6±0.5
					Executive function (divided attention)		222±63/221±92	250±58/225±75
2005 Cherrier et al.[11]	U.S.	38 Healthy older men (65±11, range 50-85)	6 weeks	Testosterone enanthate (100mg/week, intramuscular) vs. placebo	Spatial memory		42.1±14.8/50.0±12.1	37.3±12.9/43.0±12.4
					Verbal memory		42.4±7.4/48.1±13.4	46.7±10.6/48.4±12.2
					Verbal ability (fluency)		24.6±8.2/26.6±8.1	27.6±4.8/28.4±7.0
					Selective attention		52.0±18.3/47.5±14.7	52.1±23.9/47.5±16.3
					Working memory		12.5±3.7/12.45.9	12.1±5.7/11.3±11.3
2006 Lu et al.[12]	U.S.	14 Mild Alzheimer's disease and 22 healthy elderly men (mean age in each group: 61.2-70.3)	24 weeks.	Testosterone gel (75mg/day, applied to skin) vs. placebo	Alzheimer's disease group	Cognitive function	25±13.2/27.4±8.4	25.2±8.9/28.3±10.3
						Short term & verbal retention	2.3±2.7/1±2.4	1.3±1.4/0.9±1.7
						Constructional task	20±2.4/19.8±3.1	17±2.6/15.4±15.4
						Visual recognition & perception	19±7.6/20.3±7	18.1±9.9/16.5±8.7
						Visuospatial function	9.5±6.1/10.8±8	10.1±8.7/9.8±7.3
					Healthy elderly men	Cognitive function	4.3±1.6/3.7±1.6	4.4±1.7/3.4±2.2
						Short term & verbal retention	9.6±2.7/10.6±2.2	10.3±2.8/12.4±2.6
						Constructional task	25.3±1.3/26.2±1.0	25.6±1.7/25.7±2.0
						Visual recognition & perception	27.4±2.2/27.9±2.2	27.5±2.0/27.9±1.7
						Visuospatial function	29.5±6.7/28.6±8.2	34.8±9.0/33.8±8.6
2007 Vaughan et al.[13]	U.S.	47 Healthy older men with low serum Testosterone levels (70.8±4.2, range 65-83)	36 months.	Testosterone enanthate (200mg/2weeks, intramuscular) vs. placebo	Visual memory (correct)		6.33±0.27/6.50±0.46	6.17±0.38/5.50±0.51
					Visual memory (error)		5.08±0.48/4.69±0.64	5.22±0.69/6.44±0.98
					Visuospatial skill		12.38±0.42/12.63±0.50	11.96±0.48/11.94±0.42
					Attention (forward)		8.63±0.44/9.81±0.39	8.17±0.37/8.94±0.48
					Attention (backward)		7.29±0.43/8.38±0.49	6.44±0.40/6.63±0.47

					Attention (Trail A time)	39.83±2.82/37.56±3.55	40.44±2.20/37.56±5.19
					Executive functioning (Trails B)	81.83±5.39/87.31±9.28	90.43±6.70//86.88±10.77
					Verbal memory (total recall)	41.61±1.51/40.25±1.61	41.33±1.53/38.38±2.32
					Verbal memory (long term storage)	28.22±2.43/24.38±2.88	27.38±2.14/25.00±3.70
					Verbal memory (consistent long term retrieval)	18.35±2.42/15.63±2.97	17.43±1.70/16.88±3.01
					Verbal memory (delayed recall)	4.35±0.44/3.31±0.71	4.67±0.23/3.81±0.45
					Verbal memory (intrusion)	1.44±0.48/0.75±0.21	0.76±0.28/1.56±0.40
2008 Emmelot-Vonk et al.[14]	Netherlands	223 Healthy older men (67.1±5.0 in testosterone group, 67.4±4.9 in placebo group)	6 months.	Testosterone enanthate (80mg twice/day, oral) vs. placebo	Spatial perception	25.6±3.7/25.9±3.2	25.8±3.7/26.1±2.9
					Cognitive and perceptional speed	44.8±10.9/47.0±11.0	46.0±10.4/47.9±10.5
					Visuospatial performance	4.8±7.1/6.3±6.2	5.9±6.4/7.5±6.7
					Verbal episodic memory (immediate recall)	35.5±9.5/37.8±10.2	34.9±9.6/36.6±8.3
					Verbal episodic memory (delayed recall)	7.1±2.6/7.8±2.8	6.9±2.8/7.5±2.5
					Attention and mental flexibility (number)	47±18/44±16	48±16/43±13
					Attention and mental flexibility (letter)	53±33/49±28	55±34/47±22
					Attention and mental flexibility (number, letter)	108±33/49±28	101±43/95±43
2014 Cherrier et al.[15]	U.S.	19 Men with mild cognitive impairment and low testosterone levels (70.5±8.2, range 60-88)	6 months	Testosterone gel (50-100mg/day, oral) vs. placebo	Verbal memory (immediate recall)	Baseline/Change 44.7 (2.7)/-0.1 (2.2)	Baseline/Change 37.4 (2.5)/2.0(2.1)
					Verbal memory (short delay)	7.5 (1.1)/0.7 (1.0)	6.0 (1.0)/1.4 (1.0)
					Verbal memory (long delay)	6.2 (1.1)/0.9 (0.9)	4.9 (1.0)/1.5 (0.8)
					Story recall (immediate)	22.1 (2.3)/0.8 (2.4)	22.0 (2.1)/-1.7 (2.3)
					Story recall (delay)	16.4 (2.8)/2.7 (2.9)	16.5 (2.5)/-0.6 (2.8)
					Visual and spatial memory (immediate)	14.5 (2.0)/0.9 (1.6)	10.7 (1.9)/5.0 (1.7)
					Visual spatial memory (delay)	3.8 (0.7)/0.4 (0.7)	3.5 (0.6)/0.7 (0.7)
					Letter Number Sequence (span)	5.3 (0.4)/-0.5 (0.3)	5.1 (0.3)/-0.1 (0.3)
					Letter Number Sequence (total)	10.5 (0.9)/-1.4 (0.6)	9.3 (0.8)/0.3 (0.6)

					Computerized Simple reaction time (2 second)	335 (66)/30 (97)	375 (63)/ 118(92)
					Computerized Simple reaction time (5 second)	316 (23)/21 (25)	360 (22)/-31 (24)
					Computerized Choice reaction time (2 second)	494 (19)/17 (27)	553 (15)/7 (26)
					Computerized Choice reaction time (5-second)	523 (27)/3 (35)	549 (26)/11 (34)
					Visual and spatial memory (immediate)	30.7 (2.6)/-0.1 (2.9)	26.7 (2.3)/-0.6 (2.79)
					Visual and spatial memory (delay)	11.2 (1.0)/-0.7 (1.3)	10.3(1.0)/-0.5 (0.1)
					Complex design construction test (sec)	64.2 (10.2)/-5.0 (5.5)	52.1 (9.3)/0.5 (5.3)
					Verbal fluency	25.6 (2.5)/0.8 (1.9)	24.6 (2.2)/-2.3 (1.8)
					Mental Rotation	10.5(1.1)/2.1(0.9)	11.7(1.0)/2.1(0.9)

Table 2. Methodological Quality of Trials Based on the Jadad Scale (n = 10).

Study	Randomization	Description of randomization methods	Double-blind	Using identical placebos	Follow-up reporting	Total score
1994 Janowsky et al [6]	1	0	1	1	1	**4**
2001 O'Connor et al [7]	1	0	0	1	1	**3**
2002 Kenny et al [8]	1	0	0	1	1	**3**
2003 Ross et al [9]	1	1	1	1	1	**5**
2004 Kenny et al [10]	1	0	1	1	1	**4**
2005 Cherrier et al [11]	1	1	1	1	1	**5**
2005 Lu et al [12]	1	0	1	1	1	**4**
2007 Vaughan et al [13]	1	1	0	1	1	**4**
2008 Emmelot-Vonk et al [14]	1	1	1	1	1	**5**
2015 Cherrier et al [15]	1	1	1	1	1	**5**

Figure 1. Flow diagram for identification of relevant randomized controlled trials.

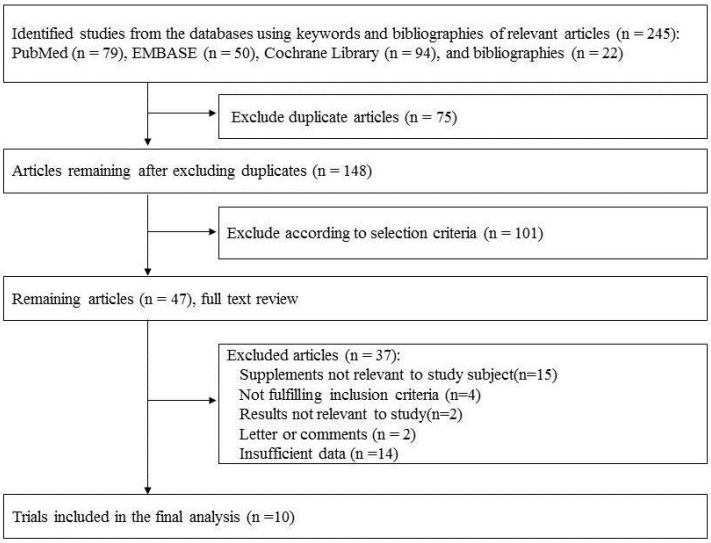
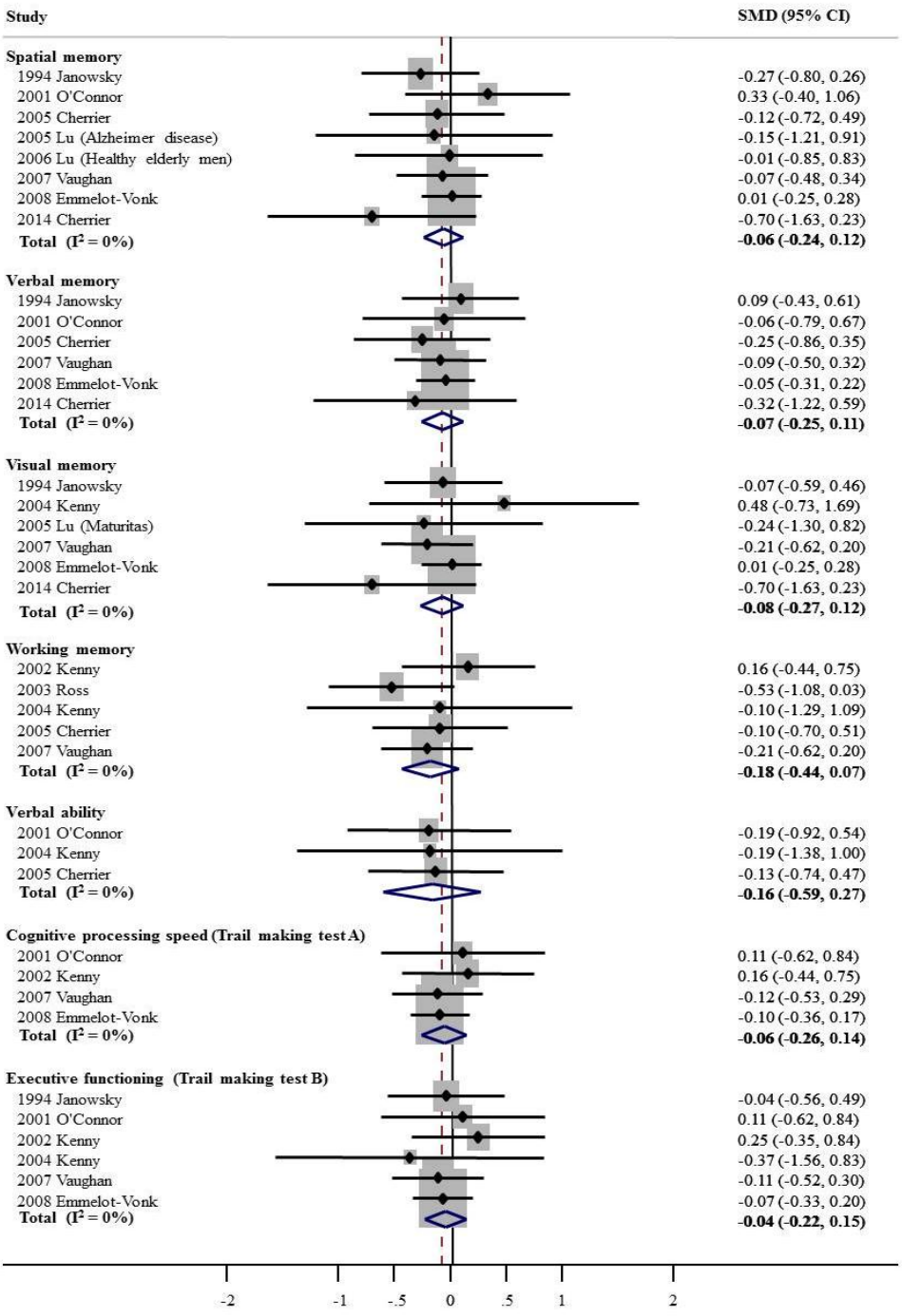
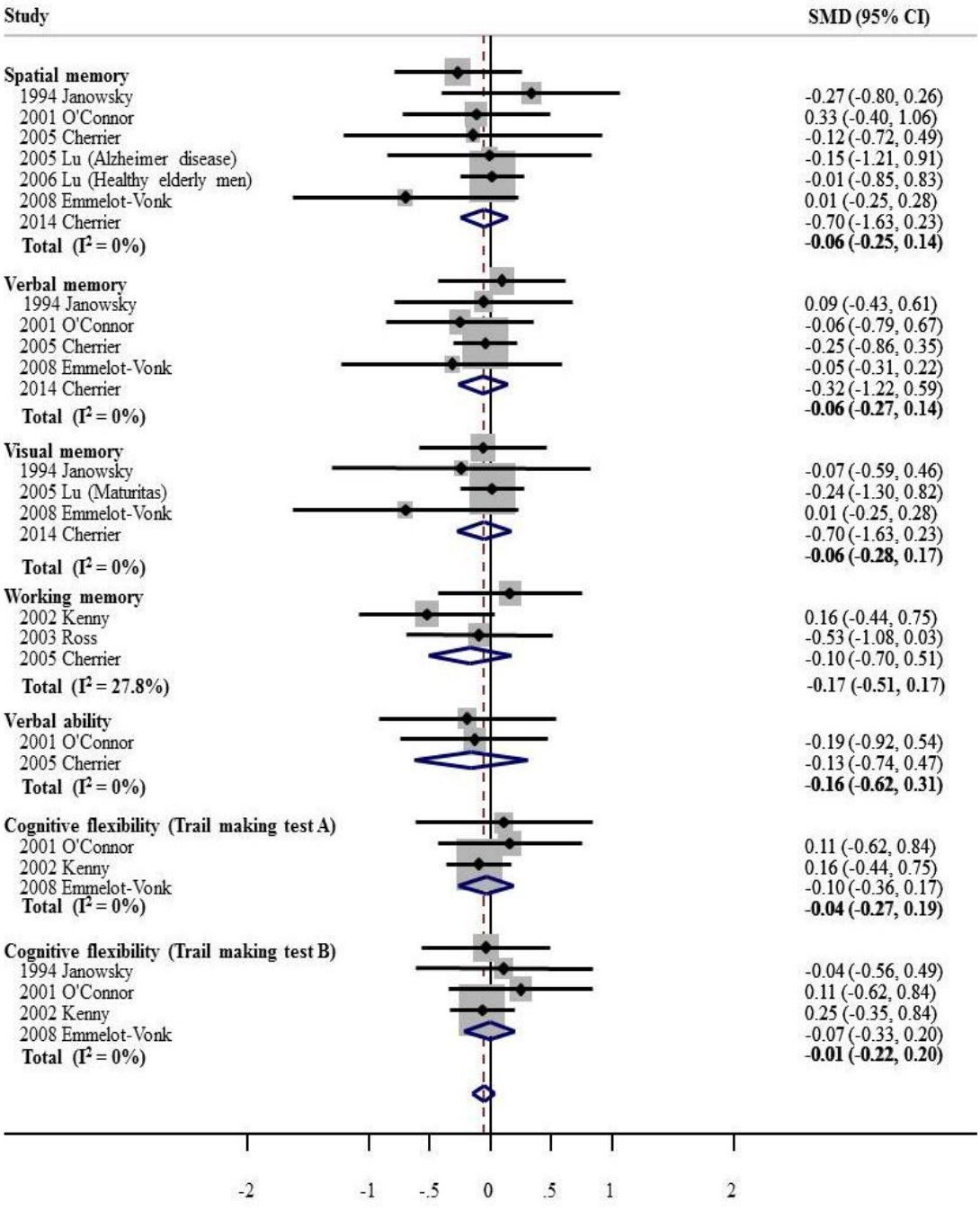


Figure 2. Efficacy of testosterone supplementation on cognitive function in the meta-analysis of randomized controlled trials by domain of cognitive function (n = 10).



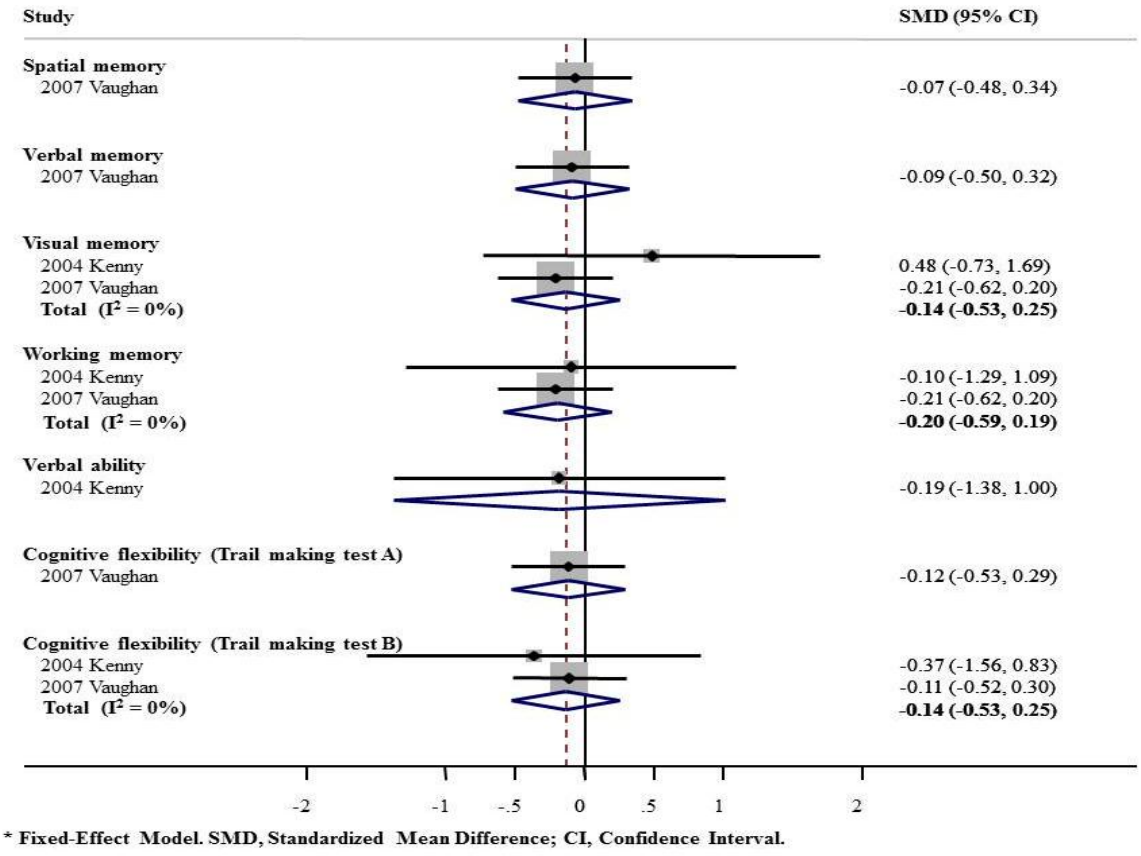
*** Fixed-Effect Model. SMD, Standardized Mean Difference; CI, Confidence Interval.**

Figure 3. Efficacy of testosterone supplementation on cognitive function in the meta-analysis of randomized controlled trials in eugonadal participants (n = 8).



* Fixed-Effect Model. SMD, Standardized Mean Difference; CI, Confidence Interval.

Figure 4. Efficacy of testosterone supplementation on cognitive function in the meta-analysis of randomized controlled trials in hypogonadal participants (n = 2).



DISSCUSSION

In the current meta-analysis of RCTs, we found that there was no efficacy of testosterone supplementation on cognitive function such as cognitive function such as spatial memory, verbal memory, visual memory, working memory, verbal ability, cognitive processing speed, and executive functioning. In addition, there was no significant association between testosterone supplementation and cognitive function in the subgroup meta-analysis by testosterone levels (hapogonadal or eugonadal).

It has been recognized that testosterone has neuroprotective effects. These effects could be through its conversion into estradiol in the brain or it could be directly, through its binding to androgen receptors [18]. In general, serum testosterone levels decrease with advancing age in men [1, 19]. This decline is thought to begin after 30 years of age, decreasing at an annual average rate of 0.2–1% for total testosterone and 2–3% for free or bioavailable testosterone [20]. There is increasing evidence that sex hormones such as testosterone and estradiol can exhibit protective properties in the brain [18]; especially in regions of the brain susceptible to Azheimer's disease pathogenesis. This includes the hippocampus, as well as cortical regions, which are known to have a high density of androgen receptors [21]. Testosterone may modulate neuronal damage caused by oxidative stress [22] (to which hippocampal neurons are particularly sensitive) and also reduce neuronal apoptosis or self programmed cell death [23], which is thought to play an important role in both Alzheimer's disease and age-related cognitive decline. Similarly, a systematic review and meta-analysis of seven prospective cohort studies published in 2015 found that low testosterone levels are significantly associated with increased risk of Alzheimer's disease in the elderly men (relative risk = 1.48; 95 % CI, 1.12-1.96) [24].

Therefore, testosterone supplementation can be a possible preventive or therapeutic modality for the prevention or treatment of cognitive disorders. Several animal studies in rats suggested that the administration of

testosterone or its metabolites improved cognitive ability such as learning and memory [25, 26]. Also, for the recent 20 years, RCTs have been published regarding the efficacy of testosterone supplementation on cognitive function. However, those findings remain inconsistent. When we reviewed all 10 RCTs on this issue which have been published as of August in 2015, six RCTs reported overall beneficial effects on cognition [6-9, 11, 13]. In contrast, the remaining four found no beneficial effects on cognition [10, 12, 14, 15]. In the current meta-analysis of these RCTs, no beneficial effect was observed.

There are possible explanations for this discrepancy in the association between testosterone levels or supplementation and cognitive function among animal studies, epidemiological studies such as cohort study, and RCTs. First, animal studies may not represent the biological processes in the human body [27]. As a similar example, although vitamin or antioxidant supplementation shows beneficial effects against certain diseases such as cancer or cardiovascular diseases in preclinical studies such as animal studies and in vitro laboratory studies, they did not show no beneficial effect or were even harmful under clinical circumstances from the findings of the meta-analysis of RCTs [28,29]. Therefore, the findings from preclinical studies such as animal studies and in vitro laboratory studies on the effects of testosterone supplementation should not be directly applied to humans. Second, even though low levels of testosterone are associated with an increased risk of cognitive decline from the findings of observational epidemiological studies such as prospective studies or case-control studies, this always does not mean that testosterone supplementation is required or beneficial for people with low levels of testosterone. We do not have any clear explanation for this. However, the level of testosterone might be just a surrogate marker for cognitive status, which is not improved by increasing the levels of testosterone via supplementation. Last, although we included 10 RCTs in this analysis, the total sample size was only 554 study participants with the 277 intervention and 277 placebo groups. The number of study participants ranged from 11 to 237 across trials. Except one trial with 223 participants [14], most trials involved only about 50 or less study participants. Therefore, the sample size of the current meta-analysis is too small to draw a definite conclusion on this issue. There are several limitations in this meta-analysis. First, as mentioned above, we only included study participants with a relatively small sample size in the current analysis because of a paucity of literature on this issue. Further larger RCTs are required to confirm our findings. Second, there was clinical heterogeneity such as characteristics of the study participants, measurement tools for assessing cognitive function, and type/dosage/duration of testosterone supplementation across trials.

Thus, individual findings might result from heterogeneity. Last, eight of 10 trials included in this analysis were conducted in the U.S. There was no trial from Asian countries. Thus, we are unable to generalize the findings from this study, especially to Asians.

CONCLUSION

In conclusion, our meta-analyses of RCTs showed no efficacy of testosterone supplements on cognitive function. Recently, including the improvement of cognitive function, the potential anti-aging effects of testosterone supplementation have been promoted by some medical professionals, specifically in Korea, and not a few people believe those effects and pay for receiving testosterone supplementation. However, the effects of testosterone supplementation on aging have provided mixed findings [14]. Specifically, testosterone supplementation has no sufficient clinical beneficial effect on cognitive function in our study. Further large-scale, randomized controlled trials are necessary to confirm our findings. Before the sufficient evidence is established, testosterone supplementation should be cautious for the purpose of the improvement of cognitive function.

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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