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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 metaanalysis 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 metaanalyses 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

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Seung-Kwon Myung Email:- msk@ncc.re.kr 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





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 \pm 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:

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

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).



				Interventio	Ι	Main Outcomes	
		Study		n (dosage		Mean±SD or	Mean (SE)
a	Coun	participa	Dur	and route of		baseline/f	ollow-up
Source	try	nts (age: years)	atio n	administrati on) vs. control group	Domains of cognitive function	Intervention group	Control group
				81	Spatial cognition	27.96±7.56/30.17±	28.72±8.61/27.90
		FC		Testosterone	(memory)	0.78	± 8.57
1994		Healthy	3	scrotal patch	recall)	9.19±2.47/10.83±2. 70	9.21±3.14/11.21± 2.23
Janows ky et	U.S.	older men (67.4,	mon	(15mg/day,	Visual memory (reproduction)	25.19±8.10/29.30± 7.00	26.21±8.83/29.59 ±7.45
al. ⁶⁾		range 60- 75)	uis.) vs.	Motor dexterity & speed	77.74±12.80/75.96 ±10.83	73.03±8.63/74.9± 11.66
				placebo	Cognitive flexibility	79.7±29.97/72.11± 19.17	87.86±32.99/78.8 3±26.71
					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)
2001		29 Eugonadal	o	Testosterone Enanthate,	Verbal fluency (category)	20.29 (0.99)/20.79 (1.46)	21.87 (1.63)/22.00 (1.60)
O'Conn or et al. ⁷⁾	U.K.	young men (28.2,	o wee ks.	intramuscula r (100mg/wee	Cognitive flexibility	27.43 (2.54)/22.42 (1.89)	26.33 (1.45)/22.41 (1.37)
		range 19- 45)		k) vs. placebo	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)
		44 Older		Testosterone	Working memory	11.4±2.6/11.5±2.5	11.8±1.8/12/4±1. 9
2002		44 Older men (76+4.	1	patch (5mg	Digit symbol	42±8/46±9	43±8/47±7
Kenny et al. ⁸⁾	U.S.	(76±4, range 65-	year	/day, transdermal)	Cognitive flexibility (sec)	42±14/38±8	39±16/38±17
		87)		vs. placebo	Perceptual motor speed (sec)	104±39/87±29	95±30/90±38
		51 Turner		Oxandrolone	Working memory	-1.2±1.3/-0.3±1.4	-0.8±1.7/-1.0±1.5
2003	ΠC	syndrome	2 year s.	(0.06mg /kg/day, oral) vs.	Spatial cognition	-2.82.4±/-2.6±2.9	-2.8±3.6/-2.8±3.1
al. ⁹⁾	0.5.	girls (range			Executive function	0.5±1.3/0.9±1.5	0.5±1.2/1.0±1.3
		10.0-14.9)		placebo	Verbal abilities	-0.1±1.6/-0.3±1.9	0.0±1.8/-0.3±1.7

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



		11 Hypogona		Testesterone	W	orking memory	15.2±1.0/15.0±2.3	13.6±6.3/12.8±6. 1
2004		dal older men with	12	Enanthate (200mg/3w	Verba	al abilities (fluency)	12.5±6.0/13.2±5.8	12.2±5.1/11.4±5. 8
Kenny et al. ¹⁰⁾	U.S.	mild cognitive	wee ks	eeks, intramuscul	Vis	uoconstruction & perception	3.8±0.4/3.8±0.4	3.0±1.7/3.6±0.5
		(80±5, range 73- 87)		ar) vs. placebo	Ex (d	ecutive function ivided attention)	222±63/221±92	250±58/225±75
				_	5	patial memory	42.1±14.8/50.0±12. 1	37.3±12.9/43.0±1 2.4
2005		38 Healthy	ć	Testosterone enanthate	Verbal memory		42.4±7.4/48.1±13.4	46.7±10.6/48.4±1 2.2
Cherrie r et	U.S.	older men (65±11,	6 wee	(100mg/wee k,	Verb	al ability (fluency)	24.6±8.2/26.6±8.1	27.6±4.8/28.4±7. 0
al. ¹¹⁾		range 50- 85)	KS	r)	Se	elective attention	52.0±18.3/47.5±14. 7	52.1±23.9/47.5±1 6.3
				vs. placebo	W	orking memory	12.5±3.7/12.45.9	12.1±5.7/11.3±11 .3
					Alz	Cognitive function	25±13.2/27.4±8.4	25.2±8.9/28.3±10 .3
					hei mer	Short term & verbal retention	2.3±2.7/1±2.4	1.3±1.4/0.9±1.7
		14 Mild			's dise	Constructional task	20±2.4/19.8±3.1	17±2.6/15.4±15.4
		's disease		Testosterone	ase gro	Visual recognition & perception	19±7.6/20.3±7	18.1±9.9/16.5±8. 7
2006		healthy elderly	24	gel (75mg/day	up	Visuospatial function	9.5±6.1/10.8±8	10.1±8.7/9.8±7.3
Lu et al. ¹²⁾	U.S.	men (mean age	wee ks.	applied to skin) vs. placebo		Cognitive function	4.3±1.6/3.7±1.6	4.4±1.7/3.4±2.2
		in each group:			Hea lthy	Short term & verbal retention	9.6±2.7/10.6±2.2	10.3±2.8/12.4±2. 6
)			elde rly	Constructional task	25.3±1.3/26.2±1.0	25.6±1.7/25.7±2. 0
					men	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
		47 Healthy		Testosterone	Visua	al memory (correct)	6.33±0.27/6.50±0.4 6	6.17±0.38/5.50±0 .51
2007		older men with low	36	enanthate (200mg/2we	Visu	al memory (error)	5.08±0.48/4.69±0.6 4	5.22±0.69/6.44±0 .98
Vaugha n et	U.S.	S. serum Testostero	erum tostero levels 8±4.2,	eks, intramuscula r)	Visuospatial skill		12.38±0.42/12.63± 0.50	11.96±0.48/11.94 ±0.42
al.15)		ne levels $(70.8\pm4.2,$			Attention (forward)		8.63±0.44/9.81±0.3 9	8.17±0.37/8.94±0 .48
	I	range 65- 83)		is. placebo	Attention (backward)		7.29±0.43/8.38±0.4 9	6.44±0.40/6.63±0 .47



					Attention (Trail A time)	39.83±2.82/37.56±	40.44±2.20/37.56
				3.33	±5.19		
					Executive functioning	81.85±5.59/87.51±	90.43±6.70//86.8
					(Trails B)	9.28	8±10.77
					verbal memory (total recall)	41.61±1.51/40.25± 1.61	$41.33\pm1.53/38.38$ ±2.32
					Verbal memory (long	28.22+2.43/24.38+	27.38+2.14/25.00
					term storage)	2.88	±3.70
					Verbal memory	19 25 10 40/15 (2)	17 42 1 70/16 99
					(consistent long	$10.53\pm2.42/15.03\pm$	$1/.45\pm1./0/10.00$
					term retrieval)	2.97	±5.01
					Verbal memory (delayed	4.35±0.44/3.31±0.7	4.67±0.23/3.81±0
					recall)	1	.45
					Verbal memory	$1.44 \pm 0.48 / 0.75 \pm 0.2$	$0.76 \pm 0.28 / 1.56 \pm 0$
					(intrusion)	1	.40
					Spatial perception	25.6±3.7/25.9±3.2	25.8±3.7/26.1±2. 9
					Cognitive and	44.8±10.9/47.0±11.	46.0±10.4/47.9±1
		222			perceptional speed	0	0.5
		Healthy			Visuospatial performance	4.8±7.1/6.3±6.2	5.9±6.4/7.5±6.7
2008 Emmel	Neth	(67.1 ± 5.0)	6	enanthate	Verbal episodic memory (immediate recall)	35.5±9.5/37.8±10.2	34.9±9.6/36.6±8. 3
ot- Vonk et	erlan	in testostero	6 (80mg mon the twice/day, (alous d month) 7.1±2.6/7.8±2.8	6.9±2.8/7.5±2.5			
al. ¹⁴⁾	u b	ne group, 67.4±4.9	uno.	oral) vs. placebo	Attention and mental	47±18/44±16	48±16/43±13
		in placebo group)			Attention and mental	53±33/49±28	44±16 48±16/43±13 '49±28 55±34/47±22
					Attention and mental		
					flexibility (number.	108+33/49+28	101+43/95+43
					letter)		
					,	Baseline/Change	Baseline/Change
					Verbal memory	Dusenne/ Change	
					(immediate recall)	44.7 (2.7)/-0.1 (2.2)	37.4
					Varhal manage (chart		(2.5)/2.0(2.1)
		19 Men			delay)	7.5 (1.1)/0.7 (1.0)	6.0 (1.0)/1.4 (1.0)
2014 Cherrie		cognitive		Testestere	Verbal memory (long delay)	6.2 (1.1)/0.9 (0.9)	4.9 (1.0)/1.5 (0.8)
	ПС	nt	6	gel (50-	Story recall (immediate)	22.1 (2.3)/0.8 (2.4)	22.0 (2.1)/-1.7 (2.3)
r et al. ¹⁵⁾	0.5.	testostero	ths	oral) vs.	Story recall (delay)	16.4 (2.8)/2.7 (2.9)	16.5 (2.5)/-0.6 (2.8)
		$(70.5\pm8.2,$		ріасево	Visual and spatial memory (immediate)	14.5 (2.0)/0.9 (1.6)	10.7 (1.9)/5.0 (1.7)
		88)			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
$2008 \text{ Emmelot-Vonk et al}_{14)}$	1	1	1	1	1	5
2015 Cherrier et al ¹⁵	1	1	1	1	1	5







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





ipatial memory -0.27 (-0.80, 0.26 2001 O Connor -0.12 (-0.72, 0.49 2005 Cherrier -0.15 (-1.21, 0.91 2005 Lu (Alzheimer disease) -0.01 (-0.25, 0.83 2006 Lu (Healthy elderly men) -0.01 (-0.25, 0.83 2014 Cherrier -0.06 (-0.25, 0.14 1994 Janowsky 0.09 (-0.43, 0.61) 2005 Cherrier -0.06 (-0.27, 0.47) 2005 Cherrier -0.05 (-0.32, 0.22) 2014 Cherrier -0.05 (-0.32, 0.23) 2005 Lu (Mataritas) -0.07 (-0.59, 0.46) 2005 Lu (Mataritas) -0.07 (-0.59, 0.46) 2005 Lu (Mataritas) -0.07 (-0.59, 0.46) 2005 Lu (Mataritas) -0.27 (-0.80, 0.25) 2005 Lu (Mataritas) -0.27 (-0.80, 0.25) 2005 Lu (Mataritas) -0.27 (-0.80, 0.25) 2005 Lu (Mataritas) -0.27 (-0.430, 0.82) 2005 Lu (D connor -0.06 (-0.28, 0.17) 2005 Lu (D connor -0.10 (-0.70, 0.51) 200	Study	SMD (95%	CI)
1994 Janowsky -0.27 (-0.80, 0.26 2001 D Connor -0.33 (-0.40, 1.06) 2005 Cherrier -0.15 (-1.21, 0.91) 2010 L (Jitheimer disease) -0.01 (-0.25, 0.83) 2010 E (Litteling elderly men) -0.01 (-0.25, 0.83) 2010 L (Jitheimer disease) -0.01 (-0.25, 0.83) 2014 Cherrier -0.01 (-0.25, 0.83) Total (I ² = 0%) -0.06 (-0.25, 0.14) /erbal memory -0.06 (-0.25, 0.14) 1994 Janowsky -0.06 (-0.25, 0.14) 2010 Connor -0.06 (-0.27, 0.14) 2010 Connor -0.06 (-0.25, 0.13, 0.22) 2011 Cherrier -0.02 (-0.31, 0.22) 2014 Cherrier -0.02 (-0.31, 0.22) 2014 Cherrier -0.02 (-0.26, 0.28) 7014 (I ² = 0%) -0.06 (-0.27, 0.14) 2002 Kenny -0.06 (-0.28, 0.17) 2002 Kenny -0.06 (-0.28, 0.17) 2003 Ross -0.07 (-1.63, 0.23) 2004 Cherrier -0.06 (-0.28, 0.17) 7001 O'Connor -0.13 (-0.44, 0.75) 2002 Kenny -0.16 (-0.44, 0.75) 2003 Ross -0.16 (-0.44, 0.75) 2004 Cherrier -0.13 (-0.44, 0.75) <tr< td=""><td>Snatial memory</td><td></td><td></td></tr<>	Snatial memory		
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2005 Lu (Abheimer disease) -0.15 (-1.21, 0.91) 2006 Lu (Hedity eddety men) -0.01 (-0.85, 0.83) 2014 Cherrier -0.06 (-0.25, 0.14) 2014 Cherrier -0.06 (-0.25, 0.14) 2005 Emmelot-Vonk -0.06 (-0.25, 0.14) 2001 CConor -0.06 (-0.27, 0.14) 2001 CConor -0.06 (-0.27, 0.14) 2014 Cherrier -0.25 (-0.86, 0.35) 2015 Cherrier -0.05 (-0.31, 0.22) 2014 Cherrier -0.25 (-0.86, 0.35) 2015 Lu (Matmina) -0.06 (-0.27, 0.14) 2005 Lu (Matmina) -0.04 (-0.25, 0.28) 2014 Cherrier -0.03 (0.31, 0.22) 2014 Cherrier -0.03 (0.32, 0.28) 1994 Janowsky -0.07 (-0.59, 0.46) 2005 Lu (Matmina) -0.24 (-1.30, 0.82) 2014 Cherrier -0.70 (-1.63, 0.23) Total (f² = 0%) -0.16 (-0.44, 0.75) 2003 Rons -0.17 (-0.51, 0.17) 2001 CConnor -0.13 (-0.22, 0.28) 2001 Connor -0.16 (-0.26, 0.31) 2001 Connor -0.16 (-0.26, 0.31) 2001 Connor -0.17 (-0.51, 0.17) 2002 Kenny -0.16 (-0.26, 0.31) <t< td=""><td>2005 Cherrier</td><td>-0.12(-0.72,</td><td>0.49)</td></t<>	2005 Cherrier	-0.12(-0.72,	0.49)
2006 Lu (Healthy elderly men) -0.01 (-0.85, 0.83) 2008 Emmelot-Vonk 0.01 (-0.25, 0.28) 2014 Cherrier -0.70 (-1.63, 0.23) 2005 Lum (Healthy elderly men) -0.01 (-0.85, 0.83) 2014 Cherrier -0.01 (-0.85, 0.83) 2005 Lum (Healthy elderly men) -0.01 (-0.45, 0.28) 2005 Lum (Healthy elderly men) -0.01 (-0.45, 0.28) 2005 Lum (Maturias) -0.01 (-0.45, 0.28) 2014 Cherrier -0.25 (-0.86, 0.35) 2015 Lu (Maturias) -0.05 (-0.31, 0.22) 2014 Cherrier -0.05 (-0.31, 0.22) 2014 Cherrier -0.05 (-0.31, 0.22) 2005 Lu (Maturias) -0.04 (-0.25, 0.28) 2014 Cherrier -0.07 (-0.59, 0.46) 2005 Lu (Maturias) -0.04 (-0.27, 0.14) 2005 Lu (Maturias) -0.07 (-0.59, 0.46) 2014 Cherrier -0.07 (-0.59, 0.46) 2005 Lu (Maturias) -0.07 (-0.59, 0.46) 2014 Cherrier -0.07 (-0.59, 0.46) 2005 Lu (Maturias) -0.07 (-0.59, 0.46) 2005 Lu (Maturias) -0.07 (-0.38, 0.17) 2003 Ross -0.05 (-0.38, 0.17) 2004 Cherrier -0.10 (-0.70, 0.51) <t< td=""><td>2005 Lu (Alzheimer disease)</td><td>-0.15(-1.21,</td><td>0.91)</td></t<>	2005 Lu (Alzheimer disease)	-0.15(-1.21,	0.91)
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2014 Cherrier -0.70(-1.63, 0.23) Total (f² = 0%) -0.06(-0.25, 0.14) Verbal memory 0.09 (-0.43, 0.61) 2005 Cherrier -0.25 (-0.48, 0.35) 2014 Cherrier -0.25 (-0.48, 0.35) 2015 Lu (Matrinas) -0.06 (-0.27, 0.14) 2005 Lu (Matrinas) -0.07 (-0.59, 0.46) 2005 Lu (Matrinas) -0.01 (-0.25, 0.28) 2014 Cherrier -0.06 (-0.27, 0.14) 7003 Ross -0.06 (-0.28, 0.17) 2003 Kenny -0.06 (-0.28, 0.17) 2003 Kenny -0.06 (-0.28, 0.17) 2003 Kenny -0.06 (-0.28, 0.17) 2003 Ross -0.01 (-0.60, 0.51) 2003 Ross -0.10 (-0.70, 0.51) 2004 Chernier -0.19 (-0.92, 0.54) 2005 Cherrier -0.16 (-0.44, 0.75) 2001 O'Connor -0.19 (-0.92, 0.54) 2002 Kenny -0.16 (-0.62, 0.31) 2003 Ross -0.10 (-0.70, 0.51) 2004 Cherrier -0.16 (-0.62, 0.31) 2005 Cherrier -0.16 (-	2008 Emmelot-Vonk	0.01 (-0.25,	0.28)
Total (I ² = 0%) -0.06 (-0.25, 0.14) Verbal memory 0.09 (-0.43, 0.61) 1994 Janowsky 0.09 (-0.43, 0.61) 2001 D'Connor -0.25 (-0.86, 0.35) 2012 Cherrier -0.32 (-1.22, 0.59) Total (I ² = 0%) -0.06 (-0.27, 0.14) 7sual memory -0.07 (-0.59, 0.46) 1994 Janowsky -0.07 (-0.59, 0.46) 2005 Cherrier -0.06 (-0.28, 0.17) Total (I ² = 0%) -0.06 (-0.28, 0.17) Norking memory -0.06 (-0.28, 0.17) 2001 Altantrias) -0.06 (-0.28, 0.17) 2002 Kernny -0.06 (-0.28, 0.17) 2003 Cherrier -0.010 (-0.70, 0.51) Total (I ² = 0%) -0.11 (-0.51, 0.17) 2001 O'Connor -0.10 (-0.70, 0.51) 2002 Kernny -0.16 (-0.62, 0.38) 2003 Dismicol-Vonk -0.16 (-0.27, 0.14) 2001 O'Connor -0.11 (-0.52, 0.84) 2002 Kernny -0.16 (-0.20, 0.31) 2003 Dismicol-Vonk -0.10 (-0.70, 0.51) 2004 Kernny -0.16 (-0.62, 0.84) 2001 O'Connor -0.11 (-0.62, 0.84) 2002 Kernny -0.21 (-0.35, 0.31) 2003	2014 Cherrier	-0.70 (-1.63,	0.23)
Verbal memory 0.09 (-0.43, 0.61) 1994 Janowsky 0.09 (-0.43, 0.61) 2001 CConor 0.25 (-0.86, 0.35) 2014 Cherrier 0.006 (-0.27, 0.14) 1994 Janowsky 0.006 (-0.27, 0.14) 2014 Cherrier 0.006 (-0.27, 0.14) 1994 Janowsky 0.007 (-0.59, 0.46) 2005 Emmelot-Vonk 0.006 (-0.27, 0.14) 2006 Emmelot-Vonk 0.001 (-0.25, 0.28) 2014 Cherrier 0.006 (-0.27, 0.14) 7 total (1 ² = 0%) 0.016 (-0.44, 0.75) Norking memory 0.16 (-0.44, 0.75) 2003 Experience 0.110 (-0.20, 0.34) 2004 Conort 0.017 (-0.51, 0.17) 2005 Cherrier 0.016 (-0.24, 0.17) 7 total (1 ² = 0%) 0.16 (-0.44, 0.75) 2005 Cherrier 0.13 (-0.74, 0.47) 7 total (1 ² = 0%) 0.11 (-0.62, 0.84) 2005 Emmelot-Vonk 0.16 (-0.44, 0.75) 2005 Emmelot-Vonk 0.16 (-0.44, 0.75) 2005 Emmelot-Vonk 0.16 (-0.42, 0.31) 2005 Emmelot-Vonk 0.16 (-0.62, 0.31) 2005 Emmelot-Vonk 0.16 (-0.62, 0.31) 2005 Emmelot-Vonk 0.10 (-0.22, 0.34) <t< td=""><td>Total $(I^2 = 0\%)$</td><td>-0.06 (-0.25,</td><td>0.14)</td></t<>	Total $(I^2 = 0\%)$	-0.06 (-0.25,	0.14)
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2001 O Connor -0.06 (-0.79, 0.6) 2005 Cherrier -0.25 (-0.86, 0.35) 2014 Cherrier -0.32 (-1.22, 0.59) 7 Dotal (1 ² = 0%) -0.06 (-0.27, 0.14) Visual memory -0.07 (-0.59, 0.46) 2008 Emmelot-Vonk -0.06 (-0.27, 0.14) 2008 Emmelot-Vonk -0.07 (-0.59, 0.46) 2005 Cherrier -0.06 (-0.27, 0.14) Total (1 ² = 0%) -0.06 (-0.28, 0.17) Vorking memory -0.06 (-0.28, 0.17) 2002 Kenny -0.06 (-0.28, 0.17) 2003 Cherrier -0.01 (-0.25, 0.28) Total (1 ² = 0%) -0.16 (-0.44, 0.75) 2001 O'Connor -0.19 (-0.92, 0.54) 2002 Kenny -0.16 (-0.44, 0.75) 2005 Cherrier -0.17 (-0.51, 0.17) 2001 O'Connor -0.19 (-0.92, 0.54) 2002 Kenny -0.16 (-0.62, 0.31) 2003 Cherrier -0.13 (-0.74, 0.47) 2004 Cherrier -0.16 (-0.62, 0.31) 2005 Cherrier -0.16 (-0.62, 0.31) 2008 Emmelot-Vonk -0.16 (-0.62, 0.31) 2008 Emmelot-Vonk -0.04 (-0.27, 0.19) 2008 Emmelot-Vonk -0.04 (-0.26, 0.49) <t< td=""><td>1994 Janowsky</td><td>- 0.09 (-0.43,</td><td>0.61)</td></t<>	1994 Janowsky	- 0.09 (-0.43,	0.61)
2005 Cheffer -0.25 (-0.36, 0.55) 2008 Emmelot-Vonk -0.05 (-0.31, 0.22) 2014 Cherrier -0.05 (-0.31, 0.22) Total (1 ² = 0%) -0.06 (-0.27, 0.14) Visual memory -0.07 (-0.59, 0.46) 2004 Emmelot-Vonk -0.06 (-0.27, 0.14) 2005 Lu (Maturitas) -0.07 (-0.59, 0.46) 2014 Cherrier -0.70 (-0.59, 0.46) Total (1 ² = 0%) -0.06 (-0.28, 0.17) Norking memory -0.16 (-0.44, 0.75) 2003 Examelot-Vonk -0.16 (-0.44, 0.75) 2003 Cherrier -0.19 (-0.92, 0.54) 7 total (1 ² = 0%) -0.17 (-0.51, 0.17) Vortal (1 ² = 0%) -0.13 (-0.27, 0.48) 2001 O'Connor -0.19 (-0.92, 0.54) 2002 Kenny -0.16 (-0.42, 0.31) 2003 Examelot-Vonk -0.16 (-0.42, 0.31) 2004 Cenny -0.16 (-0.42, 0.31) 2005 Cherrier -0.13 (-0.72, 0.44) 7 total (1 ² = 0%) -0.16 (-0.42, 0.31) 2002 Kenny -0.16 (-0.42, 0.32) 2003 Examelot-Vonk -0.10 (-0.36, 0.01) 1994 Janowsky -0.04 (-0.57, 0.49) 2004 Kenny -0.01 (-0.22, 0.20)	2001 O'Connor	-0.06(-0.79,	0.6/)
2005 Lind (Administration of the second o	2005 Chemer	-0.25 (-0.86,	0.33)
2014 Cherner -0.06 (-0.27, 0.14) 1994 Janowsky -0.07 (-0.59, 0.46) 2008 Emmelot-Vonk -0.06 (-0.28, 0.17) 2014 Cherrier -0.06 (-0.28, 0.17) 7 total (I² = 0%) -0.16 (-0.44, 0.75) Vorking memory -0.16 (-0.28, 0.17) 2002 Kenny -0.16 (-0.28, 0.17) 2003 Ross -0.10 (-0.70, 0.51) 2005 Cherrier -0.10 (-0.70, 0.51) 7 total (I² = 0%) -0.16 (-0.62, 0.38) 2005 Cherrier -0.16 (-0.62, 0.31) 7 total (I² = 0%) -0.16 (-0.62, 0.31) 2001 O'Connor -0.16 (-0.62, 0.31) 2002 Kenny -0.16 (-0.62, 0.31) 2003 Binmelot-Vonk -0.10 (-0.35, 0.20) 7 total (I² = 0%) -0.04 (-0.25, 0.48) 2002 Kenny -0.16 (-0.62, 0.31) 2003 Binmelot-Vonk -0.04 (-0.25, 0.49) 2004 Connor -0.04 (-0.25, 0.49) 2005 Kenny -0.04 (-0.25, 0.49) 2004 Connor -0.04 (-0.25, 0.49) 2005 Kenny -0.04 (-0.25, 0.49) 2004 Connor -0.04 (-0.25, 0.49) 2005 Kenny -0.04 (-0.25, 0.49) 2004 Kenny	2014 Cherrier	-0.03(-0.31	0.59)
Visual memory -0.07 (-0.59, 0.46 1994 Janowsky -0.24 (-1.30, 0.82 2005 Lu (Maturias) -0.07 (-0.59, 0.46 2005 Lu (Maturias) -0.07 (-0.59, 0.46 2014 Cherrier -0.07 (-0.59, 0.46 7 total (I ² = 0%) -0.06 (-0.28, 0.17) Norking memory -0.06 (-0.28, 0.17) 2002 Kenny -0.16 (-0.44, 0.75) 2003 Ross -0.33 (-1.08, 0.03) 2005 Cherrier -0.10 (-0.70, 0.51) Total (I ² = 27.8%) -0.17 (-0.51, 0.17) //erbal ability -0.19 (-0.92, 0.54) 2001 O'Connor -0.19 (-0.92, 0.54) 2001 O'Connor -0.16 (-0.62, 0.31) 2002 Kenny -0.16 (-0.62, 0.31) 2003 Emmelot-Vonk -0.11 (-0.62, 0.84) 2004 Conor -0.10 (-0.36, 0.17) 2005 Cherrier -0.10 (-0.36, 0.17) 2008 Emmelot-Vonk -0.04 (-0.27, 0.19) 2009 Emmelot-Vonk -0.04 (-0.26, 0.49) 2001 O'Connor -0.04 (-0.26, 0.49) 2002 Kenny -0.04 (-0.26, 0.49) 2003 Emmelot-Vonk -0.07 (-0.33, 0.20) 2004 (-0.56, 0.49) -0.01 (-0.22, 0.20) <	Total $(1^2 = 0\%)$	-0.06 (-0.27,	0.14)
1994 Janowsky -0.07 (-0.59, 0.46 2005 Lu (Maturias) -0.24 (-1.30, 0.82 2008 Emmelot-Vonk -0.01 (-0.25, 0.23) 2014 Cherrier -0.06 (-0.28, 0.017) Total (I ² = 0%) -0.16 (-0.44, 0.75) Norking memory -0.16 (-0.44, 0.75) 2003 Ross -0.10 (-0.70, 0.51) 2004 Cherrier -0.10 (-0.70, 0.51) Total (I ² = 0%) -0.19 (-0.92, 0.54) Verbal ability -0.19 (-0.92, 0.54) 2005 Cherrier -0.10 (-0.70, 0.51) Total (I ² = 0%) -0.19 (-0.92, 0.54) 2005 Cherrier -0.19 (-0.92, 0.54) 7014 (I ² = 0%) -0.10 (-0.70, 0.51) 2008 Emmelot-Vonk -0.16 (-0.62, 0.84) 2001 O'Connor 0.11 (-0.62, 0.84) 2002 Kenny -0.04 (-0.27, 0.19) 2008 Emmelot-Vonk -0.04 (-0.27, 0.19) 2009 Connor -0.04 (-0.27, 0.19) 2001 O'Connor -0.04 (-0.27, 0.19) 2003 Kenny -0.04 (-0.27, 0.19) 2004 Kenny -0.04 (-0.27, 0.19) 2005 Emmelot-Vonk -0.01 (-0.22, 0.20) 2001 O'Connor -0.01 (-0.22, 0.20) 20	Visual memory	_	
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Total (I ² = 0%)	2002 Kenny 2008 Emmelot-Vonk	0.25 (-0.35,	0.04)
	Total $(I^2 = 0\%)$	-0.01 (-0.22,	0.20)
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Research Article





Figure 4. Efficacy of testosterone supplementation on cognitive function in the meta-analysis of randomized

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 metaanalysis. 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 findings [14]. Specifically, testosterone mixed 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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