Life expectancy has steadily increased over recent decades in all high-income countries. Data from members of the Organization for Economic Cooperation and Development, including a population of about one million people among all high-income countries worldwide, suggest that by 2030 life expectancy will increase with a probability of at least 65% for women and 85% for men [1]. In particular, projection data indicate that, for men, South Korea, Australia, and Switzerland will show the best results with a 95% probability that men’s life expectancy at birth in these three countries will surpass 80 years in 2030, and 27% that it would surpass 85 years [1]. Gender differences are confirmed also by these data with women’s life expectancy projections worldwide higher when compared to men [1].

Although global aging is the result of medical, social, and economic advances over disease, it also presents important challenges. In particular, aging people are predicted to undergo a dramatic increase in the following years with more than 131.5 million people being affected by 2030. Although vascular diseases play the most important role in the pathogenesis of memory impairment in aging men, some pre-clinical and clinical evidence has suggested a possible contribution of the age-dependent reduction of testosterone (T). In this paper we have summarized and discussed all the information derived from available animal and experimental studies. In addition, we meta-analyzed data rising from all randomized placebo controlled trials (RCTs) published so far. Only limited preclinical and clinical evidence can support a possible contribution of T in the pathogenesis of the age-dependent impairment of cognitive functions. In addition, our meta-analysis did not support the use of T replacement therapy for the improvement of several cognitive domains analyzed including attention/working memory, executive function, language, verbal memory, visual memory, visuomotor ability, and visuospatial ability. However, it is important to recognize that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism preventing any final conclusion being drawn on these issues.

Keywords: Aging; Cognitive impairment; Dementia; Hypogonadism; Testosterone

Cognitive impairment and dementia are predicted to undergo a dramatic increase in the following years with more than 131.5 million people being affected by 2030. Although vascular diseases play the most important role in the pathogenesis of memory impairment in aging men, some pre-clinical and clinical evidence has suggested a possible contribution of the age-dependent reduction of testosterone (T). In this paper we have summarized and discussed all the information derived from available animal and experimental studies. In addition, we meta-analyzed data rising from all randomized placebo controlled trials (RCTs) published so far. Only limited preclinical and clinical evidence can support a possible contribution of T in the pathogenesis of the age-dependent impairment of cognitive functions. In addition, our meta-analysis did not support the use of T replacement therapy for the improvement of several cognitive domains analyzed including attention/working memory, executive function, language, verbal memory, visual memory, visuomotor ability, and visuospatial ability. However, it is important to recognize that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism preventing any final conclusion being drawn on these issues.

Keywords: Aging; Cognitive impairment; Dementia; Hypogonadism; Testosterone
characterized by chronic and progressive diseases requiring assistance during the activities of daily living. Accordingly, cognitive impairment and dementia prevalence are predicted to show a dramatic increase with a projection by 2050 of more than 131.5 million people being affected [2]. In line with these data, the economic burden of US$ 818 billion is expected to increase substantially over the next few decades [3]. In order to face this situation, the World Health Organization (WHO) in 2012 lunched a worldwide call among all the dementia stakeholders in order to finalize common solutions and plans to solve the problem [4]. This has eventually led to the organization of the first WHO Ministerial Conference on Global Action Against Dementia in March, 2015 [2]. Among the identified top ten research priorities, the most important were those related to prevention, identification, and reduction of dementia risk factors as well as those on delivery and quality of care for people with dementia and their caretakers [2].

It is quite clear that vascular diseases play an essential role in the majority of patients with dementia [5]. However, it is also important to recognize that dementia phenotype includes a wide spectrum of features with several underlying risk factors. The role of the endocrine system and, in particular, of sex steroids, is still conflicting. In men, an age-dependent reduction of testosterone (T) has been reported [6]. Late onset hypogonadism (LOH) is the most frequently used term to describe this phenomenon. A recent meta-analysis, including all available observation studies, has documented that reduced T is associated with an increased risk of cardiovascular (CV) morbidity and mortality [7]. Similarly, several data have documented a close relationship between age-dependent reduction of T levels and worse CV and metabolic profile [8-10]. In addition, both pre-clinical and clinical studies have also suggested a possible direct role of T in neuro-protective mechanisms [11,12].

The aim of the present study is to systematically summarize and discuss all the available evidence regarding the possible role of T in age-dependent male cognition impairment and dementia. Both animal and experimental data as well as results derived from randomized placebo controlled trials (RCTs) will be considered. When possible a meta-analytic approach will be used.

METHODS

A comprehensive Medline, Embase, and Cochrane search was performed including the following words: (“testosterone” [MeSH Terms] OR “testosterone” [All Fields]) AND (“cognition” [MeSH Terms] OR “cognition” [All Fields]). Publications from January 1, 1969 up to December 31st, 2019 were included. When available, meta-analytic data were preferred. In addition, a new meta-analysis on the effect of T replacement therapy (TRT) on cognition parameters with only placebo RCTs was also performed.

PRE-CLINICAL EVIDENCE

Androgen receptors (AR) are widely expressed within the central nervous system. T, in its free form, is able to cross the blood barrier and to influence neuronal cells, acting through genomic and non-genomic pathways [11,12]. Data from animal in vitro and in vivo models have reported conflicting results regarding the possible role of androgens on neuroprotection. In fact both beneficial and deleterious effects have been reported [11,12].

1. In vitro studies

Data derived from primary neurons suggested that T can act in protecting or exacerbating experimental neuronal damage depending on the concentration [13-15]. In particular, supra-physiological concentrations (10 μM) can amplify glutamate-induced excitotoxic neuronal death, whereas protection has been observed at 10 nM [16]. Although indirect effects due to T aromatization to estradiol have been reported, some evidence has also documented a direct role of androgens thought AR [13-15]. Neurotophic effects of T have also been described [17,18]. Data obtained in cultures of human neuroblastsoma cells showed that T was more effective in alleviating β-amyloid induced mitochondrial bioenergetic deficits, by regulating mitochondrial oxidative phosphorylation genes [19-21]. Finally, more recently, it has been reported that, under pathological conditions, astrocytes can mediate, at least partially, the neuroprotective effects of gonadal steroid hormones by reducing the release of pro-inflammatory molecules [11]. Given the side effects that sex steroids may have when administered systemically, a number of synthetic agonists of the receptors for gonadal steroid hormones in the nervous system have been developed, and may be considered for
clinical use after brain injury, as potential enhancers of the neuroprotective astrocytic functions [11].

2. In vivo studies

Similar to what has been observed in vitro studies, data obtained in aged rodents documented that, during stroke, maintaining T, or dihydrotestosterone, plasma levels within the low physiological range confers protection [22]. The latter effect was blunted by administration of the AR antagonist flutamide, suggesting AR-mediated mechanisms [22]. In other experimental animal models, T administration is associated with an increase in neuron somal size, neuritic growth, plasticity, and synaptogenesis in both motoneuronstes of the spinal nucleus of the bulbocavernous [23]. Finally, in male double-transgenic mice, the increase of T levels is associated with a correspondent decrease in β-secretase, an enzyme involved in the cleavage of the amyloid β protein precursor [24]. However, other authors reported that, in castrated male rats, high androgen levels exacerbate ischemic damage [25]. Similarly, a more recent study showed that chronic high-dose T administration impairs cognitive flexibility in a rat animal model [26].

Table 1. Comparisons of the available meta-analyses evaluating the relationship between androgen deprivation therapy and cognitive impairment

| Inclusion criteria | McGinty et al (2014) [32] | Sun et al (2018) [33] |
|--------------------|--------------------------|---------------------|
| No. of trials included | 14 | 6 |
| No. of patients analyzed | 414 | 122 |
| Outcomes evaluated | | |
| Visomotor domain | Yes | No |
| Attention/working memory | Yes | No |
| Executive function | Yes | No |
| Language | Yes | No |
| Verbal memory | Yes | No |
| Visual memory | Yes | No |
| Visuospatial ability | Yes | No |
| Any cognitive impairment retrospective studies | No | Yes |
| Any cognitive impairment prospective studies | No | Yes |

$^a$Scoring 1.5 or more standard deviations below published norms on 2 or more tests, or scoring 2.0 or more standard deviations below published norms on at least 1 test; $^b$Defined using International Classification of Diseases-9 diagnostic or procedure codes or other system based identification scheme.

CLINICAL EVIDENCE

Aging is associated with an impairment of cognitive ability, including memory, attention, language and visuospatial ability [2-5]. Some authors have hypothesized that the age-related reduction in cognition and the T decline are temporally related, suggesting a possible role of low T in cognition impairment [27,28]. Accordingly, cognition impairment has been considered a possible component of LOH [10,28-31].

1. Chemical castration and cognition

Up to now, two systematic meta-analyses have evaluated the relationship between androgen deprivation therapy (ADT) and cognition (Table 1). The first study included 14 RCTs with only a limited number of subjects (n=417 patients and 122 controls) [32]. Total duration of ADT ranged from a mean of 23 to 31 months, whereas mean age of the ADT groups ranged from 63.2 to 71.0 years across study samples [32]. Overall, across studies, various neuropsychological tests were used, which are divided into seven cognitive domains (Table 2) [32]. The authors concluded that patients treated with ADT performed worse than controls or than their own baseline on visuomotor domain, with larger magnitude effect in studies with a shorter follow-up. No significant effect was observed on the other six cognitive domains, including attention/working memory, executive function, language, verbal memory, visual memory, and visuospatial ability [32].

A more recent meta-analysis included two prospective and four retrospective studies, accounting for 442 and 67,644 men, respectively. Men included in the prospective studies were younger (mean 67 to 69 years old) than those evaluated in the retrospective survey studies (70 to 75 years old) [33]. When only prospective studies were considered, no difference between case and controls was observed in the risk of developing cognitive impairment, according to the International Cognition and Cancer Task Force (scoring 1.5 or more standard deviations below published norms on two or more tests, or scoring 2.0 or more standard deviations below published norms on at least one test). Similarly no increased risk of cognitive impairment was observed as defined using International Classification of Diseases-9 diagnostic or procedure codes or on other system based identification schemes (Table 2) [33].
2. Serum levels of testosterone and cognitive function in aging men

Different population-based studies have investigated a possible relationship between T levels and cognitive function in aging men (Table 3) [34-43]. The number of subjects included ranges from 310 to up to almost 6,000. Several studies have documented an association between androgen status and cognitive impairment. In particular, two studies showed that subjects with reduced total T levels have a cognitive impairment. In addition, two studies demonstrated an inverse correlation between calculated free T, and two with free T index (FTI), and impaired cognition. However, it is important to recognize that all the aforementioned studies used radioimmunoassays for T evaluation, which have demonstrated some problems of accuracy, especially in the presence of very low levels of T [44]. In addition, the use of FTI for the assessment of androgen status has been strongly criticized [45].

In apparent contrast with the aforementioned results, when mass-spectrometry was applied, the gold standard method for all steroid evaluation, no association between low T and cognitive problems was reported (Table 3).

1) Interventional studies – testosterone trials

In 2003, the US National Institute on Aging funded a set of clinical trials in order to better clarify the benefit and possible risks of TRT in the aging male.
Table 4. Characteristics and outcomes of the randomized, controlled clinical studies included in the meta-analysis

| Reference (year)          | No. of patient | Trial duration (wk) | Age (y) | Type of population | T levels | Dose (daily) | Design | Randomization | Blinding | Drop-out | Intention to treat |
|---------------------------|----------------|---------------------|---------|--------------------|----------|--------------|--------|---------------|----------|-----------|-------------------|
| Janowsky et al (1994) [52] | 56             | 12                  | 67.4    | Aging men          | Mixed    | T patch 15 mg/die | Parallel | A             | NA       | NA        | NR                |
| Janowsky et al (2000) [53] | 19             | 4                   | 67.5    | Aging men          | Eugonadal| TE 150 mg/wk     | Parallel | A             | NA       | NA        | NR                |
| Cherrier et al (2001) [54] | 25             | 6                   | 70.2    | Aging men          | Eugonadal| TE 100 mg/wk     | Parallel | NA            | NA       | A         | A                 |
| Kenny et al (2002) [55]   | 44             | 52                  | 75.5    | Aging men          | Mixed    | T patch 50 mg/d  | Parallel | NA            | NA       | A         | A                 |
| Kenny et al (2004) [56]   | 11             | 10                  | 79.6    | Mild to moderate CI| Mixed    | TE 200 mg/3 wk   | Parallel | NA            | NA       | A         | A                 |
| Cherrier et al (2005) [57] | 25             | 6                   | 70.2    | AD                | Eugonadal| TE 100 mg/wk     | Parallel | A             | NA       | A         | A                 |
| Haren et al (2005) [58]   | 76             | 52                  | 68.5    | Aging men          | Mixed    | TU 160 mg/d      | Parallel | A             | A         | A         | A                 |
| Lu et al (2006) [59]      | 18             | 24                  | 69.8    | AD                | Mixed    | TG 75 mg/d       | Parallel | A             | NA       | A         | A                 |
| Maki et al (2007) [60]    | 15             | 36                  | 73.9    | Aging men          | <8 nM    | TE 200 mg/wk     | Parallel | A             | A         | A         | A                 |
| Vaughan et al (2007) [61] | 47             | 156                 | 70.8    | Aging men          | <12 nM   | TE 200 mg/2 wk   | Parallel | A             | A         | A         | A                 |
| Emmelot-Vonk et al (2008) [62] | 237        | 24                  | 67.3    | Aging men          | <12 nM   | TE 200 mg/2 wk   | Parallel | A             | A         | A         | A                 |
| Fukai et al (2010) [63]   | 24             | 24                  | 81.0    | Mild CI            | Mixed    | TU 160 mg/d      | Parallel | A             | A         | A         | A                 |
| Bost et al (2014) [64]    | 30             | 52                  | 70.5    | Aging men          | <10.4 nM | TU 160 mg/d      | Parallel | A             | NA       | NA        | NA                |
| Cherrier et al (2015) [65] | 22             | 24                  | 70.5    | Mild CI            | <10.4 nM | TG 50 to 100 mg/d| Parallel | A             | A         | A         | A                 |
| Huang et al (2016) [66]   | 308            | 156                 | 67.6    | Aging men          | Eugonadal| TG 75 mg/d       | Parallel | A             | A         | A         | A                 |
| Wahjoepramono et al (2016) [67] | 44         | 52                  | 61.1    | Mild CI            | <10.4 nM | TG 50 mg/d       | Cross-over | A             | A         | A         | A                 |
| Resnick et al (2017) [46] | 493            | 52                  | 72.5    | Mild CI            | <8 nM    | TG 50 mg/d       | Parallel | A             | A         | A         | A                 |

T: testosterone, CI: cognitive impairment, AD: Alzheimer’s disease, TE: testosterone enanthate, TU: testosterone undecanoate, TG: testosterone gel, A: adequate, NA: not adequate, NR: not reported.
Hence, a set of seven, 52-week, randomized, placebo-controlled, double-blind trials, including overall 788 hypogonadal (total testosterone [TT]<9.4 nM) men older than 65 years were designed and planned. All men included in the active arm were treated with T 1% gel. One specific RCT, the Cognitive Function Trial, specifically investigated the efficacy of TRT on cognitive outcomes among 493 men with age-associated memory impairment [46]. The primary designated outcome of the study was verbal memory, as assessed by delayed paragraph recall performance. The latter test was selected based on prior findings in small RCTs and on its clinical importance. In fact, epidemiological data indicate that, in the years preceding clinical dementia, verbal memory impairment is accelerated [47,48]. In addition, it is important to recognize that delayed paragraph recall performance involves neurological areas of the hippocampus, which contains both androgen and estrogen receptors, supporting a physiological role of sex steroids [49,50]. However, despite this evidence, TRT for one year, as compared with placebo, was not associated with improved memory, as well as with the other cognitive functions evaluated, including visual memory, spatial ability, and executive function [46]. In the T trials the cognitive function test was also used in subjects without memory problems. When the analysis was extended to the whole population, T-treated men showed a small, but statistically significant, increase in executive function. However, the same authors recognized that treatment effect was small and the observed result does not justify the use of TRT in older men to improve cognition [51].

2) Interventional studies – meta-analysis of available randomized placebo controlled trials

Besides the T trials, several other RCTs have evaluated the effect of TRT on cognitive function in aging men. In particular, 17 studies are available overall [46,52-67]. These trials enrolled 1,438 patients with a mean age of 70.4 years and a mean follow-up of 45.6 years. The weighted standardized mean difference and 95% confidence interval for each cognitive domain at endpoint are reported in Fig. 1. The table below shows the number of trials per category, the standardized mean difference, and the 95% confidence interval for each cognitive domain:

| Source                          | #Trials | Std mean diff | Std diff in mean | LL    | UL    | p-value |
|--------------------------------|---------|---------------|------------------|-------|-------|---------|
| Attention/working memory       | 6       | -1.5 -1.0 -0.5 0 0.5 1.0 1.5 2.0 | 0.15  -0.23  0.52 0.44 |
| Overall                        | 6       |               |                  |       |       |         |
| Cognitive impairment           |         |               |                  |       |       |         |
| Executive function             | 10      | -0.8 -0.19 0.03 0.17 | 0.31  -0.31 0.04 0.14 |
| Overall                        | 10      |               |                  |       |       |         |
| Cognitive impairment           | 2       |               |                  |       |       |         |
| Verbal fluency                 | 2       | 0.10 0.13 0.33 0.38 | 0.31  -0.88 1.50 0.61 |
| Overall                        | 2       |               |                  |       |       |         |
| Cognitive impairment           | 1       |               |                  |       |       |         |
| Verbal memory (immediate recall)| 6       | 0.05 0.06 0.17 0.37 | 0.00  -0.17 0.17 0.99 |
| Overall                        | 6       |               |                  |       |       |         |
| Cognitive impairment           | 3       |               |                  |       |       |         |
| Verbal memory (delayed recall) | 10      | 0.03 0.08 0.15 0.65 | 0.11  -0.20 0.41 0.50 |
| Overall                        | 10      |               |                  |       |       |         |
| Cognitive impairment           | 4       |               |                  |       |       |         |
| Visual memory                  | 4       | 0.12 0.04 0.27 0.15 | 0.11  -0.07 0.28 0.24 |
| Overall                        | 4       |               |                  |       |       |         |
| Cognitive impairment           | 1       |               |                  |       |       |         |
| Visuomotor ability             | 5       | -0.14 -0.67 0.38 0.59 | -0.44 -1.33 0.45 0.33 |
| Overall                        | 5       |               |                  |       |       |         |
| Cognitive impairment           | 2       |               |                  |       |       |         |
| Visuospatial ability           | 5       | 0.01 0.13 0.15 0.91 | -0.01  -0.19 0.16 0.90 |
| Overall                        | 5       |               |                  |       |       |         |
| Cognitive impairment           | 2       |               |                  |       |       |         |

Fig. 1. Weighted standardized mean diff (with 95% confidence interval) of several cognitive domains at endpoint in randomized controlled trials. Std: standard deviation, diff: difference, LL: lower limit, UL: upper limit.
weeks. These trials differ in basal TT levels and type of T preparation used (Table 4). In addition, nine were performed in aging men without memory problems, five in subjects with mild to moderate cognitive impairment and two in patients with Alzheimer’s disease (Table 4). Since the classification of tests into cognitive domains differed among the included studies, the available neuropsychological tests were divided into seven cognitive domains, based on an established neuropsychological reference text [68], as previously reported (Supplementary Table 1) [32]. In order to obtain more comparable results, only trials with homogenous cognitive tests were analyzed. Combining the results of those trials, when TRT was compared to placebo, no difference in all the cognitive domains analyzed was observed (Fig. 1, Supplementary Fig. 1). In addition, no differences were also observed when depressive symptoms or score derived from Mini-Mental State Examination test were considered (Fig. 2). Similarly, no differences were observed when only patients with cognitive impairment were considered (Fig. 1, 2, Supplementary Fig. 2).

Another recent meta-analysis, including a lower number of RCTs (n=14) and of patients (n=1,406), reported that TRT improved psychomotor speed and executive function. However, the same authors recognized that the effect size was very low, although statistically significant [69].

**CONCLUSIONS**

Limited preclinical and clinical evidence suggests that T can be involved in the pathogenesis of the age-dependent impairment of cognitive functions. However, when T was evaluated with the gold standard method for sex steroid evaluation (i.e., mass spectrometry) no association between age-dependent reduction of T and memory problems was observed. In addition, the present meta-analysis does not support the use of TRT for the improvement of several cognitive domains analyzed. It is important to recognize that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism preventing any final conclusion to be drawn on these issues. In fact, positive effects of TRT were observed either on sexual function [70,71] or on body composition [72,73] only when baseline T levels were below 12 nM. Hence, further larger RCTs are advisable in order to better clarify the role of TRT in aging men, and in particular, in those with a cognitive impairment.

**Conflicts of Interest**

The authors have nothing to disclose.

**Author Contribution**

Conceptualization: GC, MM. Data curation: GC, GR, FG. Formal analysis: GC, FG. Funding acquisition: none. Investigation: GC. Methodology: GC. Project administration: GC. Resources: GC, FG. Software: GC. Supervision: GC, AS, MM. Validation: GC, MM. Visualization: GC, MM. Writing – original draft: GC, FG. Writing – review & editing: GC, FG, GR, AS, MM.
Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.200017.

REFERENCES

1. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet 2017;389:1323-35.

2. Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol 2016;15:1285-94.

3. Alzheimer’s Disease International. World Alzheimer Report 2015: the global impact of dementia [Internet]. London: Alzheimer's Disease International; c2015 [cited 2020 Jan 14]. Available from: https://www.alz.co.uk/research/world-report-2015.

4. World Health Organization, Alzheimer’s Disease International. Dementia: a public health priority. Geneva: World Health Organization; 2012.

5. Gladman JT, Corriveau RA, Debette S, Dichgans M, Greenberg SM, Sachdev PS, et al. Vascular contributions to cognitive impairment and dementia: research consortia that focus on etiology and treatable targets to lessen the burden of dementia worldwide. Alzheimers Dement (N Y) 2019;5:789-96.

6. Corona G, Maseroli E, Rastrelli G, Francomano D, Aversa A, Hackett GI, et al. Is late-onset hypogonadotropic hypogonadism a specific age-dependent disease, or merely an epiphenomenon caused by accumulating disease-burden? Minerva Endocrinol 2016;41:196-210.

7. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous testosterone levels and cardiovascular risk: meta-analysis of observational studies. J Sex Med 2018;15:1260-71.

8. Rastrelli G, Lotti F, Reisman Y, Sforza A, Maggi M, Corona G. Metabolically healthy and unhealthy obesity in erectile dysfunction and male infertility. Expert Rev Endocrinol Metab 2019;14:321-34.

9. Lotti F, Rastrelli G, Maseroi L, Cipriani S, Guaraldi F, Krausz C, et al. Impact of metabolically healthy obesity in patients with andrological problems. J Sex Med 2019;16:821-32.

10. Corona G, Vignozzi L, Sforza A, Maggi M. Risks and benefits of late onset hypogonadism treatment: an expert opinion. World J Mens Health 2013;31:103-25.

11. Acaz-Fonseca E, Avila-Rodriguez M, Garcia-Segura LM, Barreto GE. Regulation of astroglia by gonadal steroid hormones under physiological and pathological conditions. Prog Neurobiol 2016;144:5-26.

12. Liu M, Kelley MH, Herson PS, Hurn PD. Neuroprotection of sex steroids. Minerva Endocrinol 2010;35:127-43.

13. Caruso A, Di Giorgi Gerevini V, Castiglione M, Marinelli F, Tomassini V, Pozzilli C, et al. Testosterone amplifies excitotoxic damage of cultured oligodendrocytes. J Neurochem 2004;88:1179-85.

14. Ahlbom E, Prins GS, Ceccatelli S. Testosterone protects cerebellar granule cells from oxidative stress-induced cell death through a receptor mediated mechanism. Brain Res 2001;892:255-62.

15. Zhang Y, Champagne N, Beitel LK, Goodyer CG, Trifiro M, LeBlanc A. Estrogen and androgen protection of human neurons against intracellular amyloid beta42 toxicity through heat shock protein 70. J Neurosci 2004;24:5315-21.

16. Orlando R, Caruso A, Molinaro G, Motolese M, Matrisiano F, Togna G, et al. Nanomolar concentrations of anabolic-androgenic steroids amplify excitotoxic neuronal death in mixed mouse cortical cultures. Brain Res 2007;1165:21-9.

17. Beyer C, Hutchison JB. Androgens stimulate the morphological maturation of embryonic hypothalamic aromatase-immunoreactive neurons in the mouse. Brain Res Dev Brain Res 1997;98:74-81.

18. Lustig RH. Sex hormone modulation of neural development in vitro. Horm Behav 1994;28:383-95.

19. Grimm A, Biliouris EE, Lang UE, Götz J, Mensah-Nyagan AG, Eckert A. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid-β or hyperphosphorylated tau protein. Cell Mol Life Sci 2016;73:201-15.

20. Grimm A, Schmitt K, Lang UE, Mensah-Nyagan AG, Eckert A. Improvement of neuronal bioenergetics by neurosteroids: implications for age-related neurodegenerative disorders. Biochim Biophys Acta 2014;1842(12 Pt A):2427-38.

21. Vasconsuelo A, Milanesi L, Boland R. Actions of 17β-estradiol and testosterone in the mitochondria and their implications in aging. Ageing Res Rev 2013;12:907-17.

22. Pan Y, Zhang H, Acharya AB, Patrick PH, Oliver D, Morley JE. Effect of testosterone on functional recovery in a castrate male rat stroke model. Brain Res 2005;1043:195-204.

23. Cheng J, Alkayed NJ, Hurn PD. Deleterious effects of dihydrotestosterone on cerebral ischemic injury. J Cereb Blood Flow Metab 2007;27:1553-62.

24. McAllister C, Long J, Bowers A, Walker A, Cao P, Honda S, et al. Genetic targeting aromatase in male amyloid precursor protein transgenic mice down-regulates beta-secretase (BACE1) and prevents Alzheimer-like pathology and cogni-
25. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. Eur J Endocrinol 2006;155:773-81.

26. Wood RI, Serpa RO. Anabolic-androgenic steroid abuse and cognitive impairment: testosterone IMPAIRS conditional task performance in male rats. Behav Brain Res 2020;379:112339.

27. Yalamanchi S, Dobs A. Debate position: cognition and mood are not improved in men administered exogenous testosterone therapy. Curr Opin Urol 2017;27:525-31.

28. Corona G, Torres LO, Maggi M. Testosterone therapy: What we have learned from trials. J Sex Med 2020;17:447-60.

29. Corona G, Sforza A, Maggi M. Testosterone replacement therapy: long-term safety and efficacy. World J Mens Health 2017;35:65-76.

30. Giagulli VA, Guastamacchia E, Licchelli B, Triggiani V. Serum testosterone and cognitive function in ageing male: updating the evidence. Recent Pat Endocr Metab Immune Drug Discov 2016;10:22-30.

31. Ciocca G, Limoncin E, Carosa E, Di Sante S, Gravina GL, Mollaioli D, et al. Is testosterone a food for the brain? Sex Med Rev 2016;4:15-25.

32. McGinty HL, Phillips KM, Jim HS, Cessna JM, Asvat Y, Cases MG, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Support Care Cancer 2014;22:2271-80.

33. Sun M, Cole AP, Hanna N, Mucci LA, Berry DL, Basaria S, et al. Cognitive impairment in men with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. J Urol 2018;199:1417-25.

34. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999;84:3681-5.

35. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriatr Soc 2002;50:707-12.

36. Moffat SD, Zonderman AB, Metter EJ, Kawas C, Blackman MR, Harman SM, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62:188-93.

37. Fonda SJ, Bertrand R, O’Donnell A, Longcope C, McKinlay JB. Age, hormones, and cognitive functioning among middle-aged and elderly men: cross-sectional evidence from the Massachusetts male aging study. J Gerontol A Biol Sci Med Sci 2005;60:385-90.

38. Muller M, Aleman A, Grobbe DE, de Haan EH, van der Schouw YT. Endogenous sex hormone levels and cognitive function in aging men: Is there an optimal level? Neurology 2005;64:866-71.

39. Geerlings MI, Strozyk D, Masaki K, Remaley AT, Petrovitch H, Ross GW, et al. Endogenous sex hormones, cognitive decline, and future dementia in old men. Ann Neurol 2006;60:346-55.

40. Thilers PP, Macdonald SW, Herlitz A. The association between endogenous free testosterone and cognitive performance: a population-based study in 35 to 90 year-old men and women. Psychoneuroendocrinology 2006;31:565-76.

41. Yeap BB, Almeida OP, Hyde Z, Chubb SA, Hankey GJ, Jamrozik K, et al. Higher serum free testosterone is associated with better cognitive function in older men, while total testosterone is not. The health in men study. Clin Endocrinol (Oxf) 2008;68:404-12.

42. LeBlanc ES, Wang PY, Janowsky JS, Neiss MB, Fink HA, Yaffe K, et al.; Osteoporotic Fractures in Men (MrOS) Research Group. Association between sex steroids and cognition in elderly men. Clin Endocrinol (Oxf) 2010;72:393-403.

43. Wu FC, Tajer A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al.; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123-35.

44. Huhtaniemi IT, Tajer A, Lee DM, O’Neill TW, Finn JD, Bartfai G, et al.; EMAS Group. Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. Eur J Endocrinol 2012;166:983-91.

45. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018;103:1715-44.

46. Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017;317:717-27.

47. Tierney MC, Yao C, Kiss A, McDowell I. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology 2005;64:1853-9.

48. Bilgel M, An Y, Lang A, Prince J, Ferrucci L, Jedynak B, et al. Trajectories of Alzheimer disease-related cognitive measures in a longitudinal sample. Alzheimer’s Dement 2014;10:735-42.

49. Cherrier MM, Matsumoto AM, Amory JK, Ahmed S, Bremner W, Peskind ER, et al. The role of aromatization in testosterone supplementation: effects on cognition in older men. Neurology 2005;64:290-6.

50. Janowsky JS. The role of androgens in cognition and brain aging in men. Neuroscience 2006;138:1015-20.

51. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM,
52. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. Behav Neurosci 1994;108:325-32.

53. Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. J Cogn Neurosci 2000;12:407-14.

54. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57:80-8.

55. Kenny AM, Bellantionio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002;57:M321-5.

56. Kenny AM, Fabregas G, Song C, Biskup B, Bellantionio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. J Gerontol A Biol Sci Med Sci 2004;59:75-8.

57. Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Brenner W, Peskind ER, et al. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. Neurology 2005;64:2063-8.

58. Haren MT, Wittert GA, Chapman IM, Coates P, Morley JE. Effect of oral testosterone undecanoate on visuospatial cognition, mood and quality of life in elderly men with low-normal gonadal status. Maturitas 2005;50:124-33.

59. Lu PH, Masterman DA, Mulnard R, Cotman C, Miller B, Yaffe K, et al. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. Arch Neurol 2006;63:177-85.

60. Maki PM, Ernst M, London ED, Mordecai KL, Perscher P, Durso SC, et al. Intramuscular testosterone treatment in elderly men: evidence of memory decline and altered brain function. J Clin Endocrinol Metab 2007;92:4107-14.

61. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. J Androl 2007;28:875-82.

62. Emmelet-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA 2008;299:39-52.

63. Fukai S, Akishita M, Yamada S, Toba K, Ouchi Y. Effects of testosterone in older men with mild-to-moderate cognitive impairment. J Am Geriatr Soc 2010;58:1419-21.

64. Borst SE, Yarrow JE, Fernandez C, Conover CF, Ye F, Meuleman JR, et al. Cognitive effects of testosterone and finasteride administration in older hypogonadal men. Clin Interv Aging 2014;9:1327-33.

65. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen 2015;30:421-30.

66. Huang G, Wharton W, Bhasin S, Harman SM, Pencina KM, Tsitouras P, et al. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations: a prespecified secondary analysis of data from the randomised, double-blind, placebo-controlled TEAAM trial. Lancet Diabetes Endocrinol 2016;4:657-65.

67. Wahjoepramono EJ, Asih PR, Aniwiyanti V, Taddei K, Dhaliwal SS, Fuller SJ, et al. The effects of testosterone supplementation on cognitive functioning in older men. CNS Neurol Disord Drug Targets 2016;15:337-43.

68. Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. Oxford: Oxford University Press; 2004.

69. Tan S, Sohrabi HR, Weinborn M, Tegg M, Bucks RS, Taddei K, et al. Effects of testosterone supplementation on separate cognitive domains in cognitively healthy older men: a meta-analysis of current randomized clinical trials. Am J Geriatr Psychiatry 2019;27:1232-46.

70. Rastrelli G, Gualdali F, Reismann Y, Sforza A, Isidori AM, Maggi M, et al. Testosterone replacement therapy for sexual symptoms. Sex Med Rev 2019;7:464-75.

71. Rastrelli G, Corona G, Maggi M. Testosterone and sexual function in men. Maturitas 2018;112:46-52.

72. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 2016;174:R99-116.

73. Rastrelli G, Maggi M, Corona G. Pharmacological management of late-onset hypogonadism. Expert Rev Clin Pharmacol 2018;11:439-58.