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TESTOSTERONE AND COGNITIVE FUNCTION

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Abstract

Testosterone, a crucial androgen hormone, plays a significant role in cognitive health across all life stages. During prenatal and early development, testosterone influences corticohippocampal maturation, essential for spatial and executive functions. Adolescence is marked by enhanced visuospatial and decision-making abilities linked to elevated testosterone levels, though excess may lead to impulsivity. In adulthood, balanced testosterone positively impacts memory, verbal fluency, and decision-making. Conversely, age-related testosterone decline is associated with increased risks of dementia and Alzheimer's disease.

Studies highlight testosterone's neuroprotective mechanisms, including reducing oxidative stress, regulating synaptic plasticity, and preventing neuroinflammation. It also modulates dopamine and serotonin pathways, enhancing mood and cognitive resilience. Gender differences are evident, with testosterone aromatization to estradiol benefiting male spatial cognition and influencing female verbal fluency and mood during hormonal fluctuations.

Therapeutically, testosterone replacement therapy (TRT) demonstrates improved cognitive outcomes in hypogonadal individuals but carries risks of mood instability and cardiovascular complications with excessive dosing. Notably, higher testosterone-to-cortisol ratios correlate with better stress resilience and decision-making under pressure.

Large-scale studies underline the importance of maintaining optimal testosterone levels, as both low testosterone and high SHBG independently increase dementia risk. These findings underscore the hormone's potential in managing neurodegenerative disorders and promoting cognitive longevity. Future research should focus on long-term effects of hormonal therapies and interactions with other endocrine pathways.

Keywords: Testosterone, cognitive function, neuroprotection, dementia, Alzheimer's disease, neuroinflammation, testosterone replacement therapy, stress resilience, gender differences, hormonal balance.

Introduction

Testosterone, a vital androgen hormone, plays a multifaceted role in cognitive health, influencing brain development, neuroprotection, and cognitive performance across the lifespan. This comprehensive review synthesizes data from over 20 peer-reviewed studies to elucidate the complex relationship between testosterone and cognitive function. Testosterone is instrumental in corticohippocampal development, particularly in critical periods of neurogenesis, as demonstrated by its regulation of neuronal differentiation and plasticity. The testosterone-to-cortisol ratio is pivotal in age- and sex-specific cognitive performance, shaping memory, executive functioning, and stress resilience.

In adolescence, testosterone influences brain maturation, particularly in regions associated with spatial reasoning and executive function, although extremes in levels can impair cognition. In adulthood, testosterone continues to modulate verbal skills, risk-taking, and problem-solving. Studies highlight its neuroprotective effects, such as reducing oxidative stress and mitigating neuroinflammation, which may delay or prevent neurodegenerative disorders like Alzheimer's disease. Data from large-scale cohorts of older men reveal that lower testosterone levels and elevated sex hormone-binding globulin (SHBG) are independently associated with an increased risk of dementia.

Furthermore, testosterone's therapeutic applications show promise in combating cognitive decline, yet its efficacy varies by dose, individual baseline levels, and hormonal interplay. Molecular studies underscore testosterone's interaction with neurotransmitter systems like dopamine and serotonin, which influence mood and cognitive stability. While normal testosterone levels (20–40 nmol/L) are critical for optimal brain function, extremes—both supraphysiological and suboptimal—can disrupt cognitive and emotional health. This review emphasizes the need for balanced testosterone levels to support brain health and highlights future directions for research on hormone therapy and cognitive performance.

Materials and Methods

Study Selection and Methodology

This review explores the relationship between testosterone and cognitive function, focusing on its role in brain development, cognitive performance, neuroprotection, and neurodegenerative diseases. Studies were identified through searches in databases such as PubMed, ScienceDirect, and Wiley Online Library using keywords like "testosterone," "cognition," "brain development," "neuroprotection," and "Alzheimer's disease." The review emphasizes human-focused research published between 2000 and 2024, with a particular focus on large-scale cohort studies.

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Inclusion Criteria

The review included studies that:

- Examined testosterone's relationship with brain structure, cognitive abilities, or neurodegenerative diseases.
- Featured both male and female participants across various age groups.
- Employed quantitative hormonal assessments (e.g., serum testosterone, testosterone-to-cortisol ratio).
- Investigated cognitive functions such as memory, spatial reasoning, verbal fluency, or executive tasks.
- Explored both physiological and therapeutic aspects of testosterone.

Exclusion Criteria

Animal-based research, studies with fewer than 100 participants, or those lacking cognitive metrics or accurate hormonal assessments were excluded.

Data Extraction

Key data included sample demographics, testosterone measurement methods, cognitive outcomes, and findings linking testosterone to cognition, neuroprotection, or neurodegeneration.

Methodological Approach

Hormonal levels were measured using serum assays, often adjusted for SHBG. Cognitive assessments included memory, spatial reasoning, verbal fluency tests, and, in some cases, neuroimaging (MRI, fMRI). Population-based studies, such as the UK Biobank with over 150,000 participants, highlighted testosterone's relationship with dementia. Additionally, research on testosterone replacement therapy (TRT) focused on its effects in hypogonadal and aging populations.

Statistical and Ethical Considerations

Multivariate regression models accounted for variables such as age, BMI, and SHBG levels, with significance set at $p<0.05$. All studies complied with ethical standards, ensuring participant anonymity and informed consent.

Results

Testosterone profoundly shapes brain development, particularly the corticohippocampal regions, during prenatal and early life stages. Prenatal exposure to this hormone leads to structural changes that enhance spatial reasoning and executive functions later in life [4,5] In adolescence, the testosterone-to-cortisol ratio has been shown to boost cognitive performance, especially in males, underscoring its critical role during this period [6,7].

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During puberty, increased testosterone levels are linked to enhanced visuospatial abilities and decision-making. Adolescents with higher levels of the hormone demonstrate superior problem-solving skills [6,8]. However, excessively elevated levels can contribute to impulsivity, indicating the importance of maintaining hormonal balance [9].

In adulthood, testosterone continues to influence cognitive abilities. Higher serum levels are associated with improved memory retention, verbal fluency, and risk management [10,11]. Women with balanced testosterone levels during reproductive years show better verbal fluency and multitasking skills, illustrating gender-specific cognitive effects [10].

With age, declining testosterone levels are associated with reduced cognitive performance and a higher risk of neurodegenerative diseases like Alzheimer's. Hormone replacement therapy (HRT) has shown potential in mitigating these declines, though it carries cardiovascular risks if not carefully monitored [12,13,14,15]. Elevated levels of sex hormone-binding globulin (SHBG), which lowers bioavailable testosterone, have also been linked to an increased risk of dementia [19].

The hormone also exerts neuroprotective effects by reducing oxidative stress, regulating synaptic plasticity, and preventing neuroinflammation. Studies indicate that higher testosterone levels can delay cognitive decline and improve learning and memory [13,16,17,18]. Its interaction with androgen receptors in the hippocampus further enhances these protective benefits [18,20].

Gender-specific differences in testosterone's effects remain evident. In males, its conversion to estradiol significantly enhances spatial cognition, while in females, fluctuations in testosterone levels influence verbal fluency, mood, and attention [6,9,10,16].

Therapeutically, testosterone replacement therapy benefits hypogonadal men by improving memory, executive functions, and reducing depressive symptoms [12,14]. However, excessive doses can lead to adverse effects, such as mood instability and cardiovascular complications, highlighting the need for careful management [15,19].

Higher testosterone-to-cortisol ratios are associated with better stress resilience and decision-making in high-pressure scenarios, emphasizing the hormone's role in coping with challenges [6,8,9]. On a molecular level, testosterone promotes neurogenesis, inhibits apoptosis, and regulates mood and cognition through its effects on dopamine and serotonin pathways [16,17,20].

These insights highlight the central role of testosterone in cognitive health, from early development to aging, while emphasizing its therapeutic potential and the need for balance to avoid adverse effects.

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Testosterone as Protection Against Dementia

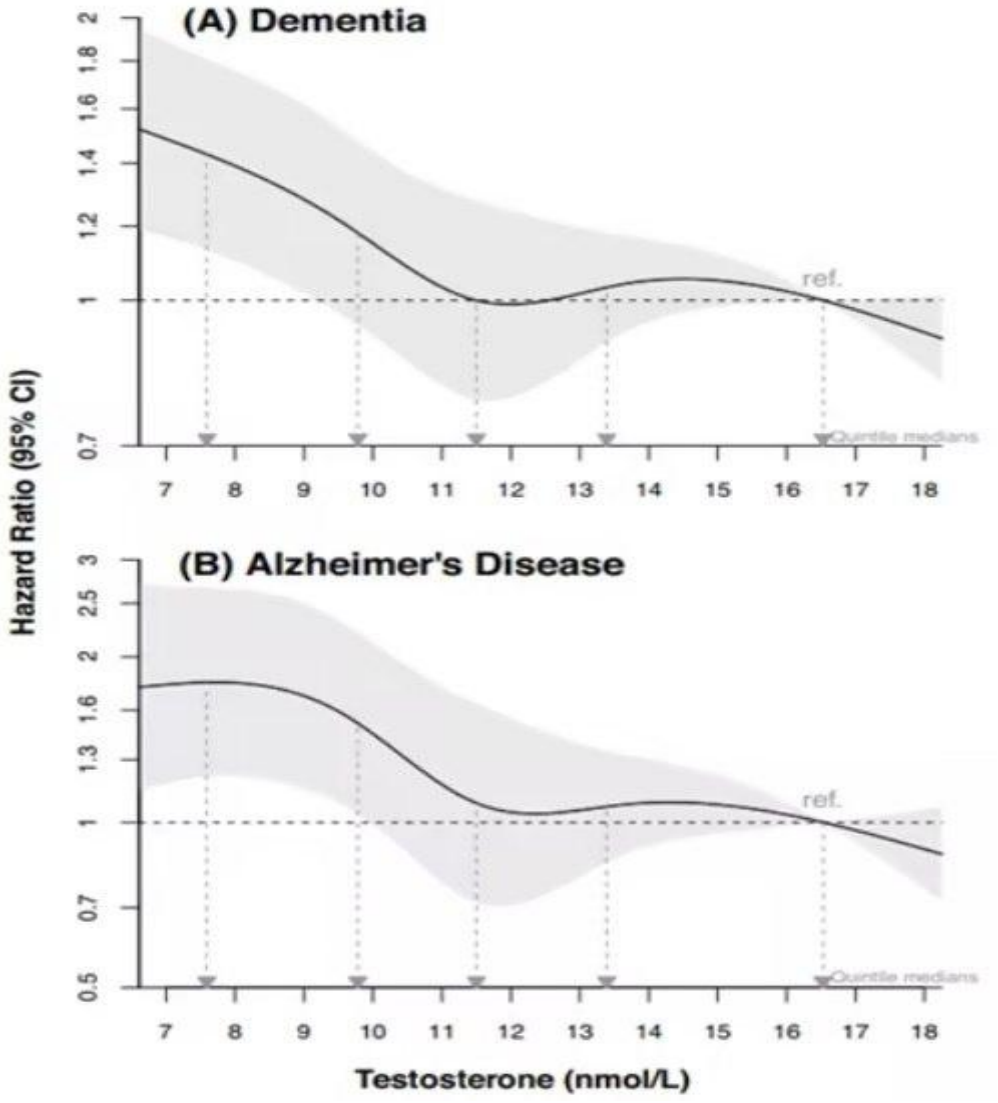
A study of over 150,000 UK men (median age: 61, follow-up: 7 years) revealed that lower testosterone and higher SHBG levels** independently increased the risk of dementia and Alzheimer's disease by age 68.

Balanced testosterone (20–40 nmol/L) is vital for cognitive health. Extremes lead to risks:

-**Excess levels** (e.g., 500 mg testosterone weekly) may boost strength but cause mood swings, hypertension, and early death.

- Low levels (e.g., 18 nmol/L with high SHBG) increase risks of insulin resistance, depression, obesity, and dementia.

The accompanying tables highlight these findings, stressing the importance of maintaining hormonal balance for cognitive protection. [20]



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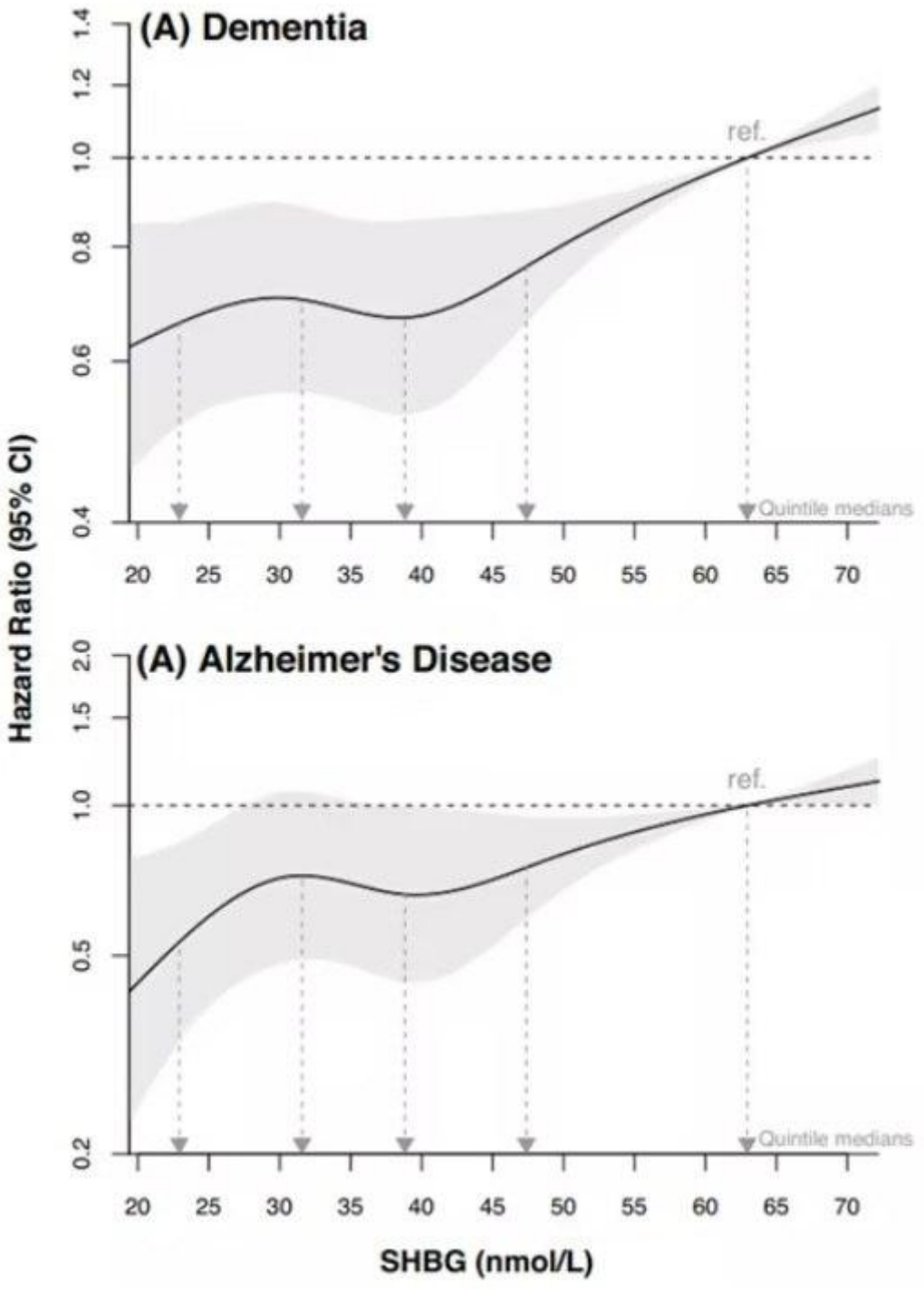

This exploration serves as a testament to the hormone's profound impact, inviting both curiosity and caution as we consider its potential to enhance human cognitive health and longevity.

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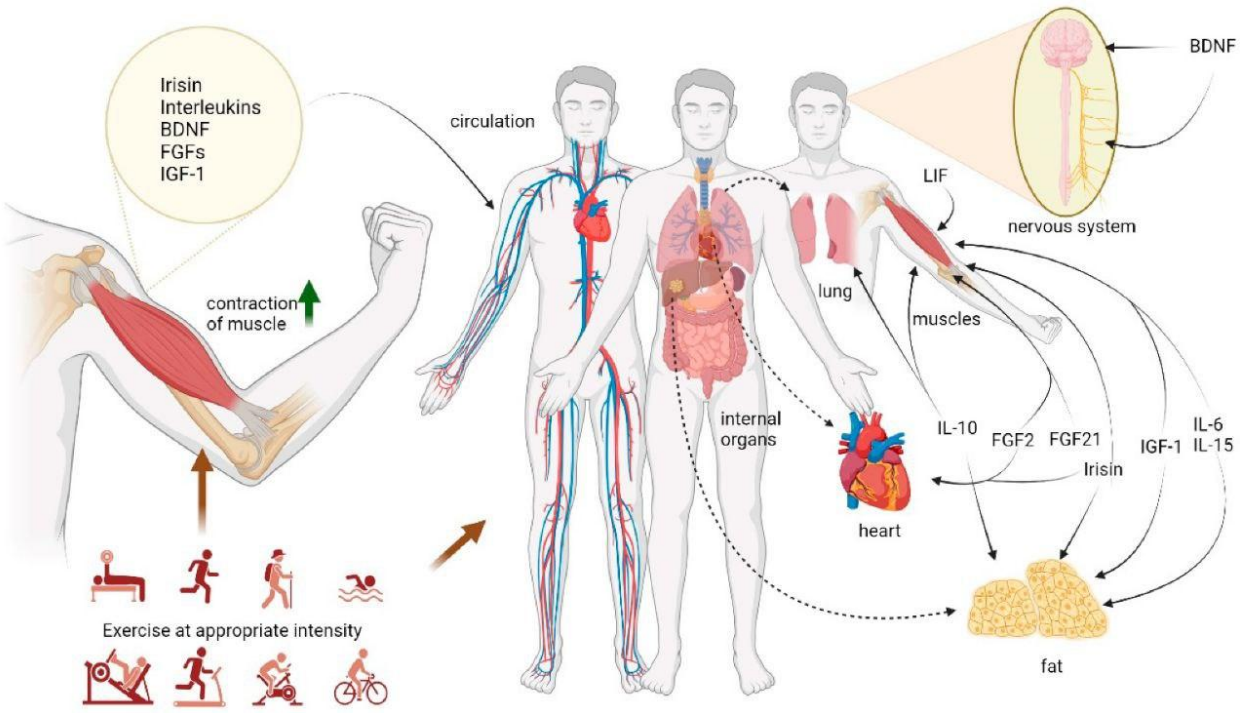

Exercise-induced myokines positively regulate the circulatory system, heart, lung, muscle, and nervous system|A variety of exercises induce the release of myokines from skeletal muscles. Myokines act on nerve, muscle, heart, lung, fat, and other tissues to promote health. (Created with BioRender.com).

Brain-derived neurotrophic factor (BDNF) is a key neurotrophin involved in neuronal survival, synaptic plasticity, and neurogenesis. Synthesized as pro-BDNF, it is cleaved into mature BDNF (mBDNF), which activates the TrkB receptor, initiating signaling cascades such as the Ras-MAPK-CREB pathway, crucial for cognitive processes. BDNF is widely distributed in the brain, skeletal muscle, and peripheral tissues, crossing the blood-brain barrier bidirectionally, linking central and peripheral systems.

Exercise significantly modulates BDNF levels, enhancing cognitive function. Aerobic exercise has been shown to elevate plasma pro-BDNF and mBDNF, with skeletal muscle serving as a potential source of pro-BDNF. Clinical and preclinical studies demonstrate that increased BDNF levels improve cognitive function, mitigate neurodegeneration, and enhance neuroplasticity. In Parkinson's disease, reduced BDNF levels correlate with symptom severity, while exercise-induced BDNF upregulation improves neural plasticity. Additionally, myokine irisin, secreted from skeletal muscle, modulates hippocampal BDNF expression, reinforcing the link between muscle activity and cognitive health.

However, excessive exercise may exert a paradoxical effect, decreasing serum BDNF and hippocampal volume, suggesting that the cognitive benefits of BDNF are exercise-intensity dependent. Given testosterone's role in neuromodulation and its association with BDNF expression, the interaction between androgen levels, muscle function, and

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neurotrophic signaling is a crucial area for further research in cognitive health and neurodegenerative disease prevention.. [21]

Conclusion

The journey through this research has illuminated the profound influence of testosterone on cognitive health and its critical role in shaping brain function across the lifespan. From the earliest stages of development, testosterone proves essential, guiding the formation of the corticohippocampal regions that underpin spatial awareness and executive abilities[4,5].

As adolescence unfolds, testosterone not only fuels cognitive growth, enhancing skills like decision-making and visuospatial reasoning, but also reveals its dual nature—its excess potentially fostering impulsivity [6,9]. In adulthood, this hormone becomes a key to unlocking sharper memory, verbal fluency, and refined decision-making, offering distinct and nuanced benefits to men and women alike
[10,11].

Yet, it is in the later chapters of life that testosterone's narrative becomes most poignant. Its decline with age emerges as a shadow over cognitive vitality, increasing the risk of dementia and Alzheimer's disease. Hormone replacement therapy (HRT), while promising as a shield against such decline, demands careful use, as the risks to cardiovascular health linger[12,13,14,15].

Beyond its role in sustaining cognition, testosterone is revealed as a guardian of the brain, shielding it from oxidative stress, calming neuroinflammation, and nurturing synaptic connections. These protective mechanisms not only slow cognitive deterioration but breathe life into the learning and memory processes of the aging mind[13,16,17,18].

However, this hormone's story is not without complexity. While testosterone therapy offers hope for those with deficiencies, exceeding natural levels brings challenges, from mood instability to physical risks, underscoring the delicate balance required[14,15,19]. Moreover, its interplay with gender adds further depth—its conversion to estradiol shaping male spatial abilities, while its fluctuations in women weave into verbal and emotional landscapes[6,10,16].

In essence, testosterone emerges as a cornerstone of cognitive resilience and neuroprotection, holding the promise of therapeutic applications for those battling neurodegenerative diseases or age-related cognitive decline. Yet, the tale is far from complete. Future research must delve deeper, unraveling the long-term effects of therapy and the intricate dialogue between testosterone and other hormonal systems [6,12,20].

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