Maturitas 214 (2026) 109124

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Hypogonadism in aging men: Impact of comorbidities, diagnosis and treatment☆

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ARTICLE INFO

Keywords:
Male hypogonadism
Functional hypogonadism
Aging
Metabolic syndrome
Obesity
Testosterone replacement therapy

ABSTRACT

Male hypogonadism is increasingly prevalent with advancing age and is particularly frequent among men with obesity, type 2 diabetes mellitus, and other cardiometabolic comorbidities (functional hypogonadism), whereas it remains relatively uncommon in younger men except in the presence of congenital or acquired disorders affecting the hypothalamic–pituitary–testicular axis (organic hypogonadism).

Historically, the relationship between testosterone decline and aging per se, as well as the contribution of comorbidities, has been debated. Similarly, uncertainty has persisted regarding the management of obesity-associated functional hypogonadism, and diagnostic thresholds remain insufficiently standardized across different guidelines.

Therefore, this narrative review addresses unresolved issues in diagnostic criteria, etiological assessment, and the impact of treatment on symptoms and long-term health outcomes in older men. It was based on a literature search conducted in PubMed using combinations of keywords such as *obesity*, *testosterone*, *male hypogonadism, functional and organic hypogonadism*, *aging men*, *metabolic syndrome*, *diabetes*, and *comorbidities*. Original research articles, systematic reviews, meta-analyses, and clinical guidelines published in English were screened, and the most relevant and high-quality publications were selected to provide a comprehensive overview of the current evidence. Additional relevant studies were identified through the reference lists of retrieved articles.

1. Introduction

Male hypogonadism (MH) is a syndrome characterized by androgen deficiency and impaired spermatogenesis. It is defined as a biochemical and clinical condition in which reduced testosterone (T) concentrations are associated with relevant and compatible symptoms or signs [2].

Its epidemiology is influenced by variability in definitions and diagnostic criteria, as well as differences in the distinction between biochemical and symptomatic hypogonadism and in the populations studied [3]. Nevertheless, the prevalence of clinically significant symptomatic MH is estimated to range between 2% and 5.3% [4,5].

According to its etiology, MH is typically classified as hypergonadotropic (primary) hypogonadism, resulting from testicular failure, and hypogonadotropic (secondary) hypogonadism, in which the underlying cause resides in hypothalamic or pituitary dysfunction. Mixed forms, meaning a reduced testicular synthesis of T due to a combination of causes, may also occur [6]. Furthermore, "compensated hypogonadism" refers to a condition in which serum T levels remain within the normal range despite elevated luteinizing hormone (LH), reflecting increased hypothalamic–pituitary stimulation to preserve T production in the presence of early or subclinical testicular dysfunction [7]. Lastly, MH may also result from impaired T bioactivity secondary to alterations in androgen receptor function or increased levels of sex hormone–binding globulin (SHBG), due to aging or the use of drugs that increase its levels [8].

Organic causes account for a minority of MH cases. The most common primary cause is Klinefelter syndrome, while other non-iatrogenic forms are rare. In contrast, iatrogenic MH is becoming increasingly common, mainly due to androgen deprivation therapy for prostate cancer, chemotherapy, radiotherapy, or gonadectomy for both oncological and non-oncological indication. Secondary MH is most often associated with traumatic brain injury, corticosteroids, opioids, anabolic–androgenic steroids, or drugs causing hyperprolactinemia, whereas pituitary tumors, hyperprolactinemia, Cushing syndrome, and iron

☆ This article is part of a Special issue entitled: 'Older Men's Health' published in Maturitas.

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https://doi.org/10.1016/j.maturitas.2026.109124
Received 31 January 2026; Received in revised form 13 August 2026; Accepted 8 September 2026
Available online 9 September 2026

overload disorders are uncommon causes [1].

Functional hypogonadism (FH), historically referred to as late-onset hypogonadism (LOH), is a more frequent condition characterized by a potentially reversible and often borderline reduction in T levels, mainly secondary to age-related comorbidities or metabolic disorders such as diabetes, obesity, or metabolic syndrome (MS), in the absence of an organic disruption of the hypothalamic–pituitary–gonadal (HPG) axis [9].

Unlike organic MH, which generally requires lifelong testosterone replacement therapy (TRT) unless contraindicated, FH is potentially reversible, with typically milder, multifactorial symptoms. Consequently, the benefits of TRT are more limited and depend on the underlying condition, making treatment indications individualized rather than routine (Table 1).

2. Clinical presentation of male hypogonadism

Signs and symptoms of MH depend on the age of onset, the severity of testosterone deficiency (TD), and the underlying cause. Prepubertal onset is characterized by delayed or incomplete puberty, with absent secondary sexual characteristics, small testes, micropenis, and cryptorchidism. In adults, the most specific manifestations are reduced libido, erectile dysfunction, and fewer spontaneous erections, while fatigue and mood disturbances are common but nonspecific. Physical findings may include gynecomastia, reduced body hair, small testes, increased fat mass, decreased muscle mass, anemia, lower age-adjusted prostate-specific antigen (PSA) levels, and reduced bone mineral density [2].

3. Diagnosis

Diagnosing MH can be challenging due to discrepancies among available assays and variability in T reference ranges. In addition, divergent diagnostic cutoffs for total testosterone (TT) and free testosterone (fT) exist among major medical societies and across regions, primarily due to differences in assay standardization, reference populations, and clinical priorities [3].

A recent article by Tsampoukas et al. [3] summarizes the differences in guidelines among nine different scientific societies. Guidelines differ in terminology (e.g., MH vs. TD, FH vs. LOH), in classification based on etiology (hypo- vs. hypergonadotropic, timing of onset, functional vs. organic), and in the inclusion of concepts such as mixed hypogonadism, decreased T bioactivity, or compensated hypogonadism. Most importantly, there is no universal consensus on diagnostic criteria based on clinical history, symptoms, and biochemical T measurements [2,7,10–15].

Regarding biochemical measurements, most clinical societies emphasize measuring TT in a fasting morning sample, typically between 7:00 and 11:00 a.m., with some recommending repeat testing to confirm the result [10,13].

Differences in total and free T diagnostic cutoffs create a diagnostic "gray zone" and contribute to variability across recommendations. While TT <8 nmol/L generally supports a diagnosis of MH and TT >12 nmol/L effectively excludes it, values between 8 and 12 nmol/L remain diagnostically uncertain [3] (Table 2).

For fT, assessed by equilibrium dialysis (gold standard) or, when unavailable, by a validated calculation such as the Vermeulen equation (based on TT, SHBG, and albumin), there is even greater variability in the recommended cutoffs. Certain societies—such as the EAA (European Academy of Andrology), SIAMS (Italian Society of Andrology and Sexual Medicine), and SfE (Society for Endocrinology) suggest a threshold of 220–225 pmol/L. [7,14] (Table 2).

Some societies also recommend measuring LH to help distinguish the underlying etiology of MH, with SIAMS suggesting that LH > 9.4 U/L indicates primary hypogonadism [10].

In most guidelines, prolactin (PRL) testing is indicated in all men with suspected secondary hypogonadism, and MRI should be performed in those with hyperprolactinemia, mass effect symptoms, panhypopituitarism, or markedly low T [11,12] (Table 2).

4. Comorbidities and hypogonadism

The prevalence of MS has increased substantially worldwide over the past two decades, with current global estimates indicating that approximately 25.7% of men are affected as of 2023 [16].

Among MS components, central/visceral adiposity is the dominant correlate of reduced T levels; in a primary-care cohort, the prevalence of biochemical low T (irrespective of symptoms) rose to 44% in men with waist circumference (WC) ≥110 cm [17].

Tsutsumi et al. highlight the bidirectional relationship between obesity and FH, which appears to be stronger in the direction from obesity to hypogonadism. At the level of the HPG axis, leptin resistance, metabolic inflammation and cytokine activity disrupt kisspeptin signalling, thereby reducing GnRH secretion in hypothalamic neurons. Peripherally, elevated leptin levels and oxidative stress impair steroidogenesis in Leydig cells. Negative feedback on GnRH due to increased oeastradiol—resulting from aromatization of T in adipose tissue—is a more debated mechanism. Finally, obesity markedly reduces SHBG levels, as inflammation decreases its hepatic synthesis, thereby affecting T bioavailability [18].

MH exacerbates adiposity and metabolic dysfunction, creating a vicious cycle. Hypogonadism promotes increased fat mass and insulin resistance through mechanisms such as elevated lipoprotein lipase (LPL) activity, reduced noradrenergic-mediated lipolysis, decreased protein synthesis, and lower physical activity. These changes further suppress the HPG axis and Leydig cell function, while promoting chronic inflammation via increased pro-inflammatory cytokines [18].

Table 1
Organic hypogonadism vs functional hypogonadism (adapted from Basaria et al, Grossman et al.) [47,48].

Feature	Organic Hypogonadism	Functional Hypogonadism
Underlying cause	Defined structural or congenital damage of the HPG axis	Likely suppressed by comorbidity without any other identifiable structural disease
Reversibility	Typically permanent and irreversible	Potentially reversible functional suppression (e.g. weight loss ≥5–10%, comorbidity control)
Clinical presentation	Specific symptoms and objective signs (e.g. low libido, small testes, gynecomastia, reduced body hair) with direct causal relationship	Less specific symptoms (e.g. erectile dysfunction, fatigue, low mood) which may overlap with comorbid conditions
Testosterone levels	Persistently and markedly reduced	More often borderline-low or fluctuating near the lower normal range
Gonadotropins	Elevated in primary forms, inappropriately normal/low in secondary forms	Usually normal, occasionally reduced
TRT indication	Definitive; lifelong	Conditional, time-limited trial for predominantly sexual symptoms, after lifestyle optimisation has failed
Expected benefits/ risks of testosterone therapy	Sexual function, BMD and fracture risk (especially Klinefelter, young onset), muscle mass, erythropoiesis, QoL	Sexual function (modest); body composition in less-complicated patients, modest BMD gain
Preferred formulation	Long-acting injectable, short-acting gel	Short-acting gel (reversibility, dose titration)

Table 2
Different total testosterone (TT) and calculated free testosterone (cfT) cutoff values for the diagnosis of male hypogonadism according to the recommendations of various scientific societies (adapted from Tsampoukas et al.) [3]. Note: TT concentrations are expressed in nmol/L; To convert TT concentrations from nmol/L to ng/dL, multiply by 28.84 (ng/dL = nmol/L × 28.84).

Society	TT suggestive of pituitary pathology	TT cutoff diagnostic of MH	TT "gray zone" and recommended next steps	TT cutoff excluding MH	cFT cutoffs diagnostic of MH
ISA, ISSAM, EAU, EAA and ASA [49]	5.2 nmol/L	8 nmol/L	8–12 nmol/L (repeat, calculate fT)	12 nmol/L	225 pmol/L
AUA [12]	5.2 nmol/L	10.4 nmol/L (repeated)	–	–	–
EAA [7]	6 nmol/L	8 nmol/L	8–12 nmol/L (repeat, fT)	12 nmol/L	–
BSSM [13]	5.2 nmol/L	8 nmol/L (repeated)	8–12 nmol/L (calculate fT)	12 nmol/L	225 pmol/L
SfE [14]	–	8 nmol/L	8–12 nmol/L	12 nmol/L	220 pmol/L
EnS [2]	5.2 nmol/L	264 ng/dL (~9.2 nmol/L). (repeated)	(repeat, calculate fT)	–	–
ISSM [15]	–	8 nmol/L (repeated)	8–12 nmol/L (repeat, calculate fT in obese and older men)	12 nmol/L	–
SIAMS/SIE	6 nmol/L	12 nmol/L (repeated)	–	–	220 pmol/L

5. Age and testosterone levels

When considering T levels alone, several epidemiological studies have consistently demonstrated a progressive decline in circulating T concentrations in men over time, with an estimated annual decrease ranging from 0.4% to 0.85% (corresponding to an average reduction of approximately 0.110 nmol/L per year) from early adulthood, despite differences in study design and methodological approaches [19,20]. The decline in fT is steeper due to age-related increases in SHBG, with fT dropping by about 1.5–2% per year [21,22].

While underlying health conditions can contribute to the reduction in androgen levels, several studies indicate that this decline is also observed in otherwise healthy men, suggesting that aging per se represents a significant risk factor [19]. However, some well-conducted longitudinal and cross-sectional studies have failed to demonstrate a significant association between age and declining T levels after controlling for comorbidities and other confounding factors, thereby questioning the role of aging per se [4,17,23].

Accumulating evidence, in fact, indicates that MH in older men is predominantly functional rather than the result of intrinsic hypothalamic–pituitary aging, with obesity, metabolic dysfunction, chronic systemic illness, and medications representing the main drivers of HPG axis suppression. Consequently, the age-related decline in T appears to reflect the cumulative burden of comorbidities rather than chronological aging itself and may be at least partially reversible following correction of these underlying conditions [4,18,24,25].

Nevertheless, a smaller but clinically relevant subgroup of men, whose prevalence increases with advanced age (particularly beyond 65–70 years), develops primary testicular dysfunction resulting from progressive Leydig cell aging and reduced steroidogenic reserve. This process is often preceded by a state of compensated primary hypogonadism which may progress to overt primary hypogonadism. Compared with FH, this phenotype is less reversible because it reflects structural and functional deterioration of the testes [24].

In conclusion, MH in older men appears to be predominantly a secondary or mixed disorder, resulting from the combined effects of age-related decline in testicular reserve and comorbidity-driven suppression of the HPG axis [4,18,24].

6. Impact of testosterone replacement therapy on metabolic health

While the bidirectional relationship between obesity and hypogonadism is well established, the effectiveness of TRT in reversing this cycle is limited. TRT leads to a significant reduction in WC and blood triglyceride levels, with modest improvements in lean body mass and LDL cholesterol. However, it has not been shown to consistently improve body weight, body mass index (BMI), blood pressure, or glycemic control [26]. Weight loss itself is more effective in improving metabolic health, and some evidence suggests that intensive lifestyle therapy benefits may be attenuated when combined with TRT [27].

Lifestyle interventions and weight loss, on the other hand, are effective in restoring T levels in obese men with MS related FH, with the magnitude of T increase proportional to the degree of weight reduction.

Among the available obesity treatments, weight loss obtained with dietary and lifestyle modification is associated with modest average T rise that can be clinically meaningful in some men (approximately 2–3 nmol/L in TT levels with 5–10% of weight loss) while bariatric surgery can produce large increases in T (approximately TT 8 nmol/L) and higher likelihood of reversing obesity-associated FH [28–30]. GLP-1 receptor agonists in this setting generally increase TT in parallel with weight loss and metabolic improvement, while evidence for dual GIP/GLP-1 agonists (e.g., tirzepatide) on the male HPG axis is newer but suggests potentially larger improvements, likely reflecting greater adiposity reduction [31,32].

However, the rise in T is often limited by a concomitant increase in SHBG, so fT may not increase to the same extent as TT and clinical symptoms may not fully resolve in all men [33].

7. Testosterone and cardiovascular risk

The adverse cardiometabolic phenotype associated with FH, particularly in men with MS, likely contributes to the increased cardiovascular risk observed in this population [34]. However, despite improving some metabolic and body composition parameters, as discussed in the previous section, TRT for MH has not been shown to consistently reduce major adverse cardiovascular events (MACE) [35].

The TRAVERSE trial, a large randomized controlled study, indeed, found that TRT was noninferior to placebo regarding MACE in 5204 men with hypogonadism and high cardiovascular risk (hazard ratio 0.96; 95% CI, 0.78–1.17), indicating no significant increase or decrease in MACE over a mean follow-up of 33 months. However, the TRAVERSE trial demonstrated a higher incidence of atrial fibrillation (AF) (3.5% vs. 2.4%) and pulmonary embolism (PE) (0.9% vs. 0.5%) in the TRT arm compared with placebo [36].

These observations are supported by the large propensity score–matched analysis by Bonnet et al., including 117,908 matched pairs of cisgender men with hypogonadism and a median follow-up of 5 years, in which TRT was associated with an increased risk of AF (HR 1.27, 95% CI 1.22–1.32; $P < 0.0001$) and acute PE/deep vein thrombosis (DVT) (HR 1.26, 95% CI 1.18–1.34; $P < 0.0001$). Collectively, these data provide convergent evidence that TRT may confer an elevated risk of AF and venous thromboembolism (VTE), particularly over longer-term exposure [37].

Therefore, despite the absolute risk of VTE is low, TRT remains contraindicated in men with known thrombophilia or a history of VTE unless anticoagulation is considered [2].

Although TRT does not appear to increase cardiovascular risk, it

should still be avoided in men who have had a recent myocardial infarction or stroke (within the last four months), and in those with severe or decompensated heart failure (NHYA III-IV), due to concerns about fluid retention and potential cardiovascular complications [38].

8. Other benefits and risks of TRT

TRAVERSE and the Testosterone Trials (TTrials) show that TRT in older men provides the most consistent benefit for sexual symptoms, with smaller/less consistent benefits for physical function, mood/vitality, anemia, and bone surrogates, and no demonstrated benefit for cognition [39,40].

Although the TRAVERSE trial was not designed to evaluate fracture outcomes, an unexpectedly higher incidence of clinical fractures was observed among men receiving TRT than among those receiving placebo, despite improvements in BMD and bone microarchitecture. Clinical fractures occurred in 91 of 2601 men (3.50%) in the TRT group compared with 64 of 2603 men (2.46%) in the placebo group over a median follow-up of 3.19 years (HR 1.43, 95% CI 1.04–1.97) [36].

However, this finding should be interpreted cautiously, as the absolute risk increase was modest (+1.04% over 3.19 years). Moreover, when analyses were restricted to non–high-impact fractures, the between-group difference was attenuated, and the incidence of major osteoporotic fractures remained low and comparable between groups [36,41]. Given the consistent evidence from randomized controlled trials demonstrating that TRT improves BMD and bone microarchitecture [42,43] the observed increase in fracture risk is unlikely to reflect impaired bone quality. Instead, it may be explained by behavioural changes associated with early symptomatic improvement, such as increased physical activity, greater risk-taking behaviour, or higher exposure to trauma before adequate musculoskeletal adaptation has occurred [41].

Nevertheless, men at high risk of fragility fractures should receive evidence-based osteoporosis treatment irrespective of TRT. If TRT is indicated for the treatment of symptomatic MH, it should be prescribed as adjunctive therapy, with patients explicitly counseled that current evidence does not demonstrate a reduction in fracture risk [44].

Although randomized trials have not demonstrated an increased incidence of prostate cancer or urinary tract symptoms(LUTS) [36,40], high-risk individuals were generally excluded, therefore older men should undergo baseline assessment for prostate cancer risk and LUTS, along with careful monitoring of PSA during treatment [2].

TRT is contraindicated in men with untreated or advanced prostate cancer, breast cancer, and those actively seeking fertility, due to the suppressive effect on spermatogenesis. Further contraindications include baseline erythrocytosis (hehaematocrit >48 or 50% according to different guidelines) and severe untreated obstructive sleep apnea (OSA), as these conditions may be exacerbated by TRT [10] (Fig. 1).

9. TRT: when and how

As previously discussed, organic MH generally warrants TRT unless contraindicated. In contrast, management of FH should primarily target reversible causes through weight loss, regular exercise, optimization of comorbidities, and discontinuation or modification of offending medications. In men with MS–related FH, lifestyle interventions, bariatric surgery when appropriate, and incretin-based therapies should be considered as first-line treatment. TRT should be reserved for carefully selected men with persistent symptomatic biochemical TD despite optimization of overall health, after individualized assessment of symptoms, T levels, and comorbidities. In this setting, the EAA guideline suggests a 3–6-month trial of transdermal TRT in men with persistent symptomatic but potentially reversible FH, with treatment discontinued if no clinical benefit is observed. Patients should be counseled about the uncertainty surrounding the long-term benefits and risks of TRT and the need for ongoing monitoring [2,6,7,11,12,45].

As sexual symptoms (reduced libido, decreased spontaneous erections, erectile dysfunction) are the most testosterone-specific and the only symptoms with consistent RCT evidence for TRT benefit, non-sexual symptoms (fatigue, mood, cognition, physical function) should not be the sole indication [45,46].

Transdermal options (gel or patch) are generally recommended as first-line therapy in older men with MH due to their ease of dose titration, lower risk of supraphysiologic peaks, favourable safety profile, and short-acting pharmacokinetics, which allow rapid discontinuation if adverse effects occur. Injectable formulations (e.g., long-acting undecanoate) may be considered for men who prefer less frequent dosing or experience adherence issues or skin irritation; however, these carry a higher risk of erythrocytosis and wider peak–trough fluctuations [10,38].

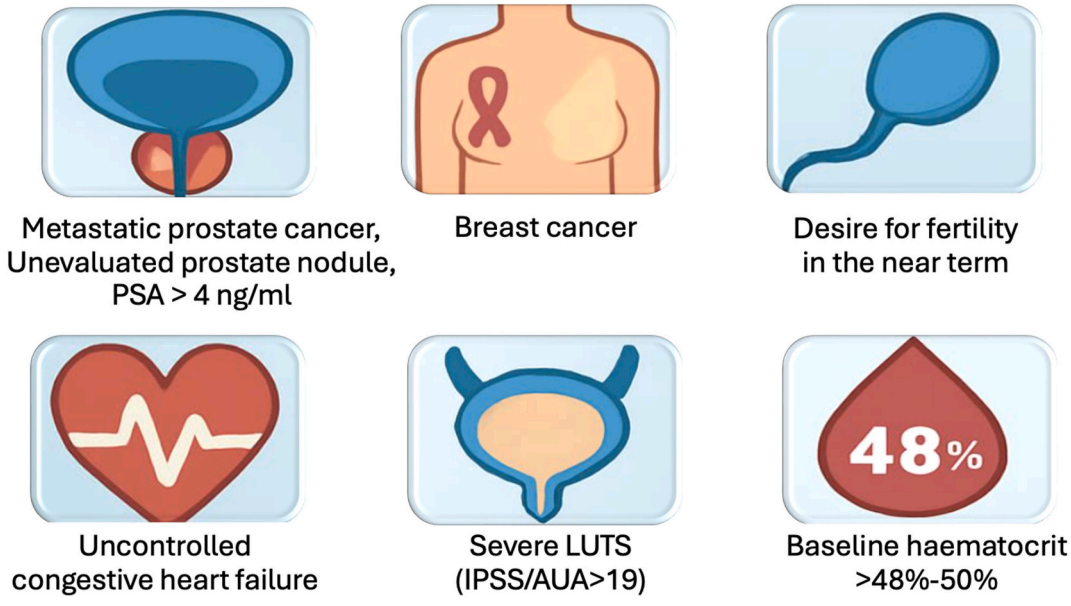

Fig. 1. Main contraindications to testosterone replacement therapy [2,7,12].

10. Treatment monitoring

Structured monitoring strategy is fundamental to ensure the efficacy and safety of TRT in men with MH.

Before treatment initiation, baseline evaluation should include serum TT, complete blood count with haematocrit, PSA and digital rectal examination (DRE) in men aged >40 years or according to individual prostate cancer risk, together with a comprehensive assessment of symptoms, treatment objectives, and cardiometabolic risk factors, including lipid and glycemic profiles [2,7,10].

During the first year of therapy, patients should undergo reassessment at 3–6 months and again at 12 months to evaluate clinical response, treatment adherence, adverse events, serum TT concentrations (to guide dose titration and maintain levels within the mid-normal physiological range), haematocrit, and prostate safety (PSA ± DRE, according to age and risk profile). Thereafter, clinical and biochemical monitoring should be performed at least annually, including periodic reassessment of metabolic parameters [2,7,10].

Particular attention should be paid to predefined safety thresholds. Haematocrit values >54% require temporary discontinuation of TRT, evaluation for reversible causes such as hypoxia or OSA, and subsequent treatment resumption at a reduced dose or with an alternative formulation once haematocrit has normalized. Similarly, a confirmed PSA concentration > 4 ng/mL, an increase in PSA >1.4 ng/mL during the first 12 months of treatment, abnormal DRE findings, or clinically significant worsening of LUTS should prompt urological evaluation and temporary discontinuation of TRT pending specialist assessment [2,7,10].

11. Conclusion

MH is increasingly recognized in older men, particularly in the setting of obesity, diabetes, MS, and multimorbidity, where FH should be viewed as a potentially reversible condition rather than an inevitable consequence of aging. Accordingly, lifestyle intervention, weight loss, and optimization of comorbidities should remain the cornerstone of management.

TRT should not be routinely prescribed in FH but may be considered in carefully selected men consistently confirmed low T levels and persistent symptoms despite appropriate lifestyle measures. Current evidence supports its greatest benefit for sexual symptoms, whereas effects on physical function, cognition, mood, and cardiometabolic outcomes remain uncertain. Given the limited long-term safety data, particularly regarding cardiovascular and prostate outcomes, individualized decision-making and regular monitoring are essential.

Future research should improve patient phenotyping and provide adequately powered trials to better define the role of TRT relative to lifestyle interventions.

Contributors

Serena Anna Ravelli conceived the review, performed the literature search, interpreted the findings, and drafted the manuscript.

Elisa Maseroli critically revised the manuscript and contributed to the interpretation of the literature.

Linda Vignozzi supervised the project and critically reviewed the manuscript.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Provenance and peer review

This article was commissioned and was externally peer reviewed.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used Open Evidence and Vera Health for bibliographic research verification and ChatGPT for minor language and stylistic editing. After using these tools, the author reviewed and edited the output as needed and take full responsibility for the content of the published article.

Funding

No funding was received for this work.

Declaration of competing interest

The authors declare that they have no competing interest.

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