MUSCULAR RESPONSES TO TESTOSTERONE REPLACEMENT VARY BY ADMINISTRATION ROUTE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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RUNNING HEAD: Muscular Responses to TRT: A Meta-Analysis

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ABSTRACT

Background: Inconsistent **fat-free mass (FFM)** and muscle strength responses have been reported in randomized clinical trials (RCTs) administering testosterone replacement therapy (TRT) to middle-aged and elderly men. Our objective was to conduct a meta-analysis to determine whether TRT improves **FFM** and muscle strength in middle-aged and elderly men, and whether the muscular responses vary by TRT administration route.

Methods: Systematic literature searches of MEDLINE/PubMed and the Cochrane Library were conducted from inception through March 31st, 2017 to identify double-blind RCTs that compared intramuscular or transdermal TRT versus placebo and that reported assessments of **FFM** or upper- or lower-extremity strength. Studies were identified and data were extracted and validated by three investigators, with disagreement resolved by consensus. Using a random effects model, individual effect sizes (ESs) were determined from 31 RCTs reporting **FFM** (sample size: n=1213 TRT, n=1168 placebo), and 17 reporting upper- or lower-extremity strength (n=2572 TRT, n=2523 placebo). Heterogeneity was examined and sensitivity analyses were performed.

Results: When administration routes were collectively assessed, TRT was associated with increases in **FFM** [ES=1.20±0.15 (95%CI: 0.91, 1.49)], total body strength [ES=0.90±0.12 (0.67, 1.14)], lower-extremity strength [ES=0.77±0.16 (0.45, 1.08)], and upper-extremity strength [ES=1.13±0.18 (0.78, 1.47)] (*P<0.001 for all*). When administration routes were evaluated separately, the ES magnitudes were larger and the percent changes were 3-5 times

greater for intramuscular TRT than for transdermal formulations versus respective placebos, for all outcomes evaluated. Specifically, intramuscular TRT was associated with a 5.7% increase in **FFM** [ES=1.49±0.18 (1.13, 1.84)] and 10-13% increases in total body strength [ES=1.39±0.12 (1.15, 1.63)], lower-extremity strength [ES=1.39±0.17 (1.07, 1.72)], and upper-extremity strength [ES=1.37±0.17 (1.03, 1.70)] (*P<0.001 for all*). In comparison, transdermal TRT was associated with only a 1.7% increase in **FFM** [ES=0.98±0.21 (0.58, 1.39)] and only 2-5% increases in total body [ES=0.55±0.17 (0.22, 0.88)] and upper-extremity strength [ES=0.97±0.24 (0.50, 1.45)] (*P<0.001*). Interestingly, transdermal TRT produced no change in lower-extremity strength versus placebo [ES=0.26±0.23 (-0.19, 0.70), *P=0.26*]. **Sub-analyses of RCTs limiting enrollment to men ≥60 years of age produced similar results.**

Conclusions: Intramuscular TRT is more effective than transdermal formulations at increasing LBM and improving muscle strength in middle-aged and elderly men, particularly in the lower-extremities.

INTRODUCTION

Serum testosterone declines by ~1.2% per year in middle-aged and older men [1]. Across the aging spectrum, hypogonadism (i.e., serum testosterone <300 ng/dL) is associated with deficits in muscle strength [2] and reduced **fat-free mass (FFM)** [3], along with a host of other health concerns [4]. **These muscular deficits develop gradually and are particularly apparent in lower extremity muscle groups involved in locomotion and balance [5], suggesting impaired physical function accompanies hypogonadism.** Several meta-analyses indicate that testosterone replacement therapy (TRT) modestly increases **FFM** [6, 7] and produces small improvements in muscle strength in middle-aged and elderly men [8, 7]. However, these relatively small muscular benefits remain an area of clinical debate, in terms of weighing the risk-to-benefit trade-off and their relevance to improved physical function [4, 9].

Despite the existing evidence, inconsistent **FFM** and muscle strength responses have been observed in double-blind, placebo-controlled randomized clinical trials (RCTs) administering TRT to middle-aged and elderly men [10]. For example, several RCTs have reported that transdermal patch- and gel-based TRT formulations produced small (0.9 – 1.9 kg) increases in **FFM** in elderly men, but did not improve muscle function in comparison with placebo [11, 12] or resulted in only minor improvements in muscle strength [13, 14]. In contrast, other RCTs indicate that elderly men exhibited relatively larger (3.1 – 4.2 kg) increases in **FFM** in response to intramuscular TRT, along with ~10-30% improvements in strength [15-17]. One explanation for these differing responses is that the musculoskeletal benefits of TRT may vary by route of administration (i.e., transdermal vs intramuscular) [10]. Indeed, transdermal and

intramuscular TRT administration routes provide different testosterone doses [9] and produce differing pharmacokinetics of androgen elevation [18, 19], which may affect musculoskeletal outcomes. **For example, intramuscular TRT formulations produce supraphysiologic testosterone concentrations for several days following injection, with values gradually declining into the physiologic range thereafter [18, 20]. In comparison, transdermal TRT formulations produce less robust testosterone elevations [19] that more consistently remain within the physiologic range [18].** The primary objectives of this systematic review and meta-analysis were to determine whether TRT improves **FFM** and muscle strength in middle-aged and elderly men, and whether the muscular responses to TRT vary by administration route. We hypothesized that intramuscular TRT would produce a greater magnitude of improvement in both **FFM** and muscle strength than transdermal TRT, when compared with respective placebos**, because 1) TRT produces dose-dependent muscular improvement in older men [21] and 2) intramuscular TRT elevates circulating testosterone to a greater magnitude than transdermal formulations [19, 18].**

METHODS

Data Sources and Searches

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Three authors systematically searched PubMed and the Cochrane Register through March 31st, 2017 using the following search strategy: (testosterone OR androgen) AND (men OR males) AND (clinical trial) AND (sarcopenia OR muscle OR lean

mass OR fat-free mass OR strength OR physical performance) and agreed upon eligibility of each study. This strategy was supplemented by manual searches of bibliographies from identified studies. Information from selected trials was extracted and verified in triplicate.

Study Selection

Inclusion criteria were pre-defined and included: 1) publications in English language-based refereed journals; 2) double-blind RCTs that compared participants receiving TRT versus placebo; 3) participant mean age of ≥45 years in the TRT and placebo groups; 4) TRT administration via intramuscular or transdermal (patch- or gel-based) formulations, with method and dose specified, for a minimum of 8 continuous weeks; 5) at least one of the following outcome measures reported: total body **FFM**, or upper-extremity or lower-extremity maximal strength; and 6) sufficient information to allow statistical comparisons among groups reported in the paper or provided by the corresponding authors during a supplemental query. We excluded trials 1) where endogenous testosterone secretion was experimentally suppressed prior to initiation of TRT because these studies did not have a true placebo group, 2) that administered androgens other than testosterone, 3) that co-administered drugs which affect muscular outcomes or sex-steroid metabolism, unless treatment arms existed that received only TRT and placebo, and 4) where exercise was combined with TRT, unless there were clearly delineated groups receiving TRT and placebo without exercise. A minimum duration of 8 continuous weeks was selected because **FFM** and strength improvements are observable within this time frame, but may not occur in studies of shorter duration. We checked for study duplication based on

authorship, study description, number of participants, and participant characteristics, to ensure that we did not include more than one study reporting the same dataset. When duplication occurred, we used the report containing the most comprehensive data for each outcome.

Data Extraction and Quality Assessment

The primary outcomes were total body **FFM** and total body strength, which represented a combination of upper- and lower-extremity strength measures. Secondary outcomes were upper- and lower-extremity strength. Data were extracted by trial arm and were validated in triplicate. Reviewers used an established tool to evaluate the quality of each trial [22]. Authors were contacted twice by email to ask for additional information if a trial met inclusionary criteria, but did not report data in a manner that would allow statistical assessment with our *a priori* methods. Studies were excluded if useable data could not be obtained with the above method.

Data Synthesis and Analysis

To account for differences in units of strength measures, we adopted the Hedge's *g*-index [23] to characterize the effect size (ES) of each data point, as shown in the following equation, with small sample size correction:

$$g = c(m)\frac{\bar{y}_d - \bar{y}_c}{S_{pooled}}$$

where $\bar{y}_d$ is the average change from baseline measurement of the drug group and $\bar{y}_c$ is the average change from baseline measurement of the control group. S_{pooled} is the pooled within-study standard deviation. c(m) is a correction factor given as the following: $c(m) = 1 - \frac{3}{4m-9}$

where m = n_d + n_p with n_d and n_p being the sample sizes in the drug and placebo group at post treatment, respectively. The converted ES and its variance for each study was included in the analysis. Heterogeneity was assessed using the Q statistic [23]. Our analysis indicated that heterogeneity was significant (<0.05) in all scenarios considered. Thus, a random effects model was fit using the DerSimonian-Laird approach to account for heterogeneity across studies [24]. Improvement was calculated as: $\frac{\bar{y}_{db}-\bar{y}_{cb}}{\bar{y}_{cb}} * 100\%$ where $\bar{y}_{db}$ is the ratio between post treatment and pre-treatment measurements of drug group and $\bar{y}_{cb}$ is the ratio between post treatment and pre-treatment measurements of placebo group.

A g-index statistic was determined for total body **FFM** and for each muscle strength measure. ESs were coded such that positive numbers reflected increasing **FFM** or strength and negative values reflected decreasing values in comparison to placebo. For each dependent measure, an ES and the accompanying 95% confidence interval (CI) are reported. ESs of 0.20-0.49 were considered small, 0.50-0.79 medium, 0.80-1.1 large, and ≥1.2 very large [25].

As noted above, several trials contained multiple upper- and/or lower-extremity strength measures. To examine bias due to lack of independent data points, we conducted sensitivity analyses on total body strength, upper-extremity strength, and lower-extremity strength by combining studies with multiple data points together using the Mantel-Haenszel method [26]. Specifically, we combined studies with multiple data points as one study, when measurement units were identical. Sensitivity analysis was not performed for **FFM** because all data points represented individual groups and the units of measurement were consistent among all studies.

To assess whether an age effect existed, we also performed subgroup analyses on all eligible RCTs that reported FFM or muscle strength outcomes and limited enrollment to men ≥60 years of age. Analyses were conducted using the open source statistical software package "metaphor" (v3.1.0) [27].

RESULTS

Study Selection and Characteristics

The initial search yielded 1227 publications, of which 127 were subjected to further scrutiny (Figure 1). From the references of these papers we identified 10 additional publications that required further review. Of these, 41 unique double-blind, placebo-controlled RCTs met our *a priori* selection criteria [28-31, 16, 32-37, 15, 38-40, 13, 41-48, 17, 49, 11, 50, 51, 14, 52-59, 12, 60, 61]. **All eligible studies were randomized, with investigators, providers, and subjects blinded to treatment allocation, and eligibility criteria were specified. Other aspects associated** with study quality assessment are reported in Table 1. We included data from 34 of these studies in the **primary** analysis, of which 15 administered intramuscular TRT and 18 administered transdermal TRT, with study characteristics reported in Table 2. **In our subgroup analysis, we included data from 19 of the above-mentioned studies that limited enrollment to men ≥60 years of age, of which 9 administered intramuscular TRT [28, 31, 16, 33, 35, 15, 17, 49, 53] and 10 administered transdermal TRT [38, 40, 13, 42, 44, 45, 11, 50, 14, 55].** We were unable to include the additional 7 RCTs that met our selection criteria [56-

59, 12, 60, 61] because data were not reported in the necessary format for our *a priori* statistical design and were not provided by authors upon query (Table 3).

Fat-Free Mass

We included 31 transdermal and intramuscular TRT studies (containing 34 ESs) that reported **FFM** (Figure 2) and obtained a pooled overall treatment ES of 1.20 (95%CI: 0.91-1.49; *P*<0.001), representing a 3.4% increase in **FFM** for TRT versus placebo (Table 4). Secondary analysis of the 15 studies evaluating intramuscular TRT produced an ES of 1.49 (1.13, 1.84; *P*<0.001), representing a 5.7% **FFM** increase. Conversely, analysis of 19 studies evaluating transdermal TRT produced an ES of 0.98 (0.58, 1.39; *P*<0.001), representing only a 1.7% increase in **FFM**.

Total Body Strength

For total body strength, we integrated 17 transdermal and intramuscular TRT studies (containing 100 ESs) that reported lower-extremity (Figure 3) or upper-extremity (Figure 4) strength measures and obtained a pooled overall treatment ES of 0.90 (0.67, 1.14; *P*<0.001), representing a 6.1% increase in strength versus placebo (Table 4). Separate analysis of the 9 intramuscular TRT studies (containing 44 ESs) resulted in an ES of 1.39 (1.15, 1.63; *P*<0.001), representing an 11.2% strength improvement. In comparison, analysis of the 8 transdermal TRT studies (containing 56 ESs) produced an ES of 0.55 (0.22, 0.88; *P*<0.001), representing only a 2.1% strength increase.

Lower Extremity Strength

For lower-extremity strength, we integrated 17 transdermal and intramuscular TRT studies (containing 62 ESs) and obtained a pooled overall treatment ES of 0.77 (0.45, 1.08; $P<0.001$), representing a 5% strength increase versus placebo (Table 4). Separate analysis of 9 intramuscular studies (containing 29 ESs) resulted in an ES of 1.39 (1.07, 1.72; $P<0.001$), representing a 10.4% increase in strength. Analysis of 8 transdermal TRT studies (containing 33 ESs) produced an ES of 0.26 (-0.19, 0.70; $P=0.26$), indicating transdermal TRT did not improve lower-extremity strength.

Upper Extremity Strength

For upper-extremity strength, we integrated 12 transdermal and intramuscular TRT studies (containing 38 ESs) and obtained a pooled overall treatment ES of 1.13 (0.78,1.47; $P<0.001$), representing a 7.8% strength increase versus placebo (Table 4). Separate analysis of the 6 intramuscular studies (containing 15 ESs) resulted in an ES of 1.37 (1.03, 1.70; $P<0.001$), representing a 12.9% increase in strength. In comparison, separate analysis of 6 transdermal TRT studies (containing 23 ESs) produced an ES of 0.97 (0.50, 1.45; $P<0.001$), representing only a 4.5% strength improvement.

Sensitivity Analysis

We conducted sensitivity analyses to ensure that RCTs containing multiple ESs for upper- and/or lower-extremity strength did not bias our outcomes. Using the Mantel-Haenszel approach [26], ESs and percent improvements were similar to the primary/secondary strength

outcomes reported above, with intramuscular TRT being associated with the largest ES magnitudes and greatest percentage improvements for all strength outcomes (Table 5).

Subgroup Analyses – Older Men

To evaluate the effects of TRT in older men, we conducted sub-analyses of RCTs that limited enrollment to men ≥60 years of age. For FFM, we included 16 transdermal and intramuscular TRT studies (containing 18 ESs) and obtained a pooled overall treatment ES of 1.36 (95%CI: 0.88, 1.83; *P*<0.001, Figure 5), representing a 4.2% increase in FFM for TRT versus placebo (Table 6). Sub-analysis of the 7 studies administering intramuscular TRT produced an ES of 1.84 (1.12, 2.55; *P*<0.001), representing a 7.3% FFM increase. In comparison, sub-analysis of the 9 studies evaluating transdermal TRT produced an ES of 1.04 (0.41, 1.67; *P*<0.001), representing only a 1.7% increase in FFM. For total body strength, we integrated 14 transdermal and intramuscular TRT studies (containing 93 ESs) that reported lower-extremity (Figure 6) or upper-extremity strength measures (Figure 7) and obtained a pooled overall treatment ES of 0.90 (0.67, 1.14; *P*<0.001), representing a 6.1% increase in strength versus placebo. The ESs and percentage increases for intramuscular and for transdermal TRT studies were similar to the primary strength outcomes reported above, with intramuscular TRT being associated with the largest ES magnitudes and greatest percent improvements (Table 6).

DISCUSSION

The increasing prevalence of TRT [62] is likely to continue, as a result of the increasing geriatric population. Previous meta-analyses of RCTs have reported that TRT positively influences health-related quality of life [63], bone mineral density (BMD) [64, 7], body composition [65, 66, 7, 6], sexual function and libido [67, 7], and several measures of metabolic health in men [65]. However, debate surrounds the potential utility of various TRT formulations in relation to promoting musculoskeletal integrity, muscular strength, and physical function in middle-aged and elderly men [9, 10]. For example, Corona et al reported that parenteral (i.e., intramuscular and transdermal) TRT collectively increased **FFM**, while oral TRT did not [65]. Tracz et al also reported that intramuscular TRT increased lumbar spine BMD, while transdermal formulations did not [64]. Similarly, meta-analyses have reported that oral TRT [19] and transdermal formulations [68] increase cardiovascular risk, while intramuscular TRT did not. These findings indicate that several risks and benefits associated with TRT may depend largely upon administration route [10]. The present meta-analysis was designed to supplement prior knowledge surrounding the effects of TRT on **FFM** and muscle strength in middle-aged and elderly men, and to determine the extent to which intramuscular and transdermal TRT administration routes effect these outcomes. Our primary findings indicate that TRT increased total body **FFM** and total body strength when intramuscular and transdermal TRT routes were examined collectively and separately versus respective placebos. Improvements in upper-extremity and lower-extremity strength were also observed when TRT administration routes were collectively analyzed. However, when evaluated separately, only intramuscular TRT

increased lower-extremity strength, with transdermal routes producing no improvement versus placebo. Interestingly, for all outcomes assessed, the ESs for intramuscular TRT were larger and the percentage improvements were 3-5 times greater than that of transdermal TRT, supporting the contention that intramuscular TRT produces greater muscular benefit than transdermal administration. **Similar results persisted when we evaluated RCTs that limited enrollment to men ≥60 years of age, which is the age-range most likely to experience hypogonadism [1], indicating that intramuscular TRT is an effective means to improve FFM and muscle strength in older men.**

*Comparison with Other Systematic Reviews - **FFM***

It is generally accepted that TRT increases **FFM** in middle-aged and elderly men [9]; although, the magnitude of this effect may vary dramatically by administration route [10]. Indeed, previous meta-analyses reported that TRT increased **FFM** from 1.6 kg (95%CI: 0.6, 2.6) [7] to 3.59 kg (2.38, 4.81) [6] when all administration routes were collectively assessed, a finding that is confirmed with our meta-analysis. Herein, we expand upon these studies by separately evaluating the effects of intramuscular and transdermal TRT on **FFM** and demonstrate a much larger magnitude of increase occurs with intramuscular TRT. Specifically, an apparent difference in percent change from baseline existed among administration routes, with a 5.7% increase in **FFM** resulting from intramuscular TRT and only a 1.7% increase resulting from transdermal formulations. From a clinical perspective and as an example, this implies that a 90 kg male would experience a 5.1 kg **FFM** increase with intramuscular TRT, as compared to a 1.5

kg **FFM** increase with transdermal formulations, providing further evidence for the **potential** utility of intramuscular TRT as means to prevent or reverse sarcopenia and frailty in hypogonadal men [10]. **However, our data should be interpreted cautiously given that 1) DXA was used to evaluate FFM in most RCTs included in our meta-analysis (see Table 2) and 2) intra- and extra-cellular water are inherently included as components of FFM assessed via DXA [69]. In this regard, TRT increases extra-cellular water by ~2 kg in hypogonadal men [70] and peripheral edema has been observed in small fraction of older men receiving TRT [56]. Other musculoskeletal imaging technologies (e.g., computed tomography, magnetic resonance imaging, or ultrasound) are considered a somewhat more reliable means to directly assess muscle mass because they are not as heavily influenced by extra-cellular fluid fluctuations [71, 72], although, few RCTs have utilized these imaging modalities to assess muscular changes resulting from TRT. Regardless, intramuscular TRT has been shown to increase muscle fiber cross-sectional area in older men, especially when administered at higher doses [73], demonstrating that testosterone produces direct myotrophic effects independent of fluid change.**

Several key differences also exist between our study and previous meta-analyses. For example, other meta-analyses assessing **FFM** included oral TRT (e.g., testosterone undecanoate, oxandrolone, and/or oxymetholone) or dihydrotestosterone formulations [65, 66, 7, 6]. We excluded RCTs administering dihydrotestosterone or oral TRT because: 1) from a clinical standpoint, these formulations are not commonly prescribed in the US [62], 2) Corona et al

recently reported that oral TRT did not increase **FFM** when evaluated separately from other parenteral TRT formulations [65], and 3) several RCTs have demonstrated that 5α-reduction of testosterone to dihydrotestosterone does not mediate improvements in **FFM** or muscular strength resulting from TRT [16, 17, 74]. Interestingly, our previous meta-analysis reported that transdermal TRT elevated circulating dihydrotestosterone to a greater magnitude than intramuscular formulations [10], likely due to the relatively higher 5α-reductase expression in skin versus skeletal muscle [75]; although, the clinical ramifications of these differing dihydrotestosterone elevations remain unknown.

Comparison with Other Systematic Reviews - Strength

Our finding that muscular strength improvements varied in middle-aged and elderly men based on TRT administration route provides evidence that accounts for the contrasting observations reported in several previous RCTs and meta-analyses [10]. For example, some RCTs reported that TRT produced pronounced **FFM** and strength improvements [15, 49], while others reported very minimal changes in comparison with placebo [12, 11, 13, 14]. Conflicting results are also present among meta-analyses, with Ottenbacher et al [8] reporting that TRT increased upper- and lower-extremity strength in middle-aged and elderly men and Isidori et al [7] reporting no improvement in knee extension, leg extension, knee flexion, or handgrip strength. In our meta-analysis, muscle strength was quantified as change from baseline, compared with respective placebo, and was comprised of three strength domains: (1) upper-extremity, (2) lower-extremity, and (3) total body. Across all strength domains, intramuscular

TRT yielded higher ESs and percent changes compared to transdermal TRT. Specifically, **within the entire cohort,** intramuscular TRT produced a very large and significant ES (ES: 1.39, 10.4% improvement) for lower-extremity strength, while transdermal TRT did not significantly improve this measure. Likewise, we observed a larger ES for upper-extremity strength for intramuscular TRT (ES: 1.37, 12.9% improvement) than for transdermal TRT (ES: 0.97, 4.5% improvement). Similarly, when upper- and lower-extremity strength measures were combined (i.e., total body strength), we observed a very large ES for intramuscular TRT (ES: 1.39, 11.2% improvement) and only a medium ES for transdermal TRT (ES: 0.55, 2.1% improvement). The most likely explanation for the differing strength outcomes reported in our meta-analysis and that of Isidori et al [7] are that we included more data points, despite limiting our selection criteria to double-blind, placebo-controlled RCTs, which was possible because we pooled upper- and lower-extremity strength assessments. Indeed, our results corroborate and update the findings of Ottenbacher et al [8], which is the only other meta-analysis of placebo-controlled RCTs that evaluated muscle strength responses in men receiving TRT, with the following caveats: (1) we evaluated total body **FFM** and report a larger magnitude of improvement with intramuscular TRT, providing a physiologic rationale for the larger strength improvements occurring with this administration route; (2) we did not include studies that administered dihydrotestosterone or oral TRT; and (3) we report that intramuscular TRT produced similar improvements for upper- and lower-extremity strength, while Ottenbacher et al reported a higher ES for lower-extremity than for upper-extremity strength, which is likely

explained by the larger number of ESs reported in our analysis (100 vs 38). **In addition, we evaluated RCTs that limited enrollment to men ≥60 years of age and observed that the magnitude of strength improvements were similar to that occurring in the entire cohort, indicating the effects of intramuscular TRT on muscle strength persist in older men.**

Clinical Relevance

The Endocrine Society recommends that the therapeutic target for adult men with classical androgen deficiency is the mid-normal range for healthy, young men (i.e., 400-750 ng/dL), with values assessed one-week post-injection for intramuscular TRT or on the day of administration for transdermal formulations [9]. To accomplish this, transdermal patch-based TRT preparations typically contain relatively low testosterone doses (35-70 mg T/week), while transdermal gel-based TRT formulations contain much higher doses **(350-1000 mg T/week)** due to low drug absorption [76, 77]. **Regardless, transdermal patch- and gel-based TRT formulations both maintain circulating testosterone in the physiologic range [19].** In comparison, intramuscular TRT typically delivers an intermediate testosterone dose (75-100 mg/week) [9], with differing pharmacokinetics than transdermal formulations, which results in substantially higher circulating testosterone for several days after administration **and values that gradually decline into the physiologic range thereafter** [18]. It is likely that the larger increase in circulating testosterone resulting from intramuscular TRT at least partially explains the greater **FFM** and strength improvements occurring with the intramuscular administration route, as TRT-induced improvements **in muscle fiber cross-sectional area [73] and muscle**

strength are dose-dependent in older men [21]. The clinical ramifications of this **apparent** dose-response effect seem clear, given that muscle quality and physical function are strongly associated [78] and that muscle strength, particularly in the lower-extremities, is independently associated with reduced mobility disability [79] and less functional decline in elderly men [80].

Limitations

No RCT to-date has directly compared muscular responses to different TRT administration routes. Our meta-analysis was designed to compare intramuscular and transdermal TRT versus respective placebos, and to infer differences among administration routes based on ES and percent change from baseline. **We believe this approach is an appropriate surrogate to a more direct dose-response analysis because 1) intramuscular TRT produces much higher circulating testosterone, on average, than transdermal TRT formulations [19, 18], 2) the different TRT formulations that we evaluated have vastly different testosterone absorption profiles and pharmacokinetics [18, 20], which limits a direct dose-response comparison, and 3) several RCTs included in our meta-analysis titrated TRT dose at the individual patient level [30, 15, 38, 13, 11, 50, 14, 55], for which TRT dose and circulating testosterone data are not readily available.** In addition, we did not selectively evaluate RCTs that enrolled men with hypogonadism because this would dramatically reduce the number of qualifying studies. However, the TRT and placebo groups from 7 intramuscular RCTs and 6 transdermal RCTs included in our analysis exhibited serum testosterone concentrations within the hypogonadal range. **As such, future RCTs comparing**

muscular responses to intramuscular and transdermal TRT formulations in hypogonadal men are warranted.

Conclusion

In summary, our meta-analysis of double-blind, placebo-controlled RCTs revealed that TRT increased **FFM**, total body strength, and upper- and lower-extremity strength when transdermal and intramuscular administration routes were evaluated collectively. Separate analysis of transdermal and intramuscular TRT versus respective placebos demonstrated that intramuscular TRT leads to larger ESs and 3-5 times greater percent improvement for all strength and **FFM** outcomes assessed. This effect was most pronounced for lower-extremity strength, which increased >10% with intramuscular TRT and did not improve with transdermal formulations. **Similar FFM and muscle strength responses were observed when selectively evaluating RCTs that limited enrollment to men ≥60 years of age.** These results suggest that intramuscular TRT is more effective than transdermal TRT in terms of preventing sarcopenia and improving muscle strength and physical function in middle-aged and elderly men.

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DISCLOSURE STATEMENT

Jared W. Skinner, Dana M. Otzel, Andrew Bowser, Daniel Nargi, Sanjay Agarwal, Mark D. Peterson, Baiming Zou, Stephen E. Borst, and Joshua F. Yarrow declare they have no conflict of interest.

FIGURE LEGEND

Figure 1. Selection process for double-blind, placebo-controlled randomized clinical trials (RCTs) assessing effects of testosterone replacement therapy (TRT) on **fat-free mass (FFM)** and/or muscle strength outcomes **in middle-aged and older men**.

Figure 2. Forest plot for **fat-free mass (FFM)** data derived from placebo-controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

Figure 3. Forest plots for lower-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

Figure 4. Forest plots for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

Figure 5. Forest plot for fat-free mass (FFM) data derived from placebo-controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

Figure 6. Forest plot for lower-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

Figure 7. Forest plot for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

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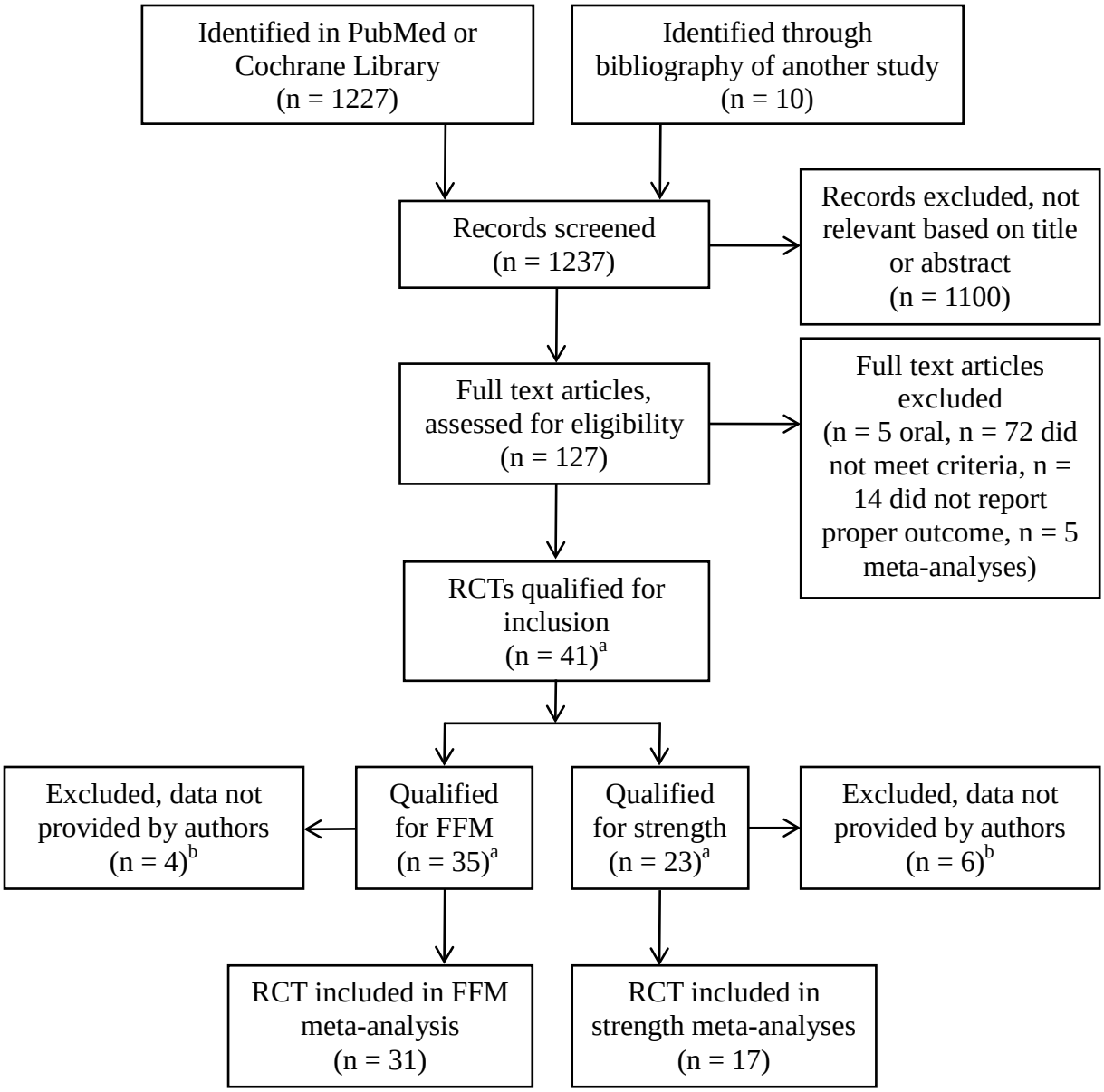
Figure 1. Selection process for double-blind, placebo-controlled randomized clinical trials (RCTs) assessing effects of testosterone replacement therapy (TRT) on **fat-free mass (FFM)** and/or muscle strength outcomes in middle-aged and older men.



[a]The discrepancy among total number of qualifying RCTs (n=41) and those qualifying for **FFM** (n=35) or strength analyses (n=23) stems from RCTs (n=17) that qualified for both analyses.

[b]RCTs (n=7) were excluded because data were not provided in a format that could be analyzed with our *a priori* statistical design, of which, n=2 qualified for both **FFM** and strength analyses.

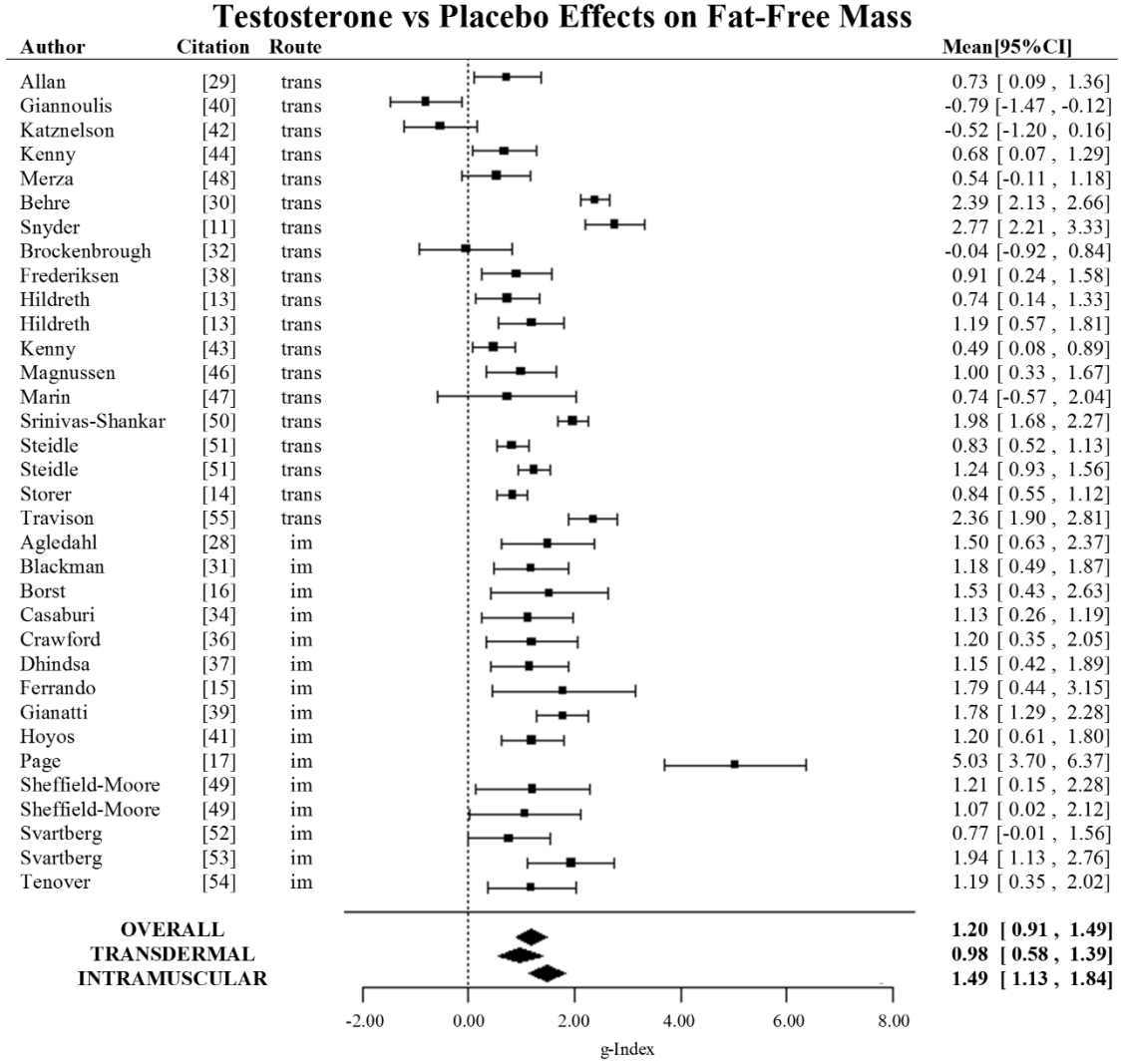


Figure 2. Forest plot for **fat-free mass (FFM)** data derived from placebo-controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

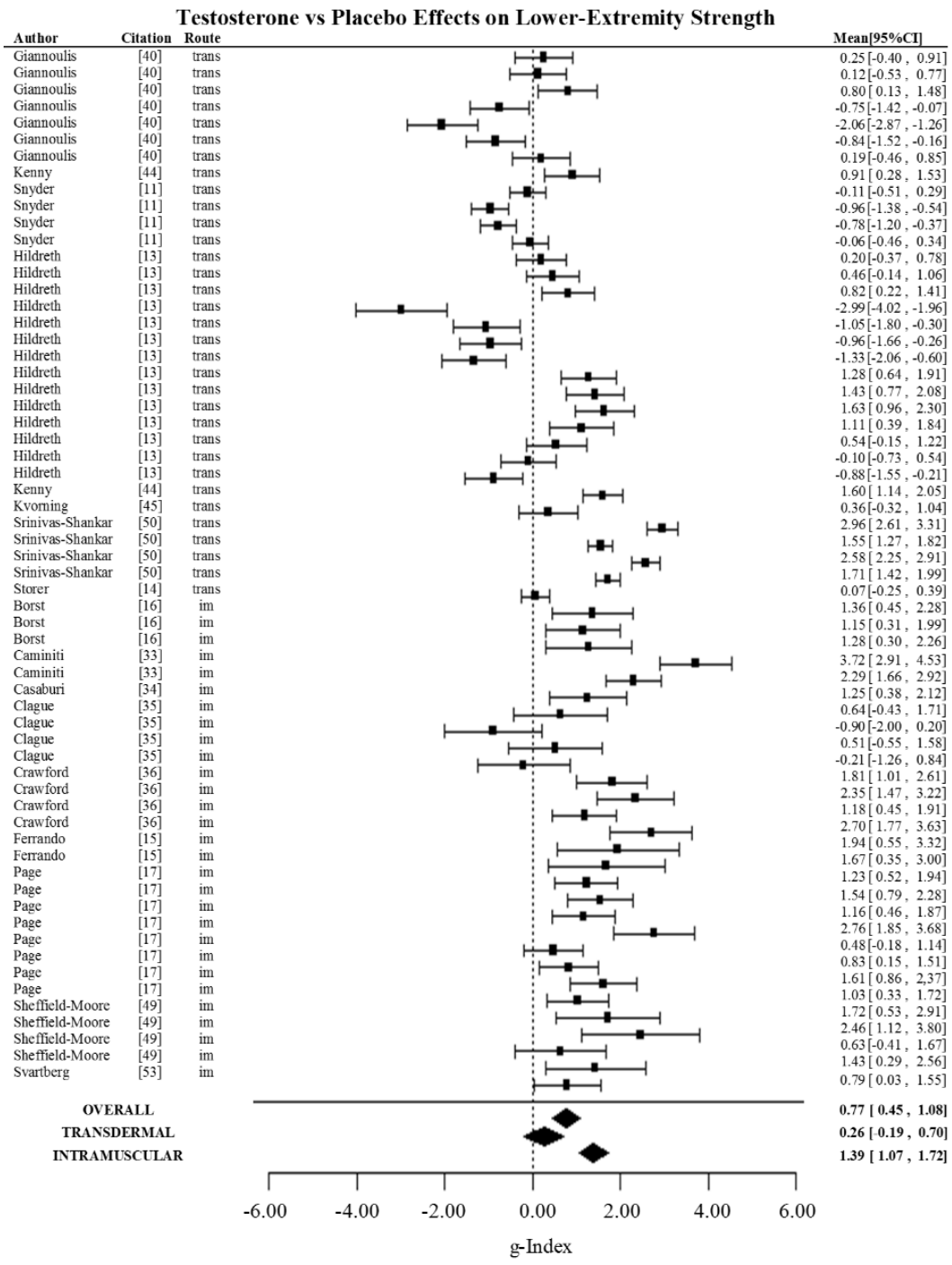


Figure 3. Forest plots for lower-extremity muscle strength data derived from placebo-

controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

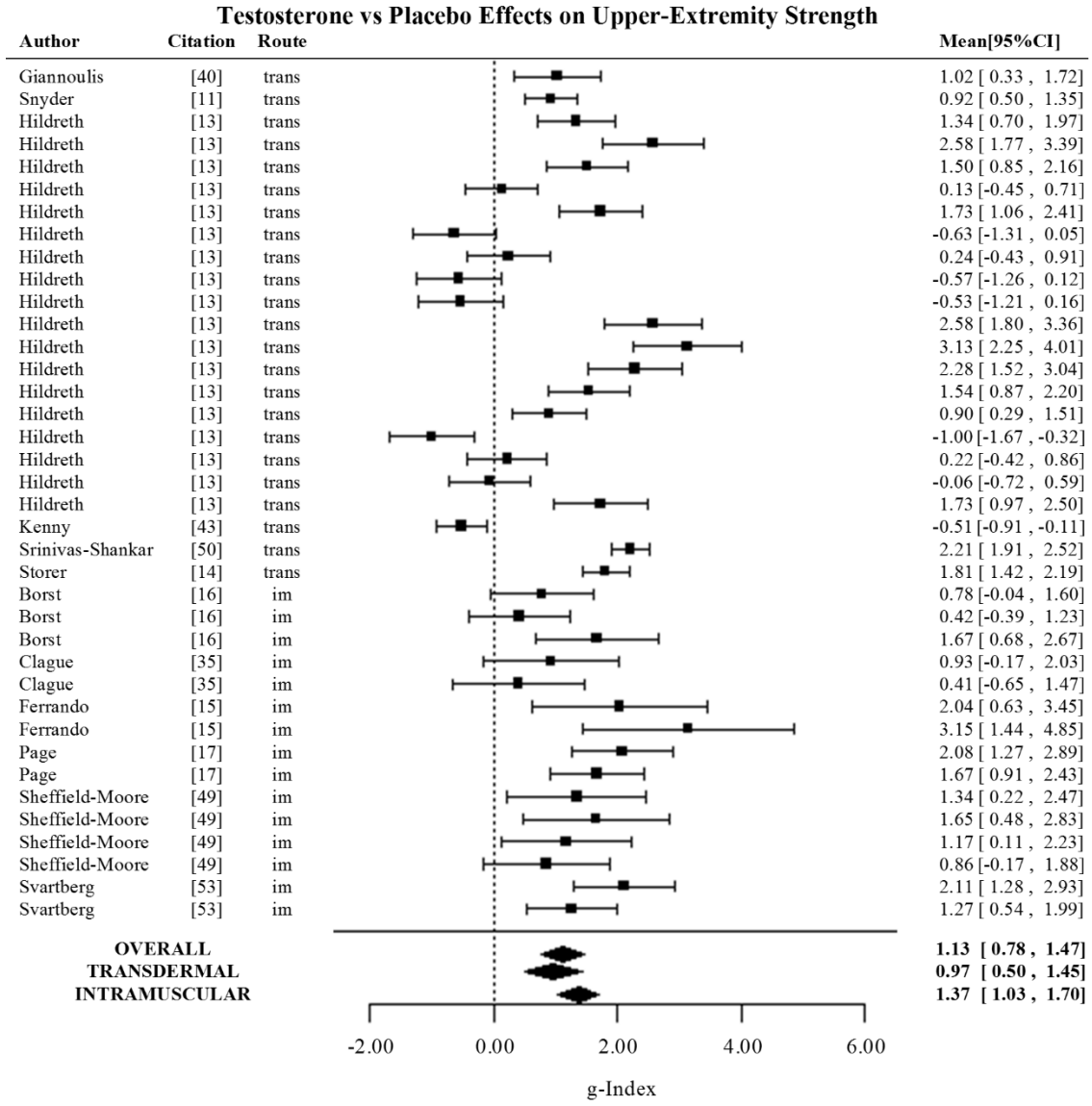


Figure 4. Forest plots for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) **of middle-aged and older men**. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT)

administration route.

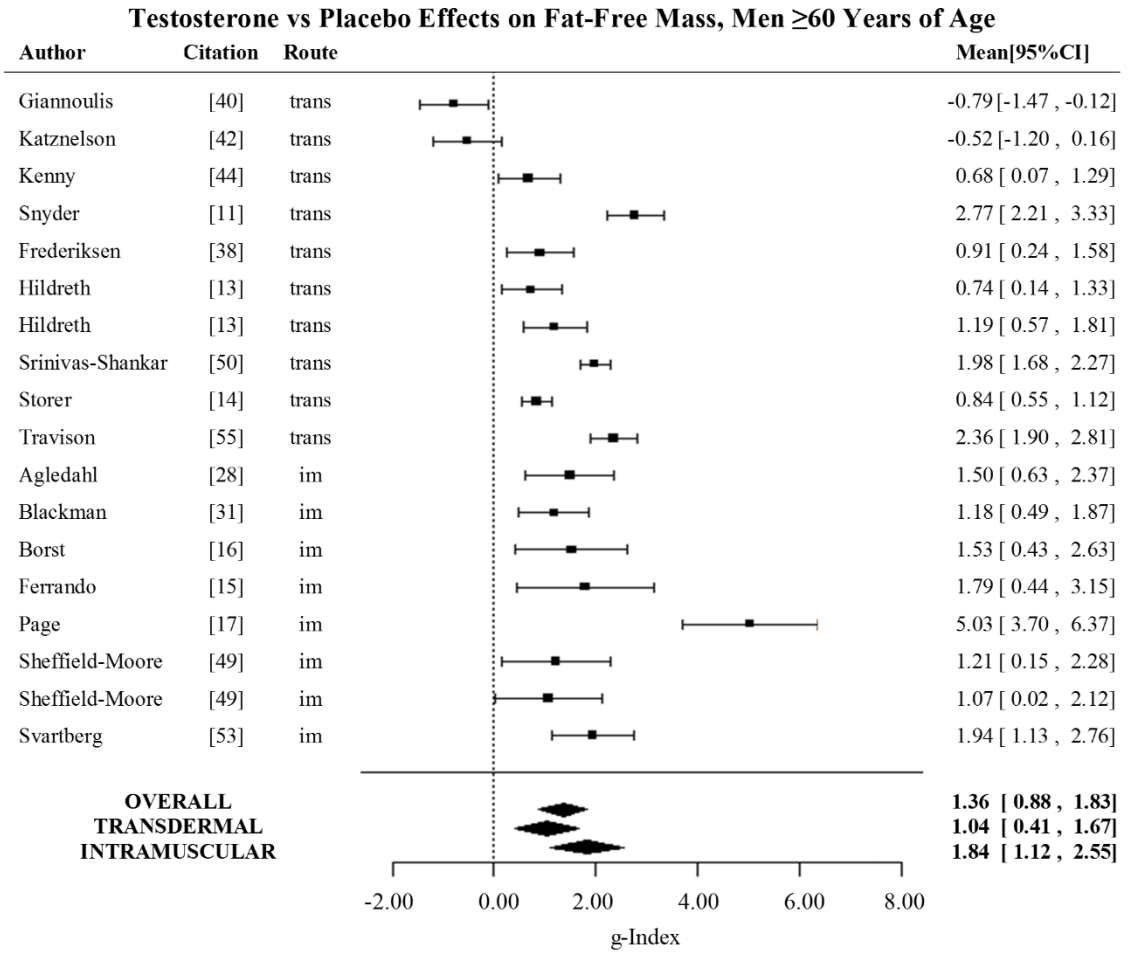


Figure 5. Forest plot for fat-free mass (FFM) data derived from placebo-controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

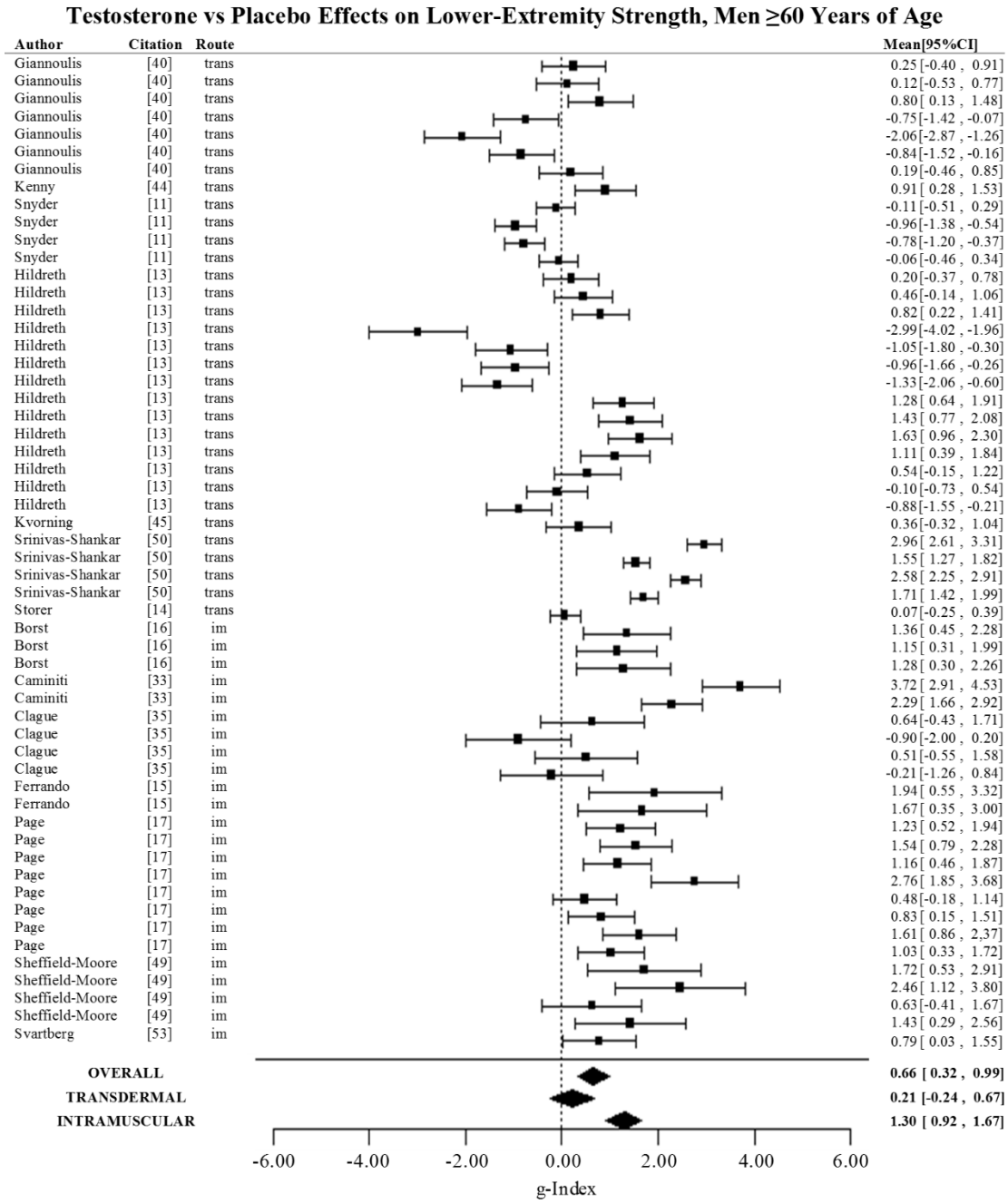


Figure 6. Forest plot for lower-extremity muscle strength data derived from placebo-

controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone replacement therapy (TRT) administration route.

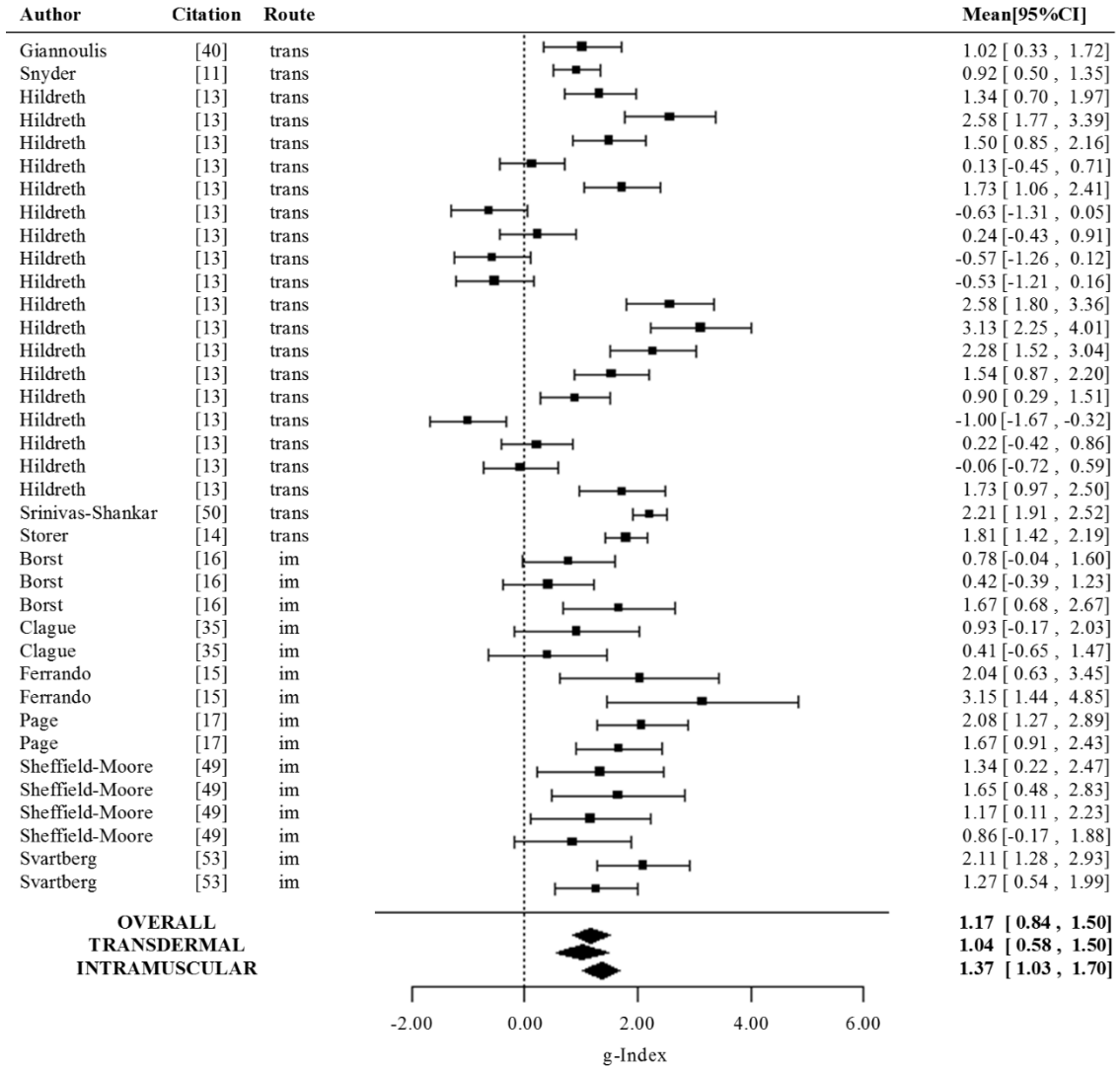


Figure 7. Forest plot for upper-extremity muscle strength data derived from placebo-controlled randomized clinical trials (RCTs) that limited enrollment to men ≥60 years of age. Values are the individual and pooled effect sizes (ESs) listed by testosterone

replacement therapy (TRT) administration route.

Table 1. Quality assessment for double-blind placebo-controlled randomized clinical trials (RCTs) evaluated, using the Delphi criteria.[a]

Article	Treatment Allocation Concealed	Groups Similar at Baseline[b]	Estimate & Variance Presented
Agledahl et al, 2008 [28]	N/R	Yes	Yes
Allan et al, 2008 [29]	Yes	N/R	Yes
Basaria et al, 2010 [56]	Yes	Yes / N/R[c]	No[d]
Behre et al, 2012 [30]	Yes	Yes	Yes
Blackman et al, 2002 [31]	Yes	Yes / No[e]	Yes
Borst et al, 2014 [16]	Yes	Yes	Yes
Brockenbrough et al, 2006 [32]	Yes	N/R	Yes
Caminiti et al, 2009 [33]	Yes	Yes	Yes
Casaburi et al, 2004 [34]	N/R	Yes / N/R[c]	Yes
Clague et al, 1999 [35]	Yes	Yes	Yes
Crawford et al, 2003 [36]	N/R	Yes / N/R[f]	Yes[g]
Del Fabbro et al, 2013 [57]	Yes	Yes	No[d]
Dhindsa et al, 2016 [37]	N/R	Yes	Yes
Dias et al, 2016 [58]	Yes	Yes	No[d]
Ferrando et al, 2002 [15]	N/R	Yes	Yes[g]

Frederiksen et al, 2012 [38]	Yes	Yes	Yes
Gianatti et al, 2014 [39]	Yes	Yes	Yes[g]
Giannoulis et al, 2006 [40]	N/R	Yes	Yes
Hildreth et al, 2013 [13]	Yes	Yes	Yes[g]
Hoyos et al, 2012 [41]	Yes	Yes	Yes[g]
Katznelson et al, 2006 [42]	N/R	Yes	Yes
Kenny et al, 2001 [44]	Yes	Yes	Yes
Kenny et al, 2010 [43]	Yes	Yes	Yes
Kvorning et al, 2013 [45]	Yes	N/R	Yes[g]
Magnussen et al, 2016 [46]	Yes	Yes	Yes
Malkin et al, 2005 [59]	N/R	Yes	No[d]
Marin et al, 1993 [47]	N/R	Yes	Yes
Merza et al, 2006 [48]	Yes	Yes	Yes
Nair et al, 2006 [12]	Yes	Yes	No[d]
Page et al, 2005 [17]	Yes	Yes	Yes[g]
Sheffield-Moore et al, 2011 [49]	N/R	Yes	Yes[g]
Sih et al, 1997 [60]	N/R	N/R	No[d]
Sinclair et al, 2016 [61]	Yes	Yes	No[d]
Snyder et al, 1999 [11]	Yes	Yes	Yes
Srinivas-Shankar et al, 2010 [50]	Yes	Yes	Yes

Steidle et al, 2003 [51]	N/R	Yes	Yes
Storer et al, 2017 [14]	Yes	Yes	Yes[g]
Svartberg et al, 2004 [52]	N/R	Yes	Yes[g]
Svartberg et al, 2008 [53]	N/R	Yes	Yes
Tenover et al, 1992 [54]	N/R	Yes	Yes
Travison et al, 2011 [55]	Yes	N/R	Yes

N/R = not reported. [a]**All RCTs were randomized, with the investigators, providers, and subjects blinded to treatment allocation, and eligibility criteria were specified.** [b]Baseline characteristics assessed were fat-free mass (FFM) and muscle strength. [c]N/R for FFM. [d]Estimate and variance were not reported in the necessary format for statistical analysis in the original article and data were not provide via author query, study was excluded from meta-analysis. [e]Difference in FFM between TRT and placebo groups at baseline. [f]N/R for strength. [g]Estimate and variance were not provided in the necessary format for statistical analysis in the original article, these data were obtained via author query.

Table 2. Characteristics of placebo-controlled randomized clinical trials (RCTs) that were included in meta-analyses.

Article	Age	Baseline		TRT Characteristics			Duration	Reported Outcomes	
	(years)	T[a]	N	Route	Mode	Dose	(months)	FFM	Strength
Agledahl et al, 2008 [28]	T: 68.9 P: 69.3	T: 245 P: 237	T: 13 P: 13	i.m.	TU	1000 mg 5x/year	12	DEXA	N/A
Allan et al, 2008 [29]	T: 62.1 P: 64.5	T: 392 P: 418	T: 31 P: 31	trans	T patch	5 mg/day	12	DEXA	N/A
Behre et al, 2012 [30]	T: 61.9 P: 62.1	T: 300 P: 306	T: 183 P: 179	trans	T gel	50-100 mg/ day	6	DEXA	N/A
Blackman et al, 2002 [31]	T: 70.0 P: 70.0	T: 409 P: 392	T: 21 P: 17	i.m.	TE	100 mg/ 2 weeks	6	DEXA	N/A
Borst et al, 2014 [16]	T: 69.2 P: 70.8	T: 245 P: 264	T: 14 P: 16	i.m.	TE	125 mg/ week	12	DEXA	L, U

Brockenbrough et al, 2006 [32]	T: 58.9 P: 53.0	T: 219 P: 202	T: 19 P: 21	trans	T gel	100 mg/day	6	DEXA	N/A
Caminiti et al, 2009 [33]	T: 71 P: 69	T: 230 P: 210	T: 35 P: 35	i.m.	TU	1000 mg/ 6 weeks	3	N/A	L
Casaburi et al, 2004 [34]	T: 66.6 P: 67.7	T: 302 P: 302	T: 12 P: 12	i.m.	TE	100 mg/ week	2.5	DEXA	L
Clague et al, 1999 [35]	T: 68.1 P: 65.3	T: 326 P: 335	T: 7 P: 7	i.m.	TE	200 mg/ 2 weeks	3	N/A	L, U
Crawford et al, 2003 [36]	T: 58.7 P: 59.9	T: 398 P: 453	T: 18 P: 16	i.m.	Mixed	200 mg/ 2 weeks	12	DEXA	L
Dhindsa et al, 2016 [37]	T: 54.7 P: 54.5	T: 252 P: 252	T: 22 P: 22	i.m.	TC	250 mg/ 2 weeks	6	DEXA	N/A
Ferrando et al, 2012 [15]	T: 68	T: N/R	T: 7	i.m.	TE	100-400 mg/	6	DEXA	L, U

	P: 67	P: N/R	P: 5			2 weeks			
Frederiksen et al, 2011 [38]	T: 68 P: 67	T: 361 P: 366	T: 23 P: 23	trans	T gel	50-100 mg/ day	6	DEXA	N/A
Gianatti et al, 2014 [39]	T: 62 P: 62	T: 251 P: 245	T: 45 P: 43	i.m.	TU	1000 mg 4x/40 weeks	9.25	DEXA	N/A
Giannoulis et al, 2006 [40]	T: 70.3 P: 69.5	T: 498 P: 432	T: 23 P: 20	trans	T patch	5 mg/day	6	DEXA	L, U
Hildreth et al, 2013 [13]	T: 66.5 P: 66.5	T: 298[b] P: 294	T: 55 P: 28	trans	T gel	25-100 mg/ day	12	DEXA	L, U
Hoyos et al, 2012 [41]	T: 48 P: 49	T: 381 P: 387	T: 33 P: 34	i.m.	TU	1000 mg/ 6 weeks	4.5	DEXA	N/A
Katznelson et al, 2006 [42]	T: 72 P: 72	T: 392 P: 421	T: 17 P: 17	trans	T patch	5 mg/day	3	DEXA	N/A

Kenny et al, 2001 [44]	T: 76 P: 75	T: 389 P: 389	T: 24 P: 20	trans	T patch	5 mg/day	12	DEXA	L
Kenny et al, 2010 [43]	T: 77.9 P: 76.3	T: 380 P: 418	T: 69 P: 62	trans	T gel	5 mg/day	12	DEXA	L, U
Kvorning et al, 2013 [45]	T: 66.6 P: 67.8	T: 147[c] P: 133[c]	T: 22 P: 23	trans	T gel	50 mg/ day	6	N/A	L
Magnussen et al, 2016 [46]	T: 61 P: 59	T: 205 P: 271	T: 22 P: 21	trans	T gel	50 mg/day	6	DEXA	N/A
Marin et al, 1993 [47]	T: 56.7 P: 58.5	T: 436 P: 447	T: 7 P: 7	trans	T gel	125 mg/day	9	^{40}K	N/A
Merza et al, 2005 [48]	T: 63.0 P: 59.7	T: 242 P: 216	T: 20 P: 19	trans	T patch	5 mg/day	6	DEXA	N/A
Page et al, 2005 [17]	T: 71	T: 286	T: 24	i.m.	TE	200 mg/	36	DEXA	L, U

	P: 71	P: 303	P: 24			2 weeks			
Sheffield-Moore et al, 2011 [49]	T: 73 P: 65	T: 349† P: 344	T: 16 P: 8	i.m.	TE	100 mg/ week	5	DEXA	L, U
Snyder et al, 1999 [11]	T: 73.1 P: 73.0	T: 367 P: 369	T: 54 P: 54	trans	T patch	4-6 mg/day	36	DEXA	L, U
Srinivas-Shankar et al, 2010 [50]	T: 73.7 P: 73.9	T: 317 P: 314	T: 130 P: 132	trans	T gel	25-75 mg/ day	6	DEXA	L, U
Steidle et al, 2003 [51]	T: 58.4 P: 56.8	T: 234† P: 228	T: 205 P: 99	trans	T gel	50-100 mg/ day	3	DEXA	N/A
Storer et al, 2017 [14]	T: 66.6 P: 68.0	T: 307 P: 302	T: 135 P: 121	trans	T gel	50-100 mg/ day	36	DEXA	L, U
Svartberg et al, 2004 [52]	T: 64.5 P: 67.5	T: 591 P: 623	T: 15 P: 14	i.m.	TE	250 mg/ 4 weeks	6	DEXA	N/A

Svartberg et al, 2008 [53]	T: 69 P: 69	T: 242 P: 237	T: 17 P: 18	i.m.	TU	1000 mg 5x/year	12	DEXA	L, U
Tenover et al, 1992 [54]	T: 67.5 P: 67.5	T: 335 P: 335	T: 13 P: 13	i.m.	TE	100 mg/ week	3	Hydro	N/A
Travison et al, 2011 [55]	T: 73.8 P: 73.9	T: 251 P: 231	T: 69 P: 69	trans	T gel	50-150 mg/ day	6	DEXA	N/A

[a]Testosterone (T) concentrations are ng/dL, rounded to the nearest whole number. [b]Indicates average T concentration from all groups receiving TRT. [c]Indicates bioavailable T concentration, total T was not reported. N = number per group; P = placebo-treated group; i.m. = intramuscular; trans = transdermal; Mixed = mixed injectable esters; TC = testosterone cypionate; TE = testosterone enanthate; TP = testosterone proprionate; TU = testosterone undecanoate; T gel = testosterone gel; T patch = testosterone patch; FFM = fat-free mass; DEXA = dual x-ray absorptiometry; ^{40}K = whole-body potassium-40 measurement; Hydro = hydrostatic weighing; L = lower-extremity; U = upper-extremity; N/A = not assessed; N/R = not reported.

Table 3. Characteristics of placebo-controlled randomized clinical trials (RCTs) that were excluded from meta-analyses due to inability to acquire data in the format necessary for our *a priori* statistical design.

Article	Age (years)	Baseline		TRT			Duration (months)	Reported Outcomes	
		T[a]	N	Route	Mode	Dose		FFM	Strength
Basaria et al, 2010 [56]	T: 74 P: 74	T: 250 P: 236	T: 106 P: 103	trans	T gel	100-150 mg/ day	6	DEXA[b]	L,U
Del Fabbro et al, 2013 [57]	T: 57 P: 63	T: N/R P: N/R	T: 16 P: 13	i.m.	TE	150-200 mg/ 2 weeks	2.4	DEXA	N/A
Dias et al, 2016 [58]	T: 72 P: 72	T: 300 P: 304	T: 13 P: 13	trans	T gel	50 mg/day	12	DEXA	N/A
Malkin et al, 2006 [59]	T: 63.1 P: 64.9	T: 401 P: 349	T: 37 P: 39	trans	T patch	5 mg/day	12	N/A	U
Nair et al, 2006 [12]	T: 66.2	T: 357	T: 27	trans	T patch	5 mg/day	24	DEXA	L,U

	P: 67.1	P: 398	P: 31						
Sih et al, 1997 [60]	T: 65 P: 68	T: 233 P: 294	T: 17 P: 15	i.m.	TC	200 mg/ 2 weeks	12	N/A	U
Sinclair et al, 2016 [61]	T: 55.5 P: 54.0	T: 267 P: 262	T: 50 P: 51	i.m.	TU	1000 mg/ 52 weeks	12	DEXA	U

[a]Testosterone (T) concentrations are ng/dL, rounded to the nearest whole number. [b]Data were included in meta-analysis, obtained from reference [55]; N = number per group; P = placebo; i.m. = intramuscular; trans = transdermal; T gel = testosterone gel; T patch = testosterone patch; TC = testosterone cypionate; TE = testosterone enanthate; TU = testosterone undecanoate; FFM = fat-free mass; DEXA = dual x-ray absorptiometry; L = lower-extremity; U = upper-extremity; N/A = not assessed; N/R = not reported

Table 4. Effect sizes and percent improvement for total body **fat-free mass (FFM)** and muscle strength outcomes **from placebo-controlled randomized clinical trials (RCTs) of middle-aged and older men**.

TRT Route	G-Index (N)	Sample Size (TRT, Placebo)	Effect Size	SE	95% CI	p-value	Improvement (%)
FAT-FREE MASS							
Overall	34	(1213, 1168)	1.200	0.150	(0.910, 1.490)	<0.001	3.4
Intramuscular	15	(242, 230)	1.490	0.180	(1.130, 1.840)	<0.001	5.7
Transdermal	19	(971, 938)	0.980	0.210	(0.580, 1.390)	<0.001	1.7
TOTAL BODY STRENGTH							
Overall	100	(2572, 2523)	0.900	0.120	(0.670, 1.140)	<0.001	6.1
Intramuscular	44	(561, 580)	1.390	0.120	(1.150, 1.630)	<0.001	11.2
Transdermal	56	(2011, 1943)	0.550	0.170	(0.220, 0.880)	<0.001	2.1
LOWER-EXTREMITY STRENGTH							

Overall	62	(1717, 1668)	0.770	0.160	(0.450, 1.080)	<0.001	5.0
Intramuscular	29	(402, 412)	1.390	0.170	(1.070, 1.720)	<0.001	10.4
Transdermal	33	(1315, 1256)	0.260	0.230	(-0.190, 0.700)	0.260	0.3
UPPER-EXTREMITY STRENGTH							
Overall	38	(855, 855)	1.130	0.180	(0.780, 1.470)	<0.001	7.8
Intramuscular	15	(159, 168)	1.370	0.170	(1.030, 1.700)	<0.001	12.9
Transdermal	23	(696, 687)	0.970	0.240	(0.500, 1.450)	<0.001	4.5

Table 5. Effect sizes and percent improvement for sensitivity analyses of muscle strength outcomes **from placebo-controlled randomized clinical trials (RCTs) of middle-aged and older men**.

Route	G-Index (N)	Sample Size (TRT, Placebo)	Effect Size[a]	SE	95% CI	p-value	Improvement (%)
TOTAL BODY STRENGTH							
Overall	35	(1175, 1126)	1.120	0.190	(0.750, 1.490)	<0.001	6.9
Intramuscular	17	(230, 244)	1.510	0.210	(1.090, 1.930)	<0.001	11.3
Transdermal	18	(945, 882)	0.790	0.270	(0.270, 1.320)	<0.001	2.7
LOWER-EXTREMITY STRENGTH							
Overall	21	(724, 695)	1.090	0.260	(0.580, 1.600)	<0.001	6.3
Intramuscular	10	(154, 161)	1.630	0.310	(1.030, 2.230)	<0.001	10.7
Transdermal	11	(570, 534)	0.650	0.360	(-0.060, 1.360)	0.070	2.4
UPPER-EXTREMITY STRENGTH							

Overall	14	(451, 431)	1.160	0.280	(0.610, 1.720)	<0.001	7.7
Intramuscular	7	(76, 83)	1.310	0.260	(0.800, 1.810)	<0.001	12.1
Transdermal	7	(375, 348)	1.020	0.430	(0.170, 1.870)	0.020	3.2

[a]Strength measures with the same units of measurement from each study were averaged to form a single effect size. Sensitivity analysis was not performed for **fat-free mass (FFM)** because all data points represented individual groups with identical units of measurement.

Table 6. Sub-analyses effect sizes and percent improvement for total body fat-free mass (FFM) and muscle strength outcomes from randomized clinical trials (RCTs) limiting enrollment to men ≥60 years of age.

TRT Route	G-Index (N)	Sample Size (TRT, Placebo)	Effect Size	SE	95% CI	p-value	Improvement (%)
FAT-FREE MASS							
Overall	18	(574, 555)	1.360	0.240	(0.880, 1.830)	<0.001	4.2
Intramuscular	8	(97, 99)	1.840	0.360	(1.120, 2.550)	<0.001	7.3
Transdermal	10	(477, 456)	1.040	0.320	(0.410, 1.670)	<0.001	1.7
TOTAL BODY STRENGTH							
Overall	93	(2382, 2355)	0.860	0.120	(0.620, 1.110)	<0.001	5.9
Intramuscular	39	(477, 504)	1.330	0.130	(1.070, 1.590)	<0.001	11.3
Transdermal	54	(1905, 1851)	0.550	0.170	(0.220, 0.880)	<0.001	2.0
LOWER-EXTREMITY STRENGTH							

Overall	56	(1580, 1546)	0.660	0.170	(0.320, 0.990)	<0.001	4.5
Intramuscular	24	(318, 336)	1.300	0.190	(0.920, 1.670)	<0.001	10.3
Transdermal	32	(1262, 1210)	0.210	0.230	(-0.240, 0.670)	0.360	0.1
UPPER-EXTREMITY STRENGTH							
Overall	37	(802, 809)	1.170	0.170	(0.840, 1.500)	<0.001	8.1
Intramuscular	15	(159, 168)	1.370	0.170	(1.030, 1.700)	<0.001	12.9
Transdermal	22	(643, 641)	1.040	0.240	(0.580, 1.500)	<0.001	4.8