Supplementary Online Content

Bhasin S, Travison TG, Storer TW, et al. Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA*. 2012;307(9):931-939.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Subjects reporting adverse sexual symptoms, fatigue, acne and oily skin.

	Dutasteride, 2.5 mg/day				Placebo			
	Testosterone Enanthate, mg / week				Testosterone Enanthate, mg / week			
	50 (n=13)	125 (n=9)	300 (n=12)	600 (n=14)	50 (n=15)	125 (n=12)	300 (n=12)	600 (n=15)
Decreased Libido	2	1	1	3	3	2	2	1
Erectile Dysfunction	3	1	0	1	1	2	1	0
Decreased Ejaculate	3	1	3	0	0	0	0	0
Delayed Orgasm	1	0	0	0	0	0	1	0
Anejaculation	0	0	0	0	0	1	0	0
Hypersexuality	0	0	1	0	1	0	0	0
Nipple Tenderness	0	0	1	1	0	0	0	0
Hot Flashes	0	0	0	1	3	0	0	1
Fatigue	1	0	1	2	2	0	0	0
Acne	2	2	10	11	8	4	4	9
Oily Skin	0	1	2	0	0	0	0	0

eTable 2. On-treatment changes in laboratory parameters by randomization in the 102 participants who completed 20 weeks of intervention and were included in the primary analysis.

	Dutasteride, 2.5 mg / day (n=48)					Placebo (n=54)					
	Testosterone Enanthate, mg / week					Testosterone Enanthate, mg / week					
	50 (n=13)	125 (n=9)	300 (n=12)	600 (n=14)	p[a]	50 (n=15)	125 (n=12)	300 (n=12)	600 (n=15)	p[b]	p[c]
Hemoglobin, g/dL	-0.4 (-0.9, 0.02)	0.5 (0.04, 0.9)	1.7 (0.6, 2.8)	1.0 (0.3, 1.6)	< 0.001	-0.2 (-0.6, 0.2)	1.1 (0.4, 1.8)	1.0 (0.5, 1.5)	1.5 (1.2, 1.9)	< 0.001	0.32
Hematocrit, %	-1.4 (-3.0, 0.2)	2.1 (0.6, 3.6)	5.3 (2.1, 8.5)	3.4 (1.5, 5.4)	< 0.001	-0.4 (-1.6, 0.7)	3.0 (1.1, 5.0)	3.6 (1.9, 5.3)	4.9 (3.6, 6.1)	< 0.001	0.43
Cholesterol, mg/dL	10.3 (-2.9, 23.6)	-2.1 (-18.3, 14.1)	-14.7 (-32.1, 2.8)	-12.3 (-24.2, -0.4)	0.04	4.9 (-3.9, 13.8)	-8.9 (-22.8, 4.9)	-13.7 (-28.1, 0.8)	-21.4 (-34.1, -8.7)	0.01	0.23
LDL-C, mg/dL	12.9 (3.1, 22.7)	-8.6 (-27.1, 10.0)	-7.8 (-22.7, 7.0)	25.7 (-42.9, 94.3)	0.54	6.1 (-1.2, 13.5)	-0.8 (-14.3, 12.8)	-6.4 (-19.9, 7.1)	-6.3 (-20.0, 7.4)	0.32	0.35
HDL-C, mg/dL	-0.9 (-6.5, 4.7)	0.7 (-2.6, 3.9)	-9.1 (-14.1, -4.1)	-12.4 (-19.1, -5.8)	0.002	-3.1 (-9.4, 3.2)	-6.2 (-11.5, -0.8)	-8.0 (-13.7, -2.3)	-14.7 (-20.0, -9.3)	0.02	0.21
Triglycerides, mg/dL	-9.5 (-31.2, 12.2)	28.9 (-40.7, 98.5)	11.3 (-19.6, 42.3)	34.2 (-21.2, 89.6)	0.45	8.5 (-16.8, 33.9)	-10.0 (-36.8, 16.8)	-12.8 (-58.3, 32.8)	-1.8 (-25.3, 21.7)	0.70	0.12
Osteocalcin, ng/mL	-1.8 (-3.6, 0.08)	2.2 (-0.8, 5.2)	0.5 (-1.9, 2.8)	0.5 (-3.1, 4.1)	0.23	-2.9 (-5.3, -0.6)	2.4 (-0.9, 5.8)	0.5 (-4.4, 5.4)	0.3 (-1.9, 2.6)	0.08	0.77
N Tx, nmol BCE/L	0.1 (-1.6, 1.9)	0.6 (-3.0, 4.3)	-1.8 (-3.7, 0.1)	-0.8 (-3.9, 2.2)	0.52	2.2 (-0.8, 5.2)	0.1 (-3.7, 4.0)	-1.5 (-3.3, 0.4)	-2.3 (-4.6, -0.1)	0.07	0.90

The data are mean (95% confidence interval).
LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; N Tx, N-telopeptide; BCE, bone collagen equivalent
[a]ANOVA for difference between Testosterone Enanthate doses among men assigned to Dutasteride
[b]ANOVA for difference between Testosterone Enanthate doses among men assigned to the Placebo
[c]ANOVA; comparison of Dutasteride vs. Placebo groups, controlling for Testosterone Enanthate dose

eTable 3. On-treatment changes in laboratory parameters by randomization group in the 139 participants who were randomized, using multiple imputation.[a]

	Dutasteride, 2.5 mg / day (n=70)					Placebo (n=69)					
	Testosterone Enanthate, mg/week					Testosterone Enanthate, mg/week					
	50 (n=19)	125 (n=16)	300 (n=17)	600 (n=18)	p[b]	50 (n=18)	125 (n=18)	300 (n=15)	600 (n=18)	p[c]	p[d]
Hemoglobin, g/dL	0.1 (-0.6, 0.8)	0.6 (-0.3, 1.6)	1.5 (0.6, 2.3)	1.0 (0.3, 1.7)	0.015	-0.1 (-0.6, 0.5)	1.1 (0.4, 1.8)	1.0 (0.3, 1.7)	1.5 (1.0, 2.0)	< 0.001	0.64
Hematocrit, %	-0.3 (-2.4, 1.9)	2.3 (-0.7, 5.4)	4.6 (2.1, 7.2)	3.4 (1.3, 5.5)	0.003	-0.1 (-1.6, 1.4)	2.8 (0.6, 5.1)	3.4 (1.3, 5.5)	4.8 (3.2, 6.3)	< 0.001	0.71
Cholesterol, mg/dL	10.9 (-3.7, 25.5)	1.2 (-20.4, 22.7)	-11.8 (-30.9, 7.3)	-10.7 (-25.9, 4.5)	0.05	5.5 (-4.8, 15.9)	-7.0 (-23.2, 9.2)	-13.1 (-30.3, 4.1)	-21 (-35.3, -6.6)	0.01	0.16
LDL-C, mg/dL	11.2 (-6.5, 29)	-1.3 (-35.3, 32.7)	-4.8 (-21.4, 11.7)	24.4 (-33.9, 82.7)	0.54	5.6 (-4.8, 16)	1.3 (-19.6, 22.2)	-4.2 (-19.3, 10.9)	-4.1 (-26.4, 18.2)	0.75	0.37
HDL-C, mg/dL	-5.2 (-13.8, 3.4)	-4.9 (-17, 7.1)	-11.2 (-18.9, -3.6)	-12.8 (-20.1, -5.5)	0.22	-5.3 (-12.7, 2.1)	-10.6 (-19.3, -1.8)	-10.7 (-18.8, -2.5)	-16.0 (-22.6, -9.3)	0.13	0.39
Triglycerides, mg/dL	-6.6 (-50.8, 37.5)	26.7 (-49.2, 102.6)	12.8 (-29.9, 55.6)	30.1 (-31.7, 91.9)	0.64	7.2 (-30.2, 44.5)	-5.3 (-61.7, 51.2)	-10.9 (-62.6, 40.8)	-2.4 (-46.9, 42)	0.93	0.22
Osteocalcin, ng/mL	-0.5 (-4.6, 3.6)	3.1 (-1.7, 7.8)	1.0 (-2.9, 4.9)	0.2 (-3.2, 3.5)	0.41	-2.4 (-5.2, 0.3)	3.2 (-1.1, 7.4)	0.8 (-4, 5.7)	0.4 (-2.6, 3.4)	0.07	0.67
N Tx, nmol BCE/L	0.5 (-3.2, 4.3)	1.2 (-3.6, 6)	-1.0 (-4.4, 2.4)	-0.4 (-3.9, 3.2)	0.71	2.3 (-0.8, 5.5)	0.6 (-3.3, 4.5)	-0.9 (-3.8, 2)	-1.9 (-4.7, 0.9)	0.12	0.97

The data are mean (95% confidence interval).

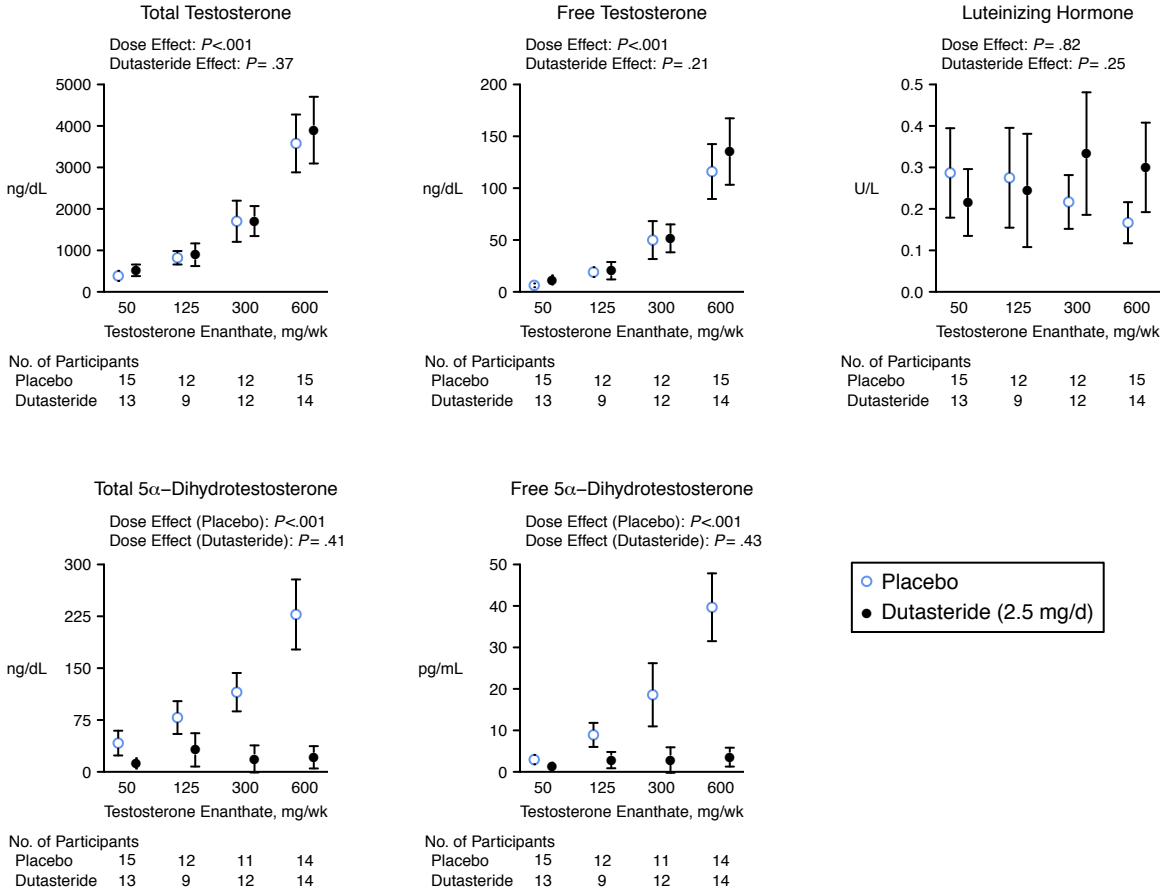
LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; N Tx, N- telopeptide; BCE, bone collagen equivalent

[a]Multiple Imputation via Predictive Mean Matching . To support analyses that were limited to participants completing the intervention treatment phase, we conducted sensitivity analyses using Multiple Imputation by Chained Equations (MICE) to obtain values for subjects with missing records. Models were fit using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). Fifty replicative data sets were created, and analyses performed on each and then pooled. Significance levels were generated using nested model comparisons.

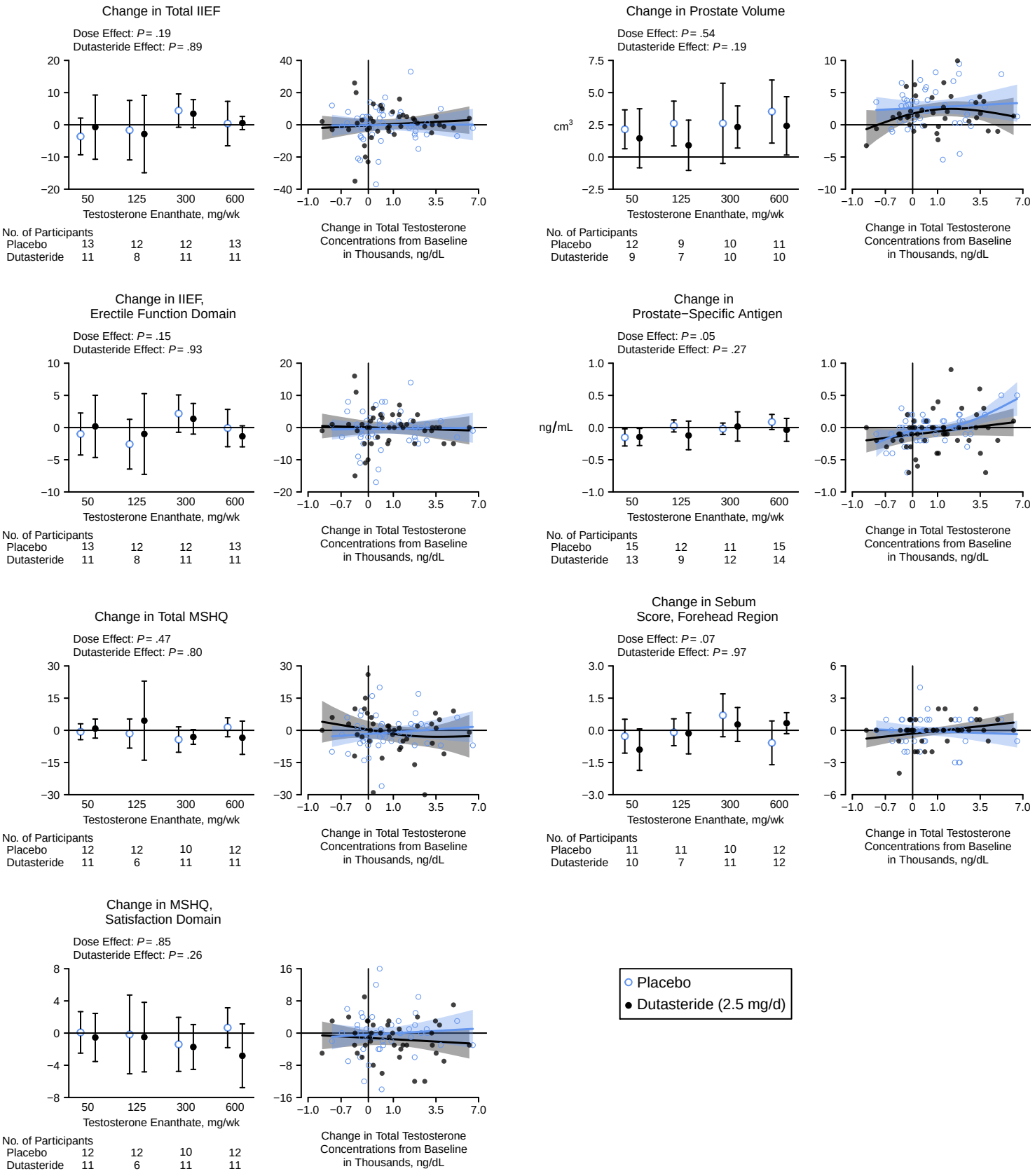
[b]ANOVA for difference between Testosterone Enanthate doses in the Dutasteride group

[c]ANOVA for difference between Testosterone Enanthate doses in the Placebo group

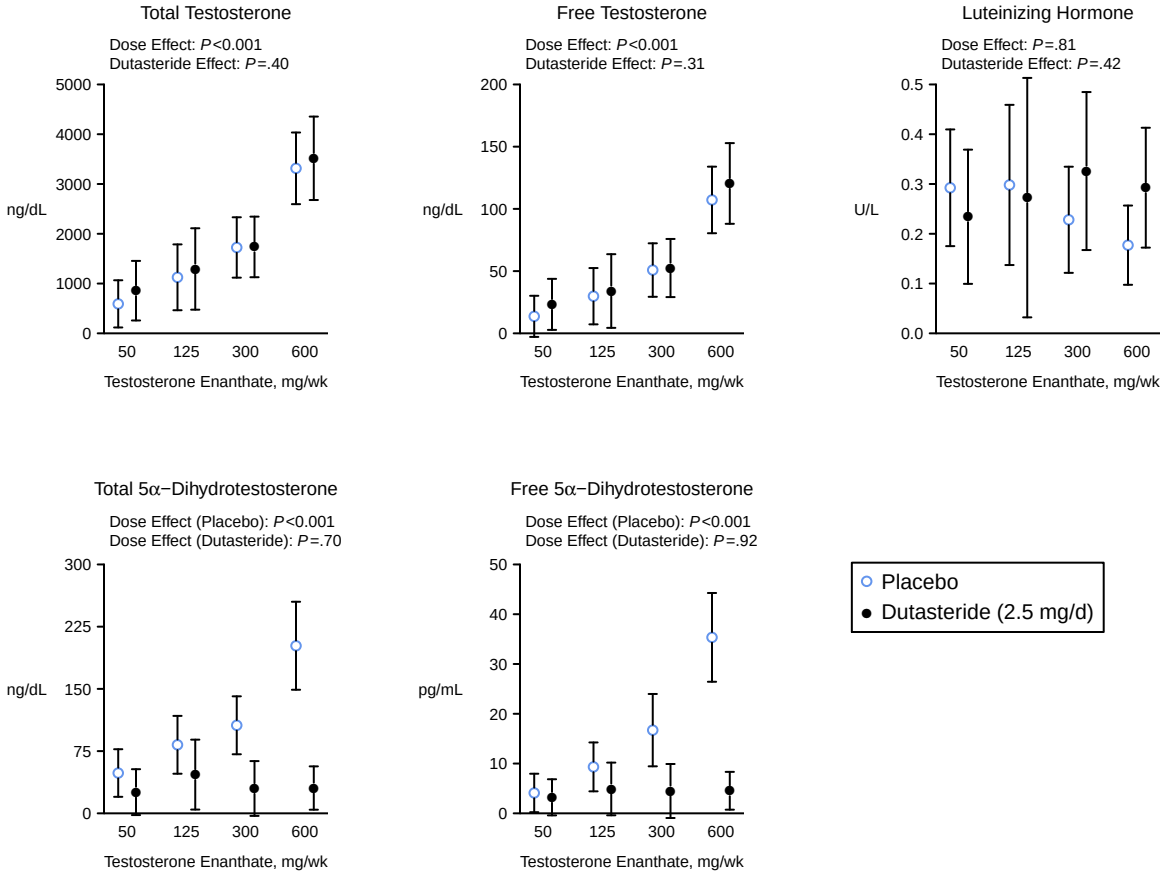
[d]Dutasteride vs. placebo, controlling for Testosterone Enanthate dose



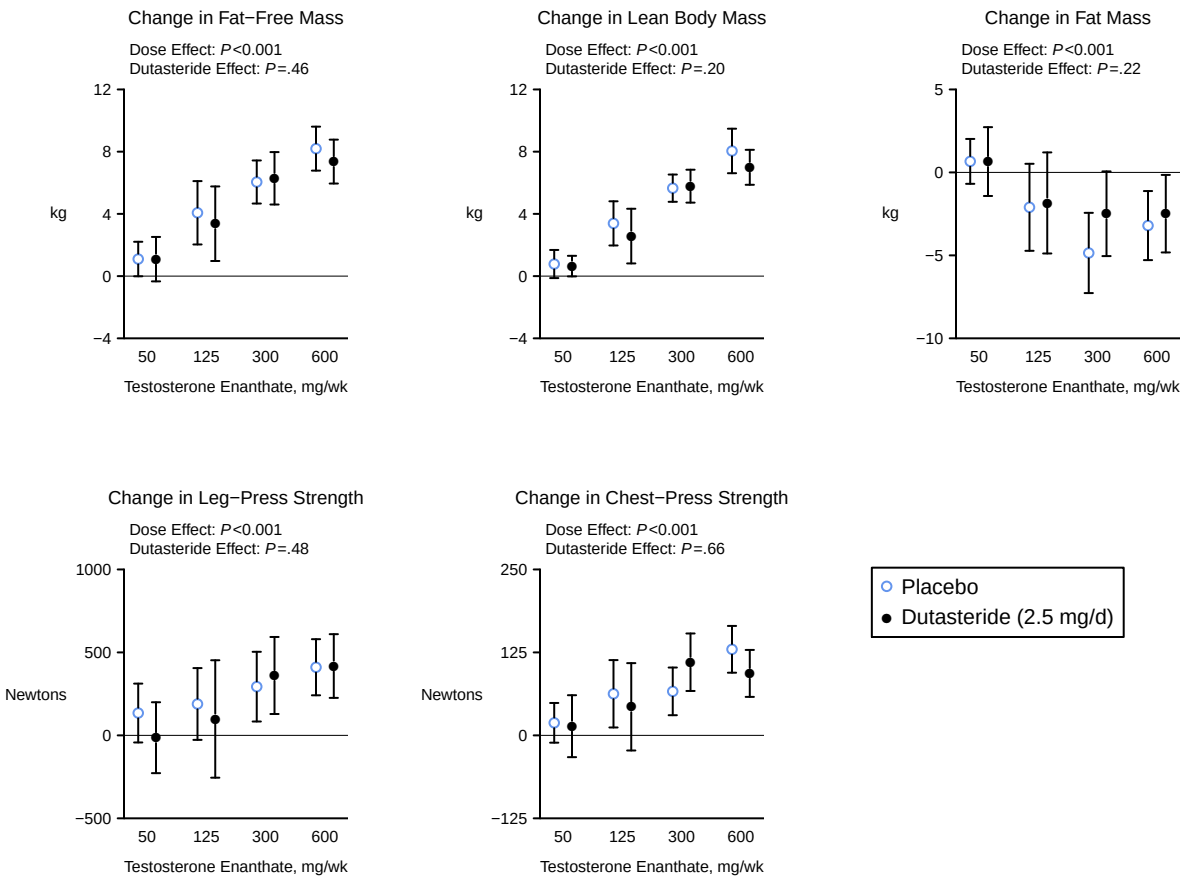
eFigure 1. On-treatment hormone concentrations, displayed by randomization group for the 102 participants who completed 20 weeks of intervention and who were included in the primary analyses. Means and 95% confidence intervals are displayed. The total numbers of subjects with nonmissing records are reported below each panel.



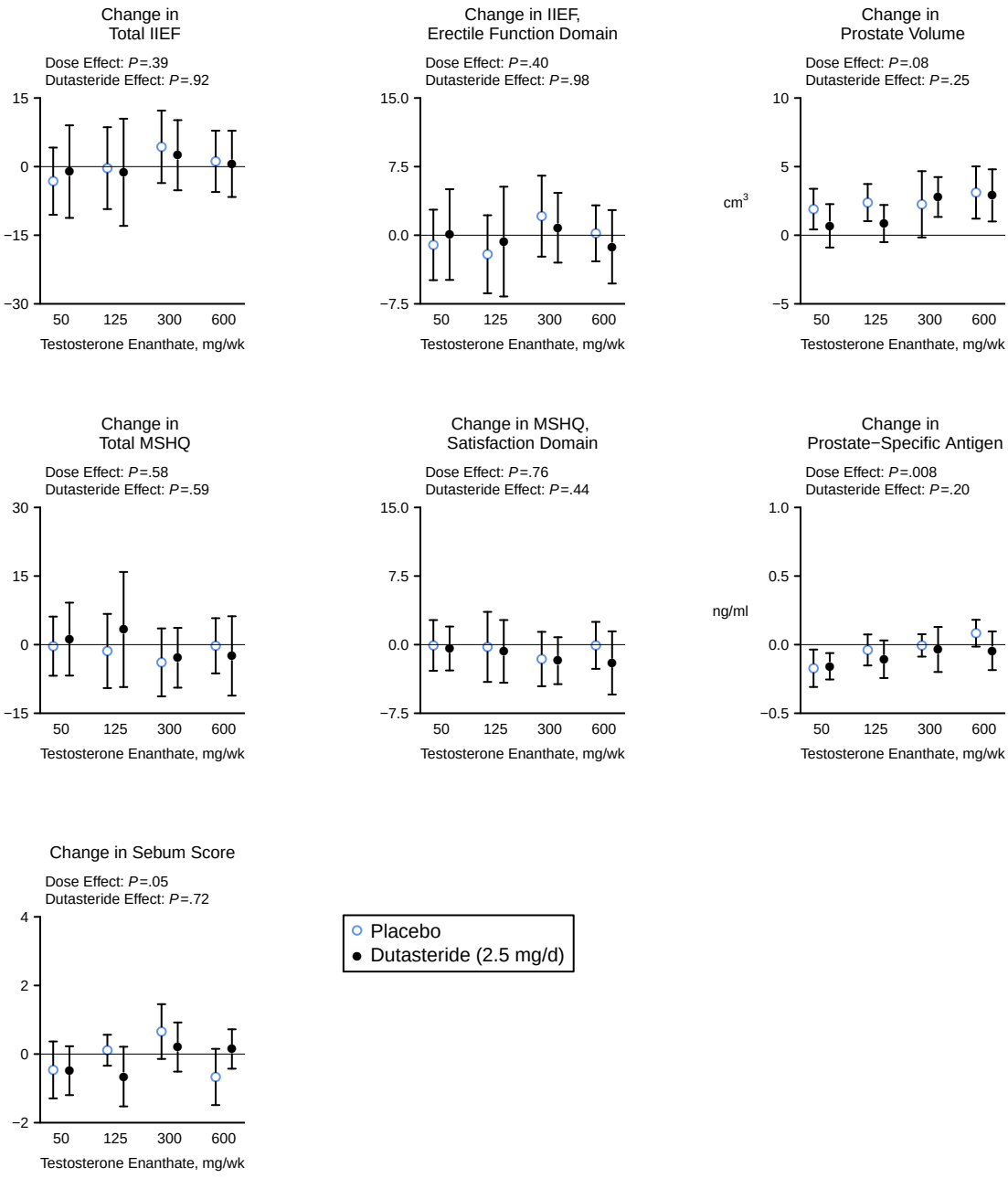
eFigure 2. Changes in sexual function scores, assessed by the International Index of Erectile Function (IIEF), and the Male Sexual Health Questionnaire (MSHQ), as well as prostate volume, prostate-specific antigen (PSA), and forehead sebum scores in the 102 participants who completed 20 weeks of intervention and who were included in the primary analyses. Means and 95% confidence intervals are shown. A single upper PSA outlier is disincluded; a computation including this observation produced no meaningful difference in results (primary result, reported in manuscript text). Smoothed curves were generated using generalized additive models; shaded areas represent corresponding 95% confidence regions.



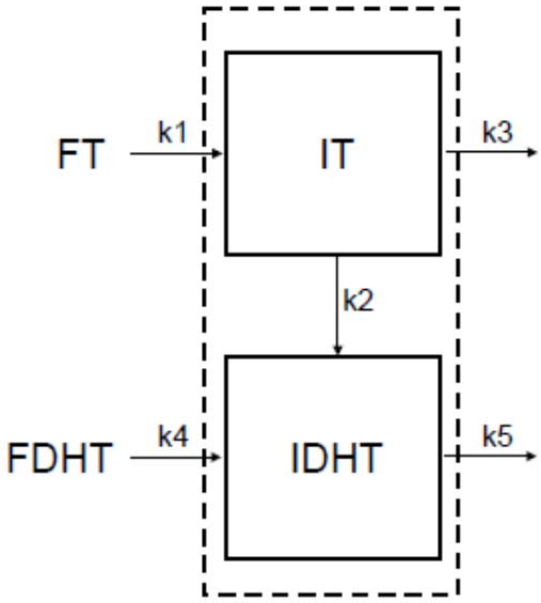
eFigure 3. On-treatment hormone concentrations in 139 participants randomized, using multiple imputation by chained equations. Means and 95% confidence intervals are displayed. Significance tests comparing randomization groups (Placebo vs. Dutasteride) and Testosterone Enanthate dose are obtained from pooled regression analyses.



eFigure 4. Change in body composition and strength parameters by randomization group, with estimation by multiple imputation for missing values, N=139. Means and 95% confidence intervals are shown.



eFigure 5. Changes in sexual function scores, assessed by the International Index of Erectile Function (IIEF) and the Male Sexual Health Questionnaire (MSHQ), along with prostate volume, prostate-specific antigen (PSA), and forehead sebum scores are presented by randomized assignment, with estimation by multiple imputation for missing values; N=139. Means and 95% confidence intervals are displayed.



eFigure 6. Schematic model of intracellular testosterone and DHT in target tissue.

The androgen effects in any tissue can be conceptualized as a function of intra-tissue testosterone (IT) and DHT (IDHT) concentrations, as shown in this model. In tissues with low 5α-reductase activity (low K2), such as the skeletal muscle and the bone, IDHT is low under basal conditions and likely negligible during Dutasteride administration. Therefore, androgen effects are mediated largely by testosterone both under basal conditions and during Dutasteride administration.

In tissues with high 5α-reductase activity, such as the prostate, IDHT is greater than IT under basal conditions. Dutasteride administration at doses (0.5-mg daily), substantially lower than those used in this trial (2.5-mg daily), has been shown to nearly completely suppress IDHT to very low levels.[20-23] As prostate volume was maintained in men treated with dutasteride and graded doses of testosterone, who presumably had very low IDHT, it follows that even in tissues with high 5α-reductase activity, such as the prostate, DHT is not essential for maintaining prostate volume in the range of testosterone concentrations achieved in this trial. It also follows from this model that administration of 5α-reductase inhibitor to men, who have low testosterone levels below the activation threshold of a particular tissue, may attenuate androgen effects in that tissue. Furthermore, at a given circulating concentration of testosterone and DHT, the activity of steroid 5α-reductase would determine the relative concentrations of testosterone and DHT in any tissue and whether testosterone or DHT may serve as the dominant androgen in that tissue. Thus, the suppression of prostate volume by dutasteride in older men with benign postatic hyperplasia suggests that DHT formation is important for amplifying testosterone's effect in this tissue at concentrations lower than those achieved in our trial. This argument is

supported by the finding that in older men with benign prostatic hyperplasia, the largest reduction in prostate volume with dutasteride is observed in men with lowest serum testosterone levels.[38] However, as circulating testosterone concentrations are raised from mid-normal (as in the men receiving the 50-mg dose in our trial) to supraphysiologic, testosterone alone can maintain prostate volumes.

K1 and K4 are coefficients representing the tissue uptake of testosterone and DHT, respectively, and K3 and K5 are coefficients representing tissue clearance of testosterone and DHT, respectively.