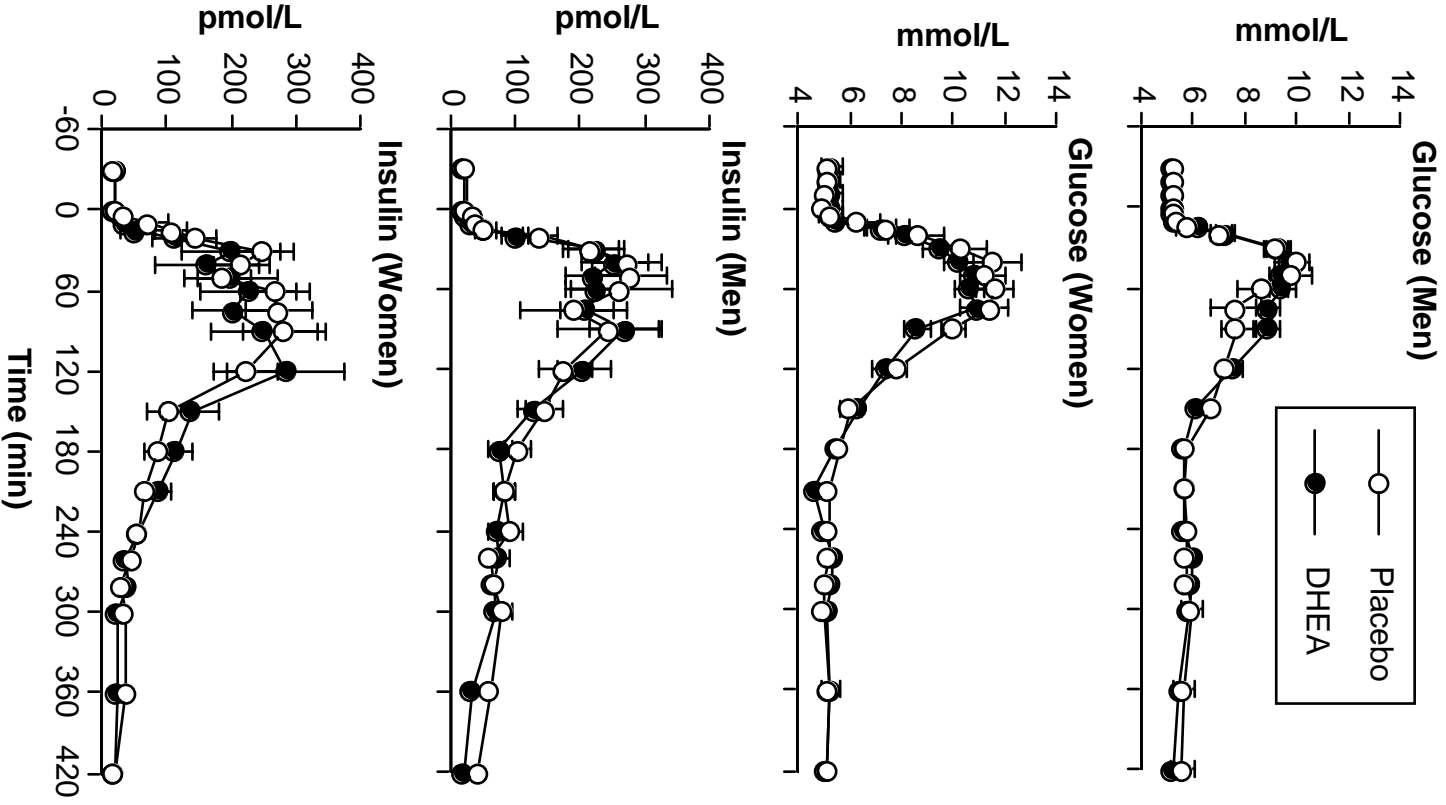


Supplementary Appendix

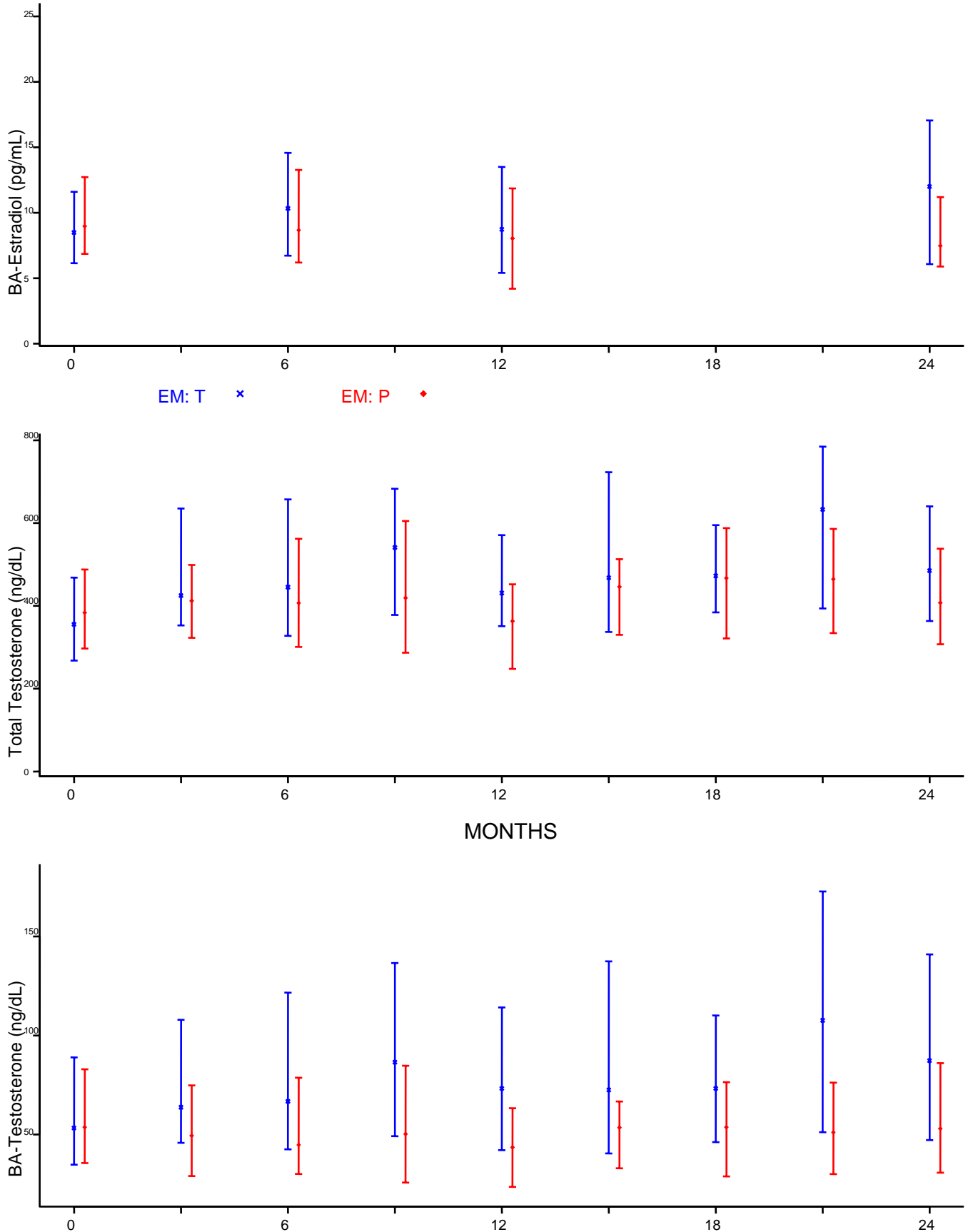
This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006;355:1647-59.

Supplement Figure 1: Glucose and insulin responses following standard meal ingestion. Values shown represent means at 24 months after adjustment for baseline value, with 95% CI. There were no significant changes between treatment groups at either 12 months (not shown) or at 24 months (based on area under curve)

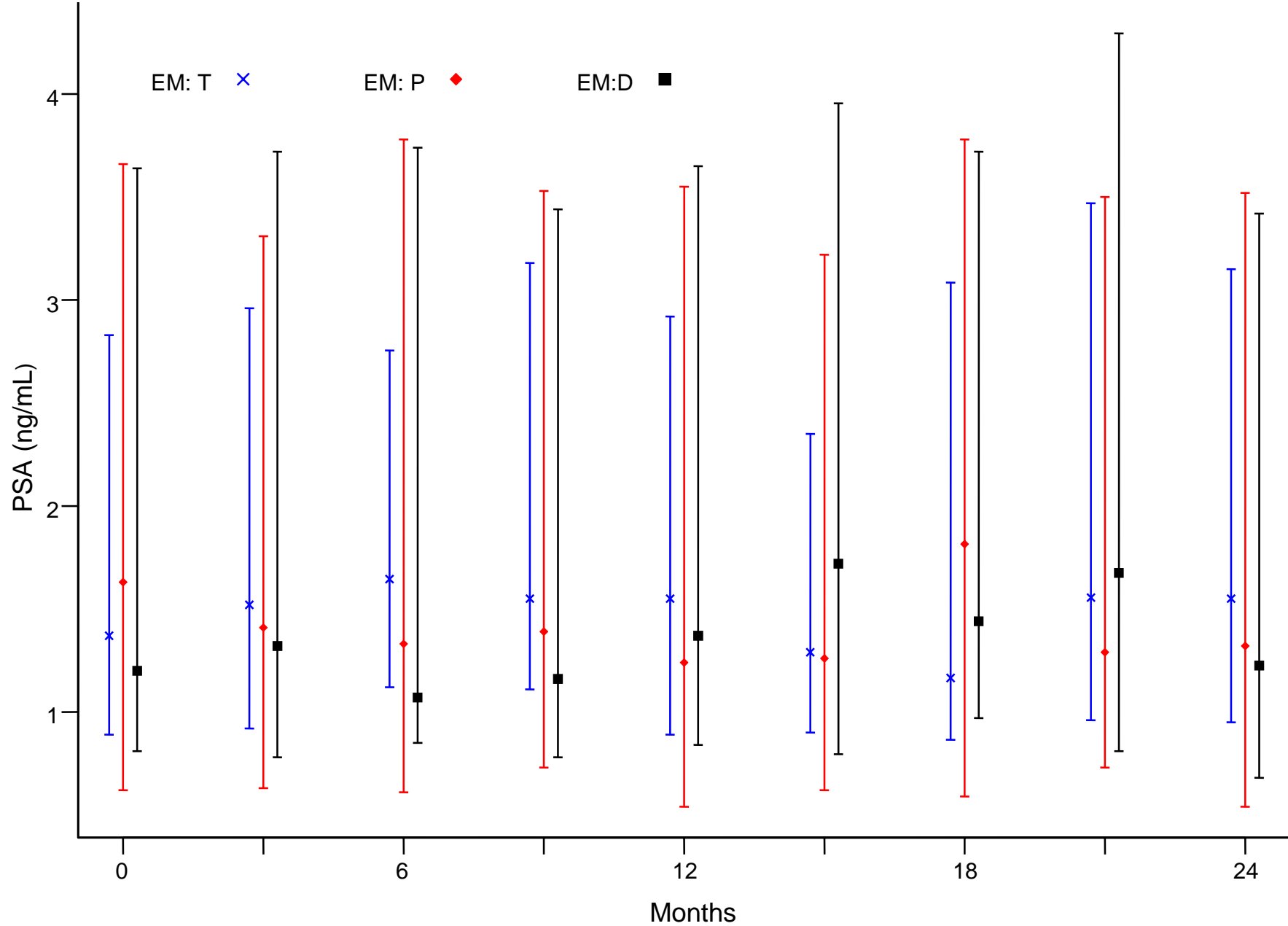


Median (IQR)



Supplemental Figure 2: Hormone levels (total and bioavailable), testosterone and bioavailable estradiol levels in elderly men on placebo (EM:P) and elderly men on testosterone (EM:T) representing random sample measurements. Table 3 provides changes in total testosterone (average of 3) and BioT (average of 10) averages of multiple samples over 24 hours

MEDIAN (IQR)



Supplemental Figure 3: Plasma concentrations of PSA in elderly men on DHEA, testosterone and placebo (EM:D, EM:T, and EM:P) showing no changes during the study period

Supplement Table 1: Exclusion criteria

1) Diseases

- Ischemic heart disease
- Renal disease
- Uncontrolled hypertension
- Diabetes mellitus
- Malignancy
- Malabsorption
- Bone disorders
- Chronic obstructive pulmonary disease
- Sleep apnea

2) Medications

- Adrenal steroids
- Anticonvulsant therapy
- Thiazide diuretics
- Estrogen replacement therapy

3) Exercise status

Volunteers who were taking medications that may affect any of the outcome measures.
People engaged in a regular exercise program lasting longer than 20 minutes involving more than 2 sessions/week were also excluded.

4) Abnormal laboratory measurements

- Serum calcium
- Phosphorus
- Alkaline phosphatase
- Aspartate aminotransferase
- Creatinine
- Urinary calcium
- Thyroid stimulating hormone
- Erythrocyte sedimentation rate

Supplemental Table 2. Baseline Characteristics of Young Subjects: Data is given as median (lower and upper quartile)		
	Young	
Parameter	Males (n=37)	Females (n=38)
Age (yrs)	23.6 (21.0, 26.0)	21.9 (20.4, 23.7)
BMI (kg/m ²)	25.5 (23.7, 27.5)	23.2 (21.8, 26.0)
BODY COMPOSITION		
Body fat (%)	21.8 (16.4, 27.2)	31.7 (27.6, 35.4)
Visceral fat/total fat ratio	0.12 (0.10, 0.14)	0.06 (0.05, 0.08)
FFM (kg)	62.3 (59.1, 65.7)	41.8 (39.6, 44.6)
BONE PARAMETERS - BMD		
AP spine (gm/cm ²)	1.30 (1.19, 1.37)	1.21 (1.16, 1.29)
Femur neck (gm/cm ²)	1.21 (1.09, 1.35)	1.05 (1.01, 1.16)
Total femur (gm/cm ²)	1.22 (1.10, 1.28)	1.09 (1.00, 1.15)
Ultradistal radius (gm/cm ²)	0.56 (0.51, 0.62)	0.43 (0.40, 0.46)
PERFORMANCE		
VO ₂ max (ml/kgFFM)	58.2 (52.5, 65.9)	54.5 (51.1, 58.6)
Seated chest press (kg)	81.6 (70.3, 90.7)	38.6 (35.2, 45.4)
Isometric knee extension (kg)	61.1 (53.5, 68.8)	37.3 (31.3, 47.4)
HORMONES AND GLUCOSE		
DHEAS levels (ug/mL)	2.53 (1.93, 3.13)	1.45 (1.13, 2.07)
Total testosterone (ng/dL)	471.8 (394.1, 534.3)	30.0 (27.6, 33.8)
Bioavailable testosterone (ng/dL)	126.1 (110.8, 175.9)	NA
Fasting glucose(mg/dL)	88.8 (87.1, 90.2)	85.7 (82.7, 88.2)
Fasting insulin (uU/mL)	3.56 (2.83, 4.45)	4.74 (3.44, 6.11)
Insulin sensitivity (10 ⁻⁴ dl/kg/min per uU/ml)	20.00 (13.10, 27.00)	10.70 (8.46, 18.70)
C-peptide (nmol/L)	0.87 (0.74, 1.05)	1.06 (0.87, 1.23)
Estradiol (pg/mL)	27.0 (20.0, 31.0)	15.0 (5.0, 56.8)
Bioavailable estradiol (pg/mL)	14.91 (11.25, 19.61)	5.52 (0.91, 20.83)
HDL cholesterol (mg/dL)	36.5 (30.5, 46.0)	47.0 (40.0, 61.0)
LDL cholesterol (mg/dL)	83.0 (67.8, 99.2)	75.8 (63.8, 93.8)
Triglycerides (mg/dL)	100.0 (84.0, 114.0)	92.0 (70.0, 119.0)

Supplemental Table 3. Changes in Study Subjects (24 Month – Baseline): Data is given as median (lower and upper quartile) in placebo (P), DHEA (D), and testosterone (T) group									
Outcome Variables	Elderly Males (EM)		EM: D vs. EM: P	Elderly Females (EF)		EF: D vs. EF: P	EM: T vs. EM: P	EM: T vs. EM: P	EM: D & EF: D vs. EM: P & EF: P
	Placebo (P)	DHEA (D)	p-values*	Placebo (P)	DHEA (D)	p-values*	Testosterone (T)	p-values*	p-values*
BODY COMPOSITION VARIABLES									
Body fat (%)	-0.60 (-1.86, 1.39)	-0.74 (-2.08, 1.77)	0.43	0.21 (-2.05, 1.07)	-2.02 (-2.75, 1.90)	0.090	-1.83 (-2.94, 0.85)	0.077	0.048
FFM (kg) [§]	-0.63 (-1.70, 0.45)	0.16 (-0.79, 1.59)	0.055	-0.06 (-0.63, 0.93)	0.70 (-0.18, 1.49)	0.19	0.58 (-0.24, 1.84)	<0.001	0.008
Visceral fat (CT & DEXA) [†]	175 (-563, 597)	114 (-491, 655)	0.88	113 (-394, 482)	-70 (-286, 168)	0.43	1 (-260, 178)	0.48	0.56
Thigh muscle (gm ²)	1.19 (-21.35, 19.74)	-10.40 (-39.25, 13.70)	0.42	-3.48 (-17.35, 5.21)	9.22 (-4.90, 13.76)	0.098	0.34 (-17.00, 9.73)	0.89	0.96
BONE MINERAL DENSITY VARIABLES									
AP spine (gm/cm ²)	0.01 (-0.01, 0.07)	0.01 (-0.01, 0.05)	0.96	-0.003 (-0.03, 0.02)	0.01 (-0.03, 0.04)	0.63	0.03 (0.003, 0.05)	0.38	0.52
Femur neck (gm/cm ²)	-0.03 (-0.05, -0.01)	-0.01 (-0.03, 0.02)	0.045	-0.02 (-0.04, -0.001)	-0.01 (-0.04, 0.00)	0.69	0.01 (-0.02, 0.03)	0.002	0.063
Total femur (gm/cm ²)	-0.001 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.30	-0.001 (-0.03, 0.02)	-0.002 (-0.01, 0.02)	0.38	0.01 (-0.01, 0.02)	0.26	0.18
Ultradistal radius (gm/cm ²)	-0.004 (-0.01, 0.01)	0.003(-0.01, 0.02)	0.58	-0.01 (-0.02, 0.01)	0.01 (-0.01, 0.02)	0.005	0.01 (0.00, 0.02)	0.064	0.016
PHYSICAL PERFORMANCE VARIABLES									
VO ₂ max (ml/kg FFM)	-1.66 (-3.84, 4.49)	-1.74 (-4.76, 0.71)	0.45	-1.84 (-3.01, 0.71)	-3.01 (-4.80, 1.66)	0.26	0.16 (-3.05, 2.78)	0.83	0.20
Leg press (kg)	2.27 (-4.54, 13.61)	4.54 (0.00, 9.07)	0.46	0.00 (-1.13, 4.54)	2.27 (0.00, 4.54)	0.92	4.54 (0.00, 13.61)	0.15	0.45
Isometric knee extension (kg)	-0.29 (-5.58, 3.63)	0.45 (-5.62, 3.40)	0.57	-2.29 (-4.31, 0.32)	-1.36 (-3.27, 2.72)	0.54	-0.59 (-6.03, 3.81)	0.82	0.68
Seated chest press (kg)	2.27 (0.00, 6.80)	4.54 (2.27, 6.80)	0.34	2.27 (0.00, 4.54)	2.27 (0.00, 6.80)	0.94	5.67 (0.00, 6.80)	0.38	0.53
QUALITY OF LIFE									
Mental component score	0.42 (-4.22, 3.80)	-0.06 (-1.92, 0.65)	0.59	-0.47 (-5.50, 3.95)	0.36 (-2.96, 3.16)	0.61	-0.14 (-1.39, 2.20)	0.38	0.48
Physical component score	-0.05 (-2.69, 3.40)	-0.70 (-2.96, 1.22)	0.12	-1.02 (-3.77, 2.25)	0.20 (-3.72, 3.54)	0.91	-0.01 (-1.68, 1.94)	0.36	0.34

HORMONAL AND METABOLIC VARIABLES									
Total Testosterone (ng/dL)	16.29 (-14.56, 60.80)	3.78 (-23.04, 28.25)	0.13	-7.71 (-12.70, -2.50)	10.40 (1.60, 25.50)	<0.001	106.43 (39.00, 246.87)	0.002	0.10
SHBG (nmol/L)	1.10 (-5.25, 5.35)	-2.97 (-5.00, 2.41)	0.053	-0.25 (-8.30, 5.05)	-11.51 (-27.15, -3.52)	<0.001	1.00 (-3.02, 5.41)	0.99	<0.001
Estradiol (pg/mL)	-0.60 (-5.00, 3.20)	19.80 (11.90, 24.00)	<0.001	0.00 (-1.10, 1.80)	20.90 (14.90, 26.40)	<0.001	1.15 (-4.30, 7.00)	0.67	<0.001
FSH (IU/L)	0.50 (-0.70, 1.70)	0.30 (-0.20, 1.10)	0.74	-2.55 (-7.30, 0.90)	-3.40 (-12.30, 0.40)	0.17	-3.00 (-4.20, -1.20)	<0.001	0.40
Luteinizing Hormone (IU/L)	0.40 (-0.60, 1.90)	0.00 (-0.70, 1.30)	0.51	-1.15 (-2.90, 2.80)	-0.50 (-5.10, 2.90)	0.80	-1.80 (-3.10, -1.10)	<0.001	0.65
Insulin (uU/mL)	0.39 (-0.11, 1.66)	0.18 (-0.28, 1.08)	0.53	0.35 (-0.27, 0.75)	0.16 (-0.53, 0.40)	0.41	-0.20 (-0.56, 0.21)	0.003	0.30
Insulin Sensitivity Index (10⁻⁴ dl/kg/min per uU/ml)	0.70 (-2.47, 3.94)	1.02 (-3.55, 4.22)	0.73	-0.64 (-2.32, 3.35)	-1.50 (-5.50, 1.73)	0.21	3.33 (-1.26, 4.97)	0.22	0.52
PSA (ng/mL)	-0.07 (-0.26, 0.60)	-0.08 (-0.22, 0.20)	0.95	NA	NA	NA	0.04 (-0.16, 0.34)	0.46	NA
Glucose (mg/dL)	-0.49 (-3.44, 1.75)	-0.49 (-3.35, 0.67)	0.58	-2.05 (-3.28, 1.19)	-1.62 (-4.72, 1.84)	0.66	1.04 (-3.22, 3.13)	0.77	0.43
HDL Cholesterol (mg/dL)	-1.50 (-6.00, 2.00)	-6.00 (-10.00, 0.00)	0.056	-4.50 (-8.00, 1.00)	-8.00 (-18.00, -4.00)	0.003	-1.00 (-4.00, 3.00)	0.80	<0.001
LDL Cholesterol (mg/dL)	-8.40 (-27.20, 9.00)	-13.20 (-26.80, 1.40)	0.41	-11.15 (-25.60, 11.00)	-4.20 (-21.20, 10.90)	0.37	-13.20 (-29.20, -0.20)	0.26	0.87
Triglycerides (mg/dL)	-3.00 (-23.00, 25.00)	-1.00 (-22.00, 11.00)	0.69	-6.50 (-28.00, 10.00)	-4.00 (-17.00, 12.00)	0.92	2.50 (-31.00, 16.00)	0.91	0.75

*Differences are DHEA minus Placebo or Testosterone minus placebo

‡P-values given are two-sided and come from a model that was adjusted for gender, age at the time of randomization, the time from randomization, and for the baseline value.

†Visceral Fat (CT & DEXA) p-values are two-sided and come from a model that adjusted for gender, age at the time of randomization, the time from randomization, the baseline value, and the difference of total body fat (DEXA).

§*Fat free mass (FFM) p-values are two-sided and come from a model that adjusted for gender, age at the time of randomization, the time from randomization, the baseline value, FFM when men and women combined (placebo: median:= -0.29, lower upper quartiles: -1.45, 0.53, and DHEA median=0.33 and quartiles: -0.44, 1.54)*

Supplement Table 4. Reported Adverse Events by Body System for all 151 randomized subjects (excluding one DHEA subject who was found to be ineligible after randomization)

System (Unique Patients)	Total	DHEA	Elderly Males		Elderly Females	
			Testosterone	Placebo	DHEA	Placebo
	151	30	30	32	29	30
Cardiovascular	20	2	5	5	6	2
Angina	1	0	0	0	1	0
Aortic aneurism	1	1	0	0	0	0
Ascending aorta dilatation	4	1	1	2	0	0
Asym.,Hypertrophic Cardiomyopathy	1	0	0	0	1	0
Atrial fibrillation	1	0	0	0	1	0
Bradycardia	1	1	0	0	0	0
CAD Stent Placement	3	0	0	1	1	1
Chest pain	2	0	0	1	1	0
Coronary Artery Bypass Graft	1	0	1	0	0	0
Coronary Artery Disease (CAD)	3	0	2	0	1	0
Deep Vein Thrombosis	1	0	0	0	1	0
Dilated Cardiomyopathy	1	0	0	0	1	0
Frequent Ventricular Ectopics	1	0	1	0	0	0
Hypertension	2	0	0	0	1	1
Hypotension	1	0	0	1	0	0
Myocardial Infarction	1	0	0	0	1	0
Palpitations	1	0	0	0	0	1
Phlebitis	3	0	1	1	1	0
Triple Bypass Surgery	1	0	1	0	0	0
Gastrointestinal	5	0	2	1	2	0
Colon Adenocarcinoma	1	0	1	0	0	0
Diarrhea	2	0	0	1	1	0
GI bleeding	1	0	0	0	1	0
Hemicolectomy	1	0	1	0	0	0
Vomiting	1	0	1	0	0	0

System (Unique Patients)	Total	DHEA	Elderly Males		Elderly Females	
			Testosterone	Placebo	DHEA	Placebo
Genitourinary	22	4	8	6	1	3
Cholecystectomy	1	0	0	1	0	0
Epididymal Cyst	1	0	1	0	0	0
Peripelvic Cyst/Mild Pyelocystitis	1	0	0	0	0	1
Testicular Pain	1	0	1	0	0	0
Vaginal Vault Repair	1	0	0	0	1	0
Prostate	12	3	5	4	0	0
BPH	1	0	0	1	0	0
Elevated PSA	2	0	0	2	0	0
PIN (Prostatic Intraepithelial Neoplasia)	3	1	1	1	0	0
Prostate Biopsy	6	1	4	1	0	0
Prostate Cancer	1	0	0	1	0	0
Prostate Nodule	1	0	1	0	0	0
Prostatism	1	1	0	0	0	0
Prostatitis	2	1	1	0	0	0
Bladder	6	1	2	1	0	2
Cystoscopy	2	0	1	1	0	0
Increased urinary frequency+/- urgency	1	0	1	0	0	0
Nocturia	1	0	1	0	0	0
Pain with urination	1	0	1	0	0	0
Post TUNA urinary symptomology	1	1	0	0	0	0
Renal Collecting System Dilatation	1	0	0	1	0	0
Right Renal Mass	1	0	0	0	0	1
Urethral Stricture	1	0	1	0	0	0
Urinary frequency	1	0	1	0	0	0
Urinary Obstruction	2	0	2	0	0	0
Urinary retention	1	0	1	0	0	0
Urinary tract infection	1	0	0	0	0	1
Hematopoietic & Lymphatic	8	0	2	2	3	1
Anemia	1	0	0	0	1	0
Bcell chronic lymphocytic leukemia	1	0	0	1	0	0
Biopsy Site Hematoma	1	0	0	0	1	0
Bruising	1	0	0	0	0	1
Elevated Liver Function Test	1	0	0	0	1	0
Erythematous Rash	1	0	0	1	0	0
Microscopic Hematoma	1	0	1	0	0	0
Pancytopenia	1	0	1	0	0	0

System (Unique Patients)	Total	DHEA	Elderly Males		Elderly Females	
			Testosterone	Placebo	DHEA	Placebo
Immunologic	12	0	6	2	3	1
Allergic Rx. to Abx.	1	0	0	0	1	0
Cellulitis	3	0	1	0	1	1
Dermatitis	2	0	2	0	0	0
Erythema at Patch Site	1	0	0	1	0	0
Infected Right Neck Phlegmon	1	0	0	0	1	0
Rash	2	0	1	0	1	0
Redness at Abdominal fat biopsy site	1	0	1	0	0	0
Soreness at Abdominal fat biopsy site	1	0	1	0	0	0
Squamous cell carcinoma on ear	1	0	0	1	0	0
Urticaria	1	0	1	0	0	0
Musculoskeletal	5	3	1	0	0	1
Fractured ribs	1	1	0	0	0	0
Fractured Wrist	1	1	0	0	0	0
Knee Arthroscopy	2	1	1	0	0	0
Total Knee Arthroplasty	3	1	1	0	0	1
Nervous	7	1	1	2	2	1
Anxiety	1	0	0	0	1	0
Death	1	0	0	0	1	0
Dizziness	1	0	1	0	0	0
General Malaise	1	0	0	0	0	1
Intracranial hemorrhage	1	0	0	0	1	0
Loss of consciousness	1	0	0	1	0	0
Pinched Back Nerve	1	1	0	0	0	0
Restless legs	1	0	0	0	0	1
Sensorineural hearing loss	1	0	0	1	0	0
Respiratory	11	3	2	3	2	1
Indeterminant Lung Nodule	1	1	0	0	0	0
Laryngospasm	1	1	0	0	0	0
Obstructive Sleep Apnea	1	0	0	1	0	0
Pneumonia	1	0	0	0	1	0
Probable Sleep Apnea	5	1	0	2	1	1
Pulmonary Nodules	1	0	1	0	0	0
Septoplasty	1	0	1	0	0	0
No Adverse Events	83	17	12	17	16	21

System (Unique Patients)	Total	DHEA	Elderly Males		Elderly Females	
			Testosterone	Placebo	DHEA	Placebo
Other	9	2	1	4	2	0
Breast Cancer	1	0	0	1	0	0
Cataract Surgery	1	1	0	0	0	0
Chills	1	0	0	1	0	0
Exhaustion	1	0	0	0	1	0
Febrile	1	0	0	1	0	0
Gynecomastia	3	1	0	2	0	0
Hemorrhoids	1	0	0	1	0	0
Hernia	1	0	0	0	1	0
Mastectomy	1	0	0	1	0	0
Right Upper Quadrant abdominal pain	1	0	1	0	0	0

NOTE: Among elderly women, there were nonsignificantly more cardiovascular events in the DHEA group than the placebo group (6/29 vs. 2/30, exact p-value=0.14). For men and women combined, the exact p-value=0.79.

Among elderly men, there were nonsignificantly more rashes, etc in the testosterone group than the placebo group (6/30 vs. 2/32, exact p-value=0.14).

Among elderly men, there were nonsignificantly more musculoskeletal events in the DHEA group than the placebo group (3/30 vs. 0/32, exact p-value 0.11). For men and women combined, the exact p-value=0.36.

No other body systems or individual adverse events showed any differences between groups (exact p-value>0.20 for all). Neither DHEA or testosterone groups had more adverse events than the placebo groups either within gender or with both genders combined (DHEA vs. placebo)(all exact p-values>0.25). The one death on study occurred in an elderly female on DHEA.

Supplement Table 5. Prostate Volume (cm³) for Elderly Male (EM) Subjects – No statistical differences between groups

		Median (IQR)	Minimum, Maximum
EM: DHEA	Baseline	31.65 (25.13, 43.07)	14.66, 124.98
	24 Month	33.32 (24.32, 44.13)	13.07, 108.86
EM: Testosterone	Baseline	28.39 (20.29, 40.00)	11.13, 60.70
	24 Month	33.62 (24.88, 47.21)	19.73, 100.83
EM: Placebo	Baseline	29.55 (19.06, 36.71)	8.79, 115.59
	24 Month	33.16 (19.45, 47.25)	0.00, 145.46

Supplement Table 6. Changes in Secondary Outcome Variables (24-month - baseline) – Median and 95% Confidence Intervals (CI) of all possible differences between groups*						
	EM:DHEA vs. EM: Placebo	P-value[‡]	EM: Testosterone vs. EM: Placebo	P-value[‡]	EF:DHEA vs. EF: Placebo	P-value[‡]
SECONDARY OUTCOME VARIABLES						
Distal 10% Radius (gm/cm²)	0.01 (-0.01, 0.02)	0.43	0.01 (-0.003, 0.02)	0.18	0.01 (-0.01, 0.03)	0.15
C-peptide (nmol/L)	-0.02 (-0.11, 0.08)	0.67	-0.06 (-0.14, 0.03)	0.16	0.11 (0.02, 0.23)	0.007
SHBG (nmol/L)	-1.98 (-5.35, 1.17)	0.053	0.75 (-2.48, 3.91)	0.99	-12.18 (-20.05, -5.90)	<0.001
Human Growth Hormone (ng/mL)	-0.13 (-0.29, -0.01)	0.036	-0.10 (-0.23, 0.04)	0.18	-0.01 (-0.16, 0.12)	0.80
ALT (U/L)	-1 (-3, 2)	0.13	1 (-2, 3)	0.46	0 (-3, 4)	0.83
AST (U/L)	-2 (-5, 2)	0.28	-1 (-5, 2)	0.80	0 (-2, 3)	0.71
Alkaline Phosphatase (U/L)	-11.0 (-38.0, 12.0)	0.38	-10.0 (-34.0, 7.0)	0.35	-14.5 (-38.0, 15.0)	0.23
Hemoglobin (g/dL)	0 (-0.4, 0.4)	0.48	0.3 (-0.2, 0.7)	0.02	0.5 (0.2, 0.9)	0.01

*Differences are DHEA minus Placebo or Testosterone minus placebo

[‡]P-values given are two-sided and come from a model that was adjusted for gender, age at the time of randomization, the time from randomization, and for the baseline value.

[†]Visceral Fat (CT & DEXA) p-values are two-sided and come from a model that adjusted for gender, age at the time of randomization, the time from randomization, the baseline value, and the difference of total body fat (DEXA).

[§]Fat free mass (FFM) p-values are two-sided and come from a model that adjusted for gender, age at the time of randomization, the time from randomization, the baseline value, and the difference of the resting energy expenditure mean.