

# The Effects of Growth Hormone on Body Composition and Physical Performance in Recreational Athletes

## A Randomized Trial

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**Background:** Growth hormone is widely abused by athletes, frequently with androgenic steroids. Its effects on performance are unclear.

**Objective:** To determine the effect of growth hormone alone or with testosterone on body composition and measures of performance.

**Design:** Randomized, placebo-controlled, blinded study of 8 weeks of treatment followed by a 6-week washout period. Randomization was computer-generated with concealed allocation. (Australian–New Zealand Clinical Trials Registry registration number: ACTRN012605000508673)

**Setting:** Clinical research facility in Sydney, Australia.

**Participants:** 96 recreationally trained athletes (63 men and 33 women) with a mean age of 27.9 years (SD, 5.7).

**Intervention:** Men were randomly assigned to receive placebo, growth hormone (2 mg/d subcutaneously), testosterone (250 mg/wk intramuscularly), or combined treatments. Women were randomly assigned to receive either placebo or growth hormone (2 mg/d).

**Measurements:** Body composition variables (fat mass, lean body mass, extracellular water mass, and body cell mass) and physical performance variables (endurance [maximum oxygen consumption], strength [dead lift], power [jump height], and sprint capacity [Wingate value]).

**Results:** Body cell mass was correlated with all measures of performance at baseline. Growth hormone significantly reduced fat mass, increased lean body mass through an increase in extracellular water, and increased body cell mass in men when coadministered with testosterone. Growth hormone significantly increased sprint capacity, by 0.71 kJ (95% CI, 0.1 to 1.3 kJ; relative increase, 3.9% [CI, 0.0% to 7.7%]) in men and women combined and by 1.7 kJ (CI, 0.5 to 3.0 kJ; relative increase, 8.3% [CI, 3.0% to 13.6%]) when coadministered with testosterone to men; other performance measures did not significantly change. The increase in sprint capacity was not maintained 6 weeks after discontinuation of the drug.

**Limitations:** Growth hormone dosage may have been lower than that used covertly by competitive athletes. The athletic significance of the observed improvements in sprint capacity is unclear, and the study was too small to draw conclusions about safety.

**Conclusion:** Growth hormone supplementation influenced body composition and increased sprint capacity when administered alone and in combination with testosterone.

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Although the World Anti-Doping Agency prohibits the use of growth hormone by competitive athletes, illicit use of the drug is widespread (1). The belief that growth hormone enhances performance is based on observations that it increases lean body mass in extremely fit persons (2, 3) and reduces body fat and increases lean mass, fitness, and strength in adults with growth hormone deficiency (4). A recent systematic review (3) highlighted the lack of evidence that growth hormone enhances performance. Athletes frequently use growth

hormone with androgenic anabolic steroids (5) on the basis of similar beliefs and evidence from studies of elderly men and men with hypopituitarism that testosterone enhances the effects of growth hormone on body composition (6). However, we do not know whether the pharmacologic improvements in body composition are associated with improvements in physical performance or whether anabolic steroids enhance the effects of growth hormone in athletes.

We previously reported findings (7) from a double-blind, randomized, placebo-controlled trial designed to detect changes in biomarkers (serum insulin-like growth factor [IGF] axis proteins and collagen peptides) in response to growth hormone administration as part of an effort to develop a test for growth hormone doping. Here, we report findings from prespecified primary analyses of secondary outcome data, which we performed to assess how growth hormone changes body composition, whether those changes enhance physical performance, and whether coadministration of testosterone enhances the effects of growth hormone on body composition and performance.

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## METHODS

The trial comprised an 8-week treatment period followed by a 6-week washout period.

### Setting and Participants

We performed our study at the clinical research facility of Garvan Institute of Medical Research, on the campus of St. Vincent's Hospital in Sydney, Australia. A trial research nurse and research medical officers enrolled participants. We recruited healthy recreational athletes aged 18 to 40 years who had engaged in regular training ( $\geq 2$  sessions/wk) for the past 12 months. We recruited from university sports centers and gymnasiums; from university sports, physical education, and medical faculties; and through publicity and advertisement at the hospital campus, fitness centers, and the wider community. Participants provided a detailed history and had a physical examination and laboratory testing at the time of screening. Participants were ineligible if they were competing at the state or national level in any sport, had abnormal chemistry and hematology blood results, reported having abused performance-enhancing drugs at any time or had positive results on urine screening for prohibited anabolic agents, or had abnormal prostate-specific antigen levels (men) or a positive pregnancy test result (women). All participants provided written informed consent. The St. Vincent's Hospital Human Research Ethics Committee approved the study.

### Interventions

Women were randomly assigned to receive either growth hormone or placebo. Men were randomly assigned to receive growth hormone plus testosterone, growth hormone plus placebo testosterone, testosterone plus placebo growth hormone, or double placebo.

Novo Nordisk (Bagsvaerd, Denmark) provided the growth hormone (somatropin, 1 mg/mL) and saline placebo, and participants self-administered the drug subcutaneously each evening at dosages of 1.0 mg/d in the first week, 1.5 mg/d in the second week, and 2.0 mg/d for the remaining 6 weeks. Cartridges were changed weekly, and we monitored adherence by the volume remaining.

A research nurse administered testosterone (Sustanon, Organon, Oss, the Netherlands), 250 mg/wk, or saline placebo intramuscularly every week for 5 weeks. Treatment began at the end of week 3, after participants reached the target growth hormone dosages of 2 mg/d, to reduce the side effects of combined treatment.

We assessed adverse effects of the study treatment by participant self-report and by clinical assessment at weekly visits during the treatment period and after treatment. If side effects occurred during the treatment period, we reduced the dosage of growth hormone or placebo to the previous dosage; we discontinued treatment if the symptoms persisted for more than 2 weeks. Similarly, if side effects occurred with testosterone (or placebo), we reduced the dosage by one half and discontinued treatment if the symptoms persisted for more than 2 weeks.

### Context

Growth hormone use is thought to be common among athletes, but its effects on athletic performance have not been carefully studied.

### Contribution

In this randomized trial, growth hormone significantly increased sprint capacity in healthy recreational athletes. The effect nearly doubled when it was given with testosterone to men. The drugs had no effect on aerobic capacity or other measures of strength or power, and the effect disappeared 6 weeks after participants discontinued therapy.

### Caution

The athletic significance of the change in sprint capacity is unknown.

### Implication

Growth hormone supplementation increased sprint capacity when given alone and in combination with testosterone. This is the first demonstration of change in physical performance with the drug.

—The Editors

### Random Assignment

The random allocation sequences were computer-generated in separate blocks for men and women (block sizes of 4 and 6, respectively) and concealed until the time of allocation. Participants and trial staff (including those measuring study outcomes and analyzing data) were blinded to the interventions at all times. Novo Nordisk generated the allocation sequence for growth hormone, prepared the growth hormone, and provided growth hormone placebo in identical matched packaging labeled with the allocation number. A statistician generated the allocation sequence for testosterone. The statistician had confidential access to the randomization list for the growth hormone assignment, to ensure balancing of the treatment groups. The statistician generated a list for assignment to testosterone or saline placebo, which was provided in a secure manner to another research nurse who administered either testosterone or placebo and was not otherwise involved in the study.

### Outcomes and Follow-up

Our primary outcomes were changes in body composition and physical performance.

### Body Composition

We studied body composition at baseline (week 0) and at the end of treatment (week 8) by using a 4-compartment model for quantifying fat mass, lean body mass, extracellular water, and body cell mass (8, 9). We measured fat mass and lean body mass by using dual-energy x-ray absorptiometry (Model DPX, software version 3.1, Lunar Radiation, Madison, Wisconsin). We measured extracellu-

lar water by using bromide dilution, as described elsewhere (10). We derived body cell mass by subtracting extracellular water mass from lean body mass (8, 9). The coefficients of variation for lean body mass and fat mass were 1.4% and 2.9%, respectively (8), and the interassay and intra-assay coefficients of variation for extracellular water were 1.6% and 0.3%, respectively.

**Physical Performance Tests**

We performed tests of physical performance before treatment (at screening and baseline), at the end of treatment (week 8), and after a 6-week washout period (week 14). We asked participants to maintain their exercise regimen throughout the study. Participants performed submaximal step, dead lift, jump height, and Wingate total work tests in a fixed order, consistent with the standards for athletic testing in Australia.

Participants first underwent a submaximal predictive step test for maximum oxygen consumption ( $\dot{V}O_{2max}$ ) on a cycle ergometer (RepcO Front-Access EX-10, Repco, Melbourne, Australia). We measured mean heart rate for

the final minute of 3 consecutive 4-minute submaximal exercise stages at fixed incremental power outputs. We derived  $\dot{V}O_{2max}$  by using individual age-predicted maximal heart rate, on the basis of a nomogram that combined heart rate, power output, and  $\dot{V}O_2$  (11). We did not adjust  $\dot{V}O_{2max}$  measures for weight because we assessed within-participant changes only and because weight is correlated with body composition, which means that differential responses of body composition to trial interventions (growth hormone or testosterone) could have influenced measures of weight-adjusted  $\dot{V}O_{2max}$  independent of fitness level.

Participants then performed an isometric dead-lift test for maximal strength by using a TTM back dynamometer (Mentone Educational, Moorabbin, Australia). Using a standardized position, participants exerted maximum extension against the dynamometer, and we recorded the best of 3 measurements.

We then measured single vertical jump height for maximal explosive power (12) by using a Yard Stick vertical jump unit (Swift Performance Equipment, Lismore,

Figure. Study flow diagram.

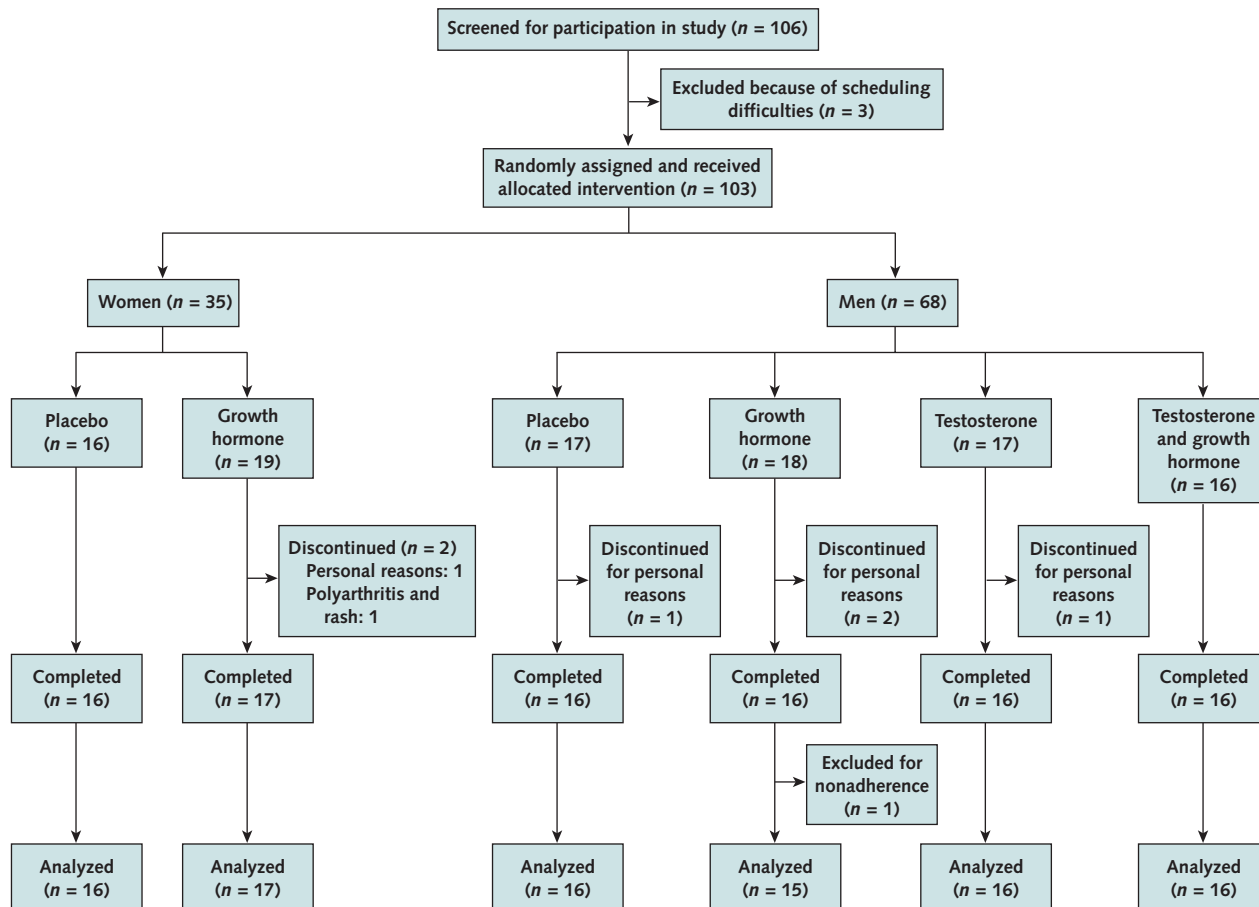


Table 1. Baseline Characteristics

| Variable                                     | Women and Men Combined |                               | Women                  |                               | Men                    |                               |                             |   |
|--|------------------------|-------------------------------|------------------------|-------------------------------|------------------------|-------------------------------|-----------------------------|---|
|  | Placebo Group (n = 32) | Growth Hormone Group (n = 32) | Placebo Group (n = 16) | Growth Hormone Group (n = 17) | Placebo Group (n = 16) | Growth Hormone Group (n = 15) | Testosterone Group (n = 16) | Growth Hormone Plus Testosterone Group (n = 16) |
| <b>Clinical</b>                              |                        |                               |                        |                               |                        |                               |                             |   |
| Mean age (SD), y                             | 28.3 (5.0)             | 27.6 (5.7)                    | 27.8 (5.0)             | 29.7 (6.2)                    | 28.9 (5.0)             | 25.2 (5.2)                    | 29 (5.7)                    | 26.8 (5.2)                                      |
| Mean height (SD), cm                         | 175 (6)                | 173 (6)                       | 164 (6)                | 169 (6)                       | 186 (5)                | 177 (6)                       | 180 (8)                     | 181 (5)   |
| Mean weight (SD), kg                         | 76.1 (10.6)            | 70.2 (10.2)                   | 61.6 (9.0)             | 65.8 (10.1)                   | 90.5 (12.2)            | 75.3 (10.4)                   | 83.3 (18.5)                 | 79.5 (10.0)                                     |
| Mean BMI (SD), kg/m <sup>2</sup>             | 24.5 (3.1)             | 23.3 (2.8)                    | 22.8 (3.2)             | 22.9 (2.8)                    | 26.1 (3.1)             | 23.8 (2.7)                    | 25.4 (3.7)                  | 24.4 (2.8)                                      |
| <b>Endocrine</b>                             |                        |                               |                        |                               |                        |                               |                             |   |
| Mean IGF-I concentration (SD), nmol/L        | 16.2 (4.9)             | 16.5 (4.9)                    | 17.9 (5.0)             | 16.2 (4.2)                    | 14.4 (4.9)             | 16.7 (4.8)                    | 16.7 (4.9)                  | 14.8 (5.2)                                      |
| Mean testosterone concentration (SD), nmol/L | 11.7 (5.2)             | 12.5 (5.4)                    | 1.4 (0.7)              | 1.2 (0.6)                     | 21.9 (7.3)             | 25.3 (7.9)                    | 23.5 (7.8)                  | 23.1 (4.99)                                     |
| Mean testosterone concentration (SD), ng/dL  | 337 (150)              | 360 (156)                     | 40 (20)                | 36 (18)                       | 631 (212)              | 729 (227)                     | 677 (224)                   | 666 (144)                                       |
| <b>Body composition*</b>                     |                        |                               |                        |                               |                        |                               |                             |   |
| Mean fat mass (SD), kg                       | 18.5 (6.8)             | 16.3 (6.2)                    | 18.2 (5.7)             | 19.4 (7.0)                    | 18.8 (7.99)            | 12.7 (5.1)                    | 16.2 (9.1)                  | 14.6 (7.7)                                      |
| Mean lean body mass (SD), kg                 | 54.1 (6.1)             | 51.3 (5.5)                    | 40.6 (5.0)             | 43.6 (4.1)                    | 67.6 (7.1)             | 59.5 (6.4)                    | 63.1 (10.2)                 | 61.9 (6.3)                                      |
| Mean extracellular water mass (SD), kg       | 19.2 (2.4)             | 17.8 (2.7)                    | 15.2 (1.8)             | 16 (1.6)                      | 23.2 (2.8)             | 19.7 (3.4)                    | 21.4 (4.0)                  | 21.4 (3.1)                                      |
| Mean body cell mass (SD), kg                 | 34.9 (4.7)             | 33.5 (4.5)                    | 25.4 (3.9)             | 27.6 (3.6)                    | 44.4 (5.3)             | 39.8 (4.9)                    | 41.8 (7.0)                  | 40.5 (4.17)                                     |
| <b>Training type, n (%)</b>                  |                        |                               |                        |                               |                        |                               |                             |   |
| Power  | 3 (9.4)                | 3 (9.4)                       | 0 (0)                  | 1 (5.9)                       | 3 (18.8)               | 2 (13.3)                      | 3 (18.8)                    | 1 (6.25)  |
| Endurance                                    | 12 (37.5)              | 6 (18.8)                      | 7 (43.8)               | 5 (29.4)                      | 5 (31.2)               | 1 (6.7)                       | 2 (12.5)                    | 2 (12.5)  |
| Mixed  | 17 (53.1)              | 23 (71.9)                     | 9 (56.2)               | 11 (64.7)                     | 8 (50.0)               | 12 (80.0)                     | 11 (68.8)                   | 13 (81.2)                                       |
| <b>Training quantity, n (%)</b>              |                        |                               |                        |                               |                        |                               |                             |   |
| 2 to 4 h                                     | 10 (31.2)              | 10 (31.2)                     | 7 (43.7)               | 7 (41.2)                      | 3 (18.8)               | 3 (20.0)                      | 1 (6.2)                     | 6 (37.5)  |
| 4 to 10 h                                    | 19 (59.4)              | 20 (62.5)                     | 8 (50.0)               | 8 (47.1)                      | 11 (68.8)              | 12 (80.0)                     | 11 (68.8)                   | 8 (50.0)  |
| >10 h  | 3 (9.38)               | 2 (6.3)                       | 1 (6.3)                | 2 (11.8)                      | 2 (12.5)               | 0 (0.0)                       | 4 (25.0)                    | 2 (12.5)  |
| <b>Performance</b>                           |                        |                               |                        |                               |                        |                               |                             |   |
| Mean $\dot{V}O_2$ max (SD), L/min            | 3.3 (0.7)              | 3.2 (0.7)                     | 2.5 (0.7)              | 2.7 (0.7)                     | 4.1 (0.7)              | 3.8 (0.7)                     | 3.8 (1.0)                   | 3.8 (0.9)                                       |
| Mean dead lift (SD), kg                      | 151 (26)               | 155 (30)                      | 118 (28)               | 131 (28)                      | 187 (22)               | 182 (32)                      | 201 (38)                    | 185 (38)  |
| Mean jump height (SD), cm                    | 44.3 (7.5)             | 46.4 (6.3)                    | 36.3 (6.9)             | 36.7 (6.2)                    | 52.7 (7.6)             | 57.4 (6.5)                    | 55.2 (9.3)                  | 53.9 (7.2)                                      |
| Mean Wingate value (SD), kJ†                 | 18.5 (3.3)             | 17.4 (3.1)                    | 13.4 (2.9)             | 13.9 (2.9)                    | 24.7 (2.6)             | 21.1 (3.1)                    | 23.3 (4.4)                  | 22.4 (3.0)                                      |

BMI = body mass index; IGF-I = insulin-like growth factor I;  $\dot{V}O_2$ max = maximum oxygen consumption.

\* We excluded data for 1 woman who received growth hormone because of technical difficulties with extracellular water measurement. We included her data for all other variables in the table.

† Total work during sprint cycle ergometry, a measure of anaerobic sprint capacity.

Australia). The best of 5 countermovement jumps made from a standing position was recorded.

Finally, we assessed total work during sprint cycle ergometry (Wingate test) for anaerobic work capacity (sprint capacity) by using a 30-second maximal test on a cycle ergometer. Participants accelerated the cycle ergometer to their maximum under verbal encouragement, and total work was recorded.

Day-to-day coefficients of variation were 5.2% for  $\dot{V}O_2$ max, 8.6% for dead lift, 8.5% for jump height, and 4.2% for the Wingate test.

### Assays

In our original trial, we measured serum IGF axis proteins (IGF-I, IGF binding protein-3, and acid labile subunit)

and collagen peptides (7). Here, we report IGF-I and testosterone concentrations only. We measured IGF-I (intra-assay and interassay coefficients of variation, <4% and <9%, respectively) by radioimmunoassay after acid-ethanol extraction (7, 13) and total testosterone by Immulite automated chemiluminescent immunoassay (Siemens Medical Solutions Diagnostics, Gwynedd, United Kingdom), with a coefficient of variation of 7.1% at 13.8 nmol/L (398 ng/dL). We collected serum samples at baseline (week 0) and at the end of treatment (week 8) and stored them at  $-80^{\circ}\text{C}$  until analysis.

### Statistical Analysis

We based our sample size calculations on previously reported changes in growth hormone biomarkers in re-

**Table 2. Between-Group Differences for Changes From Baseline in Weight, Biochemical Variables, Body Composition, and Performance**

| Variable and Time Point                                     | Women and Men Combined  |          | Women   |          |
|---|---|----------|---|----------|
|   | Change in Growth Hormone Group Minus Change in Placebo Group (95% CI) | P Value* | Change in Growth Hormone Group Minus Change in Placebo Group (95% CI) | P Value* |
| <b>Clinical</b>   |   |          |   |          |
| Weight, week 8 – week 0                                     |   |          |   |          |
| Absolute, kg  | 1.5 (0.5 to 2.6)  | <0.005   | -0.1 (-1.4 to 1.0)  | 0.86     |
| Relative, %   | 2.1 (0.7 to 3.4)  | <0.005   | -0.1 (-2.0 to 1.6)  | 0.92     |
| Body mass index, week 8 – week 0                            |   |          |   |          |
| Absolute, kg/m <sup>2</sup>                                 | 0.5 (0.1 to 0.8)  | <0.005   | -0.1 (-0.5 to 0.3)  | 0.8      |
| Relative, %   | 2.1 (0.7 to 3.4)  | <0.005   | -0.2 (-2.0 to 1.5)  | 0.88     |
| <b>Endocrine</b>  |   |          |   |          |
| Insulin-like growth factor I concentration, week 8 – week 0 |   |          |   |          |
| Absolute, nmol/L  | 17.42 (14.02 to 21.35)  | <0.005   | 12.97 (8.78 to 17.03)   | <0.005   |
| Relative, %   | 110 (86 to 139)   | <0.005   | 83 (54 to 110)  | <0.005   |
| Testosterone concentration, week 8 – week 0                 |   |          |   |          |
| Absolute nmol/L   | 0.0 (-2.1 to 2.0)   | 0.92     | 0.0 (-0.4 to 0.5)   | 0.99     |
| ng/dL   | 0.00 (-60.52 to 57.64)  |          | 0.00 (-11.53 to 14.41)  |          |
| Relative, %   | -3.2 (-23.8 to 16.7)  | 0.70     | -4.5 (-39.3 to 29.7)  | 0.8      |
| <b>Body composition†</b>                                    |   |          |   |          |
| Fat mass, week 8 – week 0                                   |   |          |   |          |
| Absolute, kg  | -1.4 (-2.1 to -0.8)   | <0.005   | -2.3 (-3.2 to -1.4)   | <0.005   |
| Relative, %   | -10.2 (-15.5 to -5.4)   | <0.005   | -12.8 (-17.6 to -8.0)   | <0.005   |
| Lean body mass, week 8 – week 0                             |   |          |   |          |
| Absolute, kg  | 2.7 (1.9 to 3.5)  | <0.005   | 2.5 (1.4 to 3.6)  | <0.005   |
| Relative, %   | 5.4 (3.7 to 7.0)  | <0.005   | 5.7 (2.9 to 8.7)  | <0.005   |
| Extracellular water mass, week 8 – week 0                   |   |          |   |          |
| Absolute, kg  | 1.8 (0.9 to 2.8)  | <0.005   | 1.2 (0.1 to 2.3)  | 0.03     |
| Relative, %   | 10.2 (4.9 to 15.5)  | <0.005   | 7.9 (0.7 to 15.2)   | 0.03     |
| Body cell mass, week 8 – week 0                             |   |          |   |          |
| Absolute, kg  | 0.9 (-0.2 to 1.9)   | 0.09     | 1.3 (-0.1 to 2.6)   | 0.07     |
| Relative, %   | 2.8 (-0.4 to 5.9)   | 0.08     | 4.4 (-1.0 to 9.7)   | 0.11     |
| <b>Performance</b>  |   |          |   |          |
| VO <sub>2</sub> max   |   |          |   |          |
| Week 8 – week 0   |   |          |   |          |
| Absolute, L/min   | -0.1 (-0.3 to 0.2)  | 0.62     | 0.1 (-0.1 to 0.3)   | 0.55     |
| Relative, %   | 0.1 (-6.2 to 6.0)   | 0.99     | 3.6 (-4.9 to 12.3)  | 0.43     |
| Week 14 – week 0  |   |          |   |          |
| Absolute, L/min   | 0.0 (-0.2 to 0.3)   | 0.83     | 0.2 (-0.1 to 0.5)   | 0.23     |
| Relative, %   | 2.8 (-4.3 to 9.9)   | 0.45     | 7.8 (-2.4 to 17.8)  | 0.14     |
| Dead lift   |   |          |   |          |
| Week 8 – week 0   |   |          |   |          |
| Absolute, kg  | -3.3 (-13.3 to 6.8)   | 0.53     | -4.5 (-16.1 to 6.4)   | 0.42     |
| Relative, %   | -2.1 (-8.6 to 4.2)  | 0.52     | -3.7 (-13.1 to 4.8)   | 0.41     |
| Week 14 – week 0  |   |          |   |          |
| Absolute, kg  | 1.8 (-8.5 to 12.5)  | 0.74     | -3.3 (-16.3 to 9.9)   | 0.63     |
| Relative, %   | -0.5 (-7.7 to 7.1)  | 0.89     | -5.6 (-16.5 to 5.5)   | 0.33     |
| Jump height   |   |          |   |          |
| Week 8 – week 0   |   |          |   |          |
| Absolute, cm  | 0.3 (-1.4 to 2.2)   | 0.73     | 1.0 (-1.4 to 3.4)   | 0.44     |
| Relative, %   | 0.8 (-3.4 to 5.1)   | 0.73     | 2.6 (-4.1 to 9.3)   | 0.45     |
| Week 14 – week 0  |   |          |   |          |
| Absolute, cm  | -1.4 (-3.6 to 0.8)  | 0.21     | -1.2 (-3.7 to 1.3)  | 0.37     |
| Relative, %   | -3.7 (-9.1 to 1.3)  | 0.16     | -4.3 (-12.1 to 3.2)   | 0.28     |
| Wingate value‡  |   |          |   |          |
| Week 8 – week 0   |   |          |   |          |
| Absolute, kJ  | 0.7 (0.1 to 1.3)  | 0.02     | 0.4 (-0.3 to 1.0)   | 0.27     |
| Relative, %   | 3.9 (0.0 to 7.7)  | 0.05     | 2.5 (-3.5 to 8.4)   | 0.42     |
| Week 14 – week 0  |   |          |   |          |
| Absolute, kJ  | 0.6 (-0.1 to 1.3)   | 0.09     | 0.2 (-0.5 to 0.9)   | 0.55     |
| Relative, %   | 3.1 (-1.5 to 7.6)   | 0.18     | 0.9 (-6.0 to 7.1)   | 0.76     |

VO<sub>2</sub>max = maximum oxygen consumption.

\* Values have not been corrected; incorporation of the Holm correction for comparison among the 4 treatment groups in men increased the P values but did not affect which changes were statistically significant.

† We excluded data for 1 woman who received growth hormone because of technical difficulties with extracellular water measurement. We have included her data for all other variables in the table.

‡ Total work during sprint cycle ergometry, a measure of anaerobic sprint capacity.

**Table 2—Continued**

| Men   |          |   |          |   |          |
|---|----------|---|----------|---|----------|
| Change in Growth Hormone Group Minus Change in Placebo Group (95% CI) | P Value* | Change in Testosterone Group Minus Change in Placebo Group (95% CI) | P Value* | Change in Growth Hormone Plus Testosterone Group Minus Change in Placebo Group (95% CI) | P Value* |
| 3.3 (1.7 to 4.9)  | <0.005   | 2.8 (1.1 to 4.6)  | <0.005   | 5.4 (3.7 to 7.2)  | <0.005   |
| 4.4 (2.3 to 6.4)  | <0.005   | 3.7 (1.6 to 5.9)  | <0.005   | 6.9 (4.7 to 9.0)  | <0.005   |
| 1.0 (0.5 to 1.5)  | <0.005   | 0.9 (0.4 to 1.5)  | <0.005   | 1.7 (1.1 to 2.2)  | <0.005   |
| 4.4 (2.4 to 6.5)  | <0.005   | 3.7 (1.7 to 6.0)  | <0.005   | 6.9 (4.8 to 9.0)  | <0.005   |
| 22.66 (16.51 to 28.95)  | <0.005   | 1.83 (−0.26 to 3.93)  | 0.10     | 22.14 (17.16 to 27.64)  | <0.005   |
| 141 (98 to 190)   | <0.005   | 6 (−11 to 20)   | 0.44     | 157 (116 to 213)  | <0.005   |
| −0.1 (−4.5 to 4.2)  | 0.92     | 13.8 (5.4 to 25.6)  | <0.005   | 8.7 (4.4 to 13.2)   | <0.005   |
| −2.88 (−129.68 to 121.04)   |          | 397.69 (155.62 to 737.75)   |          | 250.72 (126.80 to 380.40)   |          |
| −3.1 (−21.6 to 15.5)  | 0.73     | 73.3 (21.6 to 145.0)  | <0.005   | 40.6 (17.4 to 64.9)   | <0.005   |
| −0.5 (−1.6 to 0.6)  | 0.34     | 0.1 (−1.6 to 1.6)   | 0.86     | −1.0 (−2.3 to 0.2)  | 0.11     |
| −7.7 (−16.8 to 1.4)   | 0.09     | 4.2 (−5.2 to 14.6)  | 0.39     | −8.6 (−16.9 to 0.4)   | 0.06     |
| 2.9 (1.8 to 4.0)  | <0.005   | 2.4 (1.5 to 3.4)  | <0.005   | 5.8 (4.6 to 7.0)  | <0.005   |
| 5.0 (3.2 to 6.7)  | <0.005   | 3.9 (2.6 to 5.3)  | <0.005   | 9.7 (7.7 to 11.8)   | <0.005   |
| 2.4 (0.9 to 4.0)  | <0.005   | 1.2 (−0.4 to 2.9)   | 0.15     | 3.6 (1.8 to 5.3)  | <0.005   |
| 12.6 (5.1 to 20.0)  | <0.005   | 5.3 (−1.6 to 12.4)  | 0.14     | 17.1 (9.2 to 24.7)  | <0.005   |
| 0.4 (−1.1 to 1.9)   | 0.57     | 1.2 (−0.3 to 2.7)   | 0.11     | 2.3 (0.7 to 3.8)  | <0.005   |
| 1.2 (−2.3 to 4.5)   | 0.52     | 3.1 (−0.3 to 6.4)   | 0.07     | 5.8 (2.2 to 9.3)  | <0.005   |
| −0.2 (−0.5 to 0.2)  | 0.28     | 0.0 (−0.3 to 0.4)   | 0.83     | 0.1 (−0.3 to 0.4)   | 0.68     |
| −3.7 (−12.2 to 4.7)   | 0.37     | 0.9 (−7.2 to 8.3)   | 0.84     | 3.0 (−5.7 to 10.9)  | 0.48     |
| −0.1 (−0.5 to 0.2)  | 0.5      | −0.1 (−0.4 to 0.3)  | 0.72     | 0.2 (−0.2 to 0.4)   | 0.33     |
| −2.2 (−12.0 to 8.2)   | 0.64     | −1.3 (−9.7 to 6.9)  | 0.72     | 5.2 (−3.6 to 14.0)  | 0.24     |
| −1.7 (−18.7 to 15.2)  | 0.83     | −5.3 (−20.3 to 10.3)  | 0.5      | −13.1 (−31.5 to 4.0)  | 0.13     |
| −0.2 (−9.2 to 8.8)  | 0.95     | −0.4 (−9.6 to 11.1)   | 0.92     | −4.4 (−13.7 to 5.5)   | 0.37     |
| 7.1 (−9.4 to 24.0)  | 0.41     | −2.3 (−16.5 to 12.3)  | 0.77     | 0.3 (−19.9 to 19.6)   | 0.98     |
| 4.9 (−5.4 to 15.0)  | 0.36     | −3.0 (−10.7 to 4.7)   | 0.49     | 2.5 (−9.4 to 16.3)  | 0.72     |
| −0.4 (−2.8 to 2.3)  | 0.75     | −0.3 (−2.9 to 2.6)  | 0.86     | −0.9 (−3.8 to 2.1)  | 0.56     |
| −1.3 (−5.9 to 3.8)  | 0.62     | −1.3 (−6.4 to 4.0)  | 0.64     | −1.7 (−7.6 to 4.8)  | 0.6      |
| −1.6 (−5.2 to 1.8)  | 0.38     | −1.5 (−5.6 to 2.1)  | 0.44     | 0.3 (−4.1 to 4.5)   | 0.88     |
| −3.1 (−10.4 to 3.4)   | 0.38     | −2.7 (−10.6 to 4.3)   | 0.47     | 0.9 (−8.1 to 9.9)   | 0.84     |
| 1.1 (0.0 to 2.2)  | 0.05     | 0.9 (−0.2 to 2.0)   | 0.1      | 1.7 (0.5 to 3.0)  | 0.01     |
| 5.5 (0.8 to 10.5)   | 0.03     | 4.1 (−0.5 to 8.7)   | 0.08     | 8.3 (3.0 to 13.6)   | <0.005   |
| 1.0 (−0.2 to 2.3)   | 0.11     | 0.4 (−0.8 to 1.6)   | 0.54     | 0.8 (−0.5 to 2.2)   | 0.22     |
| 5.6 (−0.3 to 12.2)  | 0.07     | 1.8 (−3.2 to 6.9)   | 0.51     | 4.2 (−1.5 to 10.2)  | 0.15     |



Table 3. Adverse Events\*

| Event                                | Women and Men Combined    |                                  |   | Women                     |                                  |   |
|--------------------------------------|---------------------------|----------------------------------|---|---------------------------|----------------------------------|---|
|                                      | Placebo Group<br>(n = 32) | Growth Hormone<br>Group (n = 32) | Difference From<br>Placebo Group<br>[95% CI]† | Placebo Group<br>(n = 16) | Growth Hormone<br>Group (n = 17) | Difference From<br>Placebo Group<br>[95% CI]† |
| Swelling, n (%)                      | 9 (28)                    | 21 (66)                          | 12 (38) [12 to 63]                            | 5 (31)                    | 11 (65)                          | 6 (33) [−5 to 72]                             |
| Joint pain, n (%)                    | 6 (19)                    | 15 (47)                          | 9 (28) [3 to 53]                              | 3 (19)                    | 6 (35)                           | 3 (17) [−19 to 52]                            |
| Muscle pain, n (%)                   | 7 (22)                    | 7 (22)                           | 0 (0) [−20 to 20]                             | 2 (12)                    | 3 (18)                           | 1 (5) [−24 to 35]                             |
| Paresthesias, n (%)                  | 3 (9)                     | 9 (28)                           | 6 (19) [−3 to 40]                             | 2 (12)                    | 3 (18)                           | 1 (5) [−24 to 35]                             |
| Acne, n (%)                          | 3 (9)                     | 5 (16)                           | 2 (6) [−13 to 26]                             | 0 (0)                     | 2 (12)                           | 2 (12) [−10 to 33]                            |
| Mood changes, n (%)                  | 3 (9)                     | 2 (6)                            | −1 (−3) [−19 to 13]                           | 0 (0)                     | 0 (0)                            | 0 (0)   |
| Other, n (%)‡                        | 15 (47)                   | 14 (44)                          | −1 (−3) [−31 to 24]                           | 7 (44)                    | 6 (35)                           | −1 (−8) [−48 to 31]                           |
| Total patients with<br>events, n (%) | 23 (72)                   | 27 (84)                          | 4 (12) [−11 to 36]                            | 11 (69)                   | 13 (76)                          | 2 (8) [−29 to 44]                             |
| Total events, n                      | 46                        | 73                               | –   | 19                        | 31                               | –   |

\* For the 96 participants included in the study analysis (Figure). We excluded 1 participant from the body composition analysis only. Six additional participants started treatment and later discontinued; 5 discontinued for personal reasons after receiving treatment for 2 to 49 days, and 1 woman who received growth hormone discontinued after 28 days because of polyarthritides symptoms and rash. We excluded 1 additional participant who completed the study protocol from our analysis.

† Values in parentheses and 95% CIs are expressed as percentage points.

‡ Includes bruising from subcutaneous injections, breast tenderness, hunger, headache, and increased sweating.

sponse to exogenous growth hormone (14, 15). Our primary outcomes were biomarkers of growth hormone abuse. Our power calculations resulted in a sample size of 15 for each of the 6 study groups. We did not perform power calculations for performance outcomes.

We assessed change from baseline in participant characteristics and outcomes by using least-squares regression models, with treatment group as the main effect. We fitted the models separately for men and women and used additional models that incorporated sex as a main effect to compare the effect of treatment with growth hormone versus placebo (men and women combined). We used 5000 bootstrap samples (16) to provide robust 95% CIs for the difference between mean changes in response for the treatment groups compared with placebo groups. We also estimated *P* values for significant differences among groups from the bootstrap distributions. For men, we incorporated the Holm correction (17) for comparisons made among the 4 treatment groups. We compared the frequencies of adverse effects separately for men and women by using the Pearson chi-square test for comparing proportions, with a continuity correction (18). We performed statistical analysis of the body composition and performance variables within the R programming environment (R Foundation for Statistical Computing, Vienna, Austria).

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## RESULTS

Of 106 participants screened, 3 were not randomly assigned because of scheduling difficulties (Figure). Six of the 103 participants discontinued the study, 5 for personal reasons (unrelated to side effects) and 1 because of polyarthritides and a rash. We excluded 1 participant from analysis because of nonadherence and another from body composition analysis because of technical extracellular water measurement difficulties. Our analysis therefore included 96 participants: 33 women and 63 men (Figure). Table 1 shows the baseline characteristics of the groups, including baseline measures of body composition and performance. Body cell mass correlated significantly with each measure of performance, and fat mass was negatively correlated with jump height (Appendix, available at [www.annals.org](http://www.annals.org)).

### Effects of Treatment

Growth hormone increased IGF-I concentration compared with placebo ( $P < 0.005$ ); coadministration of testosterone did not affect the response in men (Table 2). In men, testosterone alone had no effect on IGF-I concentration, and growth hormone had no effect on testosterone concentration.

Growth hormone reduced fat mass, increased lean body mass, increased extracellular water, and increased body cell mass in all treatment groups, as did testosterone (Table 2 and Appendix Figure 1, available at [www.annals.org](http://www.annals.org)). These effects were greater with combined growth hormone and testosterone treatments. Compared with placebo, changes from baseline with growth hormone were significantly greater for fat mass (in women and in women and men combined), lean body mass (in all groups), and extracellular water (in all groups). Body cell mass changed

Table 3—Continued

| Men                       |                                  |   |                                   |   |   |   |
|---------------------------|----------------------------------|---|-----------------------------------|---|---|---|
| Placebo Group<br>(n = 16) | Growth Hormone<br>Group (n = 15) | Difference From<br>Placebo Group<br>[95% CI]† | Testosterone<br>Group<br>(n = 16) | Difference from<br>Placebo Group<br>[95% CI]† | Growth Hormone Plus<br>Testosterone Group<br>(n = 16) | Difference From<br>Placebo Group<br>[95% CI]† |
| 4 (25)                    | 10 (67)                          | 6 (42) [3 to 80]                              | 10 (62)                           | 6 (38) [−1 to 76]                             | 14 (88)   | 10 (62) [30 to 95]                            |
| 3 (19)                    | 9 (60)                           | 6 (41) [3 to 79]                              | 5 (31)                            | 2 (12) [−23 to 48]                            | 6 (38)  | 3 (19) [−18 to 55]                            |
| 5 (31)                    | 4 (27)                           | −1 (−5) [−41 to 32]                           | 10 (62)                           | 5 (31) [−8 to 70]                             | 13 (81)   | 8 (50) [14 to 86]                             |
| 1 (6)                     | 6 (40)                           | 5 (34) [0 to 68]                              | 3 (19)                            | 2 (12) [−16 to 41]                            | 5 (31)  | 4 (25) [−7 to 57]                             |
| 3 (19)                    | 3 (20)                           | 0 (1) [−28 to 30]                             | 5 (31)                            | 2 (12) [−23 to 48]                            | 7 (44)  | 4 (25) [−10 to 62]                            |
| 3 (19)                    | 2 (13)                           | −1 (−5) [−37 to 26]                           | 2 (12)                            | −1 (−6) [−38 to 25]                           | 2 (12)  | −1 (−6) [−38 to 25]                           |
| 8 (50)                    | 8 (53)                           | 0 (3) [−35 to 42]                             | 7 (44)                            | −1 (−6) [−47 to 35]                           | 7 (44)  | −1 (−6) [−47 to 35]                           |
| 12 (75)                   | 14 (93)                          | 2 (18) [−13 to 49]                            | 16 (100)                          | 4 (25) [−2 to 52]                             | 16 (100)  | 4 (25) [−2 to 52]                             |
| 27                        | 42                               | –   | 42                                | –   | 54  | –   |

significantly in participants who received both growth hormone and testosterone compared with placebo.

We detected no effects on or consistent trends in measures of physical performance due to study treatments and no correlation between changes in body composition and changes in performance (Appendix Figure 2 and Appendix Tables 1, 2, and 3 available at [www.annals.org](http://www.annals.org)), except that the Wingate value increased in all groups who received growth hormone. Sprint capacity increased significantly with growth hormone treatment compared with placebo in men and women combined (absolute increase, 0.71 kJ [95% CI, 0.1 to 1.32 kJ],  $P = 0.020$ ; relative increase, 3.9% [CI, 0.0% to 7.7%],  $P = 0.050$ ; correlation with body cell mass,  $R^2 = 0.11$ ,  $P = 0.080$ ) and in men who received both growth hormone and testosterone (absolute increase, 1.7 kJ [CI, 0.5 to 3.0 kJ],  $P = 0.010$ ; relative increase, 8.3% [CI, 3.0% to 13.6%],  $P < 0.005$ ; correlation,  $R^2 = 0.28$ ,  $P = 0.040$ ). These differences were no longer present 6 weeks after participants discontinued the study treatments.

### Adverse Events

Participants in all treatment groups reported swelling, joint and muscle pain, paresthesias, and acne (Table 3). In men and women combined, rates of swelling and joint pain differed significantly between the growth hormone and placebo groups. In men, rates of swelling, joint pain, and paresthesias differed significantly between the growth hormone and placebo groups, as did rates of swelling and muscle pain between the growth hormone plus testosterone and placebo groups. One woman skipped 3 doses of growth hormone because of numbness and tingling and then resumed treatment at the full dosage. For 1 man, we reduced both growth hormone and testosterone treatments by one half for 1 week because of joint and muscle pain, after which he resumed full dosages. One man had water retention and reported feeling angrier than usual, and we discontinued his testosterone therapy for the last 2 weeks.

### DISCUSSION

Our trial of growth hormone with and without testosterone in athletes has 4 main findings. First, body cell mass at baseline was correlated with all measures of physical performance. Second, growth hormone significantly reduced fat mass, increased lean body mass through an increase in extracellular water, and increased body cell mass when given with testosterone. Third, growth hormone led to statistically significant improvements in sprint capacity that were not maintained after a 6-week washout period in a pooled group of men and women, and the improvements were greater when growth hormone was coadministered with testosterone to men. Finally, changes in body cell mass did not correlate with improvement in sprint capacity, except when growth hormone was coadministered with testosterone. Our findings are consistent with previous observations (19) that long-term growth hormone treatment in children with the Prader–Willi syndrome increased sprint capacity.

Sprint capacity is a measure of power and anaerobic performance (20), which suggests that growth hormone may have affected muscle anabolism (power), energy supply (anaerobic performance), or both. Anabolic effects are unlikely, because the improvement in sprint capacity we observed was not accompanied by a statistically significant increase in body cell mass, the changes in these parameters did not clearly correlate, the drug had no clear effect on jump height or dynamometry, and previous studies demonstrated no beneficial effect of growth hormone on strength or power in athletes (21, 22) or on muscle protein synthesis in weight lifters (23). Microarray studies in growth hormone–deficient men (24) have also shown that growth hormone treatment had mixed effects on the genes in muscle that are involved in protein synthesis and degradation and those that encode myofibrillar proteins.

The improvement in sprint capacity with growth hormone may alternatively be explained by effects on muscle energy supply. Gene expression studies (24) indicate that



growth hormone enhances the use of glucose over fatty acids and suppresses oxidative mitochondrial energy production, which suggests regulation through anaerobic metabolism. Acute growth hormone administration caused an exaggerated increase in plasma lactate concentration during cycling in trained young men (25). Therefore, increased sprint capacity after growth hormone treatment may involve an improved ability to derive acute energy requirements from anaerobic metabolism, coupled with improved capacity to buffer against a decline in intracellular pH that would otherwise inhibit performance (26).

The athletic significance of this improvement in sprint capacity is uncertain. We do not know how an improvement in Wingate test performance translates to performance in the sporting field, but we speculate that the approximately 4% increase in sprint capacity that we observed could translate to an improvement of 0.4 second in a 10-second sprint over 100 meters or of 1.2 seconds in a 30-second swim over 50 meters.

A recent systematic review (3) concluded that claims that growth hormone enhances physical performance were premature but also highlighted the lack of well-conducted studies. One placebo-controlled study (21) with only 22 participants evaluated growth hormone treatment for more than 8 weeks. Only 8 studies investigated physical performance, and their assessments were confined to exercise capacity ( $\dot{V}O_2\text{max}$ ) and muscle strength (3). A recent study (27) has shown increased strength and peak power output in a model of abstinent anabolic or androgenic steroid-dependent persons. The systematic review (3) underscored the lack of published evidence on the physiologic effects of real-world growth hormone doping regimens, which may range from 15 to 180  $\mu\text{g}/\text{kg}$  per day (1) and may be taken in combination with other drugs, including androgens (5).

Growth hormone and testosterone induced similar changes in body composition and performance; each increased extracellular water, body cell mass, and Wingate value. Combined treatment resulted in greater increases that were statistically significant for body cell mass and Wingate value. Studies in elderly men (28, 29) have also observed that combined growth hormone and testosterone treatments result in greater changes in body composition and physical performance than with either treatment alone. In men with hypopituitarism, testosterone amplifies the metabolic actions of growth hormone, enhancing effects on resting energy expenditure, fat oxidation, protein metabolism, and fluid retention (6, 10). Our study in athletes revealed an interesting differential effect between growth hormone and testosterone: Although each increased lean body mass in men equally, growth hormone increased mass primarily by increasing extracellular water, whereas testosterone had a greater effect on body cell mass. The gain in body cell mass had a modest but statistically significant relationship ( $R^2 = 0.28$ ) with the improvement in sprint

capacity after combined growth hormone and testosterone administration.

Our study has limitations. First, we recruited recreational rather than elite athletes, because it is not ethical to administer banned agents to elite athletes. Second, we used a modest dose of growth hormone (about 30  $\mu\text{g}/\text{kg}$  for a 70-kg person) in the lower range reported for covert use (1) and for a relatively brief duration. Higher doses of the drug taken for longer durations may have greater effects on body cell mass, aerobic capacity, muscle strength or power, and lead to greater adverse effects. Third, we cannot exclude a type II error because we based the power calculations for the study on expected changes in the growth hormone biomarkers; however, we observed no trends in the other performance measures after growth hormone administration compared with placebo. Finally, although blinding of the participants to treatment should have reduced any possible effect of training on performance in this placebo-controlled study, we could not distinguish changes in performance attributable to direct effects of treatment from those attributable to increased intensity or duration of training.

In conclusion, 8 weeks of growth hormone treatment did not significantly improve strength, power, or endurance but did increase sprint capacity, an effect that was greater when we coadministered testosterone. The athletic significance of this improvement in sprint capacity is not clear. Future work should address whether growth hormone treatment for a longer period at higher doses improves aerobic performance, strength, or power, and should investigate the biochemical mechanisms that underlay growth hormone's facilitation of anaerobic capacity.

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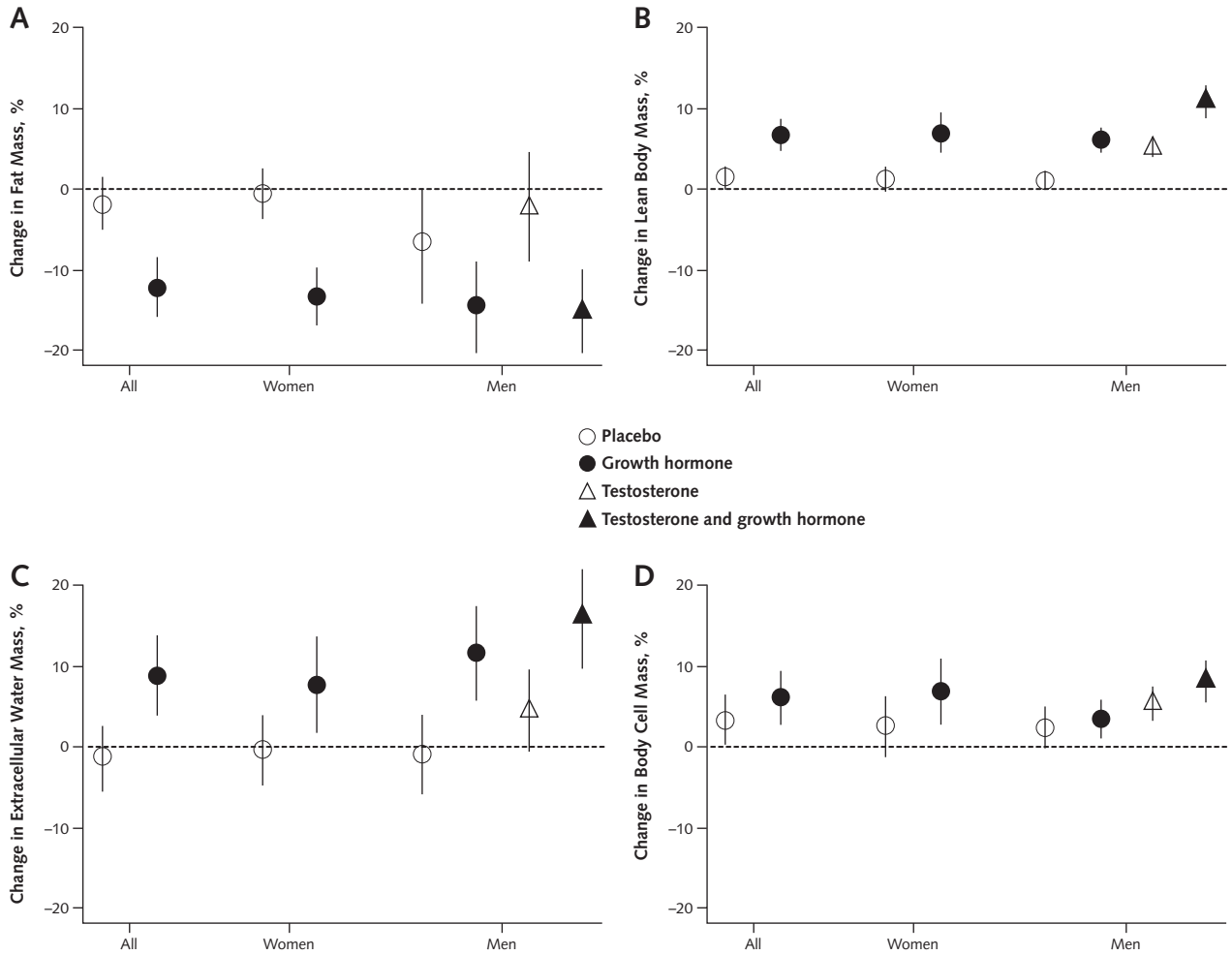
Collection and assembly of data: U. Meinhardt, A.E. Nelson, J.L. Hansen, V. Birzniece.

## APPENDIX: BASELINE ANALYSIS

We fitted regression models for each body composition variable with the measures of physical performance by using random-effects models. **Appendix Table 2** and **Appendix Figure 3** show that body cell mass was positively correlated with each measure of physical performance. Fat mass was negatively associated only with jump height.

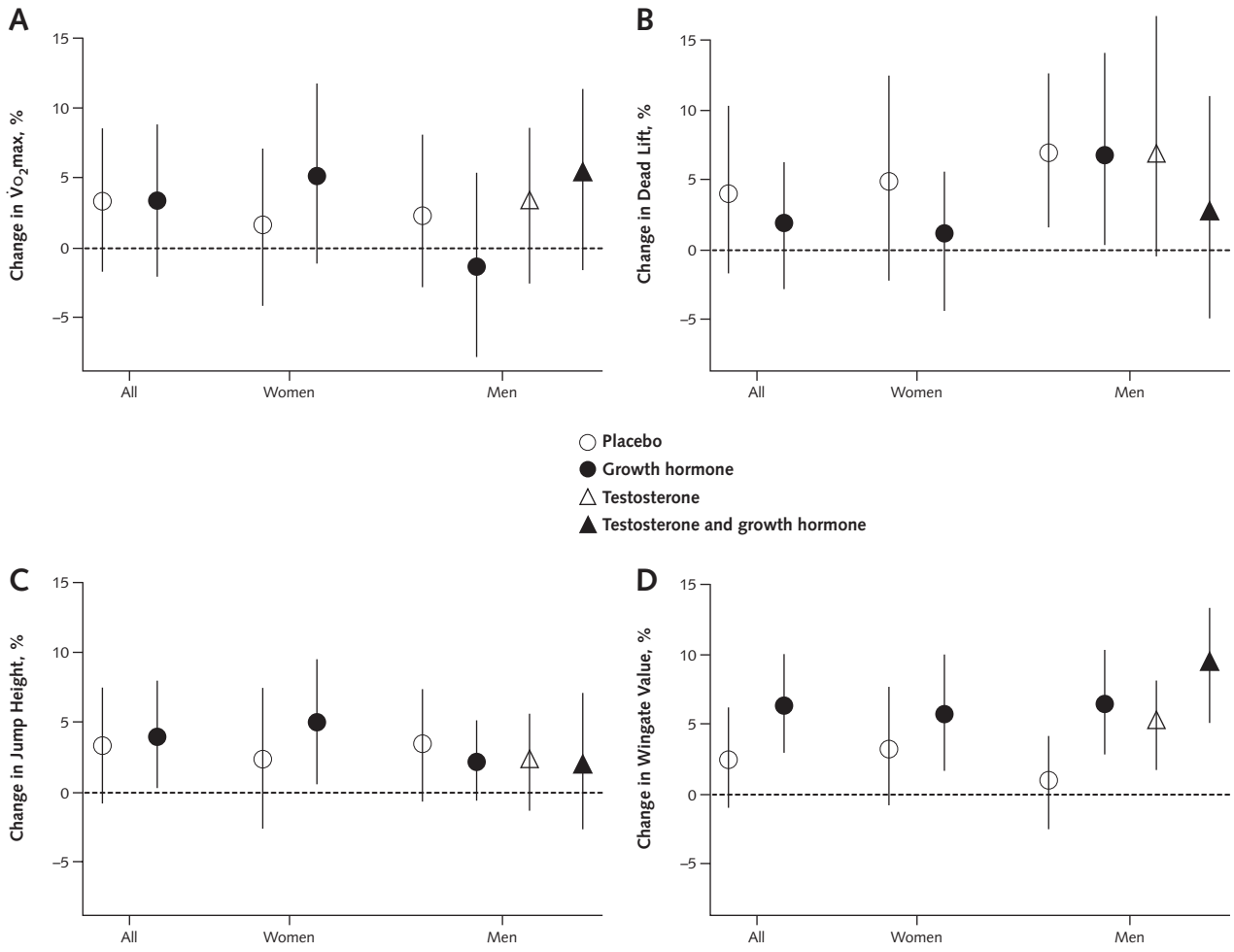
In a multiple regression analysis of performance measures that used body cell mass and fat mass as covariates, fat mass remained a significant negative predictor for jump height, accounting for 11% of residual variance ( $P < 0.001$ ). When we added sex to the model, it accounted for only 1% to 4% of additional variance for dead lift, jump height, and Wingate value ( $P < 0.050$ ), and was not a significant predictor for  $\dot{V}O_2\text{max}$ . In summary, body cell mass was strongly and positively related to all measures of performance in both men and women.

Appendix Figure 1. Percentage change in body composition variables.



Data are expressed as means (95% CIs).

Appendix Figure 2. Percentage change in performance variables.



Data are expressed as means (95% CIs).  $\dot{V}O_{2max}$  = maximum oxygen consumption.



**Appendix Table 1. Data at Baseline, Week 8, and Week 14 and Within-Group Differences From Baseline**

| Variable                         | Women and Men Combined |                               | Women                  |                               |
|----------------------------------|------------------------|-------------------------------|------------------------|-------------------------------|
|                                  | Placebo Group (n = 32) | Growth Hormone Group (n = 32) | Placebo Group (n = 16) | Growth Hormone Group (n = 17) |
| <b>Clinical</b>                  |                        |                               |                        |                               |
| Mean age (SD), y                 | 28.3 (5.0)             | 27.6 (5.7)                    | 27.8 (5.0)             | 29.7 (6.2)                    |
| Mean height (SD), cm             | 175 (6)                | 173 (6)                       | 164 (6)                | 169 (6)                       |
| Weight, kg                       |                        |                               |                        |                               |
| Mean (SD), week 0                | 76.1 (10.6)            | 70.2 (10.2)                   | 61.6 (9.0)             | 65.8 (10.1)                   |
| Mean (SD), week 8                | 75.8 (11.1)            | 71.4 (10.2)                   | 62 (8.69)              | 66 (9.43)                     |
| Mean change from week 0 (95% CI) | -0.3 (-0.9 to 0.3)     | 1.2 (0.4 to 2.0)              | 0.3 (-0.2 to 1.0)      | 0.2 (-0.9 to 1.2)             |
| BMI, kg/m <sup>2</sup>           |                        |                               |                        |                               |
| Mean (SD), week 0                | 24.5 (3.1)             | 23.3 (2.8)                    | 22.8 (3.2)             | 22.9 (2.8)                    |
| Mean (SD), week 8                | 24.4 (3.2)             | 23.7 (2.6)                    | 23 (3.1)               | 23 (2.6)                      |
| Mean change from week 0 (95% CI) | -0.1 (-0.3 to 0.1)     | 0.4 (0.1 to 0.6)              | 0.1 (-0.1 to 0.4)      | 0.1 (-0.3 to 0.4)             |
| <b>Endocrine</b>                 |                        |                               |                        |                               |
| IGF-I concentration, nmol/L      |                        |                               |                        |                               |
| Mean (SD), week 0                | 16.2 (4.9)             | 16.5 (4.9)                    | 17.9 (5.0)             | 16.2 (4.2)                    |
| Mean (SD), week 8                | 16.2 (5.2)             | 34.0 (10.9)                   | 18.0 (6.1)             | 29.4 (8.33)                   |
| Mean change from week 0 (95% CI) | 0 (-1.4 to 1.6)        | 17.5 (14.1 to 20.8)           | 0.3 (-2.1 to 2.9)      | 13.1 (9.9 to 16.5)            |
| Testosterone concentration       |                        |                               |                        |                               |
| Mean (SD), week 0                |                        |                               |                        |                               |
| nmol/L                           | 11.7 (5.2)             | 12.5 (5.4)                    | 1.4 (0.7)              | 1.2 (0.6)                     |
| ng/dL                            | 337 (150)              | 360 (156)                     | 40 (20)                | 36 (18)                       |
| Mean (SD), week 8                |                        |                               |                        |                               |
| nmol/L                           | 11.4 (4.21)            | 12.3 (6.8)                    | 1.5 (0.8)              | 1.4 (0.7)                     |
| ng/dL                            | 329 (121)              | 354 (197)                     | 43 (22)                | 40 (20)                       |
| Mean change from week 0 (95% CI) |                        |                               |                        |                               |
| nmol/L                           | -0.2 (-1.3 to 0.8)     | -0.3 (-2.0 to 1.5)            | 0.1 (-0.3 to 0.5)      | 0.1 (-0.1 to 0.4)             |
| ng/dL                            | -6 (-37 to 23)         | -9 (-58 to 43)                | 3 (-9 to 14)           | 3 (-3 to 12)                  |
| <b>Body composition*</b>         |                        |                               |                        |                               |
| Fat mass, kg                     |                        |                               |                        |                               |
| Mean (SD), week 0                | 18.5 (6.8)             | 16.3 (6.2)                    | 18.2 (5.7)             | 19.4 (7.0)                    |
| Mean (SD), week 8                | 17.9 (6.9)             | 14.2 (5.9)                    | 18.1 (5.7)             | 17 (6.6)                      |
| Mean change from week 0 (95% CI) | -0.6 (-1.1 to -0.1)    | -2.0 (-2.5 to -1.6)           | -0.1 (-0.7 to 0.4)     | -2.4 (-3.2 to -1.7)           |
| Lean body mass, kg               |                        |                               |                        |                               |
| Mean (SD), week 0                | 54.1 (6.1)             | 51.3 (5.5)                    | 40.6 (5.0)             | 43.6 (4.1)                    |
| Mean (SD), week 8                | 54.7 (6.2)             | 54.6 (6.0)                    | 41.0 (4.6)             | 46.6 (3.7)                    |
| Mean change from week 0 (95% CI) | 0.6 (0.2 to 1.0)       | 3.3 (2.6 to 4.0)              | 0.5 (-0.1 to 1.0)      | 3.0 (2.0 to 3.9)              |
| Extracellular water mass, kg     |                        |                               |                        |                               |
| Mean (SD), week 0                | 19.2 (2.4)             | 17.8 (2.7)                    | 15.2 (1.8)             | 16 (1.6)                      |
| Mean (SD), week 8                | 19 (2.5)               | 19.4 (2.8)                    | 15.1 (1.9)             | 17.1 (1.9)                    |
| Mean change from week 0 (95% CI) | -0.2 (-0.8 to 0.5)     | 1.7 (1.0 to 2.3)              | -0.1 (-0.8 to 0.6)     | 1.2 (0.3 to 2.1)              |
| Body cell mass, kg               |                        |                               |                        |                               |
| Mean (SD), week 0                | 34.9 (4.7)             | 33.5 (4.5)                    | 25.4 (3.9)             | 27.6 (3.6)                    |
| Mean (SD), week 8                | 35.7 (4.4)             | 35.1 (4.5)                    | 25.9 (3.4)             | 29.4 (3.2)                    |
| Mean change from week 0 (95% CI) | 0.8 (0.1 to 1.5)       | 1.7 (0.9 to 2.3)              | 0.5 (-0.4 to 1.3)      | 1.8 (0.7 to 2.8)              |
| <b>Training type, n (%)</b>      |                        |                               |                        |                               |
| Power                            | 3 (9.4)                | 3 (9.4)                       | 0 (0)                  | 1 (5.9)                       |
| Endurance                        | 12 (37.5)              | 6 (18.8)                      | 7 (43.8)               | 5 (29.4)                      |
| Mixed                            | 17 (53.1)              | 23 (71.9)                     | 9 (56.2)               | 11 (64.7)                     |
| <b>Training quantity, n (%)</b>  |                        |                               |                        |                               |
| 2 to 4 h                         | 10 (31.2)              | 10 (31.2)                     | 7 (43.7)               | 7 (41.2)                      |
| 4 to 10 h                        | 19 (59.4)              | 20 (62.5)                     | 8 (50.0)               | 8 (47.1)                      |
| >10 h                            | 3 (9.38)               | 2 (6.3)                       | 1 (6.3)                | 2 (11.8)                      |
| <b>Performance</b>               |                        |                               |                        |                               |
| V <sub>O</sub> 2max, L/min       |                        |                               |                        |                               |
| Mean (SD), week 0                | 3.3 (0.7)              | 3.2 (0.7)                     | 2.5 (0.7)              | 2.7 (0.7)                     |
| Mean (SD), week 8                | 3.4 (0.7)              | 3.2 (0.567)                   | 2.6 (0.7)              | 2.8 (0.6)                     |
| Mean change from week 0 (95% CI) | 0.1 (-0.1 to 0.2)      | 0.0 (-0.2 to 0.2)             | 0.0 (-0.1 to 0.2)      | 0.1 (-0.1 to 0.3)             |
| Mean (SD), week 14               | 3.5 (0.7)              | 3.4 (0.7)                     | 2.6 (0.7)              | 2.9 (0.6)                     |
| Mean change from week 0 (95% CI) | 0.2 (0.0 to 0.3)       | 0.2 (0.0 to 0.4)              | 0.1 (-0.1 to 0.2)      | 0.3 (0.0 to 0.5)              |

Appendix Table 1—Continued

| Men                    |                               |                             |   |
|------------------------|-------------------------------|-----------------------------|---|
| Placebo Group (n = 16) | Growth Hormone Group (n = 15) | Testosterone Group (n = 16) | Growth Hormone Plus Testosterone Group (n = 16) |
| 28.9 (5.0)             | 25.2 (5.2)                    | 29 (5.7)                    | 26.8 (5.2)                                      |
| 186 (5)                | 177 (6)                       | 180 (8)                     | 181 (5)   |
| 90.5 (12.2)            | 75.3 (10.4)                   | 83.3 (18.5)                 | 79.5 (10.0)                                     |
| 89.5 (13.2)            | 77.6 (10.9)                   | 85 (18.6)                   | 84 (10.5)                                       |
| -1.0 (-2.0 to 0.0)     | 2.4 (1.1 to 3.6)              | 1.9 (0.4 to 3.4)            | 4.4 (3.1 to 5.9)                                |
| 26.1 (3.1)             | 23.8 (2.7)                    | 25.4 (3.7)                  | 24.4 (2.8)                                      |
| 25.8 (3.4)             | 24.6 (2.6)                    | 26 (3.7)                    | 25.8 (3.0)                                      |
| -0.3 (-0.6 to 0.0)     | 0.7 (0.3 to 1.1)              | 0.6 (0.2 to 1.1)            | 1.4 (0.9 to 1.8)                                |
| 14.4 (4.9)             | 16.7 (4.8)                    | 16.7 (4.9)                  | 14.8 (5.2)                                      |
| 14.2 (4.1)             | 39.1 (13.2)                   | 18.3 (6.43)                 | 36.6 (13.5)                                     |
| -0.3 (-1.8 to 1.4)     | 22.3 (16.5 to 28.4)           | 1.6 (0.4 to 2.9)            | 21.8 (17.0 to 27.1)                             |
| 21.9 (7.3)             | 25.3 (7.9)                    | 23.5 (7.8)                  | 23.1 (4.99)                                     |
| 631 (212)              | 729 (227)                     | 677 (224)                   | 666 (144)                                       |
| 21.3 (5.9)             | 24.6 (10.0)                   | 36.7 (19.3)                 | 31.2 (6.65)                                     |
| 614 (170)              | 709 (287)                     | 1060 (556)                  | 899 (192)                                       |
| -0.6 (-2.7 to 1.3)     | -0.7 (-4.6 to 3.0)            | 13.2 (5.1 to 24.8)          | 8.1 (4.3 to 12.0)                               |
| -17 (-78 to 37)        | -20 (-130 to 86)              | 380 (150 to 710)            | 230 (120 to 350)                                |
| 18.8 (7.99)            | 12.7 (5.1)                    | 16.2 (9.1)                  | 14.6 (7.7)                                      |
| 17.7 (7.9)             | 11.2 (5.1)                    | 15.3 (7.9)                  | 12.5 (6.9)                                      |
| -1.1 (-2.0 to -0.1)    | -1.6 (-2.1 to -1.1)           | -1.0 (-2.4 to 0.2)          | -2.1 (-2.9 to -1.3)                             |
| 67.6 (7.1)             | 59.5 (6.4)                    | 63.1 (10.2)                 | 61.9 (6.3)                                      |
| 68.4 (7.5)             | 63.1 (7.3)                    | 66.3 (11.0)                 | 68.5 (6.3)                                      |
| 0.8 (0.2 to 1.4)       | 3.7 (2.7 to 4.6)              | 3.2 (2.5 to 4.0)            | 6.6 (5.6 to 7.7)                                |
| 23.2 (2.8)             | 19.7 (3.4)                    | 21.4 (4.0)                  | 21.4 (3.1)                                      |
| 22.9 (3.0)             | 21.9 (3.5)                    | 22.3 (5.0)                  | 24.7 (3.3)                                      |
| -0.3 (-1.4 to 0.9)     | 2.2 (1.1 to 3.2)              | 1.0 (-0.2 to 2.2)           | 3.3 (2.0 to 4.6)                                |
| 44.4 (5.3)             | 39.8 (4.9)                    | 41.8 (7.0)                  | 40.5 (4.17)                                     |
| 45.4 (5.3)             | 41.2 (5.4)                    | 44.0 (7.0)                  | 43.8 (4.4)                                      |
| 1.1 (-0.1 to 2.2)      | 1.5 (0.6 to 2.4)              | 2.3 (1.3 to 3.2)            | 3.3 (2.3 to 4.3)                                |
| 3 (18.8)               | 2 (13.3)                      | 3 (18.8)                    | 1 (6.25)  |
| 5 (31.2)               | 1 (6.7)                       | 2 (12.5)                    | 2 (12.5)  |
| 8 (50.0)               | 12 (80.0)                     | 11 (68.8)                   | 13 (81.2)                                       |
| 3 (18.8)               | 3 (20.0)                      | 1 (6.2)                     | 6 (37.5)  |
| 11 (68.8)              | 12 (80.0)                     | 11 (68.8)                   | 8 (50)  |
| 2 (12.5)               | 0 (0.0)                       | 4 (25.0)                    | 2 (12.5)  |
| 4.1 (0.7)              | 3.8 (0.7)                     | 3.8 (1.0)                   | 3.8 (0.9)                                       |
| 4.2 (0.8)              | 3.7 (0.6)                     | 3.9 (1.1)                   | 3.9 (0.8)                                       |
| 0.1 (-0.1 to 0.3)      | -0.1 (-0.4 to 0.2)            | 0.1 (-0.1 to 0.4)           | 0.1 (-0.2 to 0.4)                               |
| 4.3 (0.7)              | 3.9 (0.7)                     | 4.0 (1.1)                   | 4.1 (0.8)                                       |
| 0.2 (0.0 to 0.4)       | 0.1 (-0.2 to 0.4)             | 0.2 (-0.1 to 0.4)           | 0.4 (0.2 to 0.6)                                |

Appendix Table 1—Continued

| Parameter                        | Women and Men Combined |                               | Women                  |                               |
|----------------------------------|------------------------|-------------------------------|------------------------|-------------------------------|
|                                  | Placebo Group (n = 32) | Growth Hormone Group (n = 32) | Placebo Group (n = 16) | Growth Hormone Group (n = 17) |
| Dead lift, kg                    |                        |                               |                        |                               |
| Mean (SD), week 0                | 151 (26)               | 155 (30)                      | 118 (28)               | 131 (28)                      |
| Mean (SD), week 8                | 159 (33)               | 161 (32)                      | 123 (30)               | 132 (26)                      |
| Mean change from week 0 (95% CI) | 9 (3 to 16)            | 6 (−1 to 13)                  | 5 (−4 to 13)           | 0 (−7 to 6)                   |
| Mean (SD), week 14               | 163 (23)               | 168 (28)                      | 126 (25)               | 133 (25)                      |
| Mean change from week 0 (95% CI) | 11 (4 to 19)           | 13 (6 to 20)                  | 8 (−3 to 19)           | 5 (−2 to 11)                  |
| Jump height, cm                  |                        |                               |                        |                               |
| Mean (SD), week 0                | 44.3 (7.5)             | 46.4 (6.3)                    | 36.3 (6.9)             | 36.7 (6.2)                    |
| Mean (SD), week 8                | 45.6 (6.3)             | 47.7 (5.6)                    | 36.8 (5.9)             | 38.2 (5.1)                    |
| Mean change from week 0 (95% CI) | 1.0 (−0.4 to 2.3)      | 1.3 (0.2 to 2.5)              | 0.5 (−1.4 to 2.3)      | 1.5 (0 to 2.9)                |
| Mean (SD), week 14               | 46.4 (7.8)             | 47.2 (7.3)                    | 37.6 (6.3)             | 37.1 (6.7)                    |
| Mean change from week 0 (95% CI) | 1.8 (0.0 to 3.8)       | 0.5 (−0.6 to 1.6)             | 1.3 (−0.8 to 3.5)      | 0.1 (−1.2 to 1.5)             |
| Wingate value, k†                |                        |                               |                        |                               |
| Mean (SD), week 0                | 18.5 (3.3)             | 17.4 (3.1)                    | 13.4 (2.9)             | 13.9 (2.9)                    |
| Mean (SD), week 8                | 19.4 (2.5)             | 18 (2.9)                      | 13.7 (2.8)             | 14.5 (2.7)                    |
| Mean change from week 0 (95% CI) | 0.2 (−0.3 to 0.7)      | 0.91 (0.5 to 1.3)             | 0.3 (−0.1 to 0.8)      | 0.7 (0.2 to 1.1)              |
| Mean (SD), week 14               | 19.7 (2.7)             | 18.2 (3.0)                    | 14.0 (2.8)             | 14.5 (2.7)                    |
| Mean change from week 0 (95% CI) | 0.5 (−0.1 to 0.9)      | 1.1 (0.5 to 1.6)              | 0.6 (0.2 to 1.0)       | 0.8 (0.3 to 1.4)              |

BMI = body mass index; IGF-I = insulin-like growth factor I;  $\dot{V}O_{2max}$  = maximum oxygen consumption.

\* We excluded data for 1 woman who received growth hormone, because of technical difficulties with extracellular water measurement. We have included her data for all other variables in the table.

† Total work during sprint cycle ergometry, a measure of anaerobic sprint capacity.

Appendix Table 1—Continued

Men

| Placebo Group (n = 16) | Growth Hormone Group (n = 15) | Testosterone Group (n = 16) | Growth Hormone Plus Testosterone Group (n = 16) |
|------------------------|-------------------------------|-----------------------------|---|
| 187 (22)               | 182 (32)                      | 201 (38)                    | 185 (38)  |
| 196 (35)               | 194 (39)                      | 207 (27)                    | 185 (24)  |
| 13 (3 to 24)           | 12 (0 to 26)                  | 8 (−2 to 20)                | 0 (−15 to 13)                                   |
| 199 (21)               | 205 (28)                      | 218 (36)                    | 200 (25)  |
| 15 (5 to 25)           | 22 (9 to 35)                  | 12 (4 to 23)                | 15 (−2 to 32)                                   |
| 52.7 (7.6)             | 57.4 (6.5)                    | 55.2 (9.3)                  | 53.9 (7.2)                                      |
| 54.4 (6.6)             | 58.5 (6.1)                    | 55.3 (9.5)                  | 54.6 (6.8)                                      |
| 1.5 (−0.6 to 3.4)      | 1.1 (−0.4 to 2.8)             | 1.3 (−0.6 to 3.1)           | 0.6 (−1.5 to 2.9)                               |
| 55.1 (8.9)             | 58.1 (6.5)                    | 55 (8.3)                    | 56.6 (7.7)                                      |
| 2.3 (−0.5 to 5.5)      | 0.8 (−0.9 to 2.6)             | 0.9 (−1.7 to 2.9)           | 2.6 (−0.1 to 5.8)                               |
| 24.7 (2.6)             | 21.1 (3.1)                    | 23.3 (4.4)                  | 22.4 (3.0)                                      |
| 25.1 (2.1)             | 22.3 (2.9)                    | 23.4 (3.7)                  | 23.9 (2.4)                                      |
| 0.1 (−0.8 to 0.9)      | 1.21 (0.5 to 1.9)             | 1.0 (0.3 to 1.6)            | 1.9 (0.9 to 2.7)                                |
| 25.4 (2.6)             | 22.1 (2.7)                    | 23.9 (3.9)                  | 23.1 (3.2)                                      |
| 0.3 (−0.7 to 1.1)      | 1.3 (0.4 to 2.2)              | 0.7 (−0.2 to 1.5)           | 1.1 (0.1 to 2.1)                                |

**Appendix Table 2. Correlations Between Changes in Body Composition and Performance Variables After 8 Weeks of Treatment**

| Group and Treatment     | Body Composition Variable                 | Performance Variable  | Slope    | R <sup>2</sup>      | P Value |      |      |
|-------------------------|---|-----------------------|----------|---------------------|---------|------|------|
| <b>Women and men</b>    |   |                       |          |                     |         |      |      |
| Growth hormone (n = 32) | Fat mass                                  | VO <sub>2</sub> max   | -0.01    | 0                   | 0.93    |      |      |
|                         |   | Dead lift             | 7.04     | 0.21                | 0.010   |      |      |
|                         |   | Jump height           | -0.44    | 0.04                | 0.3     |      |      |
|                         |   | Wingate value         | -0.02    | 0                   | 0.92    |      |      |
|                         | Body cell mass                            | VO <sub>2</sub> max   | 0.07     | 0.09                | 0.110   |      |      |
|                         |   | Dead lift             | 2.38     | 0.05                | 0.22    |      |      |
|                         |   | Jump height           | 0.19     | 0.01                | 0.53    |      |      |
|                         |   | Wingate value         | 0.19     | 0.11                | 0.080   |      |      |
| <b>Women</b>            |   |                       |          |                     |         |      |      |
| Growth hormone (n = 17) | Fat mass                                  | VO <sub>2</sub> max   | 0.06     | 0.06                | 0.37    |      |      |
|                         |   | Dead lift             | 4.7      | 0.24                | 0.050   |      |      |
|                         |   | Jump height           | -0.13    | 0                   | 0.82    |      |      |
|                         |   | Wingate value         | 0.08     | 0.02                | 0.65    |      |      |
|                         | Body cell mass                            | VO <sub>2</sub> max   | 0.07     | 0.18                | 0.100   |      |      |
|                         |   | Dead lift             | 0.08     | 0                   | 0.97    |      |      |
|                         |   | Jump height           | 0.36     | 0.05                | 0.38    |      |      |
|                         |   | Wingate value         | 0.17     | 0.16                | 0.140   |      |      |
|                         |   | <b>Men</b>            |          |                     |         |      |      |
| Growth hormone (n = 15) | Fat mass                                  | VO <sub>2</sub> max   | -0.05    | 0.01                | 0.75    |      |      |
|                         |   | Dead lift             | 10.8     | 0.18                | 0.110   |      |      |
|                         |   | Jump height           | -1.28    | 0.16                | 0.140   |      |      |
|                         |   | Wingate value         | -0.55    | 0.17                | 0.150   |      |      |
|                         | Body cell mass                            | VO <sub>2</sub> max   | 0.06     | 0.04                | 0.47    |      |      |
|                         |   | Dead lift             | 6.27     | 0.22                | 0.080   |      |      |
|                         |   | Jump height           | -0.06    | 0                   | 0.89    |      |      |
|                         |   | Wingate value         | 0.25     | 0.12                | 0.22    |      |      |
|                         |   | Testosterone (n = 16) | Fat mass | VO <sub>2</sub> max | -0.03   | 0.02 | 0.59 |
|                         |   |                       |          | Dead lift           | 1.71    | 0.05 | 0.43 |
| Jump height             | -0.21                                     |                       |          | 0.02                | 0.58    |      |      |
| Wingate value           | 0.24                                      |                       |          | 0.3                 | 0.040   |      |      |
| Body cell mass          | VO <sub>2</sub> max                       |                       | 0        | 0                   | 0.95    |      |      |
|                         | Dead lift                                 |                       | -1.01    | 0.01                | 0.76    |      |      |
|                         | Jump height                               |                       | -0.33    | 0.03                | 0.56    |      |      |
|                         | Wingate value                             |                       | -0.1     | 0.02                | 0.60    |      |      |
|                         | Growth hormone plus testosterone (n = 16) |                       | Fat mass | VO <sub>2</sub> max | -0.03   | 0.01 | 0.70 |
|                         |   |                       |          | Dead lift           | -1      | 0    | 0.83 |
| Jump height             |   | 0.21                  |          | 0.01                | 0.76    |      |      |
| Wingate value           |   | -0.06                 |          | 0                   | 0.84    |      |      |
| Body cell mass          |   | VO <sub>2</sub> max   | 0.1      | 0.14                | 0.150   |      |      |
|                         |   | Dead lift             | 5.98     | 0.19                | 0.090   |      |      |
|                         |   | Jump height           | 0.15     | 0.01                | 0.79    |      |      |
|                         |   | Wingate value         | 0.47     | 0.28                | 0.040   |      |      |

VO<sub>2</sub>max = maximum oxygen consumption.

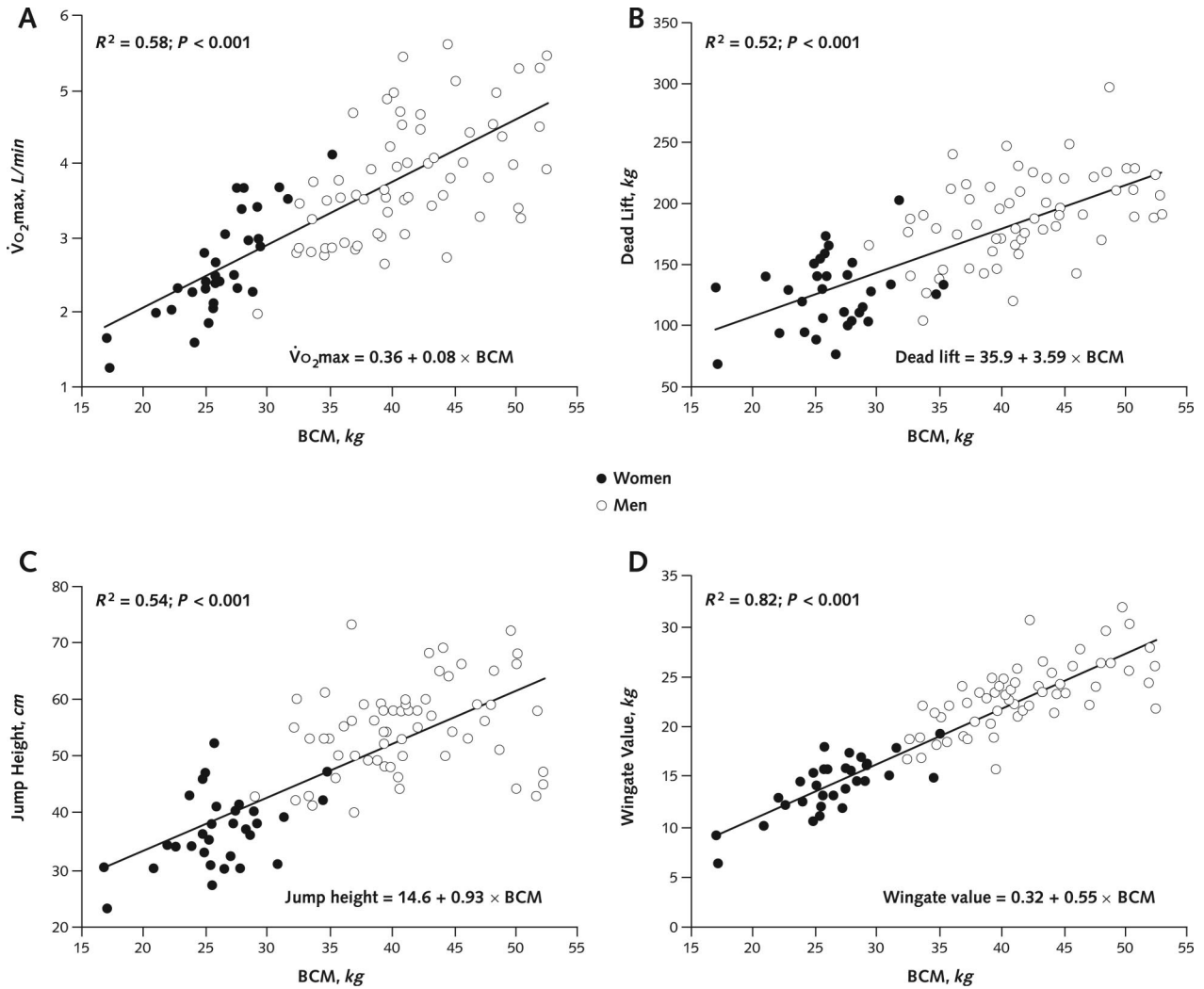
**Appendix Table 3. Univariate Analysis of Correlations Between Measures of Physical Performance and Body Composition at Baseline in Men and Women Combined**

| Variable       | VO <sub>2</sub> max |                |         | Dead Lift |                |         | Jump Height |                |         | Wingate Value |                |         |
|----------------|---------------------|----------------|---------|-----------|----------------|---------|-------------|----------------|---------|---------------|----------------|---------|
|                | Slope               | R <sup>2</sup> | P Value | Slope     | R <sup>2</sup> | P Value | Slope       | R <sup>2</sup> | P Value | Slope         | R <sup>2</sup> | P Value |
| Fat mass       | 0.01                | 0.01           | 0.45    | -0.58     | 0.01           | 0.34    | -0.52       | 0.12           | <0.005  | -0.02         | 0              | 0.78    |
| Body cell mass | 0.08                | 0.58           | <0.001  | 3.59      | 0.52           | <0.001  | 0.93        | 0.54           | <0.001  | 0.55          | 0.82           | <0.001  |

VO<sub>2</sub>max = maximum oxygen consumption.



Appendix Figure 3. Baseline relationships in women and men.



The regression lines and their corresponding equation are shown. BCM = body cell mass;  $\dot{V}O_2\text{max}$  = maximum oxygen consumption.