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Systematic Review: The Effects of Growth Hormone on Athletic Performance

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Background: Human growth hormone is reportedly used to enhance athletic performance, although its safety and efficacy for this purpose are poorly understood.

Purpose: To evaluate evidence about the effects of growth hormone on athletic performance in physically fit, young individuals.

Data Sources: MEDLINE, EMBASE, SPORTDiscus, and Cochrane Collaboration databases were searched for English-language studies published between January 1966 and October 2007.

Study Selection: Randomized, controlled trials that compared growth hormone treatment with no growth hormone treatment in community-dwelling healthy participants between 13 and 45 years of age.

Data Extraction: 2 authors independently reviewed articles and abstracted data.

Data Synthesis: 44 articles describing 27 study samples met inclusion criteria; 303 participants received growth hormone, representing 13.3 person-years of treatment. Participants were young (mean age, 27 years [SD, 3]), lean (mean body mass index, 24 kg/m^2 [SD, 2]), and physically fit (mean maximum oxygen uptake, 51 mL/kg of body weight per minute [SD, 8]). Growth hormone dosage (mean, 36 μg/kg per day [SD, 21]) and treatment duration (mean, 20 days [SD, 18] for studies giving growth hormone for >1 day) varied. Lean body mass increased in growth hormone recipients compared with participants who did not receive growth hormone (increase, 2.1 kg [95% CI, 1.3 to 2.9 kg]), but strength and exercise capacity did not seem to improve. Lactate levels during exercise were statistically significantly higher in 2 of 3 studies that evaluated this outcome. Growth hormone–treated participants more frequently experienced soft tissue edema and fatigue than did those not treated with growth hormone.

Limitations: Few studies evaluated athletic performance. Growth hormone protocols in the studies may not reflect real-world doses and regimens.

Conclusion: Claims that growth hormone enhances physical performance are not supported by the scientific literature. Although the limited available evidence suggests that growth hormone increases lean body mass, it may not improve strength; in addition, it may worsen exercise capacity and increase adverse events. More research is needed to conclusively determine the effects of growth hormone on athletic performance.

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The use of human growth hormone to improve athletic performance has recently received worldwide attention. This practice, often called *sports doping*, is banned by most professional sports leagues and associations, including the International Olympic Committee, Major League Baseball, and the National Football League (1–3). However, a wide range of athletes, including those from baseball (4–6), cycling (7, 8), and track and field (5, 9), have been implicated in or have confessed to illicit growth hormone use. The Mitchell report (10) recently identified 89 Major League Baseball players who allegedly used performance-enhancing drugs, and some of these players have subsequently admitted to using growth hormone (11, 12).

Part of the attraction of using growth hormone as a performance enhancer has been that its use is difficult to detect. The World Anti-Doping Agency, whose formation stemmed from the widely publicized doping scandal of the 1998 Tour de France (13), first used a blood test to detect exogenous growth hormone during the 2004 Olympic Games in Athens. However, according to the World Anti-Doping Agency, there have been no test-confirmed positive cases for growth hormone doping in professional or Olympic athletes (14), probably because of the limited availability and implementation of this test.

Although growth hormone is reportedly used to enhance athletic performance and has been called the "most anabolic substance known" (15), its efficacy for this purpose is not well established. Some have suggested that growth hormone is a "wonder drug" (16) that results in "ripped muscle" (17) and provides "stamina-increasing properties" (18). Exogenous growth hormone therapy in growth hormone–deficient adults (that is, those with growth hormone deficiency due to hypothalamic or pituitary defects) results in increased lean mass and decreased fat mass (19), and comparable body composition changes are seen in healthy elderly adults who receive growth hormone (20). Some experts, however, have suggested that the strength-enhancing properties of growth hormone among healthy adults have been exaggerated (15). Serious side effects, including diabetes, hepatitis, and acute renal failure, may occur in athletes using high-dose growth hormone (21). Furthermore, the use of growth hormone

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for athletic enhancement is not approved by the U.S. Food and Drug Administration, and the distribution of growth hormone for this purpose is illegal in the United States (22).

We performed a systematic review of randomized, controlled trials to determine the effects of growth hormone therapy on athletic performance in healthy, physically fit, young adults. Our primary aim was to evaluate the effects of growth hormone on body composition, strength, basal metabolism, and exercise capacity. In addition, we sought to synthesize the evidence on adverse events associated with growth hormone in the healthy young and assess the quality of the published literature.

METHODS

Literature Searches

In consultation with 2 research librarians, we developed individual search strategies to identify potentially relevant studies from the MEDLINE, EMBASE, SPORTDiscus, and Cochrane Collaboration databases. We sought English-language reports indexed through 11 October 2007 with keywords including *growth hormone* and *randomized controlled trial* (**Appendix Table 1**, available at www.annals.org). We searched bibliographies of retrieved articles for additional studies.

Study Selection

We sought randomized, controlled trials, including crossover trials, that compared growth hormone therapy with no growth hormone therapy. We included studies that 1) evaluated at least 5 participants, 2) enrolled only community-dwelling participants, 3) assessed participants with a mean or median age between 13 and 45 years, and 4) provided data on at least 1 clinical outcome of interest. We excluded studies that 1) focused solely on evaluating growth hormone secretagogues, 2) explicitly included patients with any comorbid medical condition, or 3) evaluated growth hormone as treatment for a specific illness (for example, adult growth hormone deficiency or fibromyalgia).

Data Abstraction

One author reviewed the titles and abstracts of articles identified through our search and retrieved potentially relevant studies. An endocrinologist and a physician with training in meta-analytic techniques separately reviewed the retrieved studies and abstracted data independently onto pretested abstraction forms. We resolved abstraction differences by repeated review and consensus. If a study did not present data necessary for analysis or mentioned results but did not present data, we requested additional data from study authors. If data were presented graphically, we used the graph-digitizing program DigitizeIt, version 1.5 (Share It, Braunschweig, Germany), to abstract data from the graph (23). If multiple studies presented findings from the same cohort, we used these data only once in our analysis.

We abstracted 4 types of data from each study: participant characteristics (for example, age, sex, body mass index, baseline maximum oxygen uptake [VO_2max]), study interventions (for example, dose, route, frequency, and duration of growth hormone therapy), study quality (for example, quality of randomization and blinding) (24, 25), and clinical outcomes. We included studies that provided data on at least 1 of the following clinical outcomes: body composition (for example, body weight, lean body mass, fat mass), strength (for example, biceps or quadriceps strength), basal metabolism (for example, resting energy expenditure, basal metabolic rate, heart rate, respiratory exchange ratio, or respiratory quotient), exercise capacity (for example, exercising lactate levels, exercising respiratory exchange ratio or respiratory quotient, maximum inspiratory pressure, bicycling speed, and VO_2max), or adverse events. Because the terms *lean body mass* and *fat-free mass* are typically used interchangeably in the literature, we report fat-free mass and lean body mass data as a single category of lean body mass. Similarly, we report resting energy expenditure and basal metabolic rate as a single category of basal metabolic rate.

Quantitative Data Synthesis

To describe key study characteristics, we computed mean values weighted by the number of participants in the trial. To evaluate the effects of growth hormone on body composition and strength, we computed a change score for each clinical outcome for both the treatment and control groups as the value of the outcome at trial end minus the value of the outcome at trial start. We used these change scores to calculate the weighted mean difference and standard mean difference (26) effect sizes. The weighted mean difference is reported in the same units as the clinical outcome of interest, thereby facilitating clinical interpretation. Because our outcomes were similar for both methods, we present only the outcomes from the weighted mean difference method. For studies that did not report the variance of an outcome at trial end minus the value at trial start, we calculated it as the sum of the trial-start and trial-end variances minus twice the covariance (20, 27). Because trial-start data were not available for most of the studies reporting basal metabolic outcomes, we compared trial-end results between treatment and control groups for these outcomes. We combined studies by using random-effects models (26–28) because of potential interstudy heterogeneity.

The considerable variability in exercise protocols used in the included studies reporting exercise capacity outcomes made pooling these results inappropriate. Instead, we provide a narrative, qualitative assessment of exercise capacity outcomes and report their associated published *P* values.

The variability in reporting adverse events among included studies also made a quantitative meta-analysis of these outcomes inappropriate. Instead, we calculated the

proportions of adverse events among participants who received and did not receive growth hormone in studies that reported or evaluated for each adverse event.

We performed sensitivity analyses and assessed interstudy heterogeneity to evaluate the robustness of our results. We removed each study individually to evaluate that study's effect on the summary estimates. We assessed publication bias by constructing funnel plots and calculated the number of unpublished studies required to statistically significantly change our results (28). We assessed heterogeneity among study results for each of the summary effects by calculating the Q statistic (and associated P value) and I^2 statistic (26, 28–30). We evaluated heterogeneity through predetermined subgroup analysis that stratified studies by duration of treatment. We performed analyses by using Stata software, version 9.1 (Stata, College Station, Texas); SPSS, version 15.0 (SPSS, Chicago); and Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey). We considered P values less than 0.05 (2-tailed) to indicate statistically significant differences.

Role of the Funding Source

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Results

The **Figure** summarizes the results of our literature searches. We reviewed 7599 titles from the MEDLINE, EMBASE, SPORTDiscus, and the Cochrane Collaboration databases. From our search, we reviewed 252 abstracts in detail and retrieved 56 articles for full-text evaluation. We identified 3 additional studies through searches of bibliographies. Multiple articles were often published on the same study sample: 44 articles representing 27 study samples met our inclusion criteria (**Table 1**) (31–74).

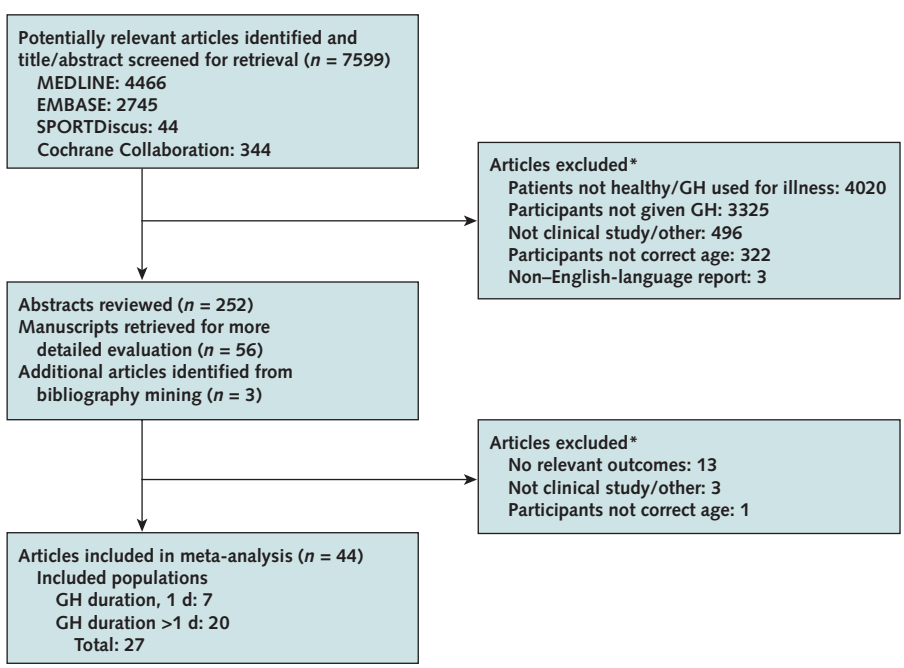
Participant Characteristics

Study participants were predominantly male (85%), young (mean age, 27 years [SD, 3]), lean (mean body mass index, 24 kg/m^2 [SD, 2]), and physically fit (mean VO_2max, 51 mL/kg per minute [SD, 8]; range, 38 to 65 mL/kg per minute) (**Table 1**).

Study Characteristics

The included studies enrolled 440 participants. Of these, 303 received growth hormone treatment, representing 13.3 person-years of treatment (**Table 1**). Study sizes were generally small (mean number of participants at enrollment, 15), and dropout rates were low (98% of participants completed the study protocols).

Figure. **Study flow diagram.**



GH = growth hormone. *Sum may be greater than total number excluded because some studies had multiple reasons for exclusion.

Table 1. **Baseline Characteristics of Participants and Study Intervention***

Study, Year (Reference)	Mean Age (SD), *y*		Men, %		Sample Size at Start and End of Study, *n/n*†	
	Growth Hormone Group	Control Group	Growth Hormone Group	Control Group	Growth Hormone Group	Control Group
Single-dose growth hormone						
Gravholt et al., 1999 (34)‡	25.5 (3.7)	25.5 (3.7)	100	100	8/8	8/8
Hansen et al., 2005 (1 d) (35)‡	25.1 (5.7)	25.1 (5.7)	100	100	8/7	8/7
Hashimoto et al., 2000 (36)	20–31‖	20–31‖	100	100	24/24	8/8
Irving et al., 2004 (37)‡	23.7 (5.7)	23.7 (5.7)	100	100	9/9	9/9
Lange et al., 2002 (38)‡	26.0 (2.6)	26.0 (2.6)	100	100	7/5**	7/7
Møller et al., 1990 (39)‡	29.0 (2.4)	29.0 (2.4)	100	100	6/6	6/6
Napoli et al., 2003 (40)‡	22.0 (2.8)	22.0 (2.8)	75	75	8/8	8/8
Multiple-dose growth hormone						
Brixen et al., 1990, 1992, 1995 (41–43)	26.0 (NA) [22–31‖]	27.0 (NA) [22–30‖]	100	100	10/9	10/10
Crist et al., 1988, 1990, 1991 (44–46)‡	27.9 (3.7)	27.9 (3.7)	63	63	8/8	8/8
Deyssig et al., 1993 (47)	23.4 (2.8)‡‡	23.4 (2.8)‡‡	100	100	11/8	11/10
Ehrnborg et al., 2005 (33, 48)	25.6 (4.2)	27.0 (4.4)	50	50	20/20	10/10
Giannoulis et al., 2005, 2002, 2000, 2000 (49–52)	25.0 (9.8)/26.3 (9.8)§§	24.9 (5.6)/24.0 (5.6)§§	51	53	39/39‖‖‖	30/30‖‖‖
Graham et al., 2007 (72–74)	32 (9)	32 (11)	100	100	24/24	24/24
Hansen et al., 2001 (53)‡	26.1 (NA) [23–31‖]	26.1 (NA) [23–31‖]	100	100	8/8	8/8
Hansen et al., 2005 (32)	24.0 (4.0)	25.0 (4.0)	100	100	8/8	8/8
Healy et al., 2006, 2003 (54, 55)	31 (NA) [23–40‖]	33 (NA) [27–42‖]	100	100	6/6	6/6
Horber et al., 1993, 1991 (31, 56)	18–36‖‡‡	18–36‖‡‡	100†††	100†††	8/8	8/8
Kniess et al., 2003 (57)	24 (NA) [21–33‖]¶¶	24 (NA) [21–33‖]¶¶	100	100	10/10	5/5
Møller et al., 1991 (58)‡	27.1 (NA) [21–33‖]	27.1 (NA) [21–33‖]	100	100	8/8	8/8
Møller et al., 1992 (59)‡	26 (NA) [21–33‖]	26 (NA) [21–33‖]	57	57	14/14	14/14
Møller et al., 1993 (60)‡	28.0 (2.4)	28.0 (2.4)	0	0	6/6	6/6
Møller et al., 1995, 1996 (61, 62)‡	26.5 (2.7)	26.5 (2.7)	100	100	8/8	8/8
Wallace et al., 2001, 2001, 1999 (63–65)	28.3 (11.2)	25.5 (6.0)	100	100	8/8	8/8
Wolthers et al., 1999, 1996, 1996 (66–68)‡	19–29‖	19–29‖	100	100	8/8	8/8
Wolthers et al., 1998 (69)‡	22–28‖	22–28‖	100	100	8/8	8/8
Yarasheski et al., 1992 (70)	27.0 (4.2)‡‡	27.0 (4.2)‡‡	100	100	9/7	9/9
Yuen et al., 2004 (71)‡	19–29‖	19–29‖	58	58	12/12	12/12

* The section on single-dose growth hormone includes studies that provided 1 dose of growth hormone therapy; the section on multiple-dose growth hormone includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. BMI = body mass index; NA = not available/unclear; $\dot{V}O_2$max = maximum oxygen uptake.
† Total does not add up to 440 participants because some studies had crossover designs, and the same participant served as treated and control participant.
‡ Crossover design.
§ Based on average body weight or height presented in article.
‖ Range.
¶ Multiple dosages provided.
** Two participants were unable to complete exercise protocol while receiving growth hormone.
†† Each dose is an average of the range of published doses.
‡‡ Data from growth hormone and non–growth hormone groups aggregated.
§§ Male data/female data.
‖‖‖ Data obtained from reference 49.
¶¶ High-dose group.
*** Assumed height and body weight for male participants: 5 feet, 11 inches, and/or 75 kg; assumed body weight for female participants, 60 kg.
††† Presumed male.
‡‡‡ Assumed mean body weight, 65 kg.

Growth hormone dosing regimens varied considerably among the included studies (**Table 1**). The studies could be divided into 2 principal types: those that evaluated the physiologic effects of a single dose of growth hormone and those that assessed the effects of longer-term dosing regimens. Seven studies evaluated the use of a single dose of growth hormone. Of these, 3 studies provided growth hormone subcutaneously (35, 36, 38) and 4 studies provided growth hormone intravenously (34, 37, 39, 40). Twenty studies provided growth hormone for more than 1 day (mean treatment duration, 20 days [SD, 18]) (**Table 1**). All of these studies provided growth hormone subcutaneously. Only 3 studies evaluated growth hormone for longer than 30 days (44–47, 70), and no study evaluated its use for more than 3 months. The mean daily dose of growth hormone was 36 μg/kg (SD, 21) among the included studies.

Study Quality

No study fulfilled all of the evaluated quality criteria, although 2 studies fulfilled 7 of 8 criteria (**Table 2**). No

Table 1—**Continued**

Mean BMI (SD), kg/m^2		Mean Baseline $\dot{V}o_2max$ (SD), *mL/kg per min*		Study Intervention	
Growth Hormone Group	Control Group	Growth Hormone Group	Control Group	Duration of Growth Hormone Therapy, *d*	Initial Growth Hormone Dosage, *μg/kg per d*
23.6 (1.7)	23.6 (1.7)	NA	NA	–	3§
22.6 (1.7)	22.6 (1.7)	62.0 (2.8)	62 (2.8)	–	33§
NA	NA	NA	NA	–	10, 25, 50, 100¶
23.6 (2.4)	23.6 (2.4)	37.9 (8.7)	37.9 (8.7)	–	10
23.0 (1.3)	23.0 (1.3)	65.0 (2.6)	65.0 (2.6)	–	33§
23.2 (1.7)	23.2 (1.7)	NA	NA	–	5
23.0 (2.8)	23.0 (2.8)	NA	NA	–	5
22.5 (NA)§	22.1 (NA)§	NA	NA	7	67
NA	NA	NA	NA	42	17, 34¶††
NA	NA	NA	NA	42	30
23.1 (2.6)	23.2 (3.9)	42.8 (7.2)	45.2 (7.2)	28	33, 67¶
22.2 (7.6)/22.5 (2.2)§§‡	23.3 (5.8)/20.7 (7.2)§§‡	55.1 (7.2)¶¶	54.3 (6.3)¶¶	28	67
27.5 (3.0)	28.0 (3.1)	41.8 (9.8)	44.8 (7.9)	6	19
NA	NA	NA	NA	6	50‖¶¶***
22.2 (2.0)	21.4 (1.6)	60.1 (9.6)	57.8 (7.2)	14	28§
24.0 (NA) [23–26‖]	25.0 (NA) [24–26‖]	54.2 (NA) [50.1–60.0‖]	53.4 (NA) [49.4–60.0]	28	67
NA	NA	NA	NA	7	100
23–27‖‡‡	23–27‖‡‡	NA	NA	14	20
NA	NA	NA	NA	14	53¶¶
23 (NA) 19–24‖	23 (NA) 19–24‖	NA	NA	10	62§‡‡‡
22.7 (1.5)	22.7 (1.5)	NA	NA	14	67¶¶
22.8 (1.7)	22.8 (1.7)	NA	NA	14	26, 52§¶
22.6 (2.8)	24.2 (3.6)	57.0 (6.4)	56.0 (6.0)	7	50
22.5–27.0‖	22.5–27.0‖	NA	NA	10	33
21.6–26.3‖	21.6–26.3‖	NA	NA	4	33
23.5 (NA)§	23.5 (NA)§	NA	NA	84	40
22.9 (13.2)	22.9 (13.2)	NA	NA	14	2

study clearly documented adequate concealment of treatment allocation at study enrollment.

Quantitative Data Synthesis

Many studies provided data on body composition and basal metabolism outcomes; however, limited data were available on strength and exercise capacity (**Appendix Table 2**, available at www.annals.org). Sixteen studies evaluated adverse events. We compared the incremental change from trial start to trial end between growth hormone–treated and non–growth hormone–treated groups to determine a summary effect size (weighted mean difference) for body composition and strength measures and compared trial-end data between groups to determine the weighted mean difference for basal metabolism outcomes.

Effects of Growth Hormone on Body Composition

Lean body mass increased significantly in growth hormone–treated groups compared with groups not treated with growth hormone (increase in lean body mass, 2.1 kg [95% CI, 1.3 to 2.9 kg]) (**Table 3** and **Appendix Figure 1**, available at www.annals.org). The decrease in fat mass approached statistical significance (change in fat mass, −0.9 kg [CI, −1.8 to −0.0 kg]). Weight increased, although the difference was not statistically significant (change in weight, 0.3 kg [CI, −0.5 to 1.1 kg]).

Effects of Growth Hormone on Strength Outcomes

Two studies evaluated change in strength (47, 70). These studies treated participants with growth hormone for 42 days (47) and 84 days (70), the longest treatment durations of all included studies. With 1-repetition maximum voluntary strength testing, growth hormone use did not improve biceps strength (change, −0.2 kg [CI, −1.5 to 1.1 kg]) or quadriceps strength (change, −0.1 kg [CI, −1.8 to 1.5 kg]) (**Table 3** and **Appendix Figure 2**, available at www.annals.org). One study evaluated 7 other muscle groups for change in maximum strength and assessed 4 measures of change in muscle circumference (70)—none of these changes significantly differed between growth hormone–treated and non–growth hormone–treated groups.

Effect of Growth Hormone on Basal Metabolism

Daily basal metabolic rate was higher in growth hormone–treated participants than in those not treated with growth hormone (basal metabolic rate, 141 kcal/d [CI, 69 to 213 kcal/d]) (**Table 3** and **Appendix Figure 3**, available

Table 2. **Study Quality***

Study, Year (Reference)	Trial Quality Measures							
	Were Growth Hormone– and Non–Growth Hormone–Treated Participants Similar at Baseline?	Was a Placebo Offered?	Was Treatment Allocation Concealed?	Were Eligibility Criteria Specified?	Were Study Participants Blinded?	Were Clinicians Blinded?	Were Point Estimates and Variability Presented?	Was an Intention-to-Treat Analysis Performed?
Single-dose growth hormone								
Gravholt et al., 1999 (34)	●	NA	NA	○	NA	NA	●	●
Hansen et al., 2005 (1 d) (35)	●	●	NA	●	●	●	●	○
Hashimoto et al., 2000 (36)	NA	●	NA	⊙	●	●	●	●
Irving et al., 2004 (37)	●	○	NA	●	○	○	●	●
Lange et al., 2002 (38)	●	●	NA	●	●	●	●	⊙
Møller et al., 1990 (39)	●	●	NA	⊙	●	●	●	●
Napoli et al., 2003 (40)	●	●	NA	⊙	●	○	●	●
Multiple-dose growth hormone								
Brixen et al., 1990, 1992, 1995 (41–43)	●	●	NA	⊙	●	●	●	○
Crist et al., 1988, 1990, 1991 (44–46)	●	●	NA	⊙	●	●	●	●
Deyssig et al., 1993 (47)	NA	●	NA	●	●	●	●	○
Ehrnborg et al., 2005 (33, 48)	●	●	NA	●	●	●	●	●
Giannoulis et al., 2005, 2002, 2000, 2000 (49–52)	●	●	NA	●	●	●	●	⊙
Graham et al., 2007 (72–74)	⊙	○	NA	●	○	○	●	●
Hansen et al., 2001 (53)	●	○	NA	○	○	○	●	●
Hansen et al., 2005 (32)	●	●	NA	●	●	●	●	●
Healy et al., 2006, 2003 (54, 55)	●	●	NA	●	●	●	●	○
Horber et al., 1993, 1991 (31, 56)	NA	●	NA	●	●	NA	●	●
Kniess et al., 2003 (57)	NA	●	NA	⊙	●	NA	⊙	NA
Møller et al., 1991 (58)	●	●	NA	⊙	●	●	●	●
Møller et al., 1992 (59)	●	●	NA	⊙	●	●	●	NA

Table 2—Continued

Study, Year (Reference)	Trial Quality Measures							
	Were Growth Hormone– and Non–Growth Hormone–Treated Participants Similar at Baseline?	Was a Placebo Offered?	Was Treatment Allocation Concealed?	Were Eligibility Criteria Specified?	Were Study Participants Blinded?	Were Clinicians Blinded?	Were Point Estimates and Variability Presented?	Was an Intention-to-Treat Analysis Performed?
Møller et al., 1993 (60)	●	●	NA	⊙	●	●	●	●
Møller et al., 1995, 1996 (61, 62)	●	●	NA	○	●	●	●	●
Wallace et al., 2001, 2001, 1999 (63–65)	⊙	●	NA	●	●	●	●	●
Wolthers et al., 1999, 1996, 1996 (66–68)	●	●	NA	⊙	●	●	⊙	●
Wolthers et al., 1998 (69)	●	●	NA	⊙	●	●	⊙	●
Yarasheski et al., 1992 (70)	NA	●	NA	⊙	●	●	●	○
Yuen et al., 2004 (71)	●	●	NA	⊙	●	●	●	●

* The section on single-dose growth hormone includes studies that provided 1 dose of growth hormone therapy; the section on multiple-dose growth hormone includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. NA = not available/unclear; ○ = quality measure not fulfilled; ⊙ = quality measure partially fulfilled; ● = quality measure fulfilled.

at www.annals.org). Resting respiratory exchange ratio or respiratory quotient was lower in growth hormone–treated participants (−0.02 [CI, −0.03 to −0.01]; mean among all participants, 0.78 [SD, 0.03]), reflecting the preferential use of lipids rather than carbohydrates for fuel at rest during growth hormone therapy. Resting heart rate was also significantly higher in growth hormone–treated participants (3.8 beats/min [CI, 0.2 to 7.4 beats/min]).

Effect of Growth Hormone on Exercise Capacity

Six studies measured exercise capacity outcomes (**Appendix Table 2**, available at www.annals.org). Given the variability in exercise interventions, we present a narrative summary rather than pooling their exercise capacity results. In growth hormone–treated participants compared with those not treated with growth hormone, lactate levels during exercise trended higher in all 3 studies evaluating this outcome, although this finding was statistically significantly higher in only 2 studies (**Table 4**). Exercising levels of plasma free fatty acids and glycerol were significantly increased in growth hormone–treated participants in all studies that evaluated these outcomes, reflecting the lipolytic properties of growth hormone. However, the exercising respiratory exchange ratio or respiratory quotient was not significantly different (35, 38, 72–74, 54, 55) in growth hormone–treated participants compared with that in those not treated with growth hormone. Exercising

Table 3. **Summary Effect Sizes for Body Composition, Strength, and Basal Metabolism***

Clinical Area and Clinical Outcome	Study Samples, *n*†	Weighted Mean Difference (95% CI)‡
Body composition		
Change in body weight	9	0.3 kg (−0.5 to 1.1 kg)
Change in fat mass	10	−0.9 kg (−1.9 to −0.0 kg)
Change in lean body mass	11	2.1 kg (1.3 to 2.9 kg)§
Strength		
Change in biceps 1RM	2	−0.2 kg (−1.5 to 1.1 kg)
Change in quadriceps 1RM	2	−0.1 kg (−1.8 to 1.5 kg)
Basal metabolism		
End basal metabolic rate	7	141 kcal/d (69 to 213 kcal/d)‖
End resting respiratory exchange ratio or respiratory quotient	7	−0.02 (−0.03 to −0.01)‖
End resting heart rate	11	3.8 beats/min (0.2 to 7.4 beats/min)¶

* 1RM = 1 repetition maximum.
† Includes subsamples based on sex and dose.
‡ Growth hormone–treated group minus non–growth hormone–treated group. The weighted mean difference provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the weighted mean value in the growth hormone–treated group was higher than the value in the group not treated with growth hormone.
§ $P < 0.01$.
‖ $P < 0.001$.
¶ $I^2 > 50\%$; $P < 0.05$.

Table 4. **Qualitative Summary for Exercise Capacity***

Clinical Outcome (during Exercise) in Study, Year (Reference)	Comparison of Values in Growth Hormone–Treated Group vs. Non–Growth Hormone–Treated Group	Published *P* Value (Comparison between Groups)
Plasma lactate level		
Hansen et al., 2005 (1 d) (35)	+	<0.001
Irving et al., 2004 (37)†	+	0.07, 0.7–1.0
Lange et al., 2002 (38)	+	<0.001
Heart rate		
Hansen et al., 2005 (1 d) (35)	+	<0.02
Irving et al., 2004 (37)†	+	0.12–1.0
Lange et al., 2002 (38)	+	<0.001
Ehrnborg et al., 2005 (33, 48)	+	0.08
Plasma free fatty acid level		
Hansen et al., 2005 (1 d) (35)	+	<0.0
Lange et al., 2002 (38)	+	<0.001
Healy et al., 2006, 2003 (54, 55)	+	<0.05
Plasma glycerol level		
Hansen et al., 2005 (1 d) (35)	+	<0.01
Lange et al., 2002 (38)	+	<0.001
Healy et al., 2006, 2003 (54, 55)	+	<0.05
Respiratory exchange ratio or respiratory quotient		
Hansen et al., 2005 (1 d) (35)	=	0.64
Lange et al., 2002 (38)	=	>0.76
Healy et al., 2006, 2003 (54, 55)	=	–‡
Graham et al., 2007 (72–74)	–	>0.05‡
Bicycling speed		
Lange et al., 2002 (38)	+	0.39
Lange et al., 2002 (38)	–	0.44
$\dot{V}O_2$max		
Ehrnborg et al., 2005 (33, 48)	+	0.76, 1.0
Graham et al., 2007 (72–74)	+	>0.05‡
Power output		
Ehrnborg et al., 2005 (33, 48)	+	0.84
Energy expenditure		
Healy et al., 2006, 2003 (54, 55)	=	–‡
Maximum inspiratory pressure (nonexercising)		
Graham et al., 2007 (72–74)	+	<0.05

* + indicates that value in growth hormone–treated group seemed higher or consistently higher than that in the non–growth hormone–treated group; – indicates that value in growth hormone–treated group seemed lower or consistently lower than that in the non–growth hormone–treated group; = indicates that values in both groups seemed similar. $\dot{V}O_2$max = maximum oxygen uptake.
† Comparison of control group with multiple growth hormone treatment groups.
‡ Comparison not reported to be significantly different between groups ($P > 0.05$) or *P* value not reported.

heart rate was significantly increased in 2 of 4 studies that evaluated this outcome (35, 38). Maximum inspiratory pressure (at rest) increased in growth hormone–treated participants compared with those not treated with growth hormone in 1 study (72–74). Groups did not differ in bicycling speed, exercising energy expenditure, and power output (1 study each) (38, 54, 55). Similarly, VO_2max was not significantly different between growth hormone–treated and non–growth hormone–treated groups (2 studies) (33, 48, 72–74).

Safety of Growth Hormone

Growth hormone–treated participants reported higher rates of adverse events than those not treated with growth hormone (**Table 5**). The former group reported more soft tissue edema and fatigue than the latter group (44% vs. 1% and 35% vs. 0%, respectively). Growth hormone–treated participants also experienced arthralgias and carpal tunnel syndrome more often than did those not treated with growth hormone.

Sensitivity Analyses

We recalculated summary effect sizes after removing each study per iteration. Removing the study by Wolthers and colleagues (66–68) resulted in a statistically significant increase in weight among growth hormone recipients. Removing 1 of 5 studies that evaluated fat mass (32, 33, 44–46, 48, 70, 72–74) or 1 of 4 studies that evaluated resting heart rate (33, 48, 53, 69, 72–74) resulted in nonsignificant differences between participants who received and those who did not receive growth hormone. The results of other clinical outcomes were robust to this analysis.

We found little evidence for statistical heterogeneity among the included studies for body composition, strength outcomes, resting respiratory exchange ratio or respiratory quotient, and resting energy expenditure (**Appendix Figures 1** to **3,** available at www.annals.org). However, the summary results for resting heart rate were statistically heterogeneous (*P* for *Q* statistic = 0.01; I^2 = 55%) (**Table 3**). Part of this heterogeneity could be explained by duration of growth hormone treatment. When we recalculated the resting heart rate from studies that provided growth hormone for at least 14 days, we found no evidence for heterogeneity (*P* for *Q* statistic = 0.26; I^2 = 22%). We found little evidence of publication bias through visual inspection of funnel plots.

DISCUSSION

Growth hormone is reported to be extensively used for illicit enhancement of athletic performance (5, 8, 75), both for its anabolic and endurance effects. However, our review of the limited published literature suggests that although growth hormone may alter body composition, it has minimal effect on key athletic performance outcomes and may, in fact, be associated with worsened exercise capacity. Our conclusions are consistent with the findings reported in the recent Mitchell report on illegal drug use in Major League Baseball, which noted the lack of evidence supporting growth hormone use and enhancement of athletic performance (10).

Table 5. **Key Adverse Events**

Adverse Event*	Studies Reporting Outcome, *n*	Events in Growth Hormone–Treated Group, *n (%)*	Events in Non–Growth Hormone–Treated Group, *n (%)*
Soft tissue edema	8	33 (44)	1 (1)
Fatigue	4	11 (35)	0 (0)
Arthralgias	2	4 (25)	0 (0)
Carpal tunnel syndrome	2	3 (15)	0 (0)
Sweating	1	3 (30)	2 (20)

* Participants may have reported more than 1 adverse event.

Athletes, in particular bodybuilders, reportedly use growth hormone to increase strength and improve muscle definition (5, 17, 76). We found that although growth hormone significantly increased lean body mass and was associated with a near-significant trend toward decreased fat mass, it did not result in gains in biceps and quadriceps strength. How can increases in lean body mass not translate into strength improvements? Because methods for evaluation of lean body mass do not reliably distinguish lean solid tissue from fluid mass (77) and because the included studies evaluated only short-term changes, we suspect that much of the increase in lean body mass from growth hormone is due to fluid retention rather than muscle hypertrophy (77–79). A nonrandomized study in experienced weightlifters supports this view. Yarasheski and colleagues (80) provided high-dose growth hormone to college football players and weightlifters and found that it did not increase muscle protein synthesis or decrease protein breakdown, suggesting that an increase in muscle mass from growth hormone use in such athletes is unlikely.

We found that growth hormone did not improve and, in fact, may worsen exercise capacity. Exercising lactate levels were significantly higher in growth hormone–treated participants than in non–growth hormone–treated participants in 2 of 3 studies that evaluated this outcome. Increased exercising lactate levels are associated with decreased exercise stamina and physical exhaustion (81). In the double-blind study by Lange and colleagues (38), 2 of 7 cyclists could complete the exercise protocol after receiving placebo but not growth hormone; this finding was replicated on repeated testing in 1 cyclist. It is not clear how growth hormone treatment increases exercising lactate levels, but it may be associated with increased action of uncoupling proteins in mitochondria or selective inhibition of pyruvate dehydrogenase (38). In addition, elevated glycerol concentrations observed during the growth hormone trials could provide an alternate gluconeogenic precursor, thus increasing blood lactate levels by reducing lactate clearance by the liver. However, our exercise capacity results must be interpreted with caution because all 3 studies evaluated exercising lactate levels after only 1 dose of growth hormone, a dosing protocol unlikely to mirror real-world regimens. Nonetheless, this finding merits further research because it suggests that endurance athletes who use growth hormone may actually be harming their athletic performance.

One recent study (72–74) included in our analysis reported respiratory function improvements (including maximum inspiratory and expiratory pressures) in participants treated with growth hormone compared with those not treated with growth hormone, although VO_2max was not reported to statistically significantly differ. Whether these findings translate into improved athletic performance is unclear. In healthy people at sea level, pulmonary function is typically not considered to be limiting to performance (82). Even during maximal exercise, participants could increase ventilation (82), suggesting an existing ventilatory reserve. Additional studies evaluating the effects of pulmonary function change on athletic performance are needed to evaluate these authors' findings.

While growth hormone therapy resulted in increased use of lipids for fuel during rest (as noted by a statistically significantly lower resting respiratory exchange ratio and respiratory quotient), this improvement did not seem to persist during exercise. Although growth hormone therapy resulted in higher exercising serum free fatty acid and glycerol levels, exercising respiratory exchange ratio and respiratory quotient levels were not reported to significantly differ in growth hormone–treated versus non–growth hormone–treated participants. Free fatty acid availability can affect free fatty acid uptake at rest and during low-intensity exercise, but exercise intensity remains the predominant determinant of substrate selection and can override other influences, especially at high rates of work output. As is the case after endurance training, a lower respiratory exchange ratio and respiratory quotient, signifying increased lipid rather than carbohydrate oxidation, are thought to contribute to improved exercise endurance due to glycogen preservation (83). The observation that respiratory exchange decrements with growth hormone did not persist during exercise suggests that short-term growth hormone treatment may not enhance endurance, at least through a mechanism of altered substrate selection. This conclusion cannot be considered definitive given the small number of included studies, but it suggests that additional research is needed to further delineate growth hormone's effects on endurance.

We found higher rates of adverse events in growth

hormone–treated participants than in non–growth hormone–treated participants. Consistent with studies in growth hormone–deficient patients (84, 85) and healthy elderly participants (20), we found higher proportions of soft tissue edema, joint pain, and carpal tunnel syndrome in participants receiving growth hormone, although variability in reporting adverse events precluded us from performing statistical analyses on these results. Adverse events related to fluid retention have been well described in growth hormone–treated patients (86, 87) and are thought to be due to growth hormone's effect on fluid homeostasis. Of note, growth hormone–treated participants reported higher rates of fatigue, consistent with our finding that growth hormone may in fact worsen exercise capacity.

Our study reflects the limitations of the included studies. First, our review highlights the lack of published evidence about the physiologic effects of growth hormone among athletic young adults. Although we reviewed thousands of studies, only 8 studies assessed strength and exercise capacity for growth hormone treatment in a randomized manner. Thus, our analysis may not have detected small but clinically relevant differences in outcomes and adverse events. Because no studies evaluated growth hormone for longer than 3 months, there is no evidence with which to evaluate the long-term use of growth hormone for athletic enhancement. In addition, because only a small percentage of participants were women, there is almost no evidence with which to evaluate the effect of growth hormone in physically fit young women. Second, published data on real-world doping regimens are limited, and growth hormone dosing regimens used in research settings may be lower than or otherwise differ from those used by athletes who engage in sports doping. Saugy and colleagues (75) reported that athletes may be using growth hormone in dosages ranging from approximately 15 to 180 μg/kg per day (75), which may be higher than dosages used in most of our included studies. Whether a graded dose response exists for growth hormone is unclear (15), and future research should evaluate growth hormone regimens used in real-world settings. Finally, anecdotal reports of sports doping regimens suggest that growth hormone is not typically used as a single agent (5), but rather is often combined with other drugs, including androgenic steroids, insulin, and antiestrogens (76). Real-world sports doping regimens may have different benefits and risks from those noted in our analyses.

Claims regarding the performance-enhancing properties of growth hormone are premature and are not supported by our review of the literature. The limited published data evaluating the effects of growth hormone on athletic performance suggest that although growth hormone increases lean body mass in the short term, it does not seem to improve strength and may worsen exercise capacity. In addition, growth hormone use in healthy young persons is frequently associated with adverse events. More research, including an identification and evaluation of real-world growth hormone doping protocols, is warranted to definitively determine the effects of growth hormone on athletic performance.

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Appendix Table 1. **Search Strategy***

Search Number (Date)	Search Terms	Articles Returned, *n*
MEDLINE		
(31 August 2006)		
1	("Growth Hormone"[MeSH] OR growth hormone*[tw])	53 732
2	("Adult"[MeSH] OR "Adolescent"[MeSH])	4 143 448
3	(randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR random allocat*[tw] OR randomly allocat*[tw] OR double-blind method [mh] OR single-blind method [mh] OR double blind*[tw] OR single blind*[tw] OR triple blind*[tw] OR clinical trial [pt] OR clinical trials [mh]) NOT (animal[mh] NOT human[mh])	591 966
4	"Middle Aged"[MeSH] OR "Aged"[MeSH]	2 585 607
5	"Child"[MeSH] OR "Child, Preschool"[MeSH] OR "Infant"[MeSH] OR "Infant, Newborn"[MeSH]	1 510 685
6	#1 AND #2 AND #3	3382
7	#1 AND #3	4202
8	#7 NOT #6	820
9	#1 AND #3 AND #4	1552
10	#1 AND #3 AND #5	1013
11	#8 NOT #9	820
12	#8 NOT #10	387
13	#8 NOT (#9 OR #10)	387
14	#8 NOT #13	433
Updated: 7 September 2006		
1	("Growth Hormone"[MeSH] OR growth hormone*[tw])	53 755
2	(randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR random allocat*[tw] OR randomly allocat*[tw] OR double-blind method [mh] OR single-blind method [mh] OR double blind*[tw] OR single blind*[tw] OR triple blind*[tw] OR clinical trial [pt] OR clinical trials [mh]) NOT (animal[mh] NOT human[mh])	592 629
3	#1 AND #2 Limits: Entrez Date from 2006/07/13 [to present]	7
Summary	Total titles identified from MEDLINE search	4180
Updated: 11 October 2007		
	Additional studies identified from MEDLINE search	286
Summary	Total titles identified from MEDLINE search	4466
EMBASE		
(7 September 2006)		
S1	Human Growth Hormone! OR growth hormone! OR growth hormone?	89 040
S3	randomi?(W)controlled(W)trial? OR DT=randomized controlled trial	385 891
S4	random?(W)alloc? OR random allocation! OR double(W)Blind? OR single(W)blind?	284 456
S5	trip?(W)blind? OR clinical trials! OR clinical trial! OR DT=clinical trial	948 086
S6	S3 OR S4 OR S5	1 064 129
S7	S6 AND S1	7634
S8	S (LT = animal or animals/df) NOT (humans/df OR human/df)	6 094 879
S9	S7 NOT S8	7245
S10	RD S9 Unique Embase records	2325
Updated: 11 October 2007		
	Additional studies identified from EMBASE search	420
Summary	Total titles identified from EMBASE search	2745
SPORTDiscus		
(7 September 2006)		
1	exp somatotropin/	725
2	growth hormone$.mp.	711
3	1 or 2	953
4	limit 3 to (article or book analytic or "book review" or microform or monograph or serial publication or "thesis or dissertation" or url)	953
5	exp ANIMAL/	10 028
6	4 not 5	925
7	4 not 6	28
8	exp clinical trial/	1084
9	double-blind method/	0
10	random$ controlled trial$.mp	976
11	double blind$.mp.	732
12	single blind$.mp.	91
9	double-blind method/	0
10	random$ controlled trial$.mp	976
11	double blind$.mp.	732

Continued on following page

Appendix Table 1—**Continued**

Search Number (Date)	Search Terms	Articles Returned, *n*
12	single blind$.mp.	91
13	triple blind$.mp	1
14	random$ alloc$.mp	82
15	8 or 9 or 10 or 11 or 12 or 13 or 14	1979
16	3 and 15	23
	Unique titles (2 eliminated, identified in prior search)	21
Updated: 11 October 2007		
	Additional studies identified from SPORTDiscus search	23
Summary	Total titles identified from SPORTDiscus search	44
Cochrane Collaboration (7 September 2006)		
1	growth hormone$.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (3371) EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2006> (36) EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (15)	3422
2	limit 2 to medline records [Limit not valid in: CDSR,DARE; records were retained] EBM Reviews Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (2591) EBM Reviews Cochrane Database of Systematic Reviews <3rd Quarter 2006> (36) EBM Reviews Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (15)	2642
3	1 not 2	780
4	limit 3 to Embase records [Limit not valid in: CDSR,DARE; records were retained]	503
5	3 not 4 EBM Reviews Cochrane Central Register of Controlled Trials <3rd Quarter 2006> (328) EBM Reviews Cochrane Database of Systematic Reviews <3rd Quarter 2006> (0) EBM Reviews Database of Abstracts of Reviews of Effects <3rd Quarter 2006> (0)	328
Updated: 11 October 2007		
	Additional studies identified from Cochrane Collaboration search	26
Summary	Total titles identified from Cochrane Collaboration search	344

* Searches current through 11 October 2007.

Appendix Table 2. Key Outcomes Available for Analysis*

Study, Year (Reference)	Body Composition			Strength Outcomes		Basal Metabolism (Nonexercising)			Exercise Capacity (Exercising)									Adverse Events Reported
	Body Weight	LBM or FFM	FM	Biceps 1RM	Quadriceps 1RM	EE or BMR	Heart Rate	RER or RQ	Heart Rate	Lactate Level	FFA or Glycerol	RER or RQ	$\dot{V}O_2$ max	Power Output	Cycling Speed	EE	MIP (Nonexercising)	
Single-dose growth hormone																		
Gravholt et al., 1999 (34)						√		√										
Hansen et al., 2005 (1 d) (35)									√	√	√	√						√
Hashimoto et al., 2000 (36)																		√
Irving et al., 2004 (37)									√	√								
Lange et al., 2002 (38)									√	√	√	√			√†			√
Møller et al., 1990 (39)						√		√										
Napoli et al., 2003 (40)							√											
Multiple-dose growth hormone																		
Brixen et al., 1990, 1992, 1995 (41–43)	√																	√
Crist et al., 1988, 1990, 1991 (44–46)		√†	√†															√
Deyssig et al., 1993 (47)		√	√	√	√													√
Ehrnborg et al., 2005 (33, 48)	√‡	√‡	√‡				√‡		√				√	√				√
Giannoulis et al., 2005, 2002, 2000, 2000 (49–52)							√†§											√†
Graham et al., 2007 (72–74)	√		√				√					√	√				√	√
Hansen et al., 2001 (53)							√											
Hansen et al., 2005 (32)	√	√	√			√												√
Healy et al., 2006, 2003 (54, 55)	√	√	√					√			√	√				√		√
Horber et al., 1993, 1991 (31, 56)						√		√										
Kniess et al., 2003 (57)																		√
Møller et al., 1991 (58)																		√
Møller et al., 1992 (59)								√										√
Møller et al., 1993 (60)						√		√										
Møller et al., 1995 (61, 62)							√†											
Wallace et al., 2001, 2001, 1999 (63–65)																		√
Wolthers et al., 1999, 1996, 1996 (66–68)	√	√				√												
Wolthers et al., 1998 (69)		√				√	√	√										
Yarasheski et al., 1992 (70)	√	√	√	√	√													√
Yuen et al., 2004 (71)	√	√	√				√											

* Upper section includes studies that provided 1 dose of growth hormone therapy; lower section includes studies that provided growth hormone for >1 day. In each section, references are arranged in alphabetical order. Check mark indicates that data were available for and are included in analysis. 1RM = 1 repetition maximum; BMR = basal metabolic rate; EE = energy expenditure; FFA = free fatty acids; FFM = fat-free mass; FM = fat mass; LBM = lean body mass; MIP = maximum inspiratory pressure; RER = respiratory exchange rate; RQ = respiratory quotient; $\dot{V}O_2$max = maximum oxygen uptake.

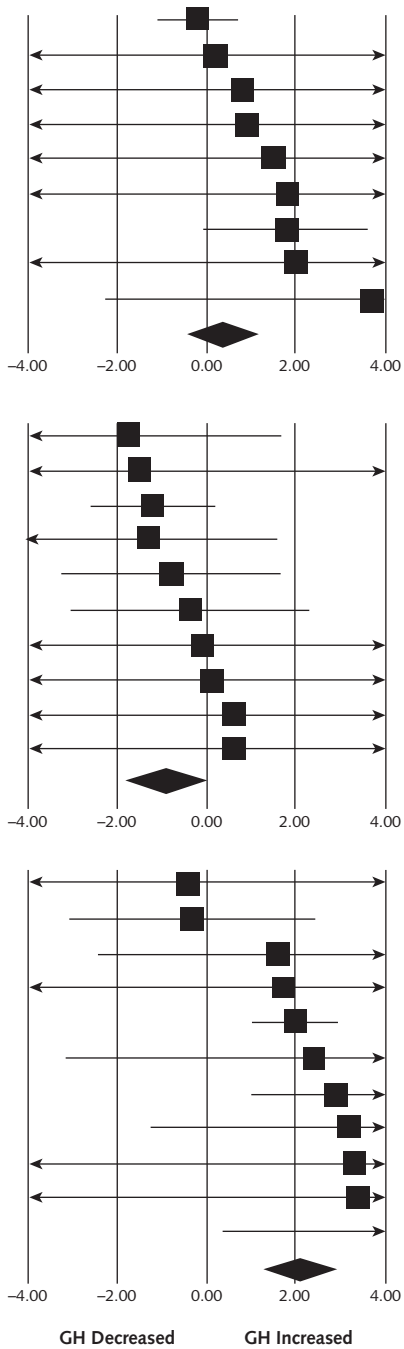
† Includes separate data for low-dose and high-dose growth hormone treatment.

‡ Includes separate data for men and women.

§ Data obtained from reference 50.

Appendix Figure 1. **Effect of growth hormone (*GH*) on body composition.**

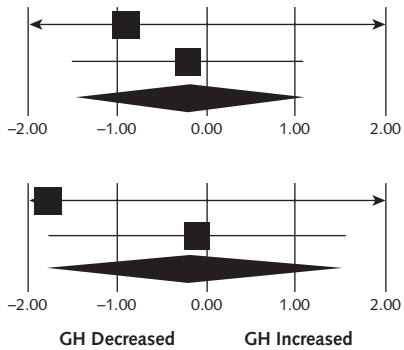
Study (Reference)	Difference in Means	Lower Limit	Upper Limit	*P* Value	GH Group	Control Group
Weight, *kg*						
Wolthers et al. (66–68)	–0.190	–1.120	0.740	0.689	8	8
Yuen et al. (71)	0.200	–9.043	9.443	0.966	12	12
Graham et al. (72–74)	0.800	–5.451	7.051	0.802	24	24
Hansen et al. (32)	0.900	–6.311	8.111	0.807	8	8
Ehrnborg et al. (33, 48)*	1.500	–8.473	11.473	0.768	10	5
Brixen et al. (41–43)	1.800	–4.080	7.680	0.549	10	10
Yarasheski et al. (70)	1.800	–0.074	3.674	0.060	7	9
Ehrnborg et al. (33, 48)†	2.000	–6.134	10.134	0.630	10	5
Healy et al. (54, 55)	3.700	–2.310	9.710	0.228	6	5
Total	0.337	–0.458	1.133	0.406	95	86
Fat mass, *kg*						
Crist et al. (44–46)‡	–1.770	–5.206	1.666	0.313	8	8
Ehrnborg et al. (33, 48)*	–1.500	–7.945	4.945	0.648	10	5
Yarasheski et al. (70)	–1.200	–2.609	0.209	0.095	7	9
Hansen et al. (32)	–1.200	–4.088	1.688	0.415	8	8
Graham et al. (72–74)	–0.800	–3.291	1.691	0.529	24	24
Crist et al. (44–46)§	–0.350	–3.045	2.345	0.799	8	8
Healy et al. (54, 55)	–0.100	–4.471	4.271	0.964	6	5
Deyssig et al. (47)	0.110	–5.468	5.688	0.969	8	10
Yuen et al. (71)	0.600	–8.242	9.442	0.894	12	12
Ehrnborg et al. (33, 48)†	0.600	–4.448	5.648	0.816	10	5
Total	–0.927	–1.852	–0.001	0.050	101	94
Lean body mass, *kg*						
Yuen et al. (71)	–0.400	–9.242	8.442	0.929	12	12
Wolthers et al. (69)	–0.300	–3.086	2.486	0.833	8	8
Ehrnborg et al. (33, 48)†	1.600	–2.449	5.649	0.439	10	5
Crist et al. (44–46)§	1.730	–8.628	12.088	0.743	8	8
Wolthers et al. (66–68)	2.000	1.020	2.980	0.000	8	8
Hansen et al. (32)	2.400	–3.207	8.007	0.402	8	8
Yarasheski et al. (70)	2.900	1.026	4.774	0.002	7	9
Healy et al. (54, 55)	3.200	–1.263	7.663	0.160	6	5
Crist et al. (44–46)‡	3.330	–7.254	13.914	0.537	8	8
Ehrnborg et al. (33, 48)*	3.400	4.933	11.733	0.424	10	5
Deyssig et al. (47)	4.100	0.358	7.842	0.032	8	10
Total	2.092	1.328	2.855	0.000	93	86



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. *Male. †Female. ‡High-dose group. §Low-dose group.

Appendix Figure 2. **Effect of growth hormone (*GH*) on strength.**

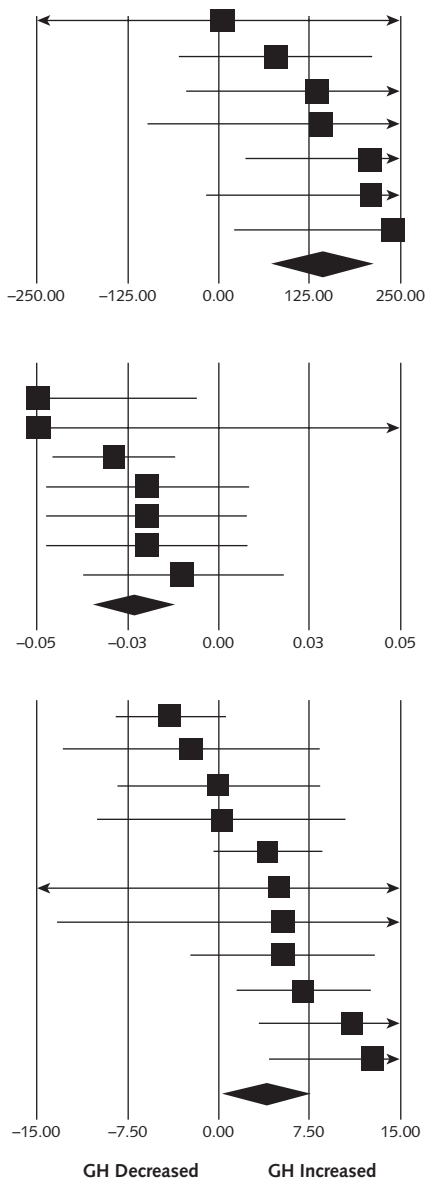
Study (Reference)	Difference in Means	Lower Limit	Upper Limit	*P* Value	GH Group	Control Group
Biceps 1RM, *kg*						
Deyssig et al. (47)	–0.900	–13.554	11.754	0.889	11	11
Yarasheski et al. (70)	–0.200	–1.515	1.115	0.766	9	9
Total	–0.207	–1.515	1.100	0.756	20	20
Quadriceps 1RM, *kg*						
Deyssig et al. (47)	–1.800	–14.114	10.514	0.774	11	11
Yarasheski et al. (70)	–0.100	–1.786	1.586	0.907	9	9
Total	–0.131	–1.802	1.539	0.878	20	20



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. 1RM = 1 repetition maximum.

Appendix Figure 3. **Effect of growth hormone (*GH*) on basal metabolism.**

Study (Reference)	Difference in Means	Lower Limit	Upper Limit	*P* Value	GH Group	Control Group
Basal metabolic rate, *kcal/d*						
Møller et al. (39)	7.000	–250.472	264.472	0.958	6	6
Gravhølt et al. (34)	79.000	–55.497	213.497	0.250	8	8
Wolthers et al. (69)	135.000	–45.508	315.508	0.143	8	8
Horber et al. (31, 56)	141.000	–99.246	381.246	0.250	8	8
Wolthers et al. (66–68)	209.000	36.056	381.944	0.018	8	8
Møller et al. (60)	210.000	–18.569	438.569	0.072	6	6
Hansen et al. (32)	239.000	19.589	458.411	0.033	8	8
Total	140.984	68.765	213.204	0.000	52	52
Resting RER or RQ						
Møller et al. (60)	–0.050	–0.094	–0.006	0.025	6	6
Møller et al. (59)	–0.500	–0.191	0.091	0.488	14	14
Møller et al. (39)	–0.029	–0.046	–0.012	0.001	6	6
Healy et al. (54, 55)	–0.020	–0.048	0.008	0.161	6	5
Wolthers et al. (69)	–0.020	–0.048	0.008	0.157	8	8
Gravhølt et al. (34)	–0.020	–0.048	0.008	0.157	8	8
Horber et al. (31, 56)	–0.010	–0.038	0.018	0.480	8	8
Total	–0.024	–0.034	–0.013	0.000	56	55
Resting heart rate, *beats/min*						
Giannoulis et al. (49–52)*†	–4.000	–8.569	0.569	0.086	17	25
Ehrnborg et al. (33, 48)*	–2.300	–12.895	8.295	0.671	10	10
Napoli et al. (40)	0.000	–8.315	8.315	1.000	8	8
Yuen et al. (71)	0.200	–10.125	10.525	0.970	12	12
Giannoulis et al. (49–52)†‡	4.000	–0.538	8.538	0.084	18	25
Møller et al. (61, 62)*	5.000	–19.811	29.811	0.693	8	8
Møller et al. (61, 62)‡	5.300	–13.410	24.010	0.579	8	8
Ehrnborg et al. (33, 48)‡	5.300	–2.385	12.985	0.176	10	10
Wolthers et al. (69)	7.000	1.456	12.544	0.013	8	8
Graham et al. (72–74)	11.000	3.232	18.768	0.006	24	24
Hansen et al. (53)	13.000	4.091	21.909	0.004	8	8
Total	3.806	0.213	7.398	0.038	131	146



We used a random-effects model and a weighted mean difference effect size to compare GH-treated and non–GH-treated participants. The black diamonds represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results with GH treatment were higher than those without GH treatment. The studies are ordered by mean effect size. RER = respiratory exchange rate; RQ = respiratory quotient. *Low-dose group; data obtained from reference 50. †Low-dose GH. ‡High-dose GH. Data obtained from reference 50. §High-dose GH.