Effects of Growth Hormone on Athletic Performance

Systematic Review: The Effects of Growth Hormone on Athletic Performance

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Background: Human growth hormone is 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: We reviewed the MEDLINE, EMBASE, SPORTDiscus, and Cochrane Collaboration databases 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 unique 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/m² [SD, 2]), and physically fit (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 [NOSP]>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 appear 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.

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, 2, 3). However, a wide range of athletes, including those from baseball (4, 5, 6), cycling (7, 8), and track and field (5, 9), have been implicated in or confessed to illicit growth hormone use. The Mitchell report (10) recently identified 89 major league baseball players who allegedly used performance-enhancing drugs, and many 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.

While 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. Reports 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 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 Collaborations 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 to 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 Inc., 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.

**Abstracted Data**
We abstracted 4 types of data from each study: participant characteristics (for example, age, sex, body mass index, baseline maximum oxygen uptake [VO$_2$max]), 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, 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$_2$max); 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, 27, 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 of 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, 29, 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 Corp, College Station, Texas); SPSS, version 15.0 (SPSS Inc., 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.

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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 unique study samples met our inclusion criteria (Table 1) (31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 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$_2$max, 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).

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 periods longer than 30 days (44, 45, 46, 47, 70), and no study evaluated its use for more than 3 months. Among the included studies, the mean daily dosage of growth hormone was 36 µg/kg per day (SD, 21).

**Study Quality**

No study fulfilled all of the evaluated quality criteria, although 2 studies fulfilled 7 of 8 criteria (Table 2). No 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. On 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 1-repetition maximum strength and assessed 4 measures of change in muscle circumference (70)—none of these changes were significantly different 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 (daily basal metabolic rate, 141 kcal/24 hours [CI, 69 to 213 kcal/24 hours]) (Table 3 and Appendix Figure 3***available 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, 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). 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, 73, 74, 54, 55) in growth hormone–treated participants compared with those not treated with growth hormone. Exercising 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, 73, 74). Groups did not differ in bicycling speed, exercising energy expenditure, and power output (1 study each) (38, 54, 55). Similarly, VO2max was not significantly different between growth hormone–treated and non–growth hormone–treated groups (2 studies) (33, 48, 72, 73, 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, 67, 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, 45, 46, 48, 70, 72, 73, 74) or 1 of 4 studies that evaluated resting heart rate (33, 48, 53, 69, 72, 73, 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 Figure 1, Appendix Figure 2, and Appendix Figure 3). However, the summary results for resting heart rate were statistically heterogeneous ($P$ for $Q$ statistic[THSP]= 0.01; $I^2[THSP]= 55\%$ [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[THSP]= 0.26; $I^2[THSP]= 22\%$). 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 published literature suggests that while 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).

Athletes, in particular body builders, 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 nonsignificant 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, 78, 79). A nonrandomized study in experienced weight lifters supports this view. Yarasheski and colleagues (80) provided high-dose growth hormone to college football players and weight lifters and found that growth hormone 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 compared with 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 raising 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, 73, 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 receiving growth hormone, although VO2max was not reported to be statistically significantly different. 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 appear 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 be significantly different 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 following 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 acute 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 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 compared with non–growth hormone–treated participants. Consistent with studies in growth hormone–deficient patients (84, 85) and the healthy elderly (20), we found higher proportions of soft tissue edema, joint pain, carpal tunnel syndrome, and sweating in participants receiving compared with those not receiving growth hormone, although variability in reporting of 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 fashion. Thus, our analysis may not have detected small but clinically relevant differences in outcomes and adverse events. Since no studies evaluated growth hormone for periods 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 appear to improve strength and may worsen exercise capacity. In addition, growth hormone in the healthy young 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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References


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Table 1. Baseline Characteristics of Participants and Study Intervention
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Figure. Trial flow. *Sum may be greater than total number excluded because some studies had multiple reasons for exclusion. GH = growth hormone.

Appendix Figure 1. Effect of growth hormone (GH) on body composition. We used a random-effects model and a weighted mean difference effect size to compare growth hormone–treated and non–growth hormone–treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results under growth hormone treatment were higher than those without growth hormone treatment. The studies are ordered by mean effect size. *Male; †Female; ‡Low-dose group; §High-dose group.
Appendix Figure 2. **Effect of growth hormone (GH) on strength.** We used a random-effects model and a weighted mean difference effect size to compare growth hormone–treated and non–growth hormone–treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results under growth hormone treatment were higher than those without growth hormone treatment. The studies are ordered by mean effect size. 1RM[THSP]= 1 repetition maximum.

Appendix Figure 3. **Effect of growth hormone (GH) on basal metabolism.** We used a random-effects model and a weighted mean difference effect size to compare growth hormone–treated and non–growth hormone–treated participants. The black diamond represents the summary effect size for the outcome of interest. Values greater than 0 indicate that results under growth hormone treatment were higher than those without growth hormone 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 growth hormone; ‡High-dose growth hormone; data obtained from reference 50; §High-dose growth hormone.