Annals of Internal Medicine | Review

Systematic Review: The Safety and Efficacy of Growth Hormone in the Healthy Elderly

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Background: Human growth hormone (GH) is widely used as an antiaging therapy, although its use for this purpose has not been approved by the U.S. Food and Drug Administration and its distribution as an antiaging agent is illegal in the United States.

Purpose: To evaluate the safety and efficacy of GH therapy in the healthy elderly.

Data Sources: The authors searched MEDLINE and EMBASE databases for English-language studies published through 21 November 2005 by using such terms as *growth hormone* and *aging*.

Study Selection: The authors included randomized, controlled trials that compared GH therapy with no GH therapy or GH and lifestyle interventions (exercise with or without diet) with lifestyle interventions alone. Included trials provided GH for 2 weeks or more to community-dwelling participants with a mean age of 50 years or more and a body mass index of 35 kg/m^2 or less. The authors excluded studies that evaluated GH as treatment for a specific illness.

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

Data Synthesis: 31 articles describing 18 unique study populations met the inclusion criteria. A total of 220 participants who received GH (107 person-years) completed their respective studies. Study participants were elderly (mean age, 69 years [SD, 6]) and overweight (mean body mass index, 28 kg/m^2 [SD, 2]). Initial daily GH dose (mean, 14 μg per kg of body weight [SD, 7]) and treatment duration (mean, 27 weeks [SD, 16]) varied. In participants treated with GH compared with those not treated with GH, overall fat mass decreased (change in fat mass, −2.1 kg [95% CI, −2.8 to −1.35] and overall lean body mass increased (change in lean body mass, 2.1 kg [CI, 1.3 to 2.9]) ($P < 0.001$), and their weight did not change significantly (change in weight, 0.1 kg [CI, −0.7 to 0.8]; $P = 0.87$). Total cholesterol levels decreased (change in cholesterol, −0.29 mmol/L [−11.21 mg/dL]; $P = 0.006$), although not significantly after adjustment for body composition changes. Other outcomes, including bone density and other serum lipid levels, did not change. Persons treated with GH were significantly more likely to experience soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia and were somewhat more likely to experience the onset of diabetes mellitus and impaired fasting glucose.

Limitations: Some important outcomes were infrequently or heterogeneously measured and could not be synthesized. Most included studies had small sample sizes.

Conclusions: The literature published on randomized, controlled trials evaluating GH therapy in the healthy elderly is limited but suggests that it is associated with small changes in body composition and increased rates of adverse events. On the basis of this evidence, GH cannot be recommended as an antiaging therapy.

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Since the 1990 publication of an article by Rudman and colleagues (1) suggesting that a short course of recombinant human growth hormone (GH) therapy could reverse decades of age-related changes in body composition in otherwise healthy elderly men, the use of GH as an antiaging therapy has increased rapidly in the United States and worldwide (2). Interest in Rudman and colleagues' results has remained high (3), spawning several popular books in the lay press (4–7). Use of GH as an antiaging therapy ranks as 1 of the most popular health-related Internet searches (8). Although the exact number of people who use GH as an antiaging therapy is unknown, Perls and colleagues (2) reported that 20 000 to 30 000 people used GH in the United States as an antiaging therapy in 2004 (9), a more than 10-fold increase since the mid-1990s (10, 11). Annual sales of GH worldwide exceed $1.5 billion (2), one third of which may be for off-label use (12). Proponents of GH for its antiaging properties claimed that more than 100 000 people received GH without a prescription in 2002 (2, 11).

The rationale for using GH as an antiaging therapy, referred to by some as the "sweet syringe of youth" (10), lies in the age-related decline in activity of the hypothalamic growth hormone–insulin-like growth factor axis, a phenomenon referred to as the "somatopause" (13–19). Some signs and symptoms of GH deficiency (that is, GH deficiency due to hypothalamic or pituitary defects), such as increased adiposity and decreased lean body mass, are similar to changes that occur with aging, suggesting that GH replacement therapy may ameliorate age-related changes. Although GH therapy improves body composition (20), bone density (20, 21), and cholesterol levels (22) and may decrease death (23) in people who are GH-deficient, its safety, efficacy, and role in the healthy elderly is highly controversial (24). Whereas proponents of GH have

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recommended its use for treating the somatopause (18, 19, 25, 26), others, including the American Association of Clinical Endocrinologists (27), have warned that such therapy is not warranted. High levels of insulin-like growth factor-1 (IGF-1), which are regulated by GH levels, may be associated with serious adverse events (12), including prostate cancer (28). Furthermore, the distribution of GH for use as an antiaging therapy in the United States is illegal (2).

We performed a systematic review and meta-analysis of randomized, controlled trials to determine the safety and efficacy of GH therapy in the healthy elderly. We aimed to evaluate the effects of GH on body composition, exercise capacity, bone density, serum lipid levels, and glucose metabolism. In addition, we sought to synthesize the evidence on adverse events associated with GH use in the healthy elderly.

Context

Human growth hormone (GH) is widely sold and used as an antiaging agent.

Contributions

The researchers reviewed all clinical trials of GH to determine if it is safe and effective in the healthy elderly. They found that GH had no important effects on body composition but led to frequent adverse effects, most notably soft tissue edema and arthralgias.

Cautions

Clinical trials of GH have been small, and they may not have been able to detect important differences.

Implications

Published data about GH use in the elderly is limited, but available evidence suggests that risks far outweigh benefits when it is used as an antiaging treatment in healthy older adults.

—The Editors

Methods

Literature Searches

An author and a professional librarian developed search strategies to identify potentially relevant studies. We searched MEDLINE and EMBASE databases for English-language studies published through 21 November 2005 using keywords including *growth hormone*; *aging*; and *randomized, controlled clinical trials* (**Appendix Table 1**, available at www.annals.org). We searched bibliographies of retrieved articles for additional studies.

Study Selection

We sought 2 types of randomized, controlled trials: those that compared injectable GH therapy with no GH therapy and those that compared injectable GH therapy plus lifestyle interventions (that is, exercise with or without a dietary intervention) with lifestyle interventions alone. We included studies that: 1) evaluated at least 10 participants; 2) included participants who received GH therapy for 2 weeks or more; 3) enrolled only community-dwelling participants; 4) assessed participants with a mean body mass index of 35 kg/m^2 or less and a mean age of 50 years or more; and 5) provided data on at least 1 clinical outcome of interest. We excluded studies that: 1) focused solely on evaluating GH-releasing factor, other GH secretagogues, or IGF-1; 2) explicitly included patients with diabetes mellitus, cardiac disease, thyroid disease, osteoporosis, or cancer; or 3) evaluated GH as a treatment for a specific illness (for example, adult GH deficiency, the HIV wasting syndrome, renal failure, or critical illness).

Data Abstraction

An author reviewed the titles and abstracts of articles identified through our search and retrieved potentially relevant studies. Two physicians with postdoctoral training in health services research, endocrinology, or both reviewed each retrieved study and abstracted data independently onto pretested abstraction forms. We resolved abstraction differences by repeated review. If a study did not present data necessary for analysis, mentioned results but did not present data, or presented data graphically, we requested additional data from study authors. If several 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: 1) study quality (for example, quality of randomization, blinding, outcomes, and statistical analyses) (29, 30); 2) study sample characteristics (for example, age, sex, weight, medical conditions, and baseline IGF-1 levels); 3) study interventions (for example, dosage, frequency, and length of GH therapy); and 4) clinical outcomes. We included studies that provided data on at least 1 of the following 6 clinical outcomes of interest: 1) body composition (for example, weight, lean body or fat-free mass, or fat mass); 2) strength or functional capacity (for example, handgrip strength or maximal rate of oxygen consumption); 3) bone dynamics (for example, femoral neck or lumbar spine bone mineral density or bone mineral content); 4) cardiovascular risk factors (for example, heart rate, total, low-density lipoprotein, and high-density lipoprotein cholesterol levels or triglyceride levels); 5) insulin resistance markers (for example, fasting glucose and insulin levels and 2-hour glucose post–75-gram oral glucose tolerance test results); 5) quality-of-life or depression scales; or 6) adverse events. Because the terms *lean body mass* and *fat-free mass* are typically used interchangeably in scientific literature, we combined data on fat-free mass and lean body mass into the single category of *lean body mass*.

Quantitative Data Synthesis

To describe key study characteristics, we computed mean values weighted by the number of participants in each trial. To evaluate the effects of GH on the outcomes of interest, we computed a change score for each clinical outcome for participants in the treatment and control groups as the value of the outcome at the end of the trial minus the value of the outcome at the start of the trial. We then used these change scores to calculate 2 study effect sizes: the Hedges' adjusted *g*, which is an estimate of the standardized mean difference (31), and the weighted mean difference (32). We calculated both study effect sizes because the Hedges' adjusted *g*, although an unbiased estimate, lacks units; whereas the results of the weighted mean difference are in the same units as the clinical outcome of interest, facilitating clinical interpretation. Our results from either method did not substantially differ, and we present effect sizes calculated by using only the weighted mean difference. If studies reported standard errors, we converted them to standard deviations. For studies that did not report the variance of an outcome at the end of the trial minus that at the start of the trial, we calculated the variance as the sum of the variances at the start and end of the trial minus twice the covariance. Calculation of the covariance between the end of the trial and the start of the trial requires the correlations from individual patient data. Because these correlations were unavailable, we computed the correlation of the reported means, which ranged from 0.61 to 0.99, and used values over this interval to estimate the covariance for each outcome. We chose a correlation of 0.80 as our baseline value, although the pooled effect sizes did not substantially change when we varied the correlation over the range of 0.61 to 0.99.

We combined studies by using the DerSimonian and Laird inverse variance weighted method (random-effects model) and the Mantel–Haenszel method (fixed-effects model) (31, 32). We present the results from only the random-effects model because of statistical heterogeneity in some clinical outcomes. For body composition measures, we calculated separate summary effect sizes for the following: 1) studies of groups receiving GH versus studies of groups not receiving GH; 2) studies of GH plus lifestyle interventions versus studies of lifestyle interventions alone; 3) studies in which researchers administered GH for less than 26 weeks versus studies in which they administered GH for 26 weeks or more; and 4) study populations in which researchers evaluated only men versus studies evaluating only women. Because few studies have reported outcomes other than body composition measures, we calculated a single effect size for other clinical outcomes.

We evaluated the effects of study heterogeneity on our summary results. We sought sources of heterogeneity affecting body composition outcomes through subgroup analysis according to intervention type, length of study, and sex. We were interested in other key factors that affect body composition (for example, participant age and method of measuring body composition variables) and the sources of heterogeneity for other clinical outcomes. However, the paucity of reported results among the included studies limited our heterogeneity assessments. We calculated the I^2 statistic, which describes the heterogeneity among study results for each summary effect (31–33). We report those summary results for which the I^2 statistic was greater than 50% (reflecting substantial heterogeneity) (33). Finally, because of heterogeneous reporting of adverse events among included studies, a quantitative meta-analysis of these outcomes was not appropriate. Instead, we calculated the proportions of adverse events among study participants who received GH therapy and those who did not receive GH therapy in studies that reported or evaluated each adverse event.

We performed sensitivity analyses to evaluate the robustness of our results. We removed each study individually to evaluate that study's effect on the summary estimates. To evaluate whether changes to the correlation between reported means altered our results, we varied the correlation between 0.40 and 0.99. We assessed publication bias by constructing funnel plots comparing the treatment effect (x-axis) to sample size (y-axis) for each clinical outcome (34). We performed analyses by using Stata, version 9.1 (StataCorp, College Station, Texas), and Review Manager, version 4.2.8 (The Cochrane Collaboration, Oxford, United Kingdom).

Role of the Funding Sources

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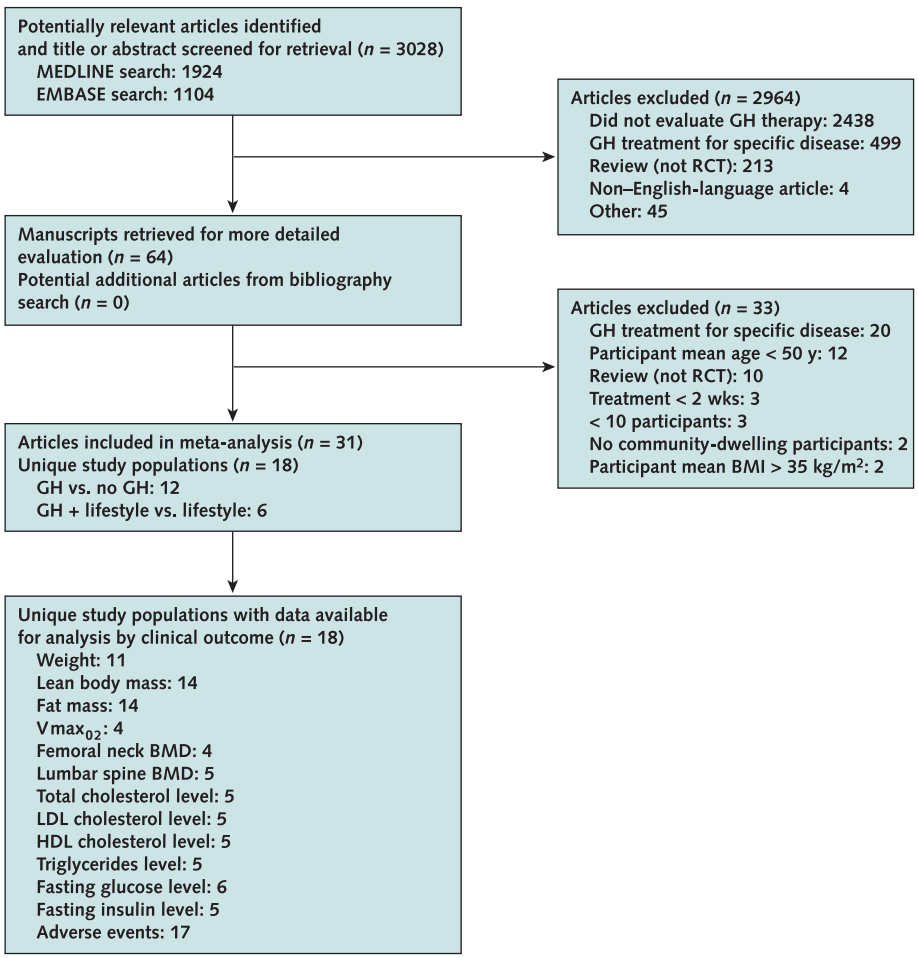
RESULTS

Figure 1 summarizes the results of our literature searches. We reviewed a total of 3028 titles from MEDLINE and EMBASE databases. We retrieved 64 articles for full-text evaluation and found no additional titles from our bibliographic search. Several articles were published on the same study population; therefore, 31 articles (1, 35–64) representing 18 unique study populations met our inclusion criteria. Twelve of these studies compared GH treatment with no GH treatment, and 6 studies compared GH plus lifestyle interventions with lifestyle interventions alone (**Table 1**). Every included study sample receiving GH treatment had a unique non–GH-treated control sample for comparison.

Study Participant Characteristics

Participants treated with and those not treated with GH were elderly (mean age, 68.7 years [SD, 5.4] vs. 68.9 years [SD, 6.1], respectively) and overweight (mean BMI,

Figure 1. **Study flow diagram.**



For excluded articles, the sums may be greater than the total numbers listed because some studies were excluded for several reasons. BMI = body mass index; BMD = bone mineral density. GH = growth hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized, controlled trial; $V\text{max}_{o2}$ = maximal rate of oxygen consumption.

27.8 kg/m^2 [SD, 2.2] vs. 27.5 kg/m^2 [SD, 2.2], respectively) (**Table 1**). They also had similar initial IGF-1 levels (mean IGF-1 level, 121 μg/L [SD, 15]vs. 125 μg/L [SD, 16], respectively). Women comprised 33% of participants at study enrollment.

Study Characteristics

No study fulfilled the evaluated quality criteria, although 2 studies fulfilled 7 of the 8 criteria (37–39, 42–44) (**Table 2**). Only 1 study (35) documented concealment of treatment allocation at study enrollment. The study by Rudman and colleagues (1, 47, 49) fulfilled only 3 of the 8 quality criteria. In particular, it did not offer a placebo, was not blinded, and did not perform an intention-to-treat analysis.

Most study sizes were small (mean study size per unique study population at enrollment, 28 participants), and some studies had high drop-out rates (**Table 1**). Two hundred twenty of 270 (82%) participants who received GH and 227 of 238 (95%) participants not receiving GH were followed until study completion. The 220 participants who received GH who completed the study represented a total of 107 person-years of GH treatment. In the largest study, which enrolled 68 participants, only 23 of the 50 (46%) participants receiving GH treatment completed the study (1, 47, 49).

Growth hormone interventions varied considerably among the included studies (**Table 1**). The initial daily dose of GH ranged from 1.7 to 43 μg per kg of body weight (mean, 14.3 μg/kg [SD, 7.3]), and final daily dose ranged from 1.7 to 25 μg/kg (mean, 11.2 μg/kg [SD, 5.3]). Serum IGF-1 levels increased an average of 88% in groups receiving GH versus 2% in groups not receiving GH. Growth hormone treatment duration ranged from 2 to 52 weeks (mean, 26.6 weeks [SD, 15.6]), and only 3 studies evaluated GH treatment for more than 26 weeks. Sample size and GH treatment duration were correlated

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

Study, Year (Reference)	Mean Age (SD), *y*		Women, %		Participants (Start of Trial/End of Trial), *n*		Mean BMI (SD), kg/m^2		IGF-1 (Start of Trial/End of Trial), *µg/L*		Study Intervention	
	GH	Control	GH	Control	GH	Control	GH	Control	GH	Control	GH Duration, *wk*	GH Initial Daily Dosage, *µg/kg* of body weight
GH-only studies												
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on women only)†	70 (4)	72 (5)	100	100	13/12	14/13	26 (3)	26 (3)	105/192	110/109	26	12.9
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on men only)†	71 (5)	70 (5)	0	0	17/16	17/17	27 (3)	27 (2)	146/244	131/138	26	12.9
Clemmesen et al., 1993 (48)	72 (3)	73 (2)	100	100	14/13	14/12	NA	NA	NA	NA	12	16.7
Franco et al., 2005 (64)	58 (NA)	57 (NA)	100	100	20/15	20/19	31 (3)	30 (4)	105/211	121/119	52	7.8
Hennessey et al., 2001 (41)	72 (5)	69 (3)	43	38	7/7	8/8	NA	NA	112/180	142/127	26	15.0
Holloway et al., 1994 (46)	65 (3)‡	69 (6)	100	100	10§/7	16/14	24 (2)‡	24 (3)	140/300‖	128/140‖	26	43.0
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	58 (NA)	58 (NA)	0	0	16/16	14/14	31 (NA)	31 (NA)	134/268	120/119	39	9.5
Jurgens et al., 2002 (35)	73 (NA)	75 (NA)	0	0	16/15	16/15	NA	NA	NA	NA	12	11.9
Lange et al., 2002 (36) and 2001 (40)¶	74 (6)	75 (3)	0	0	8/7	7/7	26 (NA)	27 (NA)	145/247	166/159	12	12.0
Papadakis et al., 1996 (45)	75 (4)	75 (4)	0	0	28/26	28/26	NA	NA	118/237	126/134	26	12.9
Rudman et al., 1990 (1) and 1991 (49)**; Cohn et al., 1993 (47)	69 (13)	69 (5)	0	0	50/23††	18/16††	27 (6)	27 (5)	0.25‡‡/NA	0.27‡‡/NA	52	12.9
Yuen et al., 2004 (63)¶	59 (3)§§	59 (3)§§	50	50	12/12	12/12	30 (6)§§	30 (6)§§	111/161	152/125	2	1.7
GH and lifestyle intervention studies												
Hennessey et al., 2001 (41)	70 (4)	74 (5)	25	38	8/8	8/8	NA	NA	128/189	109/110	26	15.0
Lange et al., 2002 (36); Hameed et al., (51) (data on men only)	73 (3)	75 (3)	0	0	8/8	8/8	28 (3)	27 (3)	123/219	138/140	12	12.0
Lange et al., 2001 (52) and 2002 (54) (data on women only)	75 (3)	75 (6)	100	100	NA/8	NA/8	28 (4)	24 (3)	139/303	143/152	12	12.0
Taafe et al., 1996 (57), 1994 (60), and 1994 (61)	70 (4)	70 (4)	0	0	13/10‖‖	8/8‖‖	26 (4)	27 (3)	114/218	97/119	10	20.0
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	70 (7)	67 (4)	100	100	9/9	7/7	31 (2)	31 (3)	94/170	96/93	12	25.0
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)¶¶	67 (3)	66 (2)	0	0	13/8	15/15	24 (NA)	26 (NA)	104/238***	125/117	16	24.0

* References are in alphabetical order. GH-only studies evaluated participants treated with GH vs. those not treated with GH. GH and lifestyle intervention studies evaluated participants receiving GH and lifestyle intervention (exercise with or without diet) vs. those receiving a lifestyle intervention alone. BMI = body mass index; GH = growth hormone; IGF-1 = insulin-like growth factor-1; NA = not available or unclear.
† Data from reference 37.
‡ Aggregate no estrogen and estrogen treatment groups.
§ Assumed 10 for no estrogen group.
‖ Estimated from graph.
¶ Includes data received from author.
** Baseline data from reference 47.
†† Start value at randomization.
‡‡ Values reported as U/mL.
§§ Aggregate GH and control.
‖‖ Data from reference 60.
¶¶ Data from reference 59.
*** Data from reference 58.

($r = 0.64$; $P = 0.004$), reflecting that many of the shortest studies were also the smallest.

All 6 studies that incorporated lifestyle interventions included an exercise program with at least 3 sessions per week (**Table 1**). Five studies incorporated resistance training as part of their exercise protocols (36, 41, 51, 53,

Table 2. **Study Quality***

Study, Year (Reference)	Did Participants Treated with GH and Those Not Treated with GH Have Similar Baseline Characteristics?	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?
GH only								
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39)	●	●	NA	●	●	●	●	●
Clemmesen et al., 1993 (48)	⊙	●	NA	●	●	●	⊙	○
Franco et al., 2005 (64)	●	●	NA	●	●	●	●	⊙
Hennessey et al., 2001 (41)	⊙	●	NA	NA	●	●	⊙	NA
Holloway et al., 1994 (46)	⊙	●	NA	●	●	●	●	○
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	●	●	NA	●	●	●	●	●
Jurgens et al., 2002 (35)	⊙	●	●	●	●	●	⊙	○
Lange et al., 2002 (36) and 2001 (40)	●	●	NA	●	●	●	●	○
Papadakis et al., 1996 (45)	⊙	●	NA	●	●	●	●	○
Rudman et al., 1990 (1) and 1991 (49); Cohn et al., 1993 (47)	●	○	NA	●	○	○	●	○
Yuen et al., 2004 (63)	●	●	Not applicable	⊙	●	●	●	●
GH and lifestyle intervention								
Hennessey et al., 2001 (41)	⊙	●	NA	NA	●	●	⊙	NA
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	⊙	●	NA	●	●	●	●	○
Lange et al., 2001 (52) and 2002 (54) (data on men only)	●	●	NA	●	●	●	●	○
Taafe et al., 1996 (57), 1994 (60), and 1994 (61)	●	●	NA	●	●	●	●	○
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	●	●	NA	●	●	●	●	○
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)	⊙	●	NA	●	●	●	●	○

* References are in alphabetical order. GH-only studies evaluated participants treated with GH vs. those not treated with GH. Growth hormone and lifestyle intervention studies evaluated participants receiving GH and lifestyle intervention (exercise with or without diet) vs. those receiving a lifestyle intervention alone. ○ = quality parameter not fulfilled; ⊙ = quality parameter partially fulfilled; ● = quality parameter fulfilled. GH = growth hormone; NA = not available or unclear.

55–61), and 1 study also incorporated a concurrent low-calorie, low-fat diet regimen (53, 55).

Quantitative Data Synthesis

Most studies provided data on body composition measures; however, few studies reported exercise capacity, bone dynamics, serum lipid values, and glucose metabolism outcomes (**Appendix Table 2**, available at www.annals.org). Lack of published data precluded us from calculating summary results for other clinical outcomes. Adverse events were reported in 17 of the 18 included studies (**Appendix Table 2**, available at www.annals.org).

Efficacy of Growth Hormone

Weight loss did not differ between participants who received GH and those not receiving GH. However, participants who received GH decreased their fat mass (change in fat mass, −2.08 kg [95% CI, −2.80 to − 1.35 kg]) and increased their lean body mass (change in lean body mass, 2.13 kg [CI, 1.32 to 2.94 kg]) compared with those not receiving GH (**Table 3**).

We found no significant differences in body composition outcomes between participants who received GH with a lifestyle intervention and those who did not (**Table 3**; **Appendix Figures 1 to 3**, and **Appendix Table 4**, available at www.annals.org). Only 1 of the included studies (36, 40, 51) was specifically designed to evaluate the independent effects of GH therapy and exercise. In that study of 22 participants who were followed for 12 weeks, participants treated with GH had a significant 2.2-kg increase in lean body mass compared with participants who received exercise therapy. Decrease in fat mass, however, did not differ between groups.

We found no significant differences in body composition outcomes between studies that administered GH for 26 weeks and those that administered GH for less than 26 weeks (**Table 3**). These results did not change when we analyzed only studies that provided GH therapy for at least 12 or 26 weeks (**Appendix Table 3**, available at www.annals.org).

Compared with men treated with GH, women treated

Table 3. **Summary Effect Sizes by Clinical Outcome***

Clinical Outcome†	Study Populations, *n*	Weighted Mean Difference (95% CI)‡	Comparison between Subgroups (*P* Value)§
Weight			
All study populations	11	0.06 kg (−0.70 to 0.83)	NA
Intervention evaluated			
GH only‖	6	−0.39 kg (−1.33 to 0.56)	0.12
GH and lifestyle intervention¶	5	0.89 kg (−0.40 to 2.17)	
Length of GH administration			
<26 weeks	7	0.21 kg (−0.60 to 1.03)	0.32
≥26 weeks	4	−0.98 kg (−3.14 to 1.18)	
Sex**			
Male	6	0.40 kg (−0.60 to 1.40)	0.32
Female	5	−0.40 kg (−1.57 to 0.78)	
Fat mass			
All study populations	14	−2.08 kg (−2.80 to −1.35)	NA
Intervention evaluated			
GH only‖	9	−2.34 kg (−3.22 to −1.45)	0.37
GH and lifestyle intervention¶	5	−1.55 kg (−2.82 to −0.27)	
Length of GH administration			
<26 weeks	7	−1.86 kg (−2.86 to −0.85)	0.57
≥26 weeks	7	−2.32 kg (−3.37 to −1.27)	
Sex**			
Male	8	−2.27 kg (−3.11 to −1.43)	0.37
Female	5	−1.55 kg (−3.03 to −0.07)	
Lean body mass			
All study populations	14	2.13 kg (1.32 to 2.94)	NA
Intervention evaluated			
GH only‖††	9	1.66 kg (0.44 to 2.88)	0.32
GH and lifestyle intervention¶	5	2.78 kg (1.85 to 3.70)	0.32
Length of GH administration			
<26 weeks	7	2.62 kg (1.90 to 3.35)	0.35
≥26 weeks††	7	1.64 kg (0.17 to 3.10)	
Sex**			
Male	8	2.62 kg (1.92 to 3.32)	0.13
Female††	5	1.39 kg (−0.39 to 3.17)	0.13
$Vmax_{o2}$	4	0.32 mL/min per kg (−1.19 to 1.84)	NA
Femoral neck BMD††	4	0.03 g/m^2 (−0.07 to 0.13)	NA
Lumbar spine BMD	5	0.00 g/m^2 (−0.04 to 0.03)	NA
Total cholesterol level	5	−0.29 mmol/L (−0.49 to −0.08)‡‡	NA
LDL cholesterol level	5	−0.12 mmol/L (−0.29 to 0.05)	NA
HDL cholesterol level	5	−0.01 mmol/L (−0.08 to 0.06)	NA
Triglycerides level††	5	−0.27 mmol/L (−0.59 to 0.04)	NA
Fasting glucose level††	6	−0.03 mmol/L (−0.28 to 0.21)	NA
Fasting insulin level††	5	3.27 pmol/L (−9.55 to 16.09)	NA

* GH-only studies evaluated participants treated with GH vs. those not treated with GH. Growth hormone and lifestyle intervention studies evaluated participants receiving GH and lifestyle intervention (exercise with or without diet) vs. those receiving a lifestyle intervention alone. To convert cholesterol values to mg/dL, divide by 0.02586. To convert triglyceride values to mg/dL, divide by 0.01129. To convert fasting glucose levels to mg/dL, divide by 0.05551. BMD = bone mineral density; GH = growth hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not available. $Vmax_{o2}$ = maximal oxygen consumption.

† For clinical outcomes other than weight, fat mass, and lean body mass, a single summary effect size is presented because of the small number of populations available for analysis. See Methods section for additional details.

‡ The weighted mean difference (groups treated with GH − groups not treated with GH) provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the increase in the weighted mean for groups treated with GH was greater than that of the groups not treated with GH. For example, a value of +2.0 kg indicates that the group treated with GH gained 2 kg compared with the group not treated with GH.

§ Comparison between those treated with and without lifestyle interventions, studies administering GH for < 26 wk and studies administering GH ≥26 wk, or all-male and all-female studies.

‖ Includes studies that did not use lifestyle intervention and compared GH treatment with no GH treatment.

¶ Includes studies that used lifestyle intervention and compared GH treatment with no GH treatment.

** Includes studies with all-male or all-female populations only; as such, sum of male and female study populations may not add up to all study populations.

†† Indicates I^2 statistic >50%.

‡‡ $P > 0.05$ after adjustment for change in fat mass.

with GH received higher initial daily doses (mean, 17.5 μg/kg [SD, 11.2] vs. 13.8 μg/kg [SD, 3.7], respectively) and final daily dosages of GH (mean, 12.8 μg/kg [SD, 6.9] vs. 11.9 μg/kg [SD, 3.2], respectively). However, women's body composition improvements were not as robust as those of men treated with GH. Women treated with GH did not significantly increase their lean body mass compared with women not treated with GH, and the decrease in fat mass among women treated with GH was only borderline statistically significant (**Table 3**). In contrast, men treated with GH had significant improvements in lean body mass and fat mass.

Total cholesterol levels decreased by 0.29 mmol/L (CI, −0.49 to −0.08 mmol/L) among participants treated with

Table 4. **Adverse Event Proportions in Participants Treated with Growth Hormone versus Those Not Treated with Growth Hormone***

Adverse Event	Studies, *n*	GH-Treated Participants		Non–GH-Treated Participants	
		Mean Proportion (Range), %†	Participants, *n*	Mean Proportion (Range), %†	Participants, *n*
Soft tissue edema‡	15	50 (23–89)	194	8 (0–25)	194
Carpal tunnel syndrome‡	16	19 (0–50)	244	1 (0–7)	212
Arthralgias‡	14	21 (0–50)	181	5 (0–25)	186
Gynecomastia§	3	6 (0–12)	95	0 (0–0)	63
New IFG, IGT, or DM	4	22 (6–53)	100	14 (0–25)	69
New DM	4	5 (0–12)	100	1 (0–5)	69

* DM = diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.
† Mean proportion weighted by study size.
‡ $P < 0.001$ for comparison between groups.
§ $P < 0.05$ for comparison between groups.

GH compared with those not treated with GH (**Table 3**); however, this decrease was not statistically significant after adjustment for decrease in fat mass. We found no significant differences in any other outcomes, including low-density lipoprotein or high-density lipoprotein cholesterol levels, triglyceride levels, maximal rate of oxygen consumption, femoral neck or lumbar spine bone density, or fasting glucose or fasting insulin levels.

We found little statistical heterogeneity among the included studies for the body composition measures of weight and fat mass. However, for lean body mass, the I^2 statistic for the summary result evaluating included studies was 41%. In subgroup analysis of this outcome, we found that statistical heterogeneity was elevated (I^2 statistic > 50%), particularly in studies that evaluated women, provided GH therapy alone without lifestyle intervention, or supplied GH therapy for 26 weeks or more (**Table 3**). Conversely, studies that evaluated men, provided GH therapy with concurrent lifestyle intervention, or provided GH therapy for fewer than 26 weeks had minimal or no statistical heterogeneity. The I^2 statistic was greater than 50% for femoral neck bone density and for triglyceride, fasting glucose, and fasting insulin levels (**Table 3**). Other outcomes showed little statistical heterogeneity.

Safety of Growth Hormone

Participants treated with GH experienced adverse events at significantly higher rates than those not treated with GH (**Table 4**). Twenty-seven percent of patients treated with GH required a dose decrease. Participants who received GH experienced higher rates of soft tissue edema, carpal tunnel syndrome, arthralgias, and gynecomastia than those not receiving GH. Soft tissue edema was a particularly common adverse event among participants treated with GH, with a range of reported edema of 23% to 89% compared with 0% to 25% among participants not treated with GH (**Table 4**). Women receiving GH were more likely to experience edema than men receiving GH (**Table 5**). However, rates of edema were not significantly greater among participants who received an initial daily dose of GH more than 20 μg/kg compared with those receiving

Table 5. **Proportion of Patients Experiencing Soft Tissue Edema***

Subgroup	Studies, *n*	GH-Treated Participants		Non–GH-Treated Participants	
		Mean Proportion (Range), %†	Participants, *n*	Mean Proportion (Range), %†	Participants, *n*
Sex‡					
Male	8	47 (23–75)	119	13 (0–25)	113
Female	5	61 (38–89)	60	2 (0–14)	65
Initial daily GH dosage					
> 0.02 mg	3	52 (23–89)	32	3 (0–14)	38
≤ 0.02 mg	12	49 (25–75)	162	10 (0–25)	156
Age					
>70 y	7	56 (25–75)	89	11 (0–25)	89
≤70 y	8	45 (23–89)	105	6 (0–21)	105

* Comparison for subgroups stratified by GH dosage or age are not significant. GH = growth hormone.
† Mean proportion is weighted by study size.
‡ $P < 0.001$ for comparison between difference in proportion between men and women.

lower dosages or among participants older than 70 years of age compared with those younger than 70 years of age.

Studies evaluating glucose metabolism–related adverse events (for example, new impaired fasting glucose levels, impaired glucose tolerance, or onset of diabetes mellitus) reported higher (albeit, not statistically significant) rates of these events in participants treated with GH compared with those not treated with GH. We could not evaluate differences in proportions among subgroups in glucose metabolism–related adverse events because of the small number of studies that reported this outcome.

No deaths or increased cancer rates directly attributable to GH use were reported, although the studies included were probably too short in duration to find these events, and no trial explicitly evaluated these outcomes.

Sensitivity Analysis

To evaluate the robustness of our results, we performed sensitivity analyses. First, we recalculated summary effect sizes after removing each study per iteration. From this analysis, the following outcomes no longer significantly differed between participants treated with GH and those not treated with GH: lean body mass in participants given GH for 26 or more weeks (3 of 7 studies) (1, 37–39, 45, 47, 49); fat mass in lifestyle intervention–treated participants (1 of 5 studies) (36, 51); fat mass in studies of women (3 of 5 studies) (37–39, 52, 54); and total cholesterol levels (1 of 5 studies) (42–44). Removing 1 study that used lifestyle intervention (36, 51) resulted in a marginally significant increase in body weight (change in weight, 1.8 kg [CI, 0.1 to 3.6 kg]) in this group of 5 studies. The results of other clinical outcomes remained robust to this analysis. Second, we varied the correlation between reported means. Assuming a correlation of 0.4 between the reported means resulted in a nonsignificant difference in total cholesterol outcomes between groups treated with GH and those not treated with GH. Results for other clinical outcomes did not change. Finally, our search strategies identified 4 non–English-language citations that we could not exclude on the basis of their title or abstract (65–68). Our summary findings on lean body mass and fat mass, for which we found no significant changes, would not differ even if each of these non–English-language studies enrolled 200 participants, which is more than any of the included studies.

Our assessment for publication bias through visual inspection of funnel plots suggested that systematic underreporting of studies with nonsignificant results did not occur, although our analysis was limited by the few studies reporting some of the outcomes. Nonetheless, our results would be strengthened only if publication bias existed and studies with negative results had not been published.

DISCUSSION

Use of GH as an antiaging therapy is widespread (2) and has been advocated in the lay press (4–7) and in scientific literature (18, 19, 25, 69). Our analysis shows that this practice is not supported by a robust evidence base, offers little clinical benefit to the healthy elderly, and is associated with high rates of adverse events.

The cumulative literature published on randomized, controlled trials evaluating GH in the healthy elderly is limited to 220 participants representing 107 person-years of total clinical evaluation from trials of variable quality. In particular, the 1990 study by Rudman and colleagues (1), which suggested that GH therapy could reverse decades of age-related changes and which is widely quoted by antiaging organizations (26, 70) and Internet GH purveyors (71–73), fulfilled only 3 out of 8 of our quality criteria, the fewest of the studies included for analysis. Moreover, their initially positive results were from a 6-month study of just 21 men (1). Only later, when GH was given for a year in a larger cohort, did high rates of adverse events and modest clinical benefit become evident (47).

Although GH therapy has been shown to improve clinical outcomes (20–22) and possibly decrease death (23) in longitudinal studies of adults who are GH-deficient, we find little evidence of clinical benefit of GH therapy in the healthy elderly. Although GH-induced body composition changes in the healthy elderly are similar to those reported in individuals who are GH-deficient (74), we find no evidence that GH replacement in the healthy elderly improves other clinically important outcomes, such as maximal oxygen consumption, bone mineral density, lipid levels, and fasting glucose and insulin levels. Many studies did not appear to adequately conceal treatment allocation; thus, improvements in body composition may be overestimated because of selection bias (75–77). Furthermore, some of the increase from GH in lean body mass may be due to fluid retention because methods evaluating lean body mass have difficulty differentiating lean solid tissue from fluid mass (78). This fluid retention may be transient (79, 80) and may account for the smaller, however not significant, difference in lean body mass seen in long-term studies compared with short-term studies. Although GH use may decrease total cholesterol levels minimally, this effect did not remain robust in sensitivity analysis and may be related to changes in body composition (81, 82) rather than to an intrinsic effect on cholesterol metabolism.

We did not find any significant differences in body composition outcomes between participants treated with GH who received a lifestyle intervention and those who did not. It is difficult to draw definitive conclusions from our analysis of the single study by Lange and colleagues (36, 40, 51), which was the only study to directly compare GH therapy alone with lifestyle interventions alone, given the small size of the study and its relatively short duration. However, their findings highlight the important need for additional research to evaluate the differential effects of exercise and GH on body composition measures.

Consistent with studies in GH-deficient populations (74, 83), we found significantly higher proportions of soft tissue edema and joint pain in participants treated with

GH than in those not treated with GH. Adverse events related to fluid retention have been well described in patients treated with GH (84, 85) and are thought to be due the effect of GH on fluid homeostasis. Although participants treated with GH tended to have higher proportions of new impaired fasting glucose levels or diabetes mellitus, this finding was nonsignificant. The effect of GH on glucose dynamics may be dose-related (63), although we did not detect a dose-related effect, possibly due to the small number of studies that evaluated these adverse events. We did not detect an association between GH dose or age and edema, as has been noted in studies of patients who are GH-deficient (86–88), although this may also be due to the small number of included studies. Because no studies lasted longer than 1 year and no study specifically evaluated cancer outcomes, we could not evaluate the effect of GH therapy on cancer risk and overall death. No evidence that we reviewed suggested that GH prolongs life.

We found that women may respond to GH therapy differently from men. Despite higher doses of GH per kilogram of body weight, women treated with GH did not increase lean body mass and achieved only borderline significant decreases in fat mass, whereas men treated with GH had significant improvements in both of these outcomes. In a similar manner, Ezzat and colleagues (74) evaluated 150 GH-deficient patients and found that increases in lean body mass and decreases in fat mass were significantly greater in men than in women (74). Women may require higher doses of GH for longer periods than men to achieve physiologic replacement levels (89). We also found that women experienced more soft tissue edema than men, although this finding may be confounded by the higher GH doses per kilogram of body weight prescribed to women. Kehely and colleagues (83) found similar adverse events rates between men and women; however, men had higher rates of supraphysiologic IGF-1 levels. Taken together, these findings suggest that men and women respond to GH differently in terms of body composition and adverse events, and further research is needed to fully explore the risks and benefits of GH therapy based on sex.

Our study reflects the limitations of the included published studies. First, studies reported only a subset of important clinical outcomes. For example, key functional outcomes, such as time to perform an activity (for example, walk a flight of stairs), psychosocial outcomes (for example, improvement in quality of life), and other clinical outcomes (for example, change in subcutaneous and central adiposity) were infrequently or heterogeneously measured and could not be synthesized. Second, given the few participants and small number of studies available for investigation, the studies we investigated and our analysis may be underpowered to detect differences in clinical outcomes and adverse events. Third, methods used to collect clinical outcomes and adverse events were heterogeneous, which may limit our ability to detect differences in outcomes or adverse events. Because of the small number of studies and incomplete reporting, we could not fully assess the effect of this heterogeneity on our results. Finally, we estimated the standard deviation of the change in treatment values at the start of the trial and at the end of the trial by using an aggregated correlation factor for studies that did not report this value. Our estimates, however, did not substantially change when we altered our assumptions over a wide range of possible values.

Although GH has been widely publicized as an antiaging therapy and initial studies suggested that it might be clinically beneficial and safe in the healthy elderly, we find little evidence to support these claims. The scant clinical experience of GH in the healthy elderly suggests that although GH may minimally alter body composition, it does not improve other clinically relevant outcomes. Substantial evidence suggests that GH use in the healthy elderly is associated with high rates of adverse events. On the basis of available evidence, GH cannot be recommended for use among the healthy elderly.

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Appendix Table 1. **Search Strategy**

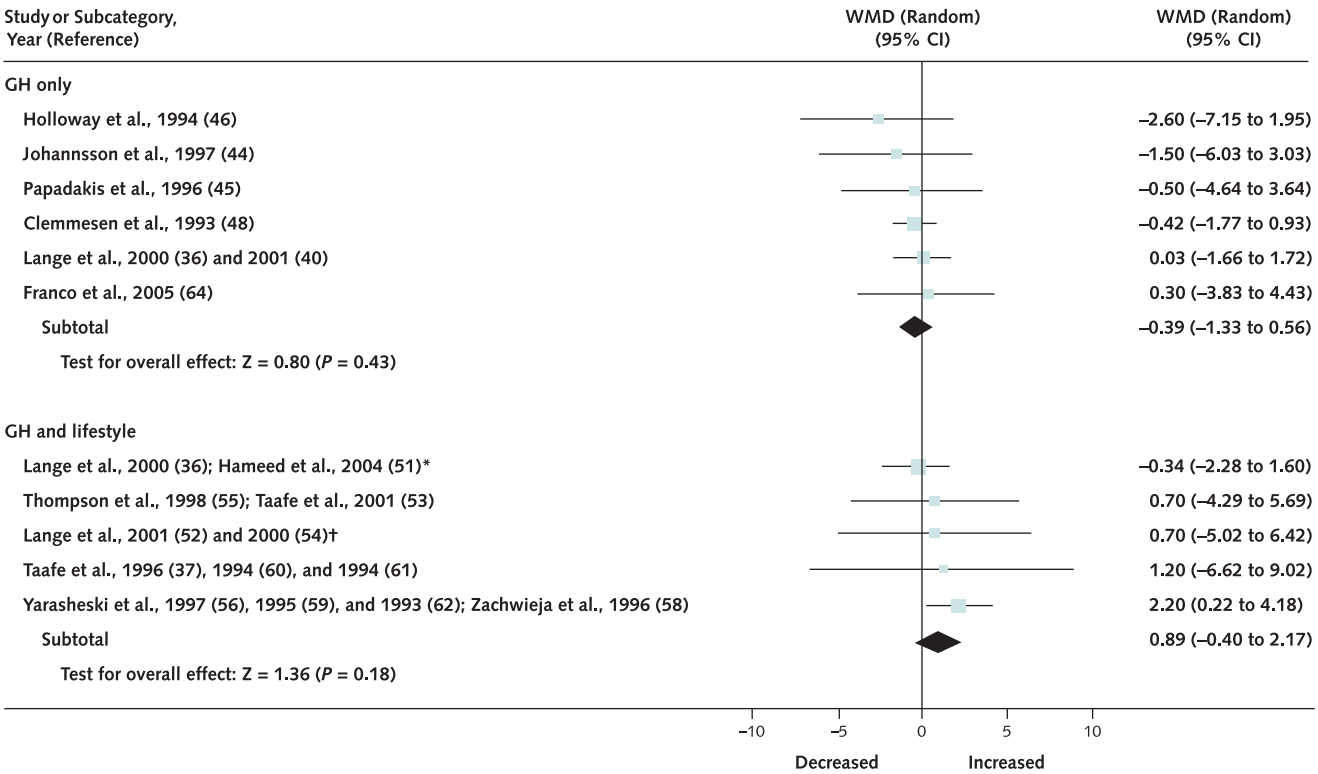
Subsearch Number	Search Terms	Articles Returned, *n*
MEDLINE		
#1	Search growth hormone* [tw] OR growth hormone [mh]	51 673
#2	Search aging	170 193
#3	Search "middle aged"[mh] OR "aged"[mh]	2 449 218
#4	Search (randomized controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] 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])	529 465
#5	Search #1 and #4 and #3	1478
#6	Search #1 and #2 and #3	567
	Total Medline: Search #5 or #6	**1924**
EMBASE		
S1	randomi?(W)controlled(W)trial? OR DT=randomized controlled trial	357 312
S2	random?(W)aloc? OR random allocation! OR double(W)blind? OR single(W)blind?	258 582
S3	trip?(W)blind? OR clinical trials! OR clinical trial! OR DT=clinical trial	892 091
S4	controlled(W)clinical(W)trial? OR controlled study!	2 082 055
S5	S1 OR S2 OR S3 OR S4	2 838 116
S6	growth hormone! OR human growth hormone! OR growth hormone?	85 263
S7	aged! OR middle aged/DE	3 250 048
S8	S5 AND S6 AND S7	2673
S9	S8/human	2371
S10	Remove duplicates	2089
	EMBASE algorithm to remove Medline duplicates – RCT search	869
S11	AGING!	198 212
S12	S6 AND S7 AND S11	767
S13	Remove duplicates	676
S14	S13/HUMAN	652
	EMBASE algorithm to remove Medline duplicates – Aging search	235
	Total EMBASE	**1104**

Appendix Table 2. Key Clinical Outcomes Available for Analysis*

Study, Year (Reference)	Body Composition			Exercise Capacity	Bone Dynamics		Cardiovascular Markers				Insulin Dynamics		
	Weight	Lean Body Mass†	Fat Mass	$Vmax_{o2}$	Femoral Neck BMD‡	Lumbar Spine BMD	Total Cholesterol Level	LDL Cholesterol Level	HDL Cholesterol Level	Triglyceride Level	Fasting Glucose Level	Fasting Insulin Level	Adverse Events Reported
GH-only studies													
Blackman, Christmas, Munzer (data on women only), (37–39)		√	√	√	√	√							√
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on men only)		√	√	√									√
Clemmesen et al., 1993 (48)	√				√	√							√§
Franco et al., 2005 (64)	√	√	√				√	√	√	√	√	√	√
Hennessey et al., 2001 (41)													√
Holloway et al., 1994 (46)	√	√	√		√	√	√	√	√	√			√
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	√	√	√				√	√	√	√	√	√	√
Jurgens et al., 2002 (35)													√
Lange et al., 2002 (36) and 2001 (40)	√	√	√										√
Papadakis et al., 1996 (45)‖	√	√	√				√	√	√	√	√		√
Rudman et al., 1990 (1) and 1991 (49); Cohn et al., 1993 (47)		√	√			√							√
Yuen et al., 2004 (63)		√	√								√	√	
GH and lifestyle intervention studies													
Hennessey et al., 2001 (41)													√
Lange et al., 2001 (52) and 2002 (54) (data on women only)	√	√	√	√							√	√	√
Lange et al., 2002 (36); Hameed et al., (51) (data on men only)	√	√	√										√
Taafe et al., 1996 (57), 1994 (60), and 1994 (61)	√	√	√										√
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	√	√	√	√			√	√	√	√			√
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)	√	√	√		√	√					√	√	√

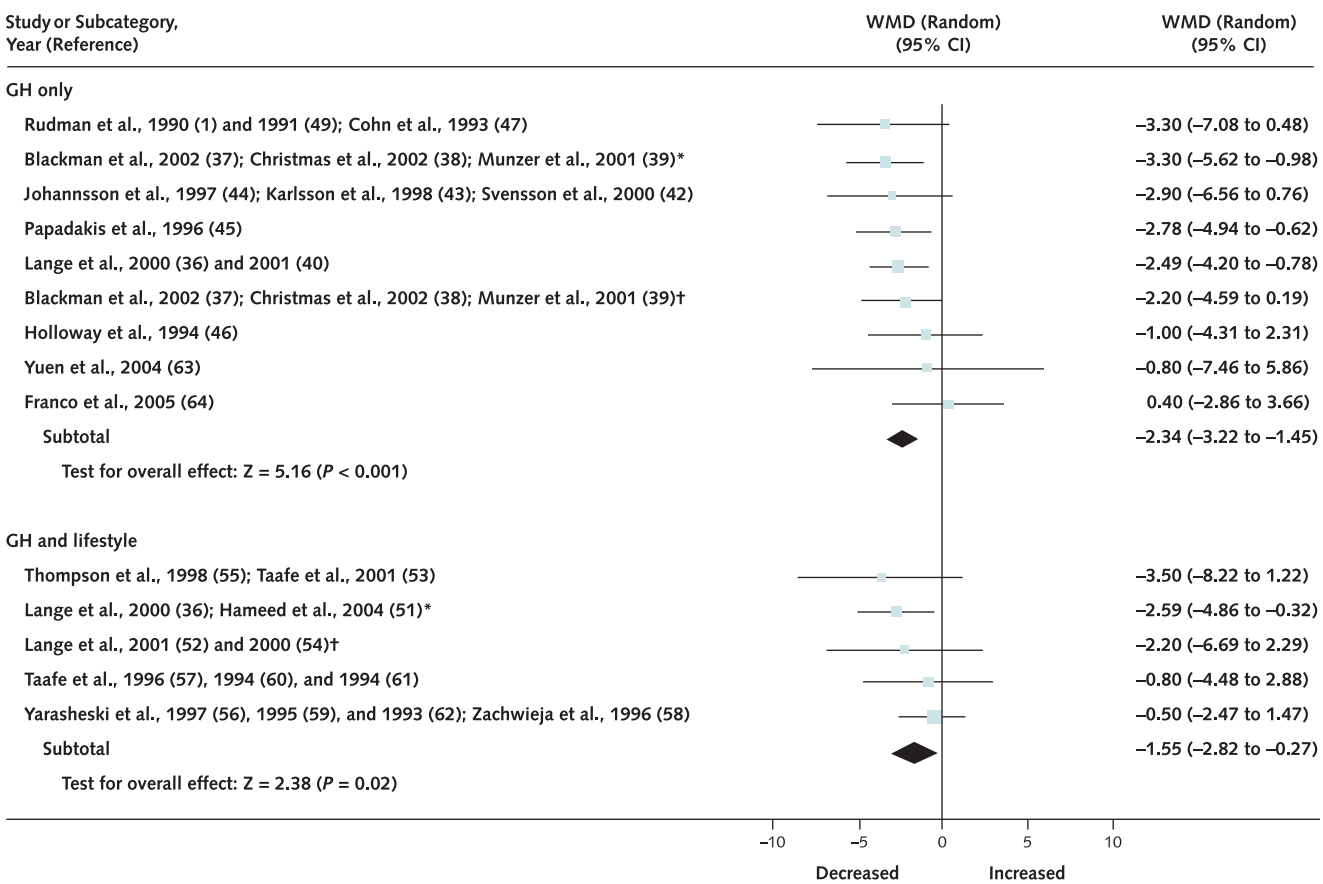
* Check mark (√) indicates data available for and included in analysis. References are in alphabetical order. GH-only studies evaluated participants treated with GH vs. those not treated with GH. Growth hormone and lifestyle intervention studies evaluated participants receiving GH and lifestyle intervention (exercise with or without diet) vs. those receiving a lifestyle intervention alone. BMD = bone mineral density; HDL = high-density lipoprotein; LDL = low-density lipoprotein; $Vmax_{o2}$ = maximal oxygen consumption.
† Includes terms lean body mass or fat-free mass.
‡ Data from total femur or proximal femur.
§ Adverse events were noted but not broken out.
‖ Standard deviation of end value not presented, assumed to be equal to start value.

Appendix Figure 1. **Meta-analysis results: change in weight.**



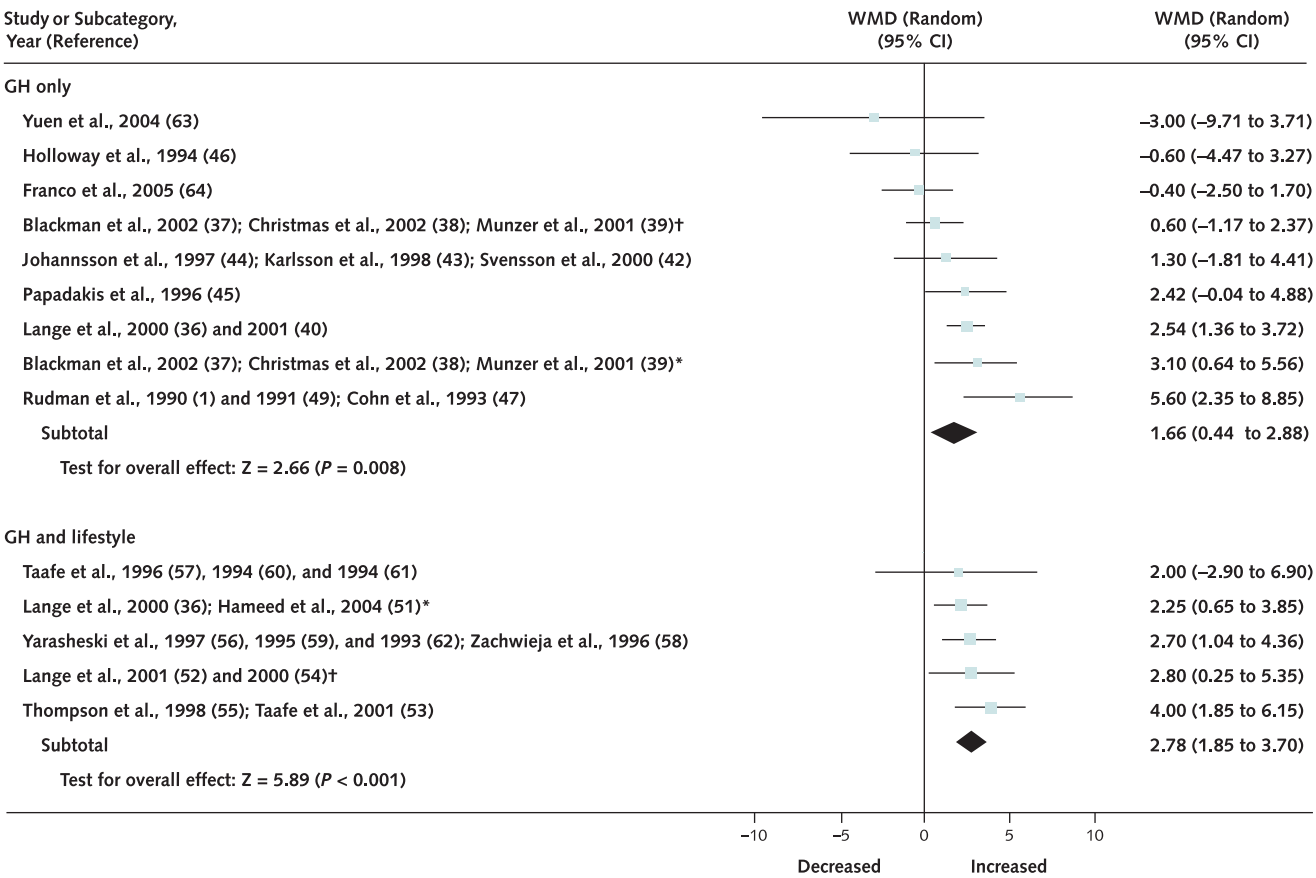
We evaluated the incremental gain or loss (in kg) of weight between participants treated with growth hormone (GH) vs. those not treated with GH in studies that treated patients with GH only (summary effect size, *upper diamond*) or GH and a lifestyle intervention (summary effect size, *lower diamond*). The studies are ordered by mean effect size. See Methods section for further details. The weighted mean difference (WMD) (groups treated with GH − groups not treated with GH) provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the increase in the weighted mean for groups treated with GH was greater than that of the groups not treated with GH. For example, a value of +2.0 kg indicates that the group treated with GH gained 2 kg compared with the group not treated with GH. * = data on men only; † = data on women only.

Appendix Figure 2. **Meta-analysis results: change in fat mass.**



We evaluated the incremental gain or loss (in kg) of fat mass between participants treated with growth hormone (GH) vs. those not treated with GH in studies that treated patients with GH only (summary effect size, *upper diamond*) or GH and a lifestyle intervention (summary effect size, *lower diamond*). The studies are ordered by mean effect size. See Methods section for further details. The weighted mean difference (WMD) (groups treated with GH − groups not treated with GH) provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the increase in the weighted mean for groups treated with GH was greater than that of the groups not treated with GH. For example, a value of +2.0 kg indicates that the group treated with GH gained 2 kg compared with the group not treated with GH. * = data on men only; † = data on women only.

Appendix Figure 3. **Meta-analysis results: change in lean body mass.**



We evaluated the incremental gain or loss of lean body mass (in kg) between participants treated with growth hormone (GH) vs. those not treated with GH in studies that treated patients with GH only (summary effect size, *upper diamond*) or GH and a lifestyle intervention (summary effect size, *lower diamond*). The studies are ordered by mean effect size. See Methods section for further details. The weighted mean difference (WMD) (groups treated with GH − groups not treated with GH) provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the increase in the weighted mean for groups treated with GH was greater than that of the groups not treated with GH. For example, a value of +2.0 kg indicates that the group treated with GH gained 2 kg compared with the group not treated with GH. * = data on men only; † = data on women only.

Appendix Table 3. **Summary Effect Sizes by Duration of Growth Hormone Therapy***

Clinical Outcome	GH Treatment Duration			
	≥12 wk		≥26 wk	
	Study Populations, *n*	Weighted Mean Difference (95% CI)†	Study Populations, *n*	Weighted Mean Difference (95% CI)†
Weight	10	0.05 kg (−0.71 to 0.82)	4	−0.98 kg (−3.14 to 1.18)
Fat mass	12	−2.15 kg (−2.89 to −1.40)	7	−2.32 kg (−3.37 to −1.27)
Lean body mass	12	2.21 kg (1.38 to 3.03)	7	1.64 kg (0.17 to 3.10)
$Vmax_{o2}$	4	0.32 mL/min per kg of body weight (−1.19 to 1.84)	2	1.64 mL/min per kg of body weight (−0.08 to 3.37)
Femoral neck BMD	4	0.03 g/m^2 (−0.07 to 0.13)	2	0.07 g/m^2 (−0.10 to 0.23)
Lumbar spine BMD	5	0.00 g/m^2 (−0.04 to 0.03)	3	−0.01 g/m^2 (−0.06 to 0.05)
Total cholesterol level	5	−0.29 mmol/L (−0.49 to −0.08)	4	−0.29 mmol/L (−0.53 to −0.04)
LDL cholesterol level	5	−0.12 mmol/L (−0.29 to 0.05)	4	−0.12 mmol/L (−0.30 to 0.06)
HDL cholesterol level	5	−0.01 mmol/L (−0.08 to 0.06)	4	0.02 mmol/L (−0.04 to 0.08)
Triglyceride level	5	−0.27 mmol/L (−0.59 to 0.04)	4	−0.33 mmol/L (−0.70 to 0.03)
Fasting glucose level	5	0.00 mmol/L (−0.26 to 0.27)	3	0.08 mmol/L (−0.06 to 0.23)
Fasting insulin level	4	0.76 pmol/L (−13.38 to 14.90)	2	−1.63 pmol/L (−49.63 to 46.36)

* To convert cholesterol values to mg/dL, divide by 0.02586. To convert triglyceride values to mg/dL, divide by 0.01129. To convert fasting glucose levels to mg/dL, divide by 0.05551. BMD = bone mineral density; HDL = high-density lipoprotein; LDL = low-density lipoprotein; $Vmax_{o2}$ = maximal oxygen consumption.
† The weighted mean difference (groups treated with GH − groups not treated with GH) provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the increase in the weighted mean for groups treated with GH was greater than that of the groups not treated with GH. For example, a value of +2.0 kg indicates that the group treated with GH gained 2 kg compared with the group not treated with GH.

Appendix Table 4. Change in Body Composition Outcomes from Study Data*

Study, Year (Reference) by Variable and Intervention	Treatment Group		Control Group	
	Participants, *n*	Mean change (SD), *kg*	Participants, *n*	Mean change (SD), *kg*
Weight				
GH only				
Clemmesen et al., 1993 (48)	13	−0.3 (1.6)	12	0.1 (1.9)
Franco et al., 2005 (64)	15	1.2 (6.0)	19	0.9 (6.2)
Holloway et al., 1994 (46)	7	−1.9 (4.9)	14	0.7 (5.2)
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	16	−1.0 (6.4)	14	0.5 (6.3)
Lange et al., 2002 (36) and 2001 (40)	7	0.2 (1.3)	7	0.2 (1.9)
Papadakis et al., 1996 (45)†	26	0.5 (8.7)	26	1.0 (6.4)
GH and lifestyle intervention				
Lange et al., 2001 (52) and 2002 (54) (data on men only)	8	0.3 (6.5)	8	−0.4 (5.0)
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	8	−0.6 (2.7)	8	−0.3 (0.9)
Taafe et al., 1996 (57), 1994 (60), and 1994 (61)	10	0.6 (8.9)	8	−0.6 (8.0)
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	7	−3.0 (4.8)	7	−3.7 (4.8)
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)	8	2.2 (2.5)	15	0.0 (1.9)
Fat mass				
GH only				
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on women only)	13	−2.5 (3.3)	14	−0.3 (3.0)
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on men only)	17	−3.3 (3.7)	17	0.0 (3.2)
Franco et al., 2005 (64)	20	1.4 (5.5)	20	1.0 (5.0)
Holloway et al., 1994 (46)	7	−1.5 (3.0)	14	−0.5 (4.6)
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	16	−3.0 (4.7)	14	−0.1 (5.4)
Lange et al., 2002 (36) and 2001 (40)	7	−2.3 (1.4)	7	0.2 (1.8)
Papadakis et al., 1996 (45)†	26	−2.8 (4.2)	26	−0.1 (3.7)
Rudman et al., 1990 (1) and 1991 (49); Cohn et al., 1993 (47)	19	−3.4 (5.7)	12	−0.1 (4.9)
Yuen et al., 2004 (63)	12	−0.6 (8.4)	12	0.2 (8.3)
GH and lifestyle intervention				
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	8	−2.8 (5.2)	8	−0.6 (3.9)
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	8	−3.2 (2.8)	8	−0.6 (1.6)
Taafe et al., 1996 (57), 1994 (60), and 1994 (61)	10	−0.8 (3.8)	8	0.0 (4.1)
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	7	−6.5 (4.0)	7	−3.0 (5.0)
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)	8	−2.6 (2.3)	15	−2.1 (2.3)
Lean body mass‡				
GH only				
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on women only)	13	1.0 (2.2)	14	0.4 (2.5)
Blackman et al., 2002 (37); Christmas et al., 2002 (38); Munzer et al., 2001 (39) (data on men only)	17	3.1 (3.3)	17	0.0 (4.0)
Franco et al., 2005 (64)	20	−0.5 (3.5)	20	−0.1 (3.3)
Holloway et al., 1994 (46)	7	−0.4 (3.4)	14	0.2 (5.6)
Johannsson et al., (44); Karlsson et al., 1998 (43); Svensson et al., 2000 (42)	16	2.0 (5.3)	14	0.7 (3.3)
Lange et al., 2002 (36) and 2001 (40)	7	2.5 (1.4)	7	−0.1 (0.9)
Papadakis et al., 1996 (45)†	26	2.4 (4.7)	26	−0.1 (4.3)
Rudman et al., 1990 (1) and 1991 (49); Cohn et al., 1993 (47)	19		12	−2.1 (4.3)
Yuen et al., 2004 (63)	12	0.2 (8.3)	12	3.2 (8.5)
GH and lifestyle intervention				
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	8	3.0 (2.9)	8	0.2 (2.3)
Lange et al., 2002 (36); Hameed et al., (51) (data on women only)	8	2.5 (1.5)	8	0.3 (1.7)
Taafe et al., 1996 (57), 1994 (60), and et al., 1994 (61)	10	1.5 (6.0)	8	−0.5 (4.6)
Thompson et al., 1998 (55); Taafe et al., 2001 (53)	7	3.9 (2.4)	7	−0.1 (1.6)
Yarasheski et al., 1997 (56), 1995 (59), and 1993 (62); Zachwieja et al., 1996 (58)	8	4.8 (1.7)	15	2.1 (2.3)

* GH-only studies evaluated participants treated with GH vs. those not treated with GH. Growth hormone and lifestyle intervention studies evaluated participants receiving GH and lifestyle intervention (exercise with or without diet) vs. those receiving a lifestyle intervention alone. For graphical summary of study data, see Appendix Figures 1–3. See Methods section for additional details. GH = growth hormone.

† Standard deviation of the end value not presented; it was assumed to be equal to the start value.

‡ Includes terms lean body mass and fat-free mass.

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