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**Review Article** 

# Impact of GH administration on athletic performance in healthy young adults: A systematic review and meta-analysis of placebo-controlled trials



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## ABSTRACT

*Objective:* Illicit use of growth hormone (GH) as a performance-enhancing drug among athletes is prevalent, although the evidence of such effects in healthy, young subjects is sparse. We therefore performed a metaanalysis of published studies on the effect of GH administration on body composition, substrate metabolism, and athletic performance in healthy, young subjects.

Design: The English-language based databases PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched, and eligible articles were reviewed in accordance with the PRISMA guidelines. Fifty-four potentially relevant articles were retrieved of which 11 were included in this analysis comprising 254 subjects. *Results:* Administration of GH significantly increased lean body mass (p < 0.01) and decreased fat mass (p < 0.01). In addition, GH increased the exercising levels of glycerol (p = 0.01) and free fatty acids (p < 0.01), but did not alter the respiratory quotient during exercise (p = 0.30). GH significantly increased anaerobic exercise capacity (p < 0.01) in the only study which investigated this, but did not over weeks to months improve muscle strength (p = 0.36) or maximum oxygen uptake (p = 0.89).

*Conclusion:* GH administration elicits significant changes in body composition, but does not increase either muscle strength or aerobic exercise capacity in healthy, young subjects.

## 1. Introduction

Illicit use of GH among elite and recreational athletes is widespread and frequently combined with other performance-enhancing drugs [1]. The salutatory effects include reduction in fat mass, increased lean body mass and increased aerobic exercise capacity, which have been documented in GH-replaced adult patients with hypopituitarism [2,3]. However, it is controversial whether GH administration exerts comparable effects in healthy subjects. Nevertheless, GH is considered a doping agent by the World Anti-Doping Agency and its use is prohibited at all times (in and out-of-competition) [4].

The aim of this meta-analysis was to assess the effects of placebocontrolled GH administration on body composition, indices of lipolysis, muscle strength, and exercise capacity in healthy, young subjects.

# 2. Materials and methods

## 2.1. Identification of relevant trials

The study was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. The English-language based databases including PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify potentially relevant studies. All databases were comprehensively searched from their respective inception until 2th December 2016 without restrictions to language or date of publication. The search was limited to human adults (19 + years of age). Where possible, the following MeSH terms were used: "growth hormone" in combination with either "sports", "performance", "exercise", or "doping" (details in Appendix A). To ensure the inclusion of studies not yet indexed with MeSH terms, a free text search was performed using the same terms. In addition, the

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Fig. 1. Flowchart of study selection.

references of relevant articles were also reviewed to identify potentially eligible articles. The literature search and data extraction was performed by one author (K Hermansen). Two other authors (M Bengtsen and JOL Jørgensen) conducted an independent review of the extracted articles, and discrepancies were solved by discussion.

# 2.2. Inclusion criteria

All randomized, double-blind, placebo-controlled trials of GH administration were included if they provided at least one of the following outcome measures: body composition (e.g. weight, lean body mass, extracellular water, body cell mass, or fat mass), strength (e.g. biceps strength, quadriceps strength, or isometric deadlift strength), indices of lipolysis (e.g. circulating levels of glycerol and/or free fatty acids, or respiratory exchange ratio) or exercise capacity (e.g. lactate

levels, bicycling speed, or maximum oxygen uptake). Restriction was applied on participants' age and health status. All participants should be healthy without evidence of pituitary disease. Moreover, studies specifically targeting children, adolescents (< 18 years of age), or older adults (> 45 years of age) were excluded. The terms *lean body mass* and *fat-free mass* are used interchangeably in the literature, why lean body mass and fat-free mass are reported as a single category of lean body mass.

## 2.3. Data extraction

The following data were extracted from each study: population characteristics (e.g. age, gender, body-mass index, maximum oxygen uptake, and initial IGF-1 levels), study interventions (e.g. dose, route, frequency, and duration of GH administration), study quality (e.g.

design, randomization, and statistical method), and clinical outcomes. Where necessary, graphical data were extracted by using the graphdigitizing program DigitizeIt, version 2.2.

#### 2.4. Risk of bias assessment

An assessment of the methodological quality of the studies was based on the Cochrane Collaboration's tool for assessing risk of bias [6]. For RCTs, this comprised the following domains: random sequence generation (i.e. selection bias); allocation concealment (i.e. selection bias); blinding of participants, personnel, and outcome assessors (i.e. performance bias); incomplete outcome data (i.e. detection bias); selective reporting and other sources of bias that may have affected the results (e.g. baseline imbalance and source of funding). For each domain, the risk of bias was assessed as low, high, or unclear. Unclear risk of bias was assigned for a domain if insufficient details were reported, or if what happened in the study was known, but its contribution to the risk of bias was unknown or unclear.

#### 2.5. Statistical analysis

The weighted mean differences with associated 95% confidence intervals (CIs) were calculated for continuous variables by using the fixed-effects inverse-variance model and DerSimonian-Laird random-effects model. Heterogeneity was assessed by using chi<sup>2</sup> and I<sup>2</sup> analyses [7]. The random-effects model was used in case of significant heterogeneity (i.e.  $I^2 \ge 50\%$ ) [8]. The fixed-effects model was used in cases without significant heterogeneity (i.e.  $I^2 < 50\%$ ). In the test for overall effect, which was given by the Z score, a two-tailed *p* value < 0.05 was considered significant. Forest plots showing the point estimate and confidence intervals were created for each outcome. All statistical analyses were performed using Review Manager 5.3 (RevMan, version 5.3; The Cochrane Collaboration, Oxford, UK).

## 3. Results

#### 3.1. Study selection

The initial search in the databases provided a total of 1441 articles (377 in PubMed, 418 in EMBASE, and 646 in Cochrane), of which 979 were unique without duplications. After screening titles and abstract, 54 potentially relevant articles remained for more detailed evaluation. Of these studies, 43 were excluded from further analysis because the studies did not meet the inclusion criteria. Any discrepancies in the articles considered important were resolved by consensus among the authors. Finally, 11 articles [9–19] were included in this review. The study search flow is shown in Fig. 1.

#### 3.2. Participants' characteristics

The enrolled participants were predominantly male (72%) with a mean age of 26.7 years [SD: 1.9] ranging between 18 and 40 years across trials. They were lean with a mean body-mass index of 23.4 kg/m<sup>2</sup> [SD: 0.8] and physically fit with a mean maximum oxygen uptake of 50.5 kg/m<sup>2</sup> [SD: 7.9]. The participants' mean IGF-1 level was 210  $\mu$ g/l [SD: 82] at baseline. The baseline characteristics of study participants are shown in Table 1.

#### 3.3. Study characteristics

In total, the included studies enrolled 224 participants. Of these, 117 participants (52%) received GH treatment representing a total of 11.7 person-years of treatment. Most study sizes were small with a mean number of participants at enrollment of 23.

The mode of GH intervention varied considerably among the included studies. Two studies [13,18] evaluated the acute effect of a single GH injection. The other studies [9–12,14–17,19] provided longer treatment duration ranging from 2 to 12 weeks with a mean of 5.2 weeks [SD: 3.3]. The daily dose of GH ranged from 25 to 67  $\mu$ g/kg with a mean of 36.5  $\mu$ g/kg [SD: 12.7] among the included studies. All the included studies provided subcutaneous GH injections.

## 3.4. Assessment of study quality

One study [19] fulfilled all the evaluated quality criteria and was the only one to document adequate concealment of treatment allocation at study enrollment. Six additional studies [9,12,15–18] fulfilled 6 of 7 criteria. Incomplete outcome data were addressed in three studies [10,11,13], and the generation of a randomized sequence was unclear in one study [11]. Caregivers, investigators, and assessors were all blind to the intervention in all the included studies [9–19]. The risk of bias is summarized in Appendix B.

#### 3.5. Quantitative data synthesis

Seven studies [9–11,14–17,19] provided data on the effects on body composition, whereas only limited data were available on the effects on lipolytic markers, strength, and exercise capacity.

## 3.6. Body composition

Weight increased significantly after GH compared to placebo (weighted mean difference in weight, 1.62 kg [95% CI, 0.79 to 2.45 kg], p < 0.01). Similarly, GH increased LBM (weighted mean difference: 2.86 kg [95% CI, 2.22 to 3.50 kg], p < 0.01). The lean body mass consists of a compartment of extracellular water and a functional cellular compartment, the body cell mass. The increase in lean body mass was accompanied by an expansion of the extracellular water (weighted mean difference: 1.77 kg [95% CI, 1.01 to 2.53 kg], p < 0.01). One study [19] observed a statistically insignificant increase in body cell mass (mean difference: 0.90 kg [95% CI, -0.09 to 1.89 kg], p = 0.07). In addition, fat mass decreased significantly in response to GH (weighted mean difference: -1.22 kg [95% CI, -1.71 to -0.74 kg], p < 0.01) (Fig. 2).

## 3.7. Indices of lipolysis

Three studies [13,14,18] employing acute GH exposure reported a significant increase in exercising levels of glycerol (weighted mean difference: 146 µmol/l [95% CI, 34 to 258 µmol/l], p = 0.01), and free fatty acids (weighted mean difference: 281 µmol/l [95% CI, 134 to 428 µmol/l], p < 0.01) after GH as compared to placebo. However, no significant decrease was observed in exercising respiratory exchange ratio (weighted mean difference: -0.03 [95% CI, -0.10 to 0.03], p = 0.30) (Fig. 3).

#### 3.8. Muscle strength

One study [11] reported that GH treatment did not increase biceps strength (mean difference: -0.90 kg [95% CI, -2.71 to 0.91 kg], p = 0.33) or quadriceps strength (mean difference: -1.00 kg [95% CI, -2.83 to 0.83 kg], p = 0.28) assessed by 1-repetition maximum voluntary strength. Another study [10] evaluated change in the strength of seven muscle groups and reported no significant difference between GH and placebo (mean difference: -0.10 kg [95% CI, -0.61to 0.41 kg], p = 0.70). Similarly, one study [19] showed that neither muscle strength nor maximal explosive power were improved by GH treatment assessed by isometric deadlift (mean difference: 2.00 kg

Table 1

Study (year)	Mean age (S (year)	SD)	Participa (n at star	nts t//end of trial)	Mean BMI ( ( <i>kg/m</i> <sup>2</sup> )	SD)	Mean VO <sub>2</sub> ma per min)	ax (SD) ( <i>ml/kg</i>	IGF-1 (SD) (μg/l)		Study inte	ervention
	GH	Control	GH	Control	GH	Control	GH	Control	GH	Control	Duration ( <i>days</i> )	Dose (µg/kg/d)
Crist et al [9]	279(37)	279(37)	8/8	8/8	NA	NA	NA	NA	NA	NA	42	38*
Yarasheski et al. [10]	27.0 (4.2) <sup>a</sup>	$27.0 (4.2)^{a}$	9/7	9/9	23.5 (NA) <sup>+</sup>	23.5 (NA) <sup>+</sup>	NA	NA	NA	NA	84	40
Deyssig et al. [11]	$23.4(2.8)^{a}$	$23.4(2.8)^{a}$	11/8	11/10	NA	NA	NA	NA	359 (NA) <sup>§</sup>	308 (NA) <sup>§</sup>	42	30
Wolthers et al. [12]	21-29#	21–29#	8/8	8/8	22.5-27.0#	22.5-27.0#	NA	NA	158 (20)	170 (37)	10	33
Lange et al. [13]	26.0 (2.6)	26.0 (2.6)	7/5	7/7	23.0 (1.3)	23.0 (1.3)	65.0 (2.6)	65.0 (2.6)	259 (NA) <sup>§</sup>	233 (NA) <sup>§</sup>	1	33 <sup>‡</sup>
Healy et al. [14]	31.0 (NA)	33.0 (NA)	6/6	6/6	24.0 (NA)	25.0 (NA)	54.2 (NA)	53.4 (NA)	188 (23)	197 (21)	28	67
Ehrnborg et al. [15]	25.6 (4.2)	27.0 (4.4)	20/20	10/10	23.1 (2.6)	23.2 (3.9)	NA	NA	310 (97)	301 (69)	28	33/67
Berggren et al. [16]	25.6 (4.2)	27.0 (4.4)	20/20	10/10	22.8 (NA) <sup>†</sup>	23.1 (NA) <sup>†</sup>	44.4 (4.3)	45.3 (4.3)	310 (100)	301 (69)	28	33/67
Hansen et al. [17]	24.0 (4.0)	25.0 (4.0)	8/8	8/8	22.2 (2.0)	21.4 (1.6)	60.1 (9.6)	57.8 (7.2)	214 (NA) <sup>§</sup>	241 (NA) <sup>§</sup>	14	$28^{*}$
Hansen et al. [18]	25.1 (5.7)	25.1 (5.7)	8/7	8/7	22.6 (1.7)	22.6 (1.7)	62.0 (2.8)	62.0 (2.8)	NA	NA	1	33 <sup>‡</sup>
Meinhardt et al. [19]	27.6 (5.7)	28.3 (5.0)	32/32	32/32	23.3 (2.8)	24.5 (3.1)	45.6 (9.9)	43.4 (9.9)	126 (37)	124 (37)	56	28 <sup>‡</sup>

BMI = body mass index; VO2 max = maximum oxygen uptake; IGF-1 = insulin-like growth factor-1.

<sup>+</sup> Based on average body weight and height presented in study.

# Reported as ranges.

\* Based on absolute doses and mean body weight presented in study.

<sup>§</sup> Data abstracted in terms of graphs by using the graph-digitizing program DigitizeIt, version 2.2.

<sup>a</sup> Data from growth hormone-treated and placebo groups aggregated.

[95% CI, -1.29 to 5.29 kg], p = 0.23) or jump height (mean difference: -1.30 cm [95% CI, -2.19 to 0.41 cm], p < 0.01), respectively. Taken together, GH administration did not improve muscle strength (relative change in muscle strength, -0.02 [95% CI, -0.05 to 0.02, p = 0.36] (Fig. 4).

## 3.9. Exercise capacity

Three studies [13,16,19] reported no significant difference in aerobic exercise capacity between GH and placebo assessed by maximum oxygen uptake (weighted mean difference in maximum oxygen uptake: 0.01 l/min [95% CI, -0.11 to 0.13 l/min], p = 0.89) (Fig. 4).

In addition, an insignificant increase in lactate levels was observed in the GH-treated groups in two studies [13,18] (mean difference: 330 µmol/l [95% CI, -341 to 1000 µmol/l], p = 0.33). Furthermore, one study [13] reported no effect on bicycling speed in growth hormone-treated participants (mean difference: 0.00 km/h [95% CI, -2.35 to 2.35 km/h], p = 1.00).

Until now, there is only one study [19] evaluating anaerobic exercise capacity. This study [19] showed a significant increase in anaerobic work capacity assessed by sprint cycle ergometry (i.e. Wingate test) (mean difference in Wingate value: 0.60 kJ [95% CI, 0.23 to 0.97 kJ], p < 0.01).

#### 4. Discussion

Growth hormone is widely used as a performance-enhancing drug in sports. The present analysis of published studies suggests that GH administration in healthy young adults primarily induces moderate changes in body composition and has limited if any effects on key performance outcomes in relation to endurance and strength dominated sports.

Administration of GH in healthy young subjects increases total body weight and lean body mass and decreases fat mass. However, methods for quantifying lean body mass (i.e. dual-energy x-ray absorptiometry) do not reliably distinguish lean solid tissue from fluid mass. In this regard, it is noteworthy that GH significantly increases extracellular water volume [20], and it is likely that fluid retention accounts for a major proportion of the increase in LBM reported in GH studies in healthy subjects. Substrate metabolism is significantly affected by acute GH exposure and a pivotal feature is stimulation of lipolysis [21]. In the present studies, the exercise-induced increase in circulating levels of glycerol and free fatty acids was significantly amplified by GH, even though an increase in lipid oxidation rates was not documented [18]. This is in accordance with data from GH-deficient adults [22] and it remains uncertain if this lipolytic effect impacts on exercise performance.

A significant GH-induced increase in plasma lactate levels to levels well above the anaerobic threshold was observed in two studies [13,18], which may be a negative determinant of exercise stamina and physical exhaustion [23]. It is believed that the increase in lactate originated from the working muscles [24], but it is unknown if this GH effect is due to increased lactate production, reduced clearance, or a combination of the two. However, Meinhardt et al. [19] reported a significant increase in anaerobic exercise capacity assessed by Wingate test and speculated that this increase in sprint capacity could translate to an improvement of 0.4 s in a 10-s sprint over 100 m. It seems unlikely that the improvement in sprint capacity is due to anabolic properties, so it is possible that GH under these conditions could regulate muscle energy metabolism and thus increase anaerobic exercise capacity which is in accordance with data from GH-deficient adults [25,26]. So far improvements in anaerobic exercise capacity has been an ignored area of exercise benefits which merits further research.

Furthermore, Meinhardt et al. reported that GH in combination with testosterone resulted in greater changes in body composition and physical performance compared to either treatment alone [19], and it is generally assumed that GH is abused in conjunction with anabolic steroids [27]. The included studies in this review show only limited evidence for efficacy of GH on athletic performance when used as a single agent. It has been hypothesized that the main performanceenhancing effect of GH is reduced recovery time via stimulation of local IGF-1 and its known musculoskeletal regenerative properties [28]. In addition, it is well-documented that GH stimulates collagen synthesis in tendon and skeletal muscle, thus strengthening the musculotendinous tissue and potentially preventing ruptures of muscle and tendons [29,30]. If this is true, GH doping may allow the athlete to train with increased frequency and higher intensities without overtraining or incurring an overuse injury, thus indirectly enhancing athletic performance.

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	G	H-treated		F	lacebo			Mean Difference			Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, 95% CI	Year		ľ	V, 95% CI	
Weighted mean diffe	erence (	kg) in wei	ight					Fixed-effects					
Yarasheski et al.	3.2	1.8	9	1.4	2.1	9	21.0%	1.80 [-0.01, 3.61]	1992				
Healy et al.	3.5	1.9416	6	-0.2	4.7371	5	3.5%	3.70 [-0.73, 8.13]	2003		-	-	
Hansen et al.	1.1	3.8897	8	0.2	4.3139	8	4.2%	0.90 [-3.13, 4.93]	2005	-		-	-
Ehrnborg et al.	1.9	3.9386	20	0.1	7.8054	10	2.6%	1.80 [-3.34, 6.94]	2005	-			
Meinhardt et al.	1.2	2.3089	32	-0.3	1.7317	32	68.6%	1.50 [0.50, 2.50]	2010				
Total (95% CI)			75			64	100.0%	1.62 [0.79, 2.45]				•	
Heterogeneity: Chi <sup>2</sup> =	1.07, df	= 4 (P = 0	).90); I <sup>≥</sup>	= 0%					-	<u> </u>	<u>    t      </u>		
Test for overall effect:	Z = 3.84	4 (P = 0.00	001)							-4	-2	0 2 4	ł
Weighted mean diffe	erence (	kg) in lea	n body	mass				Fixed-effects					
Crist et al.	2.7	5.5866	8	1	6.0208	8	1.3%	1.70 [-3.99, 7.39]	1988			2.0	
Yarasheski et al.	4.5	1.8	9	1.6	2.1	9	12.6%	2.90 [1.09, 4.71]	1992				
Deyssig et al.	5	3.1145	11	0.8	1.1314	11	10.7%	4.20 [2.24, 6.16]	1993				• •
Wolthers et al.	1.3	5.0596	8	-0.7	5.0596	8	1.7%	2.00 [-2.96, 6.96]	1999				
Healy et al.	3.4	1.6279	6	0.2	3.4655	5	3.8%	3.20 [-0.11, 6.51]	2003				
Hansen et al.	1.9	3.4655	8	-0.5	2.9069	8	4.2%	2.40 [-0.73, 5.53]	2005			· · ·	
Ehrnborg et al.	2.9	3.8792	20	0.4	6.0823	10	2.4%	2.50 [-1.64, 6.64]	2005			-	
Meinhardt et al.	3.3	2.0203	32	0.6	1.1545	32	63.3%	2.70 [1.89, 3.51]	2010				
Total (95% CI)			102			91	100.0%	2.86 [2.22, 3.50]				•	
Heterogeneity: Chi <sup>2</sup> =	2.38, df	= 7 (P = 0	).94); I <sup>z</sup>	= 0%						<u> </u>			
Test for overall effect:	Z = 8.75	5 (P < 0.00	0001)							-4	-2	0 2	4
Weighted mean diffe	erence (	kg) in ext	racellu	lar wat	er			Fixed-effects					
Ehrnborg et al.	1.8	1.4431	20	0.3	1.9251	10	31.7%	1.50 [0.15, 2.85]	2005				
Meinhardt et al.	1.7	1.876	32	-0.2	1.876	32	68.3%	1.90 [0.98, 2.82]	2010				
Total (95% CI)			52			42	100.0%	1.77 [1.01, 2.53]				•	
Heterogeneity: Chi <sup>2</sup> =	0.23, df	= 1 (P = 0	).63); I <sup>z</sup>	= 0%					-		<u> </u>		<u> </u>
Test for overall effect:	Z= 4.57	7 (P < 0.00	0001)							-4	-2	0 2	4
Weighted mean diffe	erence (	kg) in fat	mass					Fixed-effects					
Yarasheski et al.	-1.4	1.5	9	-0.2	1.5	9	12.2%	-1.20 [-2.59, 0.19]	1992				
Deyssig et al.	-0.7	3.2202	11	-0.8	2.5	11	4.0%	0.10 [-2.31, 2.51]	1993		-		
Wolthers et al.	-0.7	1.6279	8	0.8	1.2806	8	11.4%	-1.50 [-2.94, -0.06]	1999			_	
Healy et al.	0.2	2.2023	6	0.3	2.7586	5	2.6%	-0.10 [-3.09, 2.89]	2003				
Hansen et al.	-0.6	0.9723	8	0.6	1.6928	8	12.8%	-1.20 [-2.55, 0.15]	2005				
Ehrnborg et al.	-1	1.6772	20	-0.4	3.1752	10	5.3%	-0.60 [-2.70, 1.50]	2005				
Meinhardt et al.	-2	1.2988	32	-0.6	1.4431	32	51.7%	-1.40 [-2.07, -0.73]	2010		-	·	
Total (95% CI)			94			83	100.0%	-1.22 [-1.71, -0.74]			•		
Heterogeneity: Chi <sup>2</sup> =	2.45, df	= 6 (P = 0	).87); I <sup>≥</sup>	= 0%						-4	-2		4
l est for overall effect:	Z = 4.96	) (P < 0.00	JUU1)										



This analysis reveals certain limitations of the published literature. First, only 11 trials with 224 participants met the inclusion criteria wherefore the sample size may be too low. We had intended to use a standard funnel plot to help identify possible publication bias. However, we did not identify enough trials to warrant this approach. Furthermore, the relatively small sample size did not permit a subgroup analysis of the potential impact of treatment dose, duration or timing.

Second, the GH dosing regimens used in the studies may differ from those used by athletes in the context of sports doping. It is suggested that athletes use GH doses ranging from 15 to 180  $\mu$ g/kg per day three to four times a week in cycles of four to six weeks [1], which is higher than those used in most of the included studies in this review. However, it is unclear whether a graded dose-response exists for GH use. Furthermore, GH is typically co-administered with other performanceenhancing drugs [1,31] (e.g. insulin, androgenic anabolic steroids in power sports, or erythropoietin in endurance sports), and rarely used as a single agent [32]. Finally, measurement of clinical outcomes and methods were heterogeneous, which made comparisons between studies difficult.

Taken together, this meta-analysis suggests that GH administration in healthy young subjects is associated with distinct albeit moderate changes in body composition and lipolysis compatible with anabolic and lipolytic effects as previously documented in GH-deficient patients. By contrast, no consistent effects across studies were detected as regards to aerobic exercise capacity, whereas anaerobic exercise capacity may be improved by GH administration.

Conflicts of interest

The authors have nothing to disclose.

Mean Difference         <	
Study or Subgroup Mean SD Total Mean SD Total Weight N, 95% Cl Year N, 95% Cl Ye	
Weighted mean difference (µmol) in exercising levels of free fatty acids	
Lange et al. $331$ $39$ 5 105 11 7 $33,7\%$ 228.00 [190.86, 281.14] 2002 Hansen et al. II 343 54 7 162 11 7 $33.7\%$ 228.00 [140.18, 221.82] 2005 Total (65% Ct) 18 20 100.0% 146.31 [34.16, 258.46] Heterogeneity Tau <sup>9</sup> = 9397.67; Ch <sup>9</sup> = 47.01, df = 2 (P < 0.0001); P = 96% Test for overall effect Z = 2.56 (P = 0.01) Weighted mean difference (µm0) in exercising levels of free fatty acids Random effects Lange et al. 432 70 5 152 30 7 46.2% 280.00 [21.74, 345.26] 2002 Heave et al132 165 6 -215 229 6 23.1% 83.00 [+142.84, 308.84] 2003 Hansen et al. II 373 225 7 448 25 7 30.6% 431.00 [263.30, 598.70] 2005 Total (65% Ct) 18 20 100.0% 280.67 [133.53, 427.80] Heterogeneity: Tau <sup>9</sup> = 11079.95; Chi <sup>9</sup> = 6.01, df = 2 (P = 0.05); P = 67% Test for overall effect Z = 3.74 (P = 0.0002) Weighted mean difference in exercising respiratory exchange ratio Random effects Lange et al. 0.024 0.0211 5 0.014 0.0113 7 32.8% 0.01 [+0.01, 0.03] Heterogeneity: Tau <sup>9</sup> = 1.03 (P = 0.0002) Weighted mean difference in exercising respiratory exchange ratio Random effects Lange et al. 0.024 0.0211 5 0.014 0.0113 7 32.8% 0.01 [+0.01, 0.03] Hansen et al. 0.026 0.0065 7 -0.057 0.0047 7 33.8% -0.01 [+0.01, 0.03] Heterogeneity: Tau <sup>9</sup> = 0.00; Chi <sup>9</sup> = 66.36 df = 2 (P < 0.00001); P = 93% Test for overall effect Z = 1.03 (P = 0.30) Fig. 3. Effects of GH administration on lipolytic markers. Fig. 4. 0.0367 0.0367 0.1042 11 42.0% -0.0046,0.051 1982 Deyssig et al. 0.054 0.0422 11 0.104 0.1175 11 19.7% -0.056 (0.03,022] 1983 Deyssig et al. 0.054 0.0422 11 0.0438 0.0422 11 4.0428, 0.004 (0.049, 0.071 1992 Deyssig et al. 0.0564 0.0452 11 0.0438 0.0422 11 4.0438 0.04	
Heak et al. $67$ 38 6 37 41 6 33.0% 30.00 [+3.73,74.73 2003 Hansen et al. II 343 54 7 162 11 7 33.3% 181.00 [140.18,221.82] 2003 Total (95% CI) 18 20 100.0% 146.31 [34.16,258.46] Heterogeneity Tau <sup>2</sup> = 9397 67; ChF = 47 01, df = 2 (P < 0.00001); P = 96% Test for overall effect Z = 2.56 (P = 0.01) Weighted mean difference (µmol) in exercising levels of free fatty acids Random-effects Lange et al. 432 70 5 152 30 7 46.2% 280.00 [214.74,345.26] 2002 Heak et al. 132 70 5 152 7 30.6% 431.00 [263.30, 598.70] 2005 Total (95% CI) 18 20 100.0% 280.67 [133.53, 427.80] Heterogeneity Tau <sup>2</sup> = 1079.95; ChF = 6.01, df = 2 (P = 0.05); P = 67% Test for overall effect Z = 3.74 (P = 0.0002) Weighted mean difference in exercising respiratory exchange ratio Random-effects Lange et al. 0.024 0.0211 5 0.014 0.0113 7 32.8% 0.01 [-0.01, 0.03] 2002 Heak et al. 0.024 0.0211 5 0.014 0.0113 7 32.8% 0.01 [-0.01, 0.03] 2002 Heak et al. 0.026 0.0055 7 - 0.057. 0.047 7 33.8% - 0.01 E.0.11, 0.00] 2003 Total (95% CI) 18 19 100.0% -0.013 [-0.10, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; ChF = 156.56, df = 2 (P < 0.00001); F = 99% Test for overall effect Z = 1.03 (P = 0.0001) Fig. 3. Effects of GH administration on lipolytic markers. Study or Subgroup Mean SD Total Mean SD Total Weight 10.014 0.0176 11 19.7% -0.03 [-0.01, 0.02] Deyrslig et al. 0.0368 0.0346 11 0.0438 0.0342 11 42.0% -0.0012 (0.05, 1983) Deyrslig et al. 0.0368 0.0345 11 0.014 0.0176 11 19.7% -0.05 [-0.03, 0.02] 1983 Deyrslig et al. 0.0368 0.0345 11 0.0438 0.0342 11 42.0% -0.0012 (0.05, 0.02] Heterogeneity: ChF = 1.76, df = 3 (P = 0.62); F = 0% Total (95% CI) 63 63 100.0% -0.02 [-0.05, 0.02] Heterogeneity: ChF = 1.76, df = 3 (P = 0.36); F = 0% Total (95% CI) 63 63 100.0% -0.02 [-0.05, 0.02] Heterogeneity: ChF = 1.76, df = 3 (P = 0.26); F = 0% Test for overall effect Z = 0.92 (P = 0.36)	
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Weighted mean difference (umol) in exercising levels of free faity acids       Random-effects         Lange et al.       432       70       5       152       30       7       46.2%       280.00 [214.74, 345.26]       2002         Healy et al.       -132       166       6       -215       229       6       23.1%       93.00 [714.2.84, 308.84]       2003         Hear of the et al.       879       225       7       448       25       7       30.6%       431.00 [263.30, 598.70]       2005         Total (95% C1)       18       20       100.0%       280.67 [133.53, 427.80]         Helerogeneity: Tau <sup>2</sup> = 1079.95; Chi <sup>2</sup> = 6.01, df = 2 (P = 0.05); P = 67%         Test for overall effect: Z = 3.74 (P = 0.0002)         Weighted mean difference in exercising respiratory exchange ratio       Random-effects         Lange et al.       0.024 0.0211 5       0.014 0.0113 7       32.8%       0.01 [6.01, 0.03]       2002         Healy et al.       0       0.0108       6       1.00.04       0.03 [-0.10, 0.03]       2002         Healy et al.       0.02 (D1       18       19       100.0%       -0.05 [-0.1, 0.00]       2003	
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Hear yet al.       -132       103       6       -215       229       6       23.1%       83.00 [42.3.30, 598.70]       2003         Hansen et al.       879       225       7       448       25       7       30.6%       431.00 [263.30, 598.70]       2003         Total (95% C)       18       20       100.0%       280.67 [133.53, 427.80]	
$\begin{aligned} & \text{Harberh et al. II} & \text{Sr}^3 & 223 & 7 & 448 & 23 & 7 & 30.6\% & 431.00 [203.01, 99.7.0] & 2003 \\ & \text{Total (95\% CI)} & 18 & 20 & 100.0\% & 280.67 [133.53, 427.80] \\ & \text{Heterogeneity: Tau3 = 11079.95; Chi3 = 6.01, df = 2 (P = 0.05); P = 67\% \\ & \text{Test for overall effect } Z = 3.74 (P = 0.0002) \\ \end{aligned} \\ & \text{Weighted mean difference in exercising respiratory exchange ratio} & \text{Random-effects} \\ & \text{Lange et al.} & 0.024 & 0.0211 & 5 & 0.014 & 0.0113 & 7 & 32.8\% & -0.01 [-0.01, 0.03] & 2002 \\ & \text{Healy et al.} & 0 & 0.0108 & 6 & 0.1 & 0.0118 & 5 & 33.4\% & -0.01 [-0.01, -0.00] & 2003 \\ & \text{Hansen et al.} & -0.066 & 0.0065 & 7 & -0.057 & 0.0047 & 7 & 33.8\% & -0.01 [-0.01, -0.00] & 2005 \\ & \text{Total (95\% CI)} & 18 & 19 & 100.0\% & -0.03 [-0.10, 0.03] \\ & \text{Heterogeneity: Tau3 = 0.00; Chi3 = 156.56, df = 2 (P < 0.00001); P = 99\% \\ & \text{Test for overall effect } Z = 1.03 (P = 0.30) \\ & \text{Fig. 3. Effects of GH administration on lipolytic markers.} \\ & \text{GH-treated} & Placebo & Mean Difference \\ & \text{Yarasheski et al.} & 0.54 & 0.141 & 9 & 0.5 & 0.144 & 9 & 7.0\% & 0.04 [-0.09, 0.17] & 1992 \\ & Test for overall effect series and the series of the$	
Total (95% CI)       18       20       100.0% 280.67 [133.53, 427.80]         Heterogeneiky: Tau <sup>2</sup> = 11079.95; Ch <sup>2</sup> = 6.01, df = 2 (P = 0.05); P = 67%       -500       -250       0       250       500         Weighted mean difference in exercising respiratory exchange ratio       Random-effects	
Heterogeneity: Tau <sup>2</sup> = 11079.95; Ch <sup>2</sup> = 6.01, df = 2 (P = 0.05); P = 67% Test for overall effect Z = 3.74 (P = 0.0002) Weighted mean difference in exercising respiratory exchange ratio Lange et al. 0.024 0.0211 5 0.014 0.0113 7 32.8% 0.01 [-0.01, 0.03] 2002 Healy et al. 0 0.0108 6 0.1 0.0118 5 33.4% -0.10 [-0.11, -0.09] 2003 Hansen et al0.066 0.0065 7 -0.057 0.0047 7 33.8% -0.01 [-0.01, -0.00] 2005 Total (95% Cl) 18 19 100.0% -0.03 [-0.10, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 156.56, df = 2 (P < 0.00001); P = 99% Test for overall effect Z = 1.03 (P = 0.30) Fig. 3. Effects of GH administration on lipolytic markers. Study or Subgroup Mean SD Total Mean SD Total Weight N, 95% Cl Year Relative change in muscle strength Yarasheski et al. 0.54 0.0342 11 0.0438 0.0842 11 42.0% -0.00 [-0.06, 0.05] 1993 Deyssig et al. 0.0388 0.0346 11 0.0438 0.0842 11 42.0% -0.00 [-0.06, 0.05] 1993 Meinhardt et al. 0.0387 0.1303 32 0.0596 0.1242 32 31.3% -0.02 [-0.05, 0.02] Heterogeneity: Ch <sup>2</sup> = 1.76, df = 3 (P = 0.62); P = 0% Test for overall effect Z = 0.92 (P = 0.36)	
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Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 156.56, df = 2 (P < 0.00001); I <sup>2</sup> = 99%         Test for overall effect: Z = 1.03 (P = 0.30)         Fig. 3. Effects of GH administration on lipolytic markers.         GH-treated       Placebo       Mean Difference         Mean SD Total Mean SD Total Weight       IV, 95% CI         Fixed-effects         Yarasheski et al.       0.54       0.14       9         Object to the set of GH administration on lipolytic markers.         Mean Difference         Mean Difference         Mean Difference         IV, 95% CI         Fixed-effects         Yarasheski et al.       0.0504       0.04       0.01       0         Deyssig et al.       0.0388       0.0388       0.0387       0.1303       32       0.05       0.01       0.2         Object to the set of GH administration on lipolytic markers.         Total Weight       IV, 95% CI         Planewidth administration on lipolytic markers. <td< td=""></td<>	
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Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, 95% Cl         Year         IV, 95% Cl           Relative change in muscle strength         Fixed-effects         Fixed-effec	
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Fig. 4. Effects of GH administration on strength and exercise capacity.

# Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.ghir.2017.05.005.

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