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RESEARCH ARTICLE

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Exercise-induced modulation of IGF-1 in healthy, obese, and cancer populations: a systematic review and meta-analysis

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ABSTRACT

Background: This systematic review and meta-analysis evaluated the effects of chronic exercise on circulating insulin-like growth factor 1 (IGF-1) across different populations, including, healthy adults, individuals with obesity, and cancer patients or survivors. To minimize confounding, we excluded trials combining exercise with medications, hormone therapy, or structured dietary interventions.

Materials and Methods: PubMed and Embase were searched through July 2024 for randomized controlled trials (RCTs) in adults (≥18 years) with exercise interventions lasting ≥8 weeks, a non-exercise control group, and reported changes in serum IGF-1. Twenty-one RCTs with 1376 participants met the inclusion criteria. Pooled weighted mean differences (WMD) with 95% confidence intervals (CI) were calculated, and trial sequential analysis was used to assess robustness.

Results: Exercise significantly increased IGF-1 in healthy individuals (WMD=21.41, 95% CI 8.01–34.81) and in those with obesity (WMD=15.46, 95% CI -1.07–31.99), consistent with metabolic and anabolic benefits via the GH–IGF-1 axis. In contrast, exercise significantly reduced IGF-1 in cancer patients or survivors (WMD=-14.71, 95% CI -19.77 to -9.65). In studies reporting both IGF-1 and IGF-binding protein 3 (IGFBP-3), exercise increased IGFBP-3 in healthy and cancer populations, suggesting a modulatory role of IGFBP-3 in IGF-1 regulation, particularly in cancer.

Conclusion: Chronic exercise exerts health status–dependent effects on circulating IGF-1, supporting metabolic benefits in healthy and obese individuals and potentially contributing to cancer care by reducing IGF-1 in cancer patients or survivors. These findings demonstrate the complex endocrine response to exercise and support the therapeutic potential of tailored exercise prescriptions. .

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Exercise; insulin-like growth factor 1; health promotion; obesity; cancer survivors

Introduction

Insulin-like growth factor 1 (IGF-1) is a polypeptide hormone primarily synthesized in the liver in response to growth hormone (GH) stimulation. Once secreted into the bloodstream, IGF-1 exerts significant autocrine, paracrine, and endocrine effects [1]. The majority of its physiological actions are mediated through activation of the IGF-1 receptor (IGF1R), primarily *via* the Akt signaling pathway, promoting cell survival, growth, and proliferation. IGF-1 can also bind to the insulin receptor (IR), albeit with lower affinity, thereby contributing some metabolic effects of insulin [2]. Given these roles, IGF-1 has been implicated in various metabolic diseases. For instance, serum IGF-1 levels negatively correlate with obesity [3,4], the risks of ischemic stroke [5], sarcopenia in elderly men [6], Alzheimer's disease (AD) and AD-associated brain atrophy [7], and cardiovascular diseases (CVD) [8]. Notably, IGF-1 levels also exhibit a U-shaped relationship with CVD [9,10] and insulin resistance [11], wherein both low and high circulating IGF-1 concentrations are linked to increased risk.

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Although IGF-1 possesses growth-promoting and pro-metabolic properties, its relationship with adiposity remains complex. Despite early *ex vivo* reports suggesting its inhibitory effect on lipolysis by GH [12], *in vivo* studies have not demonstrated significant effects of IGF-1 on adipose tissue development or differentiation [13,14]. Conversely, the anabolic and mitogenic properties of IGF-1, alongside its oncogenic role *via* IGF1R signaling, have been implicated in the pathogenesis of several common cancers [15] and in promoting drug resistance across various tumor types [16]. Elevated IGF-1 levels have been shown to be associated with increased risks of several cancers, particularly breast [10,17], prostate [10,17], thyroid [17], and colorectal cancers [17]. Moreover, IGF-1 secreted by tumor cells and the tumor microenvironment is known to support neovascularization, as well as the maintenance, proliferation, and migration of malignant cells [18]. Conversely, higher circulating IGF-1 levels have been inversely associated with the risks of liver, esophageal, ovarian, and oral cancers. These observations reveal complex and dual nature of IGF-1's effects and suggest a need for further research to better understand its impact on health and diseases, particularly in the context of cancer.

Participation in regular physical activity has been shown to provide broad health benefits, including a reduced risk of metabolic diseases and cancers in adults [19], partly mediated by favorable endocrine adaptations [20]. Exercise promotes GH secretion across diverse populations [21,22], which, *in turn*, increases IGF-1 levels following both chronic [23,24] and acute [25] exercise. These elevations have been associated with various health-promoting effects [2]. Although debate remains regarding whether IGF-1 secreted by skeletal muscle during contraction exerts endocrine effects beyond its autocrine/paracrine actions within muscle tissue [26], emerging evidence suggests that exercise-induced IGF-1 secretion from skeletal muscle, independent of GH stimulation, may also contribute to circulating IGF-1 concentrations [27,28]. However, given IGF-1's anabolic and metabolic roles, concerns have been raised that exercise-induced increases in IGF-1 could potentially exacerbate cancer progression by enhancing cancer cell proliferation and survival. Nevertheless, substantial evidence supports that regular exercise during active cancer treatment and survivorship is both safe and beneficial. Accordingly, exercise is recommended for cancer patients and survivors to improve various aspects of quality of life, alleviate treatment-related side effects, and, although further research is warranted, potentially enhance treatment tolerance, therapeutic response, and even reduce cancer-specific mortality [29]. To advance our understanding of the complex interplay between exercise, IGF-1 regulation, and health outcomes across diverse populations, further research is needed to elucidate these relationships and to confirm the safety and efficacy of exercise interventions in both healthy and clinical populations.

The primary objective of this study is to systematically review and conduct meta-analyses to assess alterations in serum IGF-1 levels resulting from chronic exercise interventions in human randomized controlled trials (RCTs). To minimize the potential influence of significant IGF-1 modulators, including pharmacological agents [30], nutrition and structured dietary intervention [31], sex hormones therapy [32], growth hormone-replacement therapy [33], and radiotherapy [34], the present study was designed to focus on trials in which exercise was the primary intervention, thereby allowing for a more specific evaluation of exercise-induced effects on IGF-1 regulation. To enhance the clinical relevance of the primary objective, we conducted a pre-planned subgroup analysis based on population health status, healthy, obese, and cancer, to explore potential heterogeneity in IGF-1 responses. By delineating these population-specific effects, the study aims to elucidate the role of exercise in IGF-1 regulation and support the development of targeted exercise interventions to optimize health outcomes across diverse clinical contexts. To support this objective, we limited our analysis to exercise-only interventions to enhance internal validity and ensure that observed effects could be attributed primarily to exercise, thereby improving the clarity and applicability of our findings.

Materials and methods

We employed a systematic review and meta-analysis methodology to evaluate the impact of chronic exercise on serum IGF-1 levels across distinct health statuses: healthy individuals, obese individuals and cancer survivors. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines [35], and the protocol was registered in the international prospective register of systematic reviews PROSPERO under registration number CRD42024565448.

Identification and inclusion criteria

To be eligible for inclusion, studies had to meet the following criteria: 1) Participants: adults aged ≥18 years identified as healthy, as having overweight or obesity as cancer patients (physician-diagnosed malignancy) or survivors or cancer survivors after completion of primary treatment who were in follow-up/surveillance and were not receiving active anti-cancer or adjuvant therapy at enrollment, with studies involving pregnant women being excluded; 2) Intervention: supervised or unsupervised aerobic, resistance, combined or any forms of exercise involving voluntary whole-body muscle activation, lasting longer than 8 weeks with a minimum frequency of two sessions per week, excluding those used involuntary form of muscle contraction such as vibration exercises, exergaming (virtual reality-based physical activity), or similar interventions; 3) Study design: RCTs with control groups that received no active intervention (i.e. no exercise, dietary intervention, pharmacological treatment, hormone replacement therapy, radiotherapy, or structured educational programs); 4) Outcome measure: serum IGF-1 concentration reported at baseline and post-intervention. To minimize confounding and enhance comparability across studies, we excluded trials that incorporated combined dietary and exercise interventions, as well as those involving additional structured components such as hormone therapy, chemotherapy, radiotherapy, or behavioral and supportive care. These factors may independently and substantially influence IGF-1 regulation, particularly in cancer patients, thereby limiting the ability to isolate the physiological effects attributable solely to exercise. Our aim was to establish a clear relationship between physical activity and circulating IGF-1 without interference from other potent modulators of the GH–IGF-1 axis.

Literature searching and data extraction process

An electronic search of PubMed and Embase was conducted from inception to July 5, 2024, using the following terms: 'insulin-like growth factor 1', 'IGF-1', 'exercise', and 'physical activity'. The search query for each database is provided in Supplementary Method S1. Duplicate studies were excluded using reference management software (EndNote 21). Two authors (YRK and YHK) independently screened titles, abstracts, and full texts to assess eligibility for inclusion and collected the following information: (a) study details, including authors' names and years of publication; (b) participant characteristics, including sample size, gender, age, and health status; (c) intervention details, including exercise modality, training duration (*weeks*), frequency (*sessions/week*), and length of each training session (*min/session*); and (d) outcome measure (serum *free* or *total* IGF-1) for each group. A third reviewer (YSK) checked the extracted data for completeness and accuracy, and any discrepancies were resolved through review of the trial reports and discussion.

Quality evaluation of included studies

The risk of bias was assessed independently by two authors (YRK, YHK) using the revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2). The RoB2 evaluated five key domains: (1) the randomization process; (2) deviations from the intended interventions; (3) missing outcome data; (4) measurement of the outcome; and 5) selection of reported outcomes. Each domain was rated as low risk (-), some concerns (?), or high risk (+) of bias. Any disagreements were resolved by consensus with a third investigator (YSK). A graphical representation was created to visualize and report the overall risk of bias across the included studies (Supplementary Method S2).

Strategy for data synthesis

All statistical analyses were performed using STATA software (Version 19; StataCorp., College Station, TX, USA). For each outcome, baseline and post-intervention measurements of IGF-1 were extracted in their absolute units, including mean and standard deviation (SD). The pooled effect size (Cohen's d) was calculated using the within-group mean difference (MD) and expressed as the weighted mean difference (WMD). Subgroup analyses were conducted based on participants' health statuses: healthy, obese, and cancer patients or survivors. Cluster-robust point estimates with 95% confidence intervals (95% CIs) were

reported, weighted by inverse sampling variance to account for both within- and between-study variability. Statistical heterogeneity was assessed using the I^2 statistic, with values of >25% indicating low heterogeneity, >50% indicating moderate heterogeneity, and >75% indicating high heterogeneity. Publication bias was evaluated using funnel plots and Egger's test.

Trial sequential analysis

To reduce the risks of type I and type II errors inherent in cumulative meta-analyses, we conducted a Trial Sequential Analysis (TSA) using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Denmark). The TSA was applied to the primary outcome, changes in serum IGF-1 levels in response to chronic exercise interventions. Parameters were set according to previously described conventional methodology [36], assuming a two-sided α of 5%, power of 90% (β = 10%), and an anticipated effect size based on the pooled weighted mean difference (WMD) from our meta-analysis. We used the O'Brien-Fleming alpha-spending function to construct the trial sequential monitoring boundaries. The required information size (RIS) was estimated based on the diversity-adjusted model, accounting for heterogeneity across studies. If the cumulative Z-curve crossed the trial sequential monitoring boundary before reaching the RIS, the result was considered conclusive and robust, indicating sufficient evidence to confirm the effect despite the risk of random error.

Results

The literature search and characteristics of the included trials

Our search strategy initially identified a total of 841 studies. After removing 214 duplicates using a bibliographic management tool, 627 studies remained for further screening. Of these, 534 studies were excluded based on the title and abstract review. Specifically, 446 studies that employed interventions other than exercise (e.g. dietary intervention, hormone replacement therapy, drug treatment, radiotherapy), 12 studies that included participants under 18 years of age and pregnant women, 42 studies involving exercise modalities that did not require full-body voluntary movement (e.g. passive vibration exercise, blood flow restriction training) and 34 studies that featured interventions less than 8 weeks were excluded. The full texts of the remaining 85 studies were further assessed against our eligibility criteria, leading to the exclusion of 64 studies due to a lack of specific data or unavailable full text. This process resulted in a final selection of 21 studies for inclusion in the analysis. A detailed schematic of the selection process is presented in Figure 1.

Risk of bias evaluation

The risk of bias in this meta-analysis was assessed using the Cochrane RoB2 Tool by the two aforementioned researchers. Overall, the risk of bias across the included studies was considered low.

Detailed characteristics of included studies

Table 1 summarizes the characteristics of the 21 studies included in this analysis, comprising a total of 1376 participants who underwent chronic exercise interventions and reported changes in serum IGF-1 levels (mean age: 57.1 ± 5.9 years; female proportion: 90.8%). Subgroup analyses were performed based on health status: healthy individuals without diagnosed conditions ($n = 955$; mean age: 60.1 ± 5.3 years; female: 92.0%) from 11 studies [37–47], individuals with overweight or obesity ($n = 98$; mean age: 47.0 ± 4.3 years; female: 87.7%; BMI: intervention group 30.30 ± 2.69; control group 29.72 ± 1.64) from 4 studies [48–51], and cancer patients or survivors ($n = 323$; mean age: 58.5 ± 8.1 years; female: 87.9%) from 6 studies [52–57]. In the subgroup of cancer patients or survivors, one trial [53] did not report treatment status at enrollment; however, its trial registration and an associated publication under the same registration excluded prior hormone replacement therapy, chemotherapy, radiotherapy, smoking/alcohol use, and structured physical activity within the previous six months. Taken together, these sources support that, per the published eligibility for the associated population, participants were not receiving active

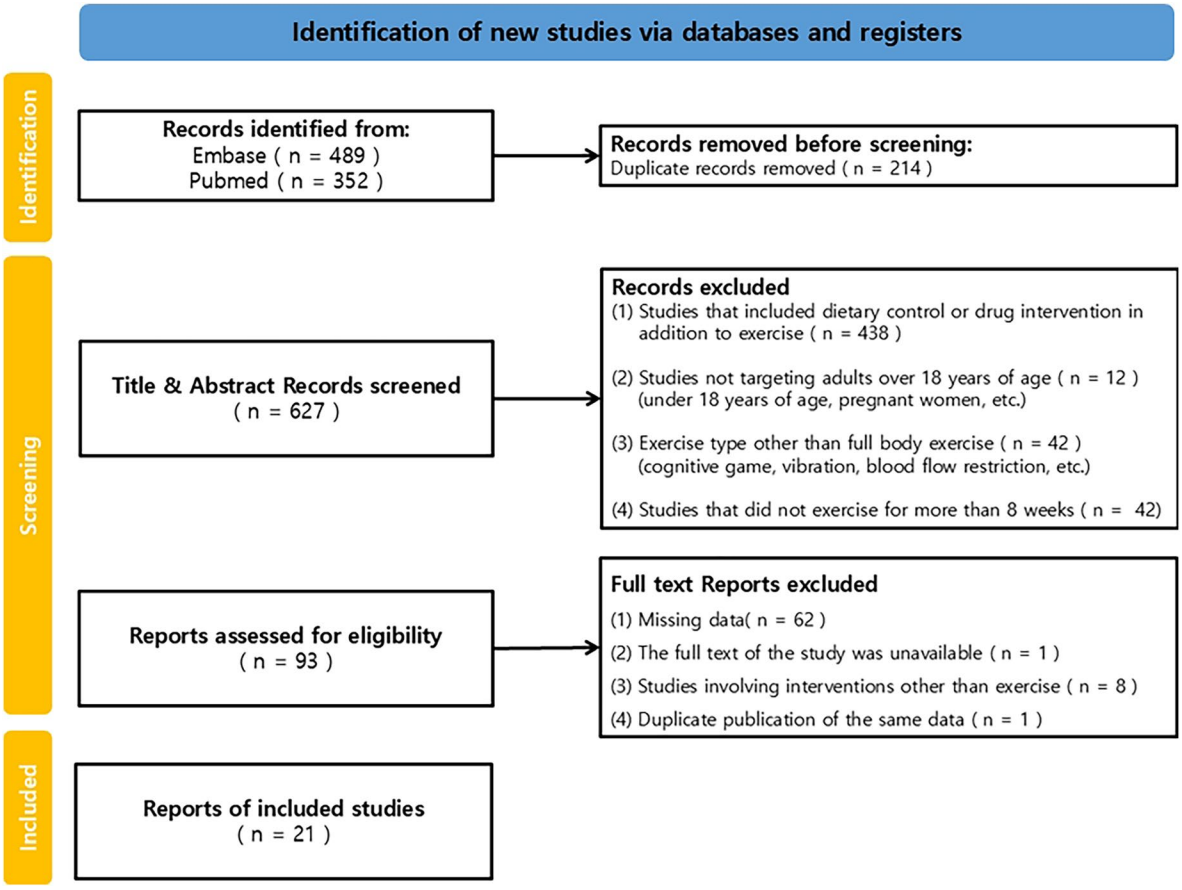

Figure 1. PRISM flow chart illustrating the different phases of the search and study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

anti-cancer or adjuvant therapy at enrollment. Cancer types included breast cancer ($n = 180$; stages 0-3b) [54,56,57], prostate cancer ($n = 39$; stages not reported) [53,55], and ovarian cancer ($n = 104$; stages 0-3a) [52]. Among the 21 studies, four were conducted in Europe (Denmark, Finland, Germany, and Poland), seven in the Americas (Brazil, Canada, Chile, and USA), and six in Asia (Iran, Republic of Korea, Taiwan).

Detailed summary of intervention

All interventions ($n = 21$) focused solely on exercise, with studies selected based on the absence of reported dietary interventions, hormone replacement therapy, drug treatment, or radiotherapy during the exercise intervention period. The duration of these interventions ranged from a minimum of 8 weeks to a maximum of 2 years, with the majority lasting 4 months or less ($n = 16$) and the remainder extending 6 months or longer [42,47,52,55,57]. Studies with fixed weekly prescriptions prescribed two or three sessions per week: 2/week in 3 trials [37,45,50] and 3/week in 12 trials [38–41,44,46–49,53,55,56]; one trial used 2–3/week [54]. One trial instructed participants to accumulate 150 min/week *ad libitum* with no minimum sessions/week specified [52]. The most common exercise modalities were resistance exercise ($n = 8$), aerobic exercise ($n = 6$), and combined exercise ($n = 5$), used in 19 trials. The remaining studies employed elastic-band exercises [41], and Tai Chi Chuan [56]. Exercise programs were supervised in 16 [37–41,44–47,49–51,53–56], semi-supervised *via* phone or web in 2 [48,52], hybrid (mixed in-person supervision & independent sessions) in 2 [42,57], and unspecified in 1 [43].

The effects of exercise intervention on IGF-1 levels

Overall, analysis of serum IGF-1 changes from pre- to post-exercise intervention across 21 included studies revealed a significant increase in post-intervention IGF-1 levels in the intervention groups

Table 1. Characteristics of the studies included in the review.

					Participants				Attrition (no. patients)		IGF-1 (△ in *ng/ml*)		IGFBP-3 (△ in *ng/ml*)	
					Exercise		*Control*							
No	Study	Health Status	Exercise	Frequency & Duration	*n*	*Age*	*n*	*Age*	*Exercise*	*Control*	*Exercise*	*Contro*	*Exercise*	*Control*
1	Schaupp et al. 2022 (Germany)	Healthy	(*Supervised:*) Resistance & Power training without use of the machine or weights	60 min, 2 times / week for 12 weeks	47 (73%*)	77.6 ± 6.1	22 (68%*)	75.9 ± 7.8	not-specified	not- specified	2.3 ± 15	−2 ± 11.5	28.9 ± 356	−107.1 ± 248
2	Castillo Quezada et al. 2021 (Chile)	Healthy	(*Supervised:*) Muscle Strength exercise Program: 50-60% of maximum load, 10-15 reps	60 min, 3 times / week for 12 weeks	14*	69.39 ± 6.48	15*	69.39 ± 6.48	loss of follow-up (6)	loss of follow-up (8)	21.72 ± 36.9	0.93 ± 17.8		
3	Cunha et al. 2020 (Brazil)	Healthy	(*Supervised:*) Resistance training with multiple sets included 8 whole body exercises	45 min, 3 times / week for 12 weeks	20*	68.60 ± 4.44	21*	68.04 ± 4.38	loss of follow-up (3)	loss of follow-up (2)	10.11 ± 20.7	−2.4 ± 23.6		
4	Banitalebi et al. 2018 (Iran)	Healthy	(*Supervised:*) Resistance training before Aerobic training	70 min, 3 times / week for 12 weeks	10*	55.38 ± 5.74	9*	55.38 ± 5.74	loss of follow-up (5)	loss of follow-up (6)	31.71 ± 7.2	−2.22 ± 8.4		
5	So et al. 2013 (Korea)	Healthy	(*Supervised:*) Elastic band exercise: 2-3 sets, 15-25 reps	60 min, 3 times / week for 12 weeks	18 (12*)	71.6 ± 5.5	22 (15*)	68.4 ± 5.8	loss of follow-up (5)		29.8 ± 49.4	16.5 ± 34.6	−1132.9 ± 759.59	−1125.2 ± 720.88
6	Friedenrei-ch et al. 2011 (Canada)	Healthy	(*3d Supervised; 2d Unsupervised:*) Aerobic exercise: 70-80% HRR	45 min, 5 times / week for 1 year	154*	61.2 ± 5.4	156*	60.6 ± 5.7	loss of follow-up (5), not-specified (1)	loss of follow-up (3), died (1)	−2 ± 27	−4 ± 28.5	−100 ± 490	0 ± 683
7	Arikawa et al. 2010 (USA)	Healthy	(*n.a*) Weight-bearing aerobic exercise: 80-85% HRmax	30 min, 5 times / week for 16 weeks	165*	25.4 ± 3.4	151*	25.3 ± 3.5	high follow-up insulin level (1)	high follow-up insulin level (2)	−8.7 ± 5.7	−12.6 ± 6	18.7 ± 552.9	−103.1 ± 523.8
8	Seo et al. 2010 (Korea)	Healthy	(*Supervised:*) Walked and aerobic exercise: 60-80% HRR	3 times / week for 12 weeks	7*	55 ± 4.8	7*	58 ± 4.2	not-specified	not-specified	38.7 ± 99.4	−4.6 ± 74.4		
9	Sillanpää et al. 2010 (Finland)	Healthy	(*Supervised:*) Combined training: periodization program, 3-4 sets	2 times / week for 21 weeks	22*	51 (7)	9*	53 (8)	not-specified	not-specified	5 ± 29.2	−3 ± 27.2		
10	Orsatti et al. 2008 (Brazil)	Healthy	(*Supervised:*) Resistance training: periodically adjusted; dynamic exercise	60 min, 3 times / week for 16 weeks	21*	57.8 ± 8.0	22*	59.3 ± 6.2	non-adherence (6)	scheduling conflicts (1)	0.56 ± 60.2	−0.16 ± 38.7		

(*Continued*)

Table 1. Continued.

No	Study	Health Status	Exercise	Frequency & Duration	Participants				Attrition (no. patients)		IGF-1 (△ in *ng/ml*)		IGFBP-3 (△ in *ng/ml*)	
					Exercise		*Control*							
					n	*Age*	*n*	*Age*	*Exercise*	*Control*	*Exercise*	*Contro*	*Exercise*	*Control*
11	Cassilhas et al. 2007 (Brazil)	Healthy	(*Supervised:*) Resistance training: 80% 1RM	60 min, 3 times / week for 24 weeks	20	68.4 ± 0.67	23	67.04 ± 0.54	not-specified	not-specified	80.73 ± 22.3	−25.4 ± 25.7		
12	Cartmel et al. 2023 (USA)	Ovarian cancer	(*Semi-supervised:*) Aerobic home-based exercise program: moderate-intensity	150 min / week for 6 months	53*	56.8 (9.4)	51*	57.2 (8.1)	loss of follow-up (21)	loss of follow-up (19)	−10.3 ± 32	3.9 ± 33.5		
13	Jafari et al. 2019 (Iran)	Prostate cancer	(*Supervised:*) Resistance training: 60-70% 1RM; Aerobic training: 60% VO2max	3 sessions / week for 8 weeks	10	62.6 ± 7.71	10	62.6 ± 7.71	not-specified	not-specified	−4.39 ± 1.5	8.72 ± 1.6	3.65 ± 1.30	−0.8 ± 0.59
14	Dieli-Conwright et al. 2018 (USA)	Breast Cancer	(*Supervised:*) Aerobic/ Resistance training: ACSM/ACS guidelines for survivors of cancer	150 min of AE; 2-3 days of RE / week for 16 weeks		52.8 (10.6)	45*	53.6 (10.1)	loss of follow-up (4)	loss of follow-up; scheduling conflicts (5)	−12.1 ± 23.1	8.1 ± 26	6.9 ± 3.25	−1.2 ± 2.64
15	Hvid et al. 2016 (Denmark)	Prostate Cancer	(*Supervised:*) Endurance training: 50-100% VO_{2max}	45 min, 3 times / week for 2 years	12	69.8 ± 2.9	7	68.0 ± 6.1	non-adherence (5)	non-adherence (1)	−4.8 ± 10.5	−1.6 ± 10.1	10.757 ± 14.14	5.766 ± 10.05
16	Janelsins et al. 2011 (USA)	Breast Cancer	(*Supervised:*) Tai chi Chuan: 15-move short form of Yang-style	60 min, 3 times / week for 12 weeks	9*	54.33 (10.64)	10*	52.70 (6.67)	non-adherence (8)	non-adherence (4)	−27.32 ± 45.1	−16.64 ± 66.5	0.89 ± 3.12	0.700 ± 3.77
17	Irwin et al. 2009 (USA)	Breast Cancer	(*3d Supervised; 2d Unsupervised:*) Combined training: moderate-intensity	150 min, 5 times / week for 6 months	36*	56.4 (9.5)	32*	55.6 (7.7)	non-adherence (1)	non-adherence (6)	−7.36 ± 6	12.7 ± 6.4	−190 ± 480	150 ± 570
18	Ratajczak et al. 2024 (Poland)	Obesity	(*Semi-supervised:*) Combined strength and endurance circuit training	33 min, 3 times / week for 12 weeks	19*	33.37 ± 4.5	8*	32.13 ± 5.1	non-adherence (9)	non-adherence (6)	−0.63 ± 10.1	−1.77 ± 10		
19	Mahmoud et al. 2022 (Iran)	Obesity	(*Supervised:*) Resistance training: nonlinear periodization, 60-90% 1RM	3 sessions / week for 12 weeks	9*	37.2 ± 4.7	9*	37.2 ± 4.7	non-adherence (5)	non-adherence (4)	41.6 ± 11.2	6.6 ± 8		
20	Chen et al. 2017 (Taiwan)	Obesity	(*Supervised:*) Resistance training: 60-70% 1RM, 3 sets, 8-12 repetitions	60min, 2 times / week for 8 weeks	15 (12*)	68.9 ± 4.4	15 (13*)	68.6 ± 3.1	scheduling conflicts (3), not-specified (4)	scheduling conflicts (7)	0.07 ± 1.7	−0.95 ± 1		
21	Irving et al. 2009 (USA)	Obesity	(*Supervised:*) Moderate-high intensity exercise: 3 days /week at RPE 15-17, 2 days / week at RPE 10-12	5 times / week for 16 weeks	13 (10*)	49.0 ± 2.9	10 (6*)	49.2 ± 4.8	not-specified	not-specified	6 ± 8.2	−20 ± 13.2		

compared to their respective control groups. The random effects model yielded a weighted mean difference (WMD) of 9.13 ng/mL (95% CI [3.17, 15.10], $p < 0.001$), with high heterogeneity across studies (I^2 = 97.9%), indicating substantial between-study variability (Figure 2). Subgroup analysis by health status revealed divergent patterns in IGF-1 responses to chronic exercise. In healthy individuals (11 studies), serum IGF-1 levels significantly increased following exercise interventions (WMD = 21.41 ng/mL, 95% CI [8.01, 34.81], $p < 0.001$), accompanied by high heterogeneity (I^2 = 96.2%) (Figure 3). Similarly, among obese individuals (four studies), exercise also led to a significant increase in IGF-1 levels (WMD = 15.46 ng/mL, 95% CI [−1.07, 31.99], $p < 0.001$), with comparably high heterogeneity (I^2 = 96.3%) (Figure 4). In contrast, cancer patients and survivors (six studies) exhibited a significant decrease in serum IGF-1 levels following exercise (WMD = −14.71 ng/mL, 95% CI [−19.77, −9.65], $p < 0.001$), with moderate-to-high heterogeneity observed (I^2 = 79.2%) (Figure 5).

The effects of exercise intervention on IGFBP-3 levels

A subgroup meta-analysis was conducted on studies that reported both exercise-induced changes in circulating IGF-1 and insulin insulin-like growth factor binding protein 3 (IGFBP-3) levels. Among healthy

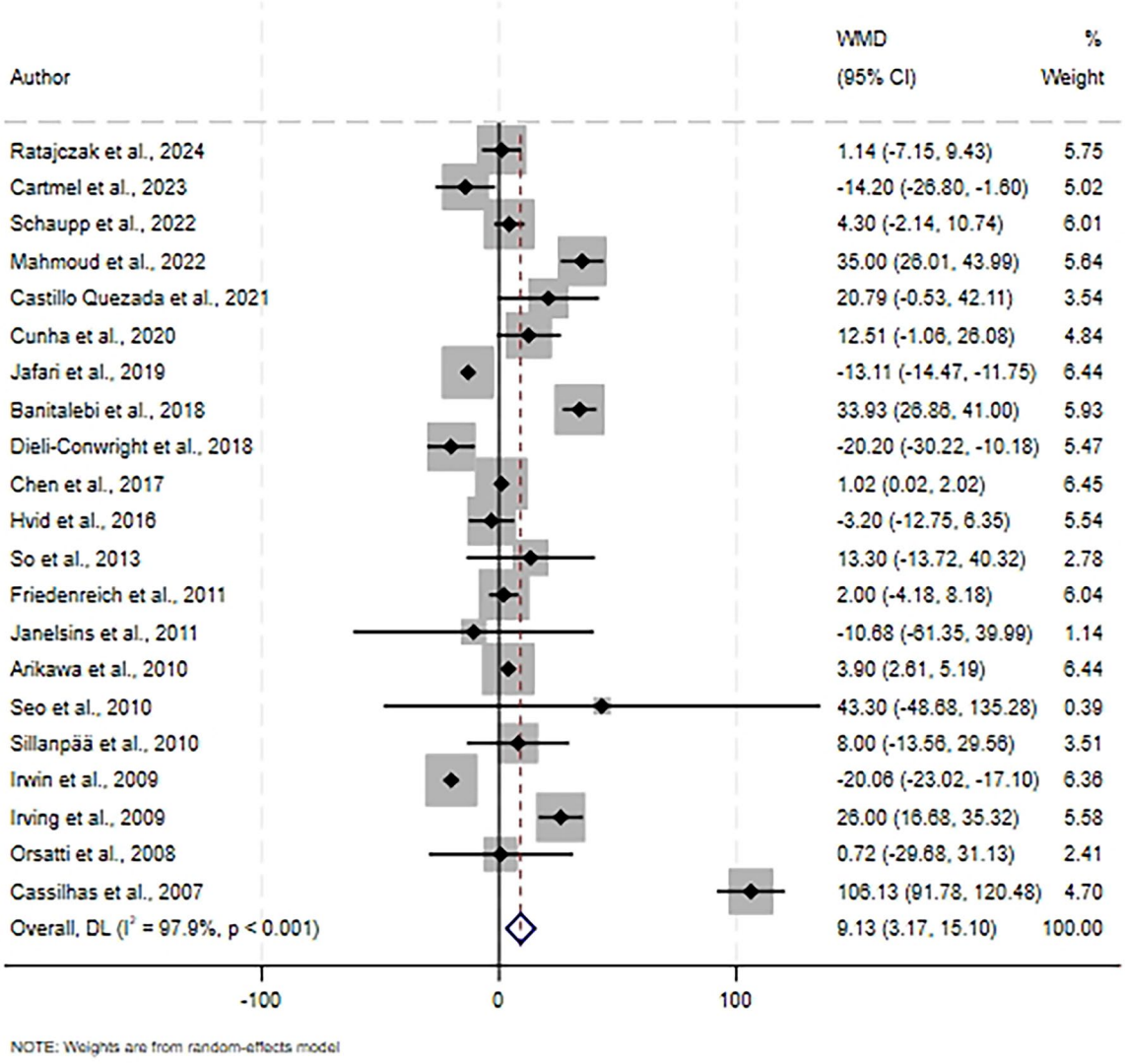

Figure 2. Forest plot of exercise-induced changes in IGF-1 levels compared to controls. Forest plot showing the weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of chronic exercise on circulating IGF-1 levels. The overall meta-analytic effect size is represented by the center of the diamond, with its width indicating the 95% CI.

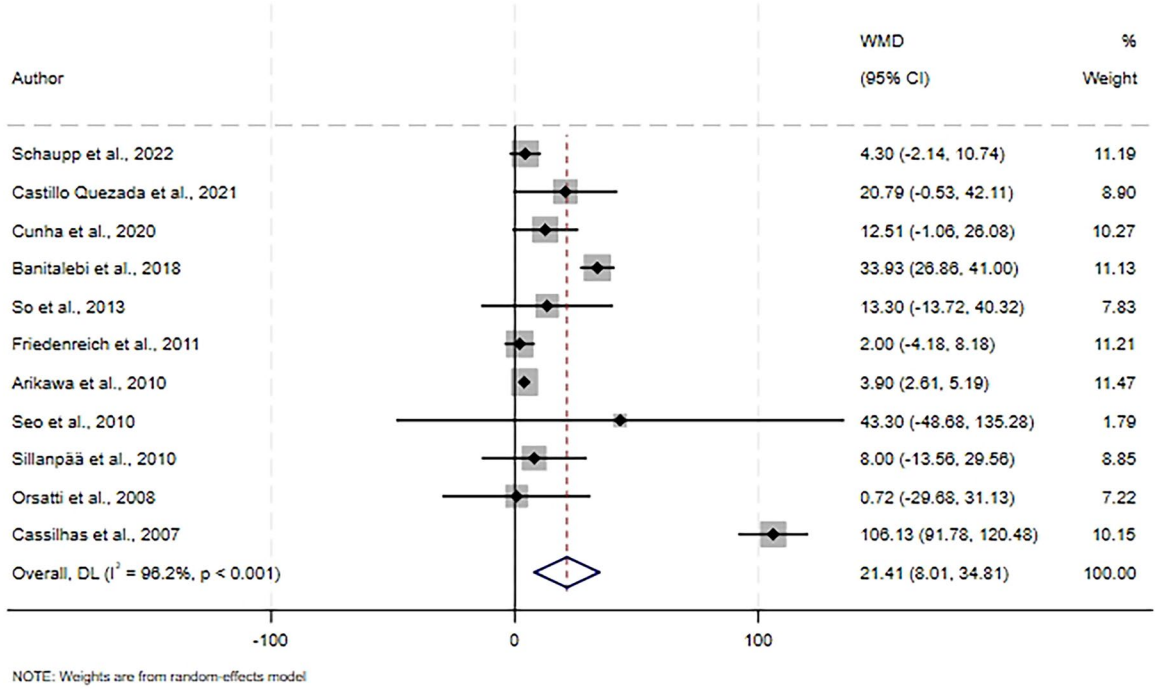

Figure 3. Forest plot of exercise-induced changes in IGF-1 levels in healthy individuals compared to controls. Forest plot showing the weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of chronic exercise on circulating IGF-1 levels in healthy individuals. The overall meta-analytic effect size is represented by the center of the diamond, with its width indicating the 95% CI.

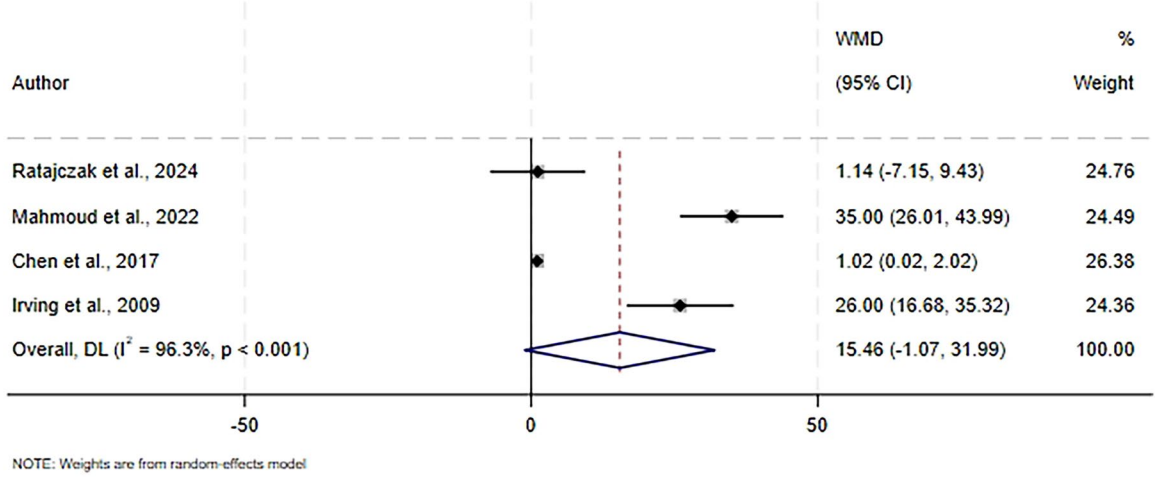

Figure 4. Forest plot of exercise-induced changes in IGF-1 levels in individuals with obesity compared to controls. Forest plot showing the weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of chronic exercise on circulating IGF-1 levels in individuals with obesity. The overall meta-analytic effect size is represented by the center of the diamond, with its width indicating the 95% CI.

individuals, exercise tended to increase IGFBP-3 (WMD = 48.23 ng/mL, 95% CI [–84.20, 180.65, $p = 0.051$), accompanied by moderate heterogeneity (I^2 = 61.3%) (Supplementary Result S1). In cancer patients or survivors, exercise significantly increased IGFBP-3 levels (WMD = 4.58 ng/mL, 95% CI [–1.36, 7.79, $p < 0.001$), with high heterogeneity (I^2 = 91.4%) (Supplementary Result S2). One study conducted in cancer survivors [57] was excluded from this analysis due to its extremely low statistical weight (0.01%), which may have disproportionately influenced the pooled estimate and variance. None of the studies conducted in individuals with overweight or obesity reported both IGF-1 and IGFBP-3 outcomes, precluding subgroup analysis for this population.

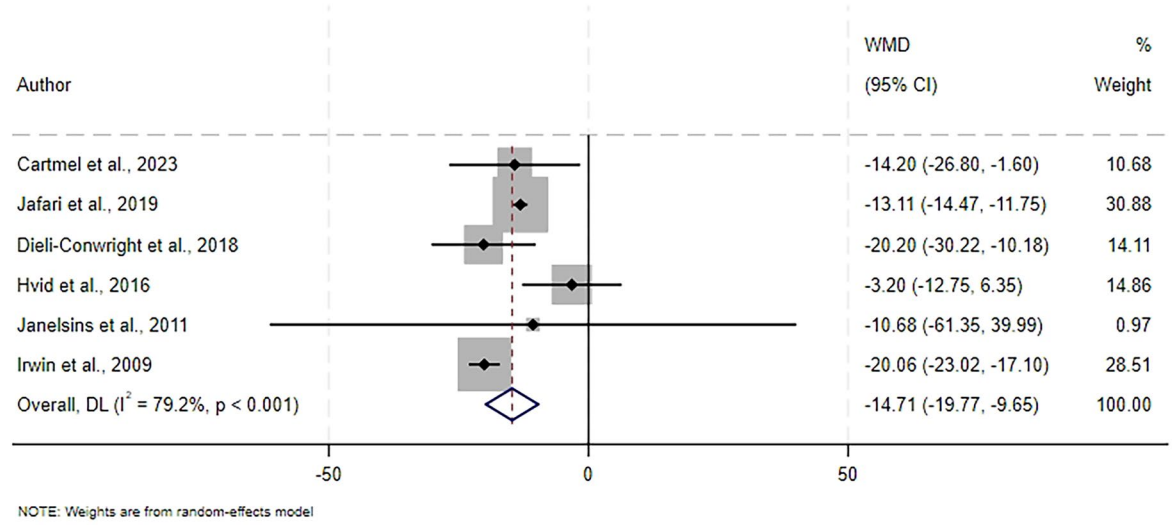

Figure 5. Forest plot of exercise-induced changes in IGF-1 levels in individuals with cancer compared to controls. Forest plot showing the weighted mean difference (WMD) and 95% confidence intervals (CIs) for the effect of chronic exercise on circulating IGF-1 levels in cancer patients or survivors. The overall meta-analytic effect size is represented by the center of the diamond, with its width indicating the 95% CI.

Assessment of cumulative evidence using trial sequential analysis

The TSA showed that the cumulative *Z*-curve crossed both the conventional significance boundary and the O'Brien–Fleming trial sequential monitoring boundary before reaching the required information size (RIS) (Figure 6a). The RIS was estimated to be 1628 participants, while the accrued sample size in the meta-analysis was 1372 participants. Despite falling slightly short of the RIS, the crossing of the monitoring boundary indicates that the observed significant increase in IGF-1 levels following chronic exercise interventions is statistically robust and unlikely to be a false-positive finding due to random error.

Publication bias

Publication bias was assessed using Egger's test and visual inspection of the funnel plot. Egger's test showed no significant evidence of publication bias ($p = 0.277$). Consistently, the funnel plot demonstrated a symmetrical distribution (Figure 6c), further suggesting that publication bias is unlikely to have substantially influenced the findings of this meta-analysis.

Discussion

In this systematic review and meta-analysis, we included 22 studies investigating the effects of chronic exercise on modulating serum IGF-1 levels across various health conditions, including healthy individuals, individuals with overweight or obesity, and cancer patients or survivors. This study sought to minimize confounding factors such as medications, hormone therapy, and structured dietary interventions by excluding studies that explicitly combined these factors with exercise, thereby enabling a focused evaluation of exercise-specific effects. The results demonstrate that exercise training led to a significant increase in serum IGF-1 levels in both healthy individuals and those with overweight or obesity, supporting the notion that exercise may mediate health benefits partially through the GH-IGF-1 axis [58]. Conversely, in cancer patients or survivors, exercise was associated with a significant reduction in IGF-1 levels, suggesting a more complex interaction between exercise and IGF-1 regulation in this population. While these findings emphasize the modulatory role of exercise in modulating serum IGF-1, they also highlight its diverse effects of exercise on IGF-1 across different populations, emphasizing its therapeutic potential and the need for tailored exercise interventions.

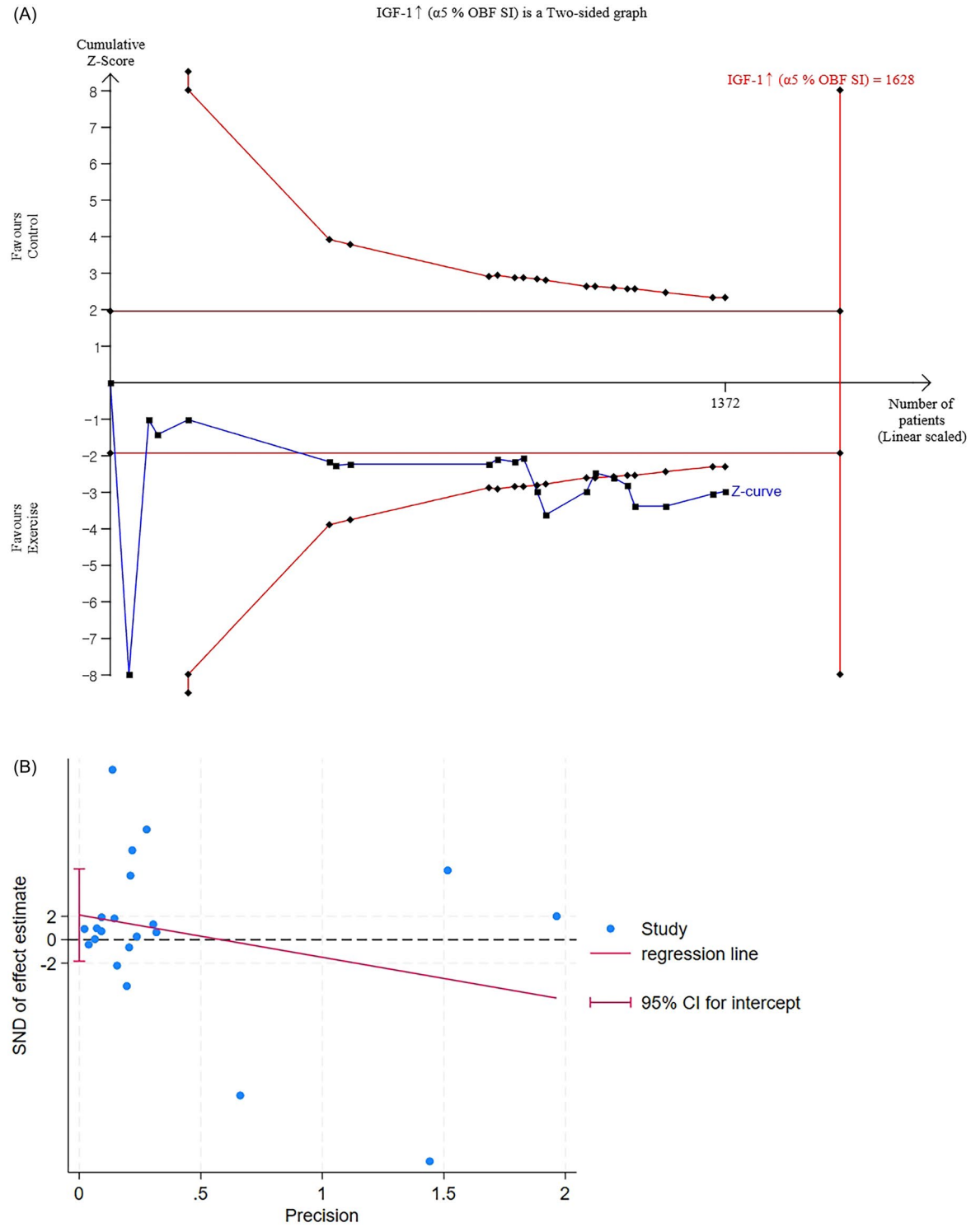

Figure 6. A. Trial sequential analysis of the effect of chronic exercise on IGF-1. Trial sequential analysis demonstrating the cumulative Z-curve (blue line) plotted against the trial sequential monitoring boundaries (red lines) for a two-sided α of 5% with a required information size (RIS) of 1,628 participants. The cumulative Z-curve crossed both the conventional significance boundary and the O'Brien–Fleming monitoring boundary before reaching the RIS (accrued sample size: 1,372), supporting the robustness of the observed exercise-induced increase in circulating IGF-1 levels while adjusting for random errors and repeated significance testing. B. Egger's test with pseudo 95% confidence limits. The non-significant result ($p = 0.277$) indicates no strong evidence of publication bias among the included studies. C. Funnel plot with pseudo 95% confidence limits. The plot supports the conclusion that potential publication bias does not substantially affect the interpretation of the meta-analysis results.

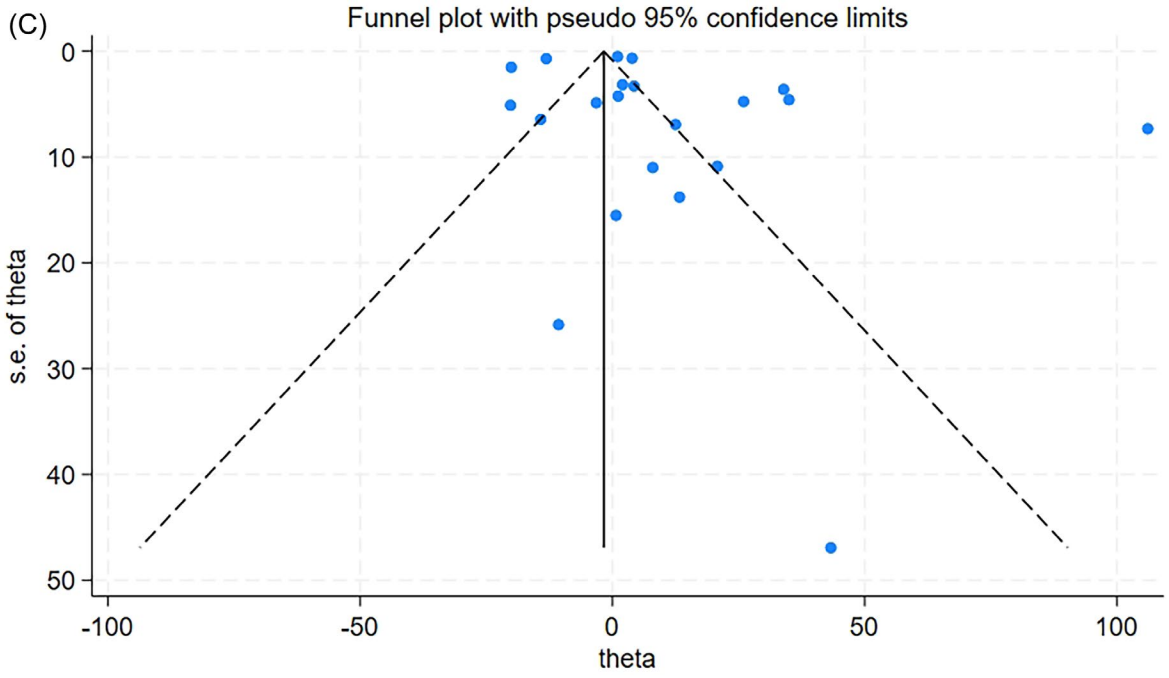

Figure 6. Continued.

Beyond physical activity, circulating IGF-1 levels can also be influenced by hormonal and nutritional factors. For instance, estrogen-based hormone replacement therapy (HRT) has been shown to decrease IGF-1 levels [59–61], whereas testosterone and growth hormone (GH) therapies tend to elevate IGF-1, particularly in healthy males across age groups [62–64]. While such interventions may offer theoretical benefits in attenuating age-related declines in IGF-1, concerns about potential oncogenic risks often outweigh their use in otherwise healthy individuals [65–67]. Additionally, higher dietary protein intake has been positively associated with serum IGF-1 levels [31,68], with some studies suggesting this association may be stronger than that of physical activity [69]. However, examining the independent role of dietary protein is challenging due to its correlation with increased caloric and carbohydrate intake, which may also stimulate IGF-1 *via* insulin-mediated pathways [31,70]. Importantly, an isocaloric protein-restricted diet did not significantly reduce serum IGF-1 [71], suggesting that protein intake alone may not be a sufficient determinant. Collectively, these findings emphasize the complexity and potential risks of modulating IGF-1 through exogenous or dietary means, further reinforcing the appeal of exercise as a safer and more physiologically congruent intervention. In support of this, our review found that exercise interventions were generally well tolerated across populations. Only two studies mentioned safety-related outcomes; one study with healthy individuals excluded a small number of participants due to elevated insulin levels not attributed to the intervention [43], and another study with cancer patients excluded the participants due to disease recurrence, which is unrelated to the exercise protocol [52]. The most commonly reported dropouts were predominantly due to non-specific reasons such as loss to follow-up, non-adherence, or personal scheduling conflicts, rather than adverse events. These findings suggest that chronic exercise programs can be safely implemented across diverse clinical contexts.

In this context, accumulating evidence supports regular exercise as an effective and independent strategy for increasing IGF-1 levels, particularly in healthy individuals. Although some studies report no significant IGF-1 response to exercise training over similar durations in comparable age groups [37,41,42,44], evidence from multiple RCTs suggests that regular exercise lasting beyond 8 weeks is positively associated with elevated serum IGF-1 levels in healthy individuals. Specifically, significant increases have been observed following resistance exercise training [38,39,46,47], aerobic exercise training [38], and combined exercise training [40,45]. Additionally, meta-analyses have further confirmed that both acute bouts of aerobic and resistance exercise [25] and sustained resistance training [72] can significantly elevate serum IGF-1 levels, supporting the anabolic and metabolic roles of exercise [22]. These

findings are particularly relevant for older adults, a demographic commonly featured in the included studies (age >50), where natural age-related declines in IGF-1 are well documented [73]. Importantly, our analysis indicate that such exercise-induced IGF-1 enhancement occurs even in the absence of pharmacological agents [30], nutritional interventions [31], or hormone therapy, emphasizing the independent efficacy of physical activity in activating the GH–IGF-1 axis. This aligns with the established physiological benefits of exercise in promoting muscle growth, tissue repair, and metabolic regulation [74], reinforcing its role as a key strategy for ameliorating age-related endocrine decline. This is particularly relevant, as this population typically experiences a significant decline in serum IGF-1 level [73], indicating the potential of exercise to attenuate age-related reductions in IGF-1 mediated health benefits. This pattern of exercise-induced IGF-1 elevation has also been examined in broader meta-analytic frameworks. For instance, a recent meta-analysis [75] evaluated the effects of physical activity on circulating IGF-1 levels exclusively in female populations, regardless of health status. However, interpretation of their results is complicated by methodological limitations, including heterogeneity and potential bias. In contrast, our meta-analysis, which included both male and female participants and incorporated stratification by health status, revealed a more differentiated pattern, in which exercise increased IGF-1 in healthy and obese individuals while decreasing it in cancer patients or survivors. These differences indicate the importance of participant characteristics and methodological rigor when interpreting exercise-induced IGF-1 modulation. In a qualitative, hypothesis-generating inspection of intervention features across the included trials, resistance-training programs performed at least three times per week, with sessions exceeding 60 min and continued for at least eight weeks, appeared more frequently among trials reporting IGF-1 increases in healthy individuals. These observations are descriptive rather than meta-analytic; given the small number of modality-specific trials and heterogeneous prescriptions, we did not conduct a modality-stratified meta-analysis, and robust recommendations would require pre-specified, adequately powered subgroup analyses stratified by exercise characteristics.

Along with the increasing prevalence of obesity, the association between IGF-1 levels with obesity has been of interest, as IGF-1's strong anabolic effects may counteract certain health benefits by amplifying obesogenic effects. Although some conflicting results exist [76], several recent clinical studies have demonstrated a negative association between obesity and IGF-1 [3,4,77], with this association appearing stronger in older populations [3]. This may be attributed to the obesity-related GH resistance in the liver, leading to attenuated IGF-1 production and subsequently lower serum IGF-1 levels [78]. Additionally, decreased ghrelin secretion from the stomach in obesity may blunt GH secretion from the pituitary, further contributing to reduced serum IGF-1 level [79]. Furthermore, IGF-1–mediated signaling has been reported to contribute only marginally to adipose tissue formation [13], playing a more critical role in the differentiation of pre-adipocytes than in the maturation and hypertrophy of adipocytes [80]. Consequently, IGF-1 itself appears to have a limited direct impact on adipose tissue deposition and adipocyte hypertrophy, while exerting beneficial effects across various other health domains. This suggests that obese individuals who engage in regular exercise are likely to experience positive outcomes, potentially benefiting from IGF-1's metabolic and anabolic effects without significantly promoting adiposity. Our meta-analysis of four eligible studies suggests that regular exercise is associated with increased serum IGF-1 levels in obese individuals. However, IGF-1 responses differed by participant characteristics and exercise protocols within overweight and obese cohorts. Resistance-focused programs in overweight women at high loads [49] and in sarcopenic-obese older adults using resistance or combined training [50] showed increases. In contrast, a mixed-circuit program in insulin-resistant women [48] and a predominantly endurance program delivered five times per week in adults with metabolic syndrome [51] showed marginal or no between-group differences. Although all four cohorts were overweight or obese, these divergent findings likely reflect differences in concurrent disease context, exercise modality and dose, and non-uniform post-intervention sampling windows, each of which can influence GH/IGF-1 axis activation and recovery dynamics. This variability warrants further investigation, though our overall result supports that regular exercise can increase IGF-1 levels in this population.

Exercise has been shown to exert direct effects on tumor-intrinsic factors, influence systemic physiological responses, alleviate cancer-related adverse events, and enhance treatment efficacy [81]. However, the anabolic and metabolic effects mediated by IGF-1 raise concerns regarding its potential role in exacerbating cancer progression and neoplastic processes [82]. The IGF-1 axis is known to contribute to

proliferation, survival, metastasis, and inhibition of apoptosis of cancer cells through both direct and indirect mechanisms [83]. Indeed, recent large cohort studies have demonstrated that elevated IGF-1 levels are associated with a higher incidence of various cancers [10,83] and increased cancer-related mortality [10], with the strongest associations observed in prostate, breast, and colorectal cancers [84]. Moreover, tissue expression of IGF1R is often elevated in cancer patients, particularly those with lung, gastric, endometrial, and breast cancers, compared to controls [83]. These findings suggest that serum IGF-1 levels and related components should be carefully considered in the management of cancer patients or survivors. Physical activity is recommended for its ability to improve various health outcomes and enhance treatment tolerance and response in this population [29], and a substantial proportion of cancer survivors have been reported to meet the recommended physical activity guidelines [85]. Our meta-analysis demonstrated a significant reduction in serum IGF-1 levels following chronic exercise in cancer survivors, alleviating concerns regarding exercise-induced IGF-1 elevation and its potential oncogenic implications. This finding is consistent with prior meta-analyses that observed moderate decreases in circulating IGF-1 following exercise interventions in breast cancer survivors [86–89]. Additionally, another meta-analysis with breast cancer patients found a trend towards decreased IGF-I levels following exercise interventions, though this reduction did not reach statistical significance [90]. In contrast, other reviews reported no significant changes in IGF-1 in response to exercise in similar populations [91,92], suggesting a more limited endocrine responsiveness under certain conditions. These discrepancies may due to the differences in study populations and methodological stringency. Specifically, the previous analyses focused exclusively on female breast cancer survivors, whereas our study included a more heterogeneous oncologic population, comprising individuals with breast, ovarian, and prostate cancers, and incorporated both male and female participants. Furthermore, our meta-analysis applied more rigorous inclusion criteria by excluding trials in which control groups received structured non-exercise interventions (e.g. educational or behavioral support), thereby improving the specificity with which exercise-induced effects on IGF-1 modulation could be assessed.

Given that exercise promotes GH secretion across various populations, subsequently increasing IGF-1 levels [21,22], and stimulates IGF-1 secretion from skeletal muscle independently of GH's action on the liver [27,28], there is limited specific literature explaining differential IGF-1 responses to exercise across varying health statuses, particularly in cancer contexts. This may be largely due to the complex roles IGF-1 plays in various metabolic and pathological processes, including cancer progression, which may alter its regulation in distinct ways. Although exercise-induced reductions in IGF-1 may be beneficial for tumor suppression in cancer patients or survivors, regular exercise provides extensive therapeutic and health benefits beyond IGF-1 modulation. Thus, regular exercise is recommended as a supportive intervention for cancer patients or survivors, offering multifaceted health advantages. Further research is necessary to clarify how IGF-1 reductions impact other health statuses and to determine the suitability of exercise recommendations for cancer patients based on these effects.

IGFBP-3 functions as the primary circulating carrier of IGF-1, modulating its bioavailability, prolonging its half-life, and regulating its interaction with IGF-1 receptors. Beyond its carrier role, IGFBP-3 also exerts IGF-1–independent biological actions, including pro-apoptotic and anti-proliferative effects, which may hold particular relevance in oncological settings [93]. In our subgroup meta-analysis restricted to studies concurrently reporting both IGF-1 and IGFBP-3 outcomes, exercise appeared to increase both circulating IGF-1 and IGFBP-3 levels in healthy individuals, which align with the recognized anabolic and metabolic roles of exercise. By contrast, in cancer patients or survivors, exercise was associated with a significant increase in IGFBP-3 levels alongside a reduction in circulating IGF-1 concentrations. This differential response suggests that elevated IGFBP-3 may contribute to the exercise-induced suppression of IGF-1 in cancer populations, potentially through sequestration of free IGF-1 or modulation of IGF-1 receptor availability, mechanisms that could attenuate IGF-1–mediated oncogenic signaling [94]. Supporting this notion, epidemiological evidence has indicated that higher circulating IGF-1 concentrations combined with lower IGFBP-3 levels are associated with an increased risk of breast [95] and colorectal cancers [96]. Accordingly, our observation of exercise-induced IGFBP-3 elevation concurrent with IGF-1 reduction in cancer populations may represent a potentially beneficial adaptive response. Nevertheless, considering the heterogeneity of prior findings regarding the relationship between IGF-1 and IGFBP-3 in cancer populations [97,98], as well as inconsistent reports from meta-analyses evaluating the effects of exercise on IGFBP-3

[86,88,91,99,100], this interpretation remains speculative. Further mechanistic studies are warranted to elucidate the interplay between exercise, IGF-1, and IGFBP-3, particularly in the context of cancer.

In this meta-analysis, we sought to minimize key confounding factors, such as pharmacological treatments, hormone therapy, and structured dietary interventions, by excluding studies that explicitly combined these factors with exercise. However, we acknowledge that dietary intake was not systematically assessed in the majority of included studies. Although some trials instructed participants to maintain their habitual diet, such guideline alone may not adequately control for dietary variability, which remains a potential source of residual confounding. This methodological limitation constrains our ability to attribute observed IGF-1 changes solely to exercise. Moreover, evidences suggest that energy availability as a critical determinant of IGF-1 regulation, independent of exercise. For instance, caloric restriction has been reported to markedly blunt IGF-1 responses despite elevated GH levels, indicating a state of anabolic resistance [101]. Additional studies have demonstrated that energy deficits suppress IGF-1 secretion in a dose-dependent manner [102,103], overriding the anabolic signaling typically induced by physical activity. These results indicate the importance of considering both caloric intake and total energy balance when interpreting exercise-induced IGF-1 modulation. In particular, the reduction in IGF-1 levels observed among cancer survivors and patients and survivors in this meta-analysis may, in part, reflect population-specific alterations in energy balance. Prospective cohort data indicate that cancer survivors frequently exhibit sustained reductions in caloric intake following diagnosis [104], which may result in a net energy deficit sufficient to suppress hepatic IGF-1 production when combined with increased energy expenditure from exercise. Accordingly, the decrease in IGF-1 in this population may represent an adaptive endocrine response to caloric insufficiency, which has been shown to suppress hepatic IGF-1 synthesis [101–103]. While the underlying mechanisms warrant further investigation, these considerations call for the need to account for energy balance when evaluating endocrine dynamics to exercise, particularly in in oncological contexts where baseline nutritional status may already be compromised.

Several limitations should be acknowledged. First, the high degree of statistical heterogeneity observed across studies is a notable methodological consideration. The overall meta-analysis revealed substantial heterogeneity (I^2=97.9%), with similarly high values in subgroup analyses of healthy individuals (I^2=96.2%) and obese individuals (I^2=96.3%), and moderate-to-high heterogeneity among cancer patients or survivors (I^2=79.2%). However, such levels of heterogeneity are not uncommon in exercise-based meta-analyses; previous meta-analyses conducted in breast cancer populations have reported I^2 values as high as 84.15% [75] and even 99% [91]. This variability likely reflects differences in exercise modalities [25,105], participant characteristics such as age, sex, and baseline IGF-1 levels [72,106], and intervention duration [72]. The inclusion of both male and female participants in our study, unlike prior meta-analyses that focused exclusively on women with breast cancer [75,89,91], may have further contributed to between-study heterogeneity. These findings highlight the inherent difficulty of standardizing lifestyle interventions across heterogeneous populations and study protocols, underscoring the need for more uniformly designed future trials. Nevertheless, despite the observed variability, the overall consistency in directionality across subgroups suggests a robust signal. To further validate the reliability of this effect and minimize the risks of random error and cumulative type I error, we performed TSA over the primary outcome. Results from the trial sequential analysis confirmed the robustness of our main finding, lending additional support to the conclusion that exercise significantly increases circulating IGF-1 levels. This result reinforces the credibility of our findings and strengthens confidence in the exercise-induced modulation of IGF-1 despite high heterogeneity. Furthermore, our inclusion criteria limited the diversity of exercise interventions, particularly modality, intensity, and volume; and because these dimensions may differentially influence the GH/IGF-1 axis, our dataset, constrained by few trials per modality and heterogeneous prescriptions, was insufficient for robust modality-specific subgrouping, underscoring the need for adequately powered, modality-stratified trials. The study population was predominantly female (91%) and relatively older (mean age: 57.1 ± 5.9 years), which may limit the generalizability of our findings. In addition, our analysis of IGFBP-3 was restricted to a subset of studies reporting both IGF-1 and IGFBP-3 outcomes, preventing comprehensive evaluation of their interplay across all populations. Future studies with standardized dietary assessments, broader participant demographics, and consistent measurement of IGF-1–related biomarkers are needed to clarify the mechanisms underlying exercise-induced IGF-1 modulation across different clinical and physiological contexts.

Conclusion

In conclusion, this systematic review and meta-analysis demonstrates that regular exercise exerts differential effects on circulating IGF-1 levels depending on health status. Exercise significantly increased IGF-1 in healthy individuals and those with overweight or obesity, supporting its role in promoting metabolic and anabolic health. In contrast, exercise was associated with a reduction in IGF-1 among cancer patients or survivors, a response that may be partially mediated by concurrent increases in IGFBP-3 levels. Taken together, these findings indicate divergent physiological responses across clinical contexts and highlight the need for further work to delineate mechanisms and the broader clinical implications of exercise-induced IGF-1 modulation.

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Authors' contribution

CRediT: **Yu Rim Kwon**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft; **Yehee Kim**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft; **YuSik Kim**: Conceptualization, Investigation, Supervision, Validation, Data curation, Formal analysis, Methodology, Writing – review & editing.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Puche JE, Castilla-Cortazar I. Human conditions of insulin-like growth factor-I (IGF-I) deficiency. J Transl Med. 2012;10(1):224. doi:10.1186/1479-5876-10-224.
[2] LeRoith D, Yakar S. Mechanisms of disease: metabolic effects of growth hormone and insulin-like growth factor 1. Nat Clin Pract Endocrinol Metab. 2007;3(3):302–310. doi:10.1038/ncpendmet0427.
[3] Sherlala RA, Kammerer CM, Kuipers AL, et al. Relationship between serum IGF-1 and BMI differs by age. J Gerontol A Biol Sci Med Sci. 2021;76(7):1303–1308. doi:10.1093/gerona/glaa282.
[4] Kubo H, Sawada S, Satoh M, et al. Insulin-like growth factor-1 levels are associated with high comorbidity of metabolic disorders in obese subjects; a Japanese single-center, retrospective-study. Sci Rep. 2022;12(1):20130. doi:10.1038/s41598-022-23521-1.
[5] Li Y, Yang W, Li J, et al. Relationship between serum insulin-like growth factor 1 levels and ischaemic stroke: a systematic review and meta-analysis. BMJ Open. 2022;12(6):e045776. doi:10.1136/bmjopen-2020-045776.
[6] Jiang JJ, Chen SM, Chen J, et al. Serum IGF-1 levels are associated with sarcopenia in elderly men but not in elderly women. Aging Clin Exp Res. 2022;34(10):2465–2471. doi:10.1007/s40520-022-02180-2.
[7] Westwood AJ, Beiser A, Decarli C, et al. Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology. 2014;82(18):1613–1619. doi:10.1212/WNL.0000000000000382.

[8] Li T, Zhao Y, Yang X, et al. Association between insulin-like growth factor-1 and cardiovascular events: a systematic review and dose-response meta-analysis of cohort studies. J Endocrinol Invest. 2022;45(12):2221–2231. doi:10.1007/s40618-022-01819-1.
[9] Lin J, Yang L, Huang J, et al. Insulin-like growth factor 1 and risk of cardiovascular disease: results from the UK Biobank Cohort Study. J Clin Endocrinol Metab. 2023;108(9):e850–e60. doi:10.1210/clinem/dgad105.
[10] Mukama T, Srour B, Johnson T, et al. IGF-1 and risk of morbidity and mortality from cancer, cardiovascular diseases, and all causes in EPIC-Heidelberg. J Clin Endocrinol Metab. 2023;108(10):e1092–e105. doi:10.1210/clinem/dgad212.
[11] Friedrich N, Thuesen B, Jørgensen T, et al. The association between IGF-I and insulin resistance: a general population study in Danish adults. Diabetes Care. 2012;35(4):768–773. doi:10.2337/dc11-1833.
[12] Pascual M, Larralde J, Martínez JA. Insulin-like growth factor I (IGF-I) affects plasma lipid profile and inhibits the lipolytic action of growth hormone (GH) in isolated adipocytes. Life Sci. 1995;57(12):1213–1218. doi:10.1016/0024-3205(95)02067-s.
[13] Boucher J, Softic S, El Ouaamari A, et al. Differential roles of insulin and IGF-1 receptors in adipose tissue development and function. Diabetes. 2016;65(8):2201–2213. doi:10.2337/db16-0212.
[14] Klöting N, Koch L, Wunderlich T, et al. Autocrine IGF-1 action in adipocytes controls systemic IGF-1 concentrations and growth. Diabetes. 2008;57:2074–2082.
[15] Wang P, Mak VC, Cheung LW. Drugging IGF-1R in cancer: new insights and emerging opportunities. Genes Dis. 2023;10(1):199–211. doi:10.1016/j.gendis.2022.03.002.
[16] Hua H, Kong Q, Yin J, et al. Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: a challenge for cancer therapy. J Hematol Oncol. 2020;13(1):64. doi:10.1186/s13045-020-00904-3.
[17] Knuppel A, Fensom GK, Watts EL, et al. Circulating insulin-like growth factor-I concentrations and risk of 30 cancers: prospective analyses in UK Biobank. Cancer Res. 2020;80(18):4014–4021. doi:10.1158/0008-5472.CAN-20-1281.
[18] Nwabo Kamdje AH, Seke Etet PF, Kipanyula MJ, et al. Insulin-like growth factor-1 signaling in the tumor microenvironment: carcinogenesis, cancer drug resistance, and therapeutic potential. Front Endocrinol (Lausanne). 2022;13:927390. doi:10.3389/fendo.2022.927390.
[19] Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. JAMA. 2018;320(19):2020–2028. doi:10.1001/jama.2018.14854.
[20] Athanasiou N, Bogdanis GC, Mastorakos G. Endocrine responses of the stress system to different types of exercise. Rev Endocr Metab Disord. 2023;24(2):251–266. doi:10.1007/s11154-022-09758-1.
[21] Jansson D, Lindberg AS, Lundberg E, et al. Effects of resistance and endurance training alone or combined on hormonal adaptations and cytokines in healthy children and adolescents: a systematic review and meta-analysis. Sports Med Open. 2022;8(1):81. doi:10.1186/s40798-022-00471-6.
[22] Zouhal H, Jayavel A, Parasuraman K, et al. Effects of exercise training on anabolic and catabolic hormones with advanced age: a systematic review. Sports Med. 2022;52(6):1353–1368. doi:10.1007/s40279-021-01612-9.
[23] Rodríguez-Gutiérrez E, Torres-Costoso A, Pascual-Morena C, et al. Effects of resistance exercise on neuroprotective factors in middle and late life: a systematic review and meta-analysis. Aging Dis. 2023;14(4):1264–1275. doi:10.14336/AD.2022.1207.
[24] Ye G, Xiao Z, Luo Z, et al. Resistance training effect on serum insulin-like growth factor 1 in the serum: a meta-analysis. Aging Male. 2020;23(5):1471–1479. doi:10.1080/13685538.2020.1801622.
[25] de Alcantara Borba D, da Silva Alves E, Rosa JPP, et al. Can IGF-1 serum levels really be changed by acute physical exercise? A systematic review and meta-analysis. J Phys Act Health. 2020;17(5):575–584. doi:10.1123/jpah.2019-0453.
[26] Birzniece V. Exercise and the growth hormone–insulin-like growth factor axis. Curr Opin Endocr Metab Res. 2019;9:1–7. doi:10.1016/j.coemr.2019.04.006.
[27] Brahm H, Piehl-Aulin K, Saltin B, et al. Net fluxes over working thigh of hormones, growth factors and biomarkers of bone metabolism during short lasting dynamic exercise. Calcif Tissue Int. 1997;60(2):175–180. doi:10.1007/s002239900210.
[28] Adams GR, Haddad F, Bodell PW, et al. Combined isometric, concentric, and eccentric resistance exercise prevents unloading-induced muscle atrophy in rats. J Appl Physiol (1985). 2007;103(5):1644–1654. doi:10.1152/japplphysiol.00669.2007.
[29] Rock CL, Thomson CA, Sullivan KR, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin. 2022;72(3):230–262. doi:10.3322/caac.21719.
[30] Klement RJ, Fink MK. Dietary and pharmacological modification of the insulin/IGF-1 system: exploiting the full repertoire against cancer. Oncogenesis. 2016;5(2):e193–e193. doi:10.1038/oncsis.2016.2.
[31] Watling CZ, Kelly RK, Tong TYN, et al. Associations of circulating insulin-like growth factor-I with intake of dietary proteins and other macronutrients. Clin Nutr. 2021;40(7):4685–4693. doi:10.1016/j.clnu.2021.04.021.
[32] Veldhuis JD, Frystyk J, Iranmanesh A, et al. Testosterone and estradiol regulate free insulin-like growth factor I (IGF-I), IGF binding protein 1 (IGFBP-1), and dimeric IGF-I/IGFBP-1 concentrations. J Clin Endocrinol Metab. 2005;90(5):2941–2947. doi:10.1210/jc.2004-1314.
[33] van Bunderen CC, Meijer RI, Lips P, et al. Titrating growth hormone dose to high-normal IGF-1 levels has beneficial effects on body fat distribution and microcirculatory function despite causing insulin resistance. Front Endocrinol (Lausanne). 2020;11:619173. doi:10.3389/fendo.2020.619173.

[34] Cheng Y, Li W, Gui R, et al. Dual characters of GH-IGF1 signaling pathways in radiotherapy and post-radiotherapy repair of cancers. Front Cell Dev Biol. 2021;9:671247. doi:10.3389/fcell.2021.671247.
[35] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100.
[36] Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol. 2017;17(1):39. doi:10.1186/s12874-017-0315-7.
[37] Schaupp A, Bidlingmaier M, Martini S, et al. Resistance training-induced improvement in physical function is not associated to changes in endocrine somatotropic activity in prefrail older adults. Arch Gerontol Geriatr. 2022;103:104792. doi:10.1016/j.archger.2022.104792.
[38] Castillo Quezada H, Martínez-Salazar C, Fuentealba-Urra S, et al. Effects of two physical training programs on the cognitive status of a group of older adults in Chile. Int J Environ Res Public Health. 2021;18(8):4186. doi:10.3390/ijerph18084186.
[39] Cunha PM, Nunes JP, Tomeleri CM, et al. Resistance training performed with single and multiple sets induces similar improvements in muscular strength, muscle mass, muscle quality, and IGF-1 in older women: a randomized controlled trial. J Strength Cond Res. 2020;34(4):1008–1016. doi:10.1519/JSC.0000000000002847.
[40] Banitalebi E, Faramarzi M, Bagheri L, et al. Comparison of performing 12 weeks' resistance training before, after and/or in between aerobic exercise on the hormonal status of aged women: a randomized controlled trial. Horm Mol Biol Clin Investig. 2018;35(3):20180020. doi:10.1515/hmbci-2018-0020.
[41] So W-y, Song M, Park Y-h, et al. Body composition, fitness level, anabolic hormones, and inflammatory cytokines in the elderly: a randomized controlled trial. Aging Clin Exp Res. 2013;25(2):167–174. doi:10.1007/s40520-013-0032-y.
[42] Friedenreich CM, Neilson HK, Woolcott CG, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. Endocr Relat Cancer. 2011;18(3):357–369. doi:10.1530/ERC-10-0303.
[43] Arikawa AY, Kurzer MS, Thomas W, et al. No effect of exercise on insulin-like growth factor-I, insulin, and glucose in young women participating in a 16-week randomized controlled trial. Cancer Epidemiol Biomarkers Prev. 2010;19(11):2987–2990. doi:10.1158/1055-9965.EPI-10-0828.
[44] Seo DI, Jun TW, Park KS, et al. 12 weeks of combined exercise is better than aerobic exercise for increasing growth hormone in middle-aged women. Int J Sport Nutr Exerc Metab. 2010;20(1):21–26. doi:10.1123/ijsnem.20.1.21.
[45] Sillanpää E, Häkkinen A, Laaksonen DE, et al. Serum basal hormone concentrations, nutrition and physical fitness during strength and/or endurance training in 39-64-year-old women. Int J Sports Med. 2010;31(2):110–117. doi:10.1055/s-0029-1242811.
[46] Orsatti FL, Nahas EA, Maesta N, et al. Plasma hormones, muscle mass and strength in resistance-trained postmenopausal women. Maturitas. 2008;59(4):394–404. doi:10.1016/j.maturitas.2008.04.002.
[47] Cassilhas RC, Viana VAR, Grassmann V, et al. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc. 2007;39(8):1401–1407. doi:10.1249/mss.0b013e318060111f.
[48] Ratajczak M, Krzywicka M, Szulińska M, et al. Effects of 12-week combined strength and endurance circuit training program on insulin sensitivity and retinol-binding protein 4 in women with insulin-resistance and overweight or mild obesity: a randomized controlled trial. Diabetes Metab Syndr Obes. 2024;17:93–106. doi:10.2147/DMSO.S432954.
[49] Mahmoud N, Mohammadreza HA, Abdolhosein TK, et al. Serum myokine levels after linear and flexible non-linear periodized resistance training in overweight sedentary women. Eur J Sport Sci. 2022;22(4):658–668. doi:10.1080/17461391.2021.1895893.
[50] Chen HT, Chung YC, Chen YJ, et al. Effects of different types of exercise on body composition, muscle strength, and IGF-1 in the elderly with sarcopenic obesity. J Am Geriatr Soc. 2017;65(4):827–832. doi:10.1111/jgs.14722.
[51] Irving BA, Weltman JY, Patrie JT, et al. Effects of exercise training intensity on nocturnal growth hormone secretion in obese adults with the metabolic syndrome. J Clin Endocrinol Metab. 2009;94(6):1979–1986. doi:10.1210/jc.2008-2256.
[52] Cartmel B, Li F-Y, Zhou Y, et al. Randomized trial of exercise on cancer-related blood biomarkers and survival in women with ovarian cancer. Cancer Med. 2023;12(14):15492–15503. doi:10.1002/cam4.6187.
[53] Jafari A, Arazi H, Ghadian A, et al. The impact of combined (aerobic-resistance) training on serum levels of IGF-I and IGFBP-3 in men with prostate cancer. J Adv Med Biomed Res. 2019;27(122):35–41. doi:10.30699/jambs.27.122.35.
[54] Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial. J Clin Oncol. 2018;36(9):875–883. doi:10.1200/JCO.2017.75.7526.
[55] Hvid T, Lindegaard B, Winding K, et al. Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. Cancer Causes Control. 2016;27(2):165–174. doi:10.1007/s10552-015-0694-1.
[56] Janelsins MC, Davis PG, Wideman L, et al. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer. 2011;11(3):161–170. doi:10.1016/j.clbc.2011.03.013.
[57] Irwin ML, Varma K, Alvarez-Reeves M, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. Cancer Epidemiol Biomarkers Prev. 2009;18(1):306–313. doi:10.1158/1055-9965.EPI-08-0531.

[58] Frystyk J. Exercise and the growth hormone-insulin-like growth factor axis. Med Sci Sports Exerc. 2010;42(1):58–66. doi:10.1249/MSS.0b013e3181b07d2d.
[59] Sonnet E, Lacut K, Roudaut N, et al. Effects of the route of oestrogen administration on IGF-1 and IGFBP-3 in healthy postmenopausal women: results from a randomized placebo-controlled study. Clin Endocrinol (Oxf). 2007;66(5):626–631. doi:10.1111/j.1365-2265.2007.02783.x.
[60] Stanosz S, Zochowska E, Safranow K, et al. Influence of modified transdermal hormone replacement therapy on the concentrations of hormones, growth factors, and bone mineral density in women with osteopenia. Metabolism. 2009;58(1):1–7. doi:10.1016/j.metabol.2008.07.016.
[61] Davis SR, Stuckey BG, Norman RJ, et al. Effects of the route of estrogen administration on insulinlike growth factor-I, IGF binding protein-3, and insulin resistance in healthy postmenopausal women: results from a randomized, controlled study. Menopause. 2008;15(6):1065–1069. doi:10.1097/gme.0b013e318174f16e.
[62] Hobbs CJ, Plymate SR, Rosen CJ, et al. Testosterone administration increases insulin-like growth factor-I levels in normal men. J Clin Endocrinol Metab. 1993;77:776–779.
[63] Duschek EJ, Gooren LJ, Netelenbos C. Comparison of effects of the rise in serum testosterone by raloxifene and oral testosterone on serum insulin-like growth factor-1 and insulin-like growth factor binding protein-3. Maturitas. 2005;51(3):286–293. doi:10.1016/j.maturitas.2004.08.011.
[64] Muniyappa R, Sullivan SD, Tella SH, et al. Effects of growth hormone administration on luteinizing hormone secretion in healthy older men and women. Physiol Rep. 2017;5(23):e13516. doi:10.14814/phy2.13516.
[65] Giordano R, Bonelli L, Marinazzo E, et al. Growth hormone treatment in human ageing: benefits and risks. Hormones (Athens). 2008;7(2):133–139. doi:10.1007/BF03401504.
[66] Harper-Harrison G, Carlson K, Shanahan MM. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC; 2024. Hormone Replacement Therapy.
[67] Giannoulis MG, Martin FC, Nair KS, et al. Hormone replacement therapy and physical function in healthy older men. Time to talk hormones? Endocr Rev. 2012;33(3):314–377. doi:10.1210/er.2012-1002.
[68] Donnelly K, Beare T, Clapper J, et al. The effects of dietary protein on serum IGF-1 levels in adult humans. The FASEB Journal. 2008;22(S1):883.8. doi:10.1096/fasebj.22.1_supplement.883.8.
[69] Gulick CN, Peddie MC, Cameron C, et al. Physical activity, dietary protein and insulin-like growth factor 1: cross-sectional analysis utilising UK Biobank. Growth Horm IGF Res. 2020;55:101353. doi:10.1016/j.ghir.2020.101353.
[70] Kaklamani VG, Linos A, Kaklamani E, et al. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol. 1999;17(10):3291–3298. doi:10.1200/JCO.1999.17.10.3291.
[71] Cagigas ML, Fiorito G, Bertozzi B, et al. Effects of protein restriction on insulin-like growth factor (IGF)-1 in men with prostate cancer: results from a randomized clinical trial. Biomark Res. 2024;12(1):68. doi:10.1186/s40364-024-00613-w.
[72] Jiang Q, Lou K, Hou L, et al. The effect of resistance training on serum insulin-like growth factor 1(IGF-1): A systematic review and meta-analysis. Complement Ther Med. 2020;50:102360. doi:10.1016/j.ctim.2020.102360.
[73] Zhu H, Xu Y, Gong F, et al. Reference ranges for serum insulin-like growth factor I (IGF-I) in healthy Chinese adults. PLoS One. 2017;12(10):e0185561. doi:10.1371/journal.pone.0185561.
[74] Song YH, Song JL, Delafontaine P, et al. The therapeutic potential of IGF-I in skeletal muscle repair. Trends Endocrinol Metab. 2013;24(6):310–319. doi:10.1016/j.tem.2013.03.004.
[75] Swain CTV, Drummond AE, Milne RL, et al. Linking physical activity to breast cancer risk via insulin/insulin-like growth factor signaling system, part 1: the effect of physical activity on the insulin/insulin-like growth factor signaling system. Cancer Epidemiol Biomarkers Prev. 2022;31(12):2106–2115. doi:10.1158/1055-9965.EPI-22-0504.
[76] Hjelholt A, Høgild M, Bak AM, et al. Growth hormone and obesity. Endocrinol Metab Clin North Am. 2020;49(2):239–250. doi:10.1016/j.ecl.2020.02.009.
[77] Muller YL, Hanson RL, Mahkee D, et al. Low serum insulinlike growth factor II levels correlate with high BMI in American Indian adults. Obesity (Silver Spring). 2020;28(3):676–682. doi:10.1002/oby.22741.
[78] Juiz-Valiña P, Pena-Bello L, Cordido M, et al. Altered GH-IGF-1 axis in severe obese subjects is reversed after bariatric surgery-induced weight loss and related with low-grade chronic inflammation. J Clin Med. 2020;9(8):2614. doi:10.3390/jcm9082614.
[79] Pena-Bello L, Pertega-Diaz S, Outeiriño-Blanco E, et al. Effect of oral glucose administration on rebound growth hormone release in normal and obese women: the role of adiposity, insulin sensitivity and ghrelin. PLoS One. 2015;10(3):e0121087. doi:10.1371/journal.pone.0121087.
[80] Bäck K, Arnqvist HJ. Changes in insulin and IGF-I receptor expression during differentiation of human preadipocytes. Growth Horm IGF Res. 2009;19(2):101–111. doi:10.1016/j.ghir.2008.06.004.
[81] Hojman P, Gehl J, Christensen JF, et al. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018;27(1):10–21. doi:10.1016/j.cmet.2017.09.015.
[82] Khandwala HM, McCutcheon IE, Flyvbjerg A, et al. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev. 2000;21(3):215–244. doi:10.1210/edrv.21.3.0399.
[83] Kasprzak A, Kwasniewski W, Adamek A, et al. Insulin-like growth factor (IGF) axis in cancerogenesis. Mutat Res Rev Mutat Res. 2017;772:78–104. doi:10.1016/j.mrrev.2016.08.007.

[84] Thomas R, Kenfield SA, Yanagisawa Y, et al. Why exercise has a crucial role in cancer prevention, risk reduction and improved outcomes. Br Med Bull. 2021;139(1):100–119. doi:10.1093/bmb/ldab019.
[85] Baughman C, Norman K, Mukamal K. Adherence to American Cancer Society Nutrition and Physical Activity Guidelines Among Cancer Survivors. JAMA Oncol. 2024;10(6):789–792. doi:10.1001/jamaoncol.2024.0470.
[86] Zhou Y, Jia N, Ding M, et al. Effects of exercise on inflammatory factors and IGF system in breast cancer survivors: a meta-analysis. BMC Womens Health. 2022;22(1):507. doi:10.1186/s12905-022-02058-5.
[87] Kang XY, Xu QY, Yu Z, et al. The effects of physical activity on physiological markers in breast cancer survivors: A meta-analysis. Medicine (Baltimore). 2020;99(20):e20231. doi:10.1097/MD.0000000000020231.
[88] Meneses-Echávez JF, Jiménez EG, Río-Valle JS, et al. The insulin-like growth factor system is modulated by exercise in breast cancer survivors: a systematic review and meta-analysis. BMC Cancer. 2016;16(1):682. doi:10.1186/s12885-016-2733-z.
[89] Hu C, Tang J, Gao Y, et al. Effects of physical exercise on body fat and laboratory biomarkers in cancer patients: a meta-analysis of 35 randomized controlled trials. Support Care Cancer. 2022;30(9):1–12. doi:10.1007/s00520-022-07013-6.
[90] Han JK, Kim G. Role of physical exercise in modulating the insulin-like growth factor system for improving breast cancer outcomes: A meta-analysis. Exp Gerontol. 2021;152:111435. doi:10.1016/j.exger.2021.111435.
[91] Kang DW, Lee J, Suh SH, et al. Effects of exercise on insulin, IGF axis, adipocytokines, and inflammatory markers in breast cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2017;26(3):355–365. doi:10.1158/1055-9965.EPI-16-0602.
[92] Zhu G, Zhang X, Wang Y, et al. Effects of exercise intervention in breast cancer survivors: a meta-analysis of 33 randomized controlled trails. Onco Targets Ther. 2016;9:2153–2168. doi:10.2147/OTT.S97864.
[93] Varma Shrivastav S, Bhardwaj A, Pathak KA, et al. Insulin-like growth factor binding protein-3 (IGFBP-3): unraveling the role in mediating IGF-independent effects within the cell. Front Cell Dev Biol. 2020;8:286. doi:10.3389/fcell.2020.00286.
[94] Baxter RC. Signaling pathways of the insulin-like growth factor binding proteins. Endocr Rev. 2023;44(5):753–778. doi:10.1210/endrev/bnad008.
[95] Sarkissyan M, Mishra DK, Wu Y, et al. IGF gene polymorphisms and breast cancer in African-American and Hispanic women. Int J Oncol. 2011;38(6):1663–1673. doi:10.3892/ijo.2011.990.
[96] Keku TO, Vidal A, Oliver S, et al. Genetic variants in IGF-I, IGF-II, IGFBP-3, and adiponectin genes and colon cancer risk in African Americans and Whites. Cancer Causes Control. 2012;23(7):1127–1138. doi:10.1007/s10552-012-9981-2.
[97] Tas F, Bilgin E, Tastekin D, et al. Serum IGF-1 and IGFBP-3 levels as clinical markers for patients with lung cancer. Biomed Rep. 2016;4(5):609–614. doi:10.3892/br.2016.629.
[98] Ciulei G, Orășan OH, Cozma A, et al. Exploring vitamin D deficiency and IGF axis dynamics in colorectal adenomas. Biomedicines. 2024;12(8):1922. doi:10.3390/biomedicines12081922.
[99] Bueno-Notivol J, Calvo-Latorre J, Alonso-Ventura V, et al. Effect of programmed exercise on insulin sensitivity in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2017;24(12):1404–1413. doi:10.1097/GME.0000000000000936.
[100] Riley EC, Rai S, Pan J, et al. Uninsured utilization of the mobile mammography: 10-year analysis. J Clin Oncol. 2014;32(26_suppl):12–12. doi:10.1200/jco.2014.32.26_suppl.12.
[101] Murphy C, Koehler K. Caloric restriction induces anabolic resistance to resistance exercise. Eur J Appl Physiol. 2020;120(5):1155–1164. doi:10.1007/s00421-020-04354-0.
[102] Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab. 2003;88(1):297–311. doi:10.1210/jc.2002-020369.
[103] Clemmons DR.viiviii Metabolic actions of insulin-like growth factor-I in normal physiology and diabetes. Endocrinol Metab Clin North Am. 2012;41(2):425–443. –. doi:10.1016/j.ecl.2012.04.017.
[104] Ishii Y, Takachi R, Ishihara J, et al. Prospective study of dietary changes in cancer survivors for five years including pre- and post- diagnosis compared with those in cancer-free participants. Sci Rep. 2023;13(1):982. doi:10.1038/s41598-023-27820-z.
[105] Khalafi M, Kheradmand S, Habibi Maleki A, et al. The effects of concurrent training versus aerobic or resistance training alone on body composition in middle-aged and older adults: a systematic review and meta-analysis. Healthcare (Basel). 2025;13(7):776. doi:10.3390/healthcare13070776.
[106] Stojanovic M, Popevic M, Pekic S, et al. Serum insulin-like growth factor-1 (IGF-1) age-specific reference values for healthy adult population of Serbia. Acta Endocrinol (Buchar). 2021;17(4):462–471. doi:10.4183/aeb.2021.462.