

## REVIEW ARTICLE

# A meta-analysis of the effect of chromium supplementation on anthropometric indices of subjects with overweight or obesity

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## Summary

The role of chromium as a weight loss agent remains questionable, and although previous meta-analyses findings have reported small reductions in body weight in individuals with overweight/obesity following chromium supplementation, there have been significant limitations with these findings. The objective of this meta-analysis was to evaluate the current evidence for the efficacy of oral chromium supplementation in individuals with overweight/obesity from randomized controlled trials. Studies were identified by a search of electronic databases from inception to November 2018 and combined and stratified analyses were used. Twenty-one trials from 19 studies were identified which met all inclusion criteria which were suitable for statistical pooling, and data from 1316 participants were included. Pooled analysis showed significant reductions in anthropometric indices associated with body composition; for weight loss (weighted mean difference [WMD]:  $-0.75$  kg, 95% confidence interval [CI],  $-1.04$ ,  $-0.45$ ,  $P < 0.001$ ), body mass index (WMD:  $-0.40$ , 95% CI,  $-0.66$ ,  $-0.13$ ,  $P = 0.003$  and body fat percentage (WMD:  $-0.68\%$ , 95% CI,  $-1.32$ ,  $-0.03$ ,  $P = 0.04$ ) in individuals with overweight/obesity. No changes were detected in controls. Subgroup analysis showed significant improvements in weight loss and body fat percentage, particularly for study durations  $\leq 12$  weeks and doses  $\leq 400$   $\mu\text{g}/\text{d}$ . Chromium supplementation was associated with some improvements in body composition in subjects with obesity/overweight. The effect size was medium and the clinical relevance of chromium as a weight loss aid remains uncertain. Further investigation from larger and well-designed randomized controlled studies, especially in patients with diabetes, is warranted.

## KEYWORDS

BMI, body weight, chromium, meta-analysis, systematic review

## 1 | INTRODUCTION

Obesity and overweight, are associated with several comorbidities and metabolic abnormalities; dyslipidaemia, insulin resistance and hypertension, and as such are well-established risk factors for chronic

diseases including type-2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).<sup>1,2</sup>

Therapeutic approaches include dietary management, however; poor compliance with conventional weight management programmes highlight the need for further safe and efficacious treatments.<sup>3</sup>

Chromium (III) or trivalent chromium, is a trace element widely distributed in the human diet, and food sources including meat, nuts, cereal grains, molasses, and brewer's yeast provide an especially abundant source. It is estimated that around 1% to 2% of ingested chromium is absorbed from the diet, and current dietary recommendations suggest a daily intake range between 25 and 45  $\mu\text{g}/\text{d}$  for adults.<sup>4</sup>

The exact mechanism of chromium is not well understood, however, it is believed to be associated with carbohydrate and lipid metabolism, where it may be important in promoting the action of insulin in the control of blood glucose.<sup>5</sup> Chromium is widely marketed as an aid to weight loss because of its potential ability to regulate eating behaviour and food cravings, suppress appetite, stimulate thermogenesis, enhance resting energy expenditure and improve insulin sensitivity.<sup>6-8</sup>

However, the role of chromium as a weight loss aid remains questionable, and although evidence from previous meta-analyses of RCT's have reported small reductions in body weight in individuals with overweight and obesity following chromium supplementation, there have been significant limitations with these findings.<sup>9,10</sup> Therefore, the purpose of the present study was to investigate and update the efficacy of chromium supplementation on anthropometric indices related to body composition in individuals with obesity, overweight and diabetes including data from recent RCT's.

## 2 | MATERIALS AND METHODS

### 2.1 | Search strategy and selection

Systematic literature searches were conducted using the data sources PubMed, The Cochrane Library, Web of Knowledge and Scopus, from its inception until November 2018. Bibliographies from located articles were also searched for additional studies. The search terms included the following combinations of keywords: (chromium OR "chromium picolinate" OR "chromium nicotinate") AND (overweight OR "body-mass index" OR weight OR BMI OR "body fat percentage" OR "waist circumference" OR diabetes OR T2DM). Our search was limited to studies published in English or Persian, and only randomized placebo-controlled trials (RCTs) were included. To be considered for inclusion, RCTs had to meet the following criteria<sup>1</sup>: studies which investigated the association between chromium supplementation and at least one anthropometric index<sup>2</sup>; studies which included adult subjects aged  $\geq 18$  years<sup>3</sup>; studies which included healthy and subjects with diabetes, overweight and/or obesity with a body mass index (BMI) of  $\geq 25 \text{ kg}/\text{m}^2$ <sup>4</sup>; studies reporting changes in body weight (kg), BMI ( $\text{kg}/\text{m}^2$ ), body fat (%) or waist circumference (cm), with associated standard deviations (SD), for both intervention and placebo groups. Trials were excluded if they lasted  $\leq 2$ -weeks, were unpublished reports, case series, case reports, editorials, and reviews. In addition, we tried to contact the corresponding authors of the studies with limited data for statistical pooling (eg, the net changes and their associated SD, or the reported data for calculating them including the median and confidence intervals [CI] of anthropometric indices) to

achieve the required data for further inclusion of trials. The present meta-analysis was carried out according to PRISMA guidelines.<sup>11</sup>

### 2.2 | Data extraction

Two reviewers (M.T. and E.A.) independently assessed the eligibility of the studies and any possible disagreements were resolved by consensus and discussion with a third reviewer (S.J.). The following items were extracted: author's first name, year of publication, country of origin, study design, subject characteristics (including sample size of both intervention and control groups, gender and age), duration of supplementation and follow-up, dosage of chromium (micrograms or milligrammes per day), type and route of administration, clinical condition of subjects, observed significant outcomes and study quality.

### 2.3 | Quality assessment

The Jadad Scale was used to assess the methodological quality of included RCT's, with scores ranging from 0 (very low quality) to 5 (very high quality) based on three distinct parts of randomization, double blinding, and follow-up.<sup>12</sup> This scale assigns one point for mentioning randomization in the text, one point for mentioning blinding in the text, and one point for the proper description of the fate of all subjects. Moreover, one point belongs to the study if the randomization method was appropriate (-1 if inappropriate) and one point if the double-blinding was appropriate (-1 if inappropriate).<sup>12</sup>

### 2.4 | Statistical analysis

All analyses were carried out using Review Manager Software (Review Manager 5.3; Cochrane 100 Collaboration, Oxford, England, UK) and Comprehensive Meta-Analysis (version 3.2; Biostat). The pooled weighted mean difference (WMD) and its 95% confidence interval (CI) was used to assess the effects of chromium supplementation on anthropometric indices. The SDs of the changes of indices including body weight (kg), BMI ( $\text{kg}/\text{m}^2$ ), body fat (%) and waist circumference (cm) were calculated by the method of Higgins et al,<sup>13</sup> if the included studies did not report these parameters. Statistical heterogeneity was estimated using I<sup>2</sup> test (I<sup>2</sup> < 50%) and  $\chi^2$  test on Cochrane's Q statistic. Random effects models were used in the present meta-analysis. Stratified analyses were conducted according to the Cochrane guidelines<sup>14</sup> to identify the influence of other modulators including, duration of follow-up and supplementation, chromium dosage, the clinical condition of participants and the quality of studies. Additionally, sensitivity and pre-specified subgroup analyses were performed according to the Cochrane guidelines to evaluate possible sources of heterogeneity within the included trials.<sup>15</sup> In the sensitivity analysis, a single study was omitted each time and the effect size was re-calculated to investigate its influence on the overall effect size.<sup>16</sup> Moreover, weighted random effect meta-regressions using unrestricted maximum likelihood models were performed to determine the effects of potential moderators like chromium dosage and duration of supplementation. We assessed the publication bias by

visual inspection of funnel plots test. The asymmetric shape of funnel-plot can be indicative of publication bias. Begg's rank correlation test and Egger's weighted regression test were used to investigate any possible bias.<sup>16</sup> A *P*-value of  $\leq 0.05$  was considered as statistically significant.

### 3 | RESULTS

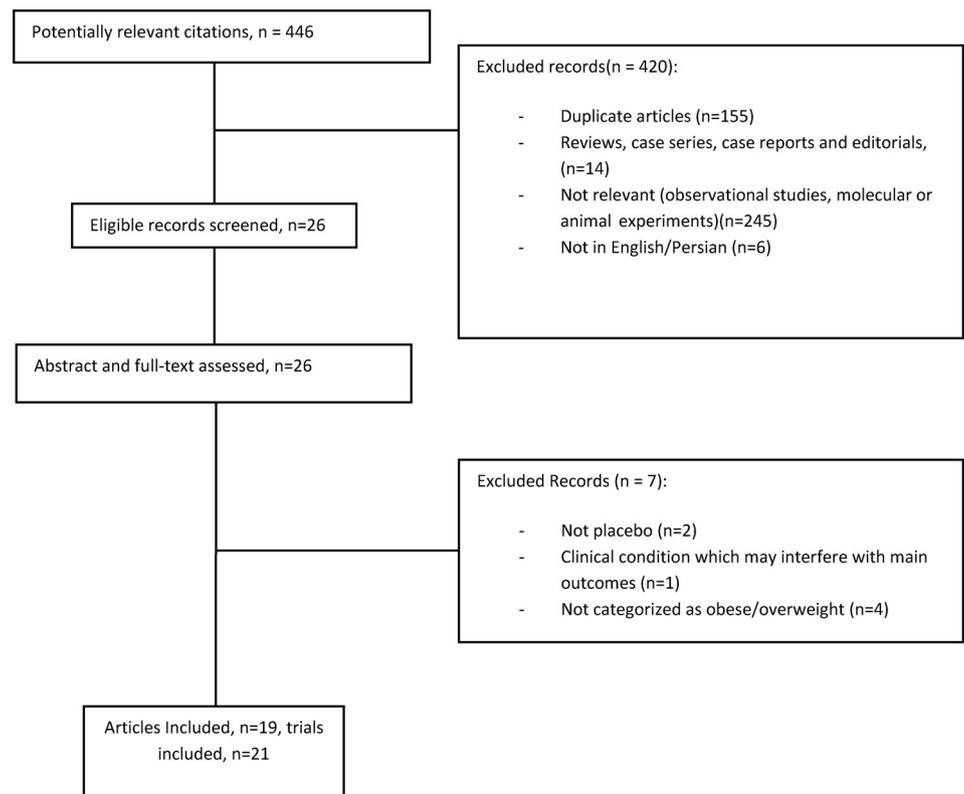
#### 3.1 | Study selection

The literature search and study selection flow chart is presented in Figure 1. Of 446 trials identified, 420 trials were excluded, because they were duplicate studies ( $n = 155$ ), reviews/editorials ( $n = 14$ ), irrelevant studies including observational studies, molecular or animal experiments ( $n = 245$ ) and six trials were excluded because there were not published in English/Persian languages. After abstracts and full-text screening of 26 eligible records, seven were excluded for the following reasons: no placebo groups in the studies ( $n = 2$ ). Another one study were excluded because of clinical condition of included patients, which may interfere with the measured outcomes, as they were patients with poly-cystic ovarian syndrome with complex complications, which may interfere with overall results. Additionally, four studies were excluded because the participants were not all reported as overweight/obese. Finally 19 studies with, 1316 participants in total (666 in intervention and 650 in control groups), were finally included for meta-analysis, which were all randomized, controlled trials. Grant et al and Kaats et al investigated the effect of chromium on two different groups separated by different forms of chromium (chromium

picolinate and nicotinate) and dosage (400 vs 200  $\mu\text{g}/\text{d}$ ) and based on the Cochrane Handbook for Systematic Reviews of Interventions,<sup>14</sup> each group was considered separately in the analysis. Therefore, we analysed 21 distinct trials extracted from 19 studies in the present meta-analyses.

#### 3.2 | Characteristics of included studies

The characteristics of the included studies and participants are shown in Table 1. The studies were published from 1996 to 2017, in which 10 studies were conducted in United States,<sup>17-26</sup> two studies in Iran<sup>27,28</sup> and one was conducted in Brasil<sup>29</sup>, Canada,<sup>30</sup> Denmark,<sup>31</sup> Greece,<sup>32</sup> Norway<sup>33</sup>, Taiwan<sup>34</sup> and New Zealand.<sup>26</sup> Twelve of the included studies were conducted on both males and females<sup>12,18-20,22-27,29,31,32</sup> and the remaining studies on females.<sup>17,21,28,30,33</sup> The number of participants ranged from 9 to 70 with a sum of total sample size of 1316 (a sum of 666 in the intervention and 650 in the control groups). Of the 21 trials, 12 included participants with overweight and obesity, seven included patients with type 2 diabetes mellitus and remaining two included patients with other clinical conditions including infection and schizophrenia. Different forms of chromium were used in the included trials. Of all included trials, 17 trials administered chromium picolinate,<sup>12,17-24,26-28,30,33</sup> two trials administered the intervention as chromium-enriched yeast<sup>31,32</sup> and three trials used the nicotinate form of chromium as the interventional compound.<sup>21,25,29</sup> Duration of chromium supplementation varied between 9 and 24 weeks with a median of 12 weeks. Dosages of supplementation ranged from 200 to



**FIGURE 1** Study flow chart showing process for study selection and inclusion of randomized clinical trials

**TABLE 1** Reporting criteria and characteristics of 20 included studies used for the present meta-analyses

Author	Year	Country	Design	DB, 23 PC	No. of subjects in case	No. of controls	Gender	Age (mean)	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Aghdassi	2010	Canada	R, DB, 23 PC	23	F/M	46.8; control: 50.2	Intervention: Blood glucose ≥6.1 mmol/L, triglycerides ≥2.0 mmol/L, total cholesterol ≥5.5 mmol/L, HDL ≤0.9 mmol/L	Infection	16	Chromium nicotinate: 400 mg/d	No co-supplement	Significant decrease in HOMA-IR, insulin, triglycerides, total body fat mass and trunk fat mass, chromium improved insulin resistance, metabolic abnormalities and body composition	4		
Aghdassi	2010	Canada	R, DB, 23 PC	23	F/M	46.8; control: 50.2	Intervention: Blood glucose ≥6.1 mmol/L, triglycerides ≥2.0 mmol/L, total cholesterol ≥5.5 mmol/L, HDL ≤0.9 mmol/L	Infection	16	Chromium nicotinate: 400 mg/d	No co-supplement	Significant decrease in HOMA-IR, insulin, triglycerides, total body fat mass and trunk fat mass, chromium improved insulin resistance, metabolic abnormalities and body composition	4		
Calbasi	2014	Iran	R, DB, 28 PC	27	F	NS	BMI range 25 to 35 kg/m <sup>2</sup> , treated with oral medications or insulin and anti-diabetes treatment that remained stable over the next 3 months, glycosylated haemoglobin (7%-10%)	Type 2 diabetes	12	Chromium picolinate: 200 mg/d	No co-supplement	Significant decrease in TG, HbA1c, FPG, body weight, waist circumference	5		
Campbell	1999	USA	R, DB, 9 PC	9	F	Intervention: Age range 50 to 60; control: 63	Age range 50 to 75 years, BMI range of 27 to 34 kg/m <sup>2</sup> , nondiabetic, physically able to safely engage in all aspects of the study	Overweight	12	Chromium picolinate: 924 mg/d	No co-supplement	High-dose CrPic supplementation did not enhance muscle size, strength, or power development or lean body mass accretion in older	4		

TABLE 1 (Continued)

Author	Year	Country	Design	No. of subjects in case	No. of controls	Gender	Age (mean)	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Cefalu	2010	USA	R, DB, 70 PC	67	F/M		Intervention: Type 2 DM subjects (age, 30-70 years) 58.7; control: 51.6	Type 2 DM subjects (age, 30-70 years) with a BMI range of 25 to 40 and with a fasting plasma glucose of at least 6.94 mmol/L (125 mg/dL)	Type 2 diabetes	24	Chromium picolinate: 1000 mg/d	No co-supplement	men during a RT programme, which had significant, independent effects on these measurements. Chromium may reduce myocardial lipids and enhance insulin sensitivity in subjects with type 2 diabetes mellitus, myocardial lipids were significantly decreased, decrease insulin sensitivity and increase fasting glucose and A1c	3
Chen	2014	Taiwan	R, DB, 38 PC	28	F/M		Intervention: Within the age of 30 to 75 years, have been diagnosed with T2D for at least 4 months before study entry, FPG between 140 and 250 mg/dL, HbA1c of 7.5% to 12%, BMI between 20 and 35 kg/m <sup>2</sup> 53.3; control: 54.2	Type 2 diabetes	Type 2 diabetes	16	Chromium chloride-containing milk powder (GalaChrom): 200 mg/d	Chloride, galactose	Insulin sensitivity was significantly improved, the static insulin responsiveness index was significantly higher after the treatment, a significant decrease in the IL-6 level	3
Crawford	1999	USA	R, DB, 23 PC	23	F	NS	Who desired to lose weight.	Overweight	Overweight	8	Niacin-bound chromium: 600 mg/d	Niacin	Fat loss was significantly greater, non fat body mass loss significantly less with chromium intake.	4
Grant	1997	USA	R, PC	11	F		Total: 24.4	Obesity	Obesity	9	Chromium picolinate/ icotinate: 200 mg/d	No co-supplement	Cr picolinate supplementation resulted in significant	1

TABLE 1 (Continued)

Author	Year	Country	Design	No. of subjects in case group	No. of controls	Age (mean)	Gender	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Guimares	2016	Brazil	R, DB, 13 PC	13	13	F/M	Intervention: 52.94; control: 51	Type 2 diabetic individuals, body mass index greater than 25 kg/m <sup>2</sup> , increased waist circumference (men ≥102 cm and women ≥88 cm). Individuals taking insulin; with chronic complications of diabetes,	Type 2 diabetes	13	Chromium nicotinate: 50 mg/d	No co-supplement	There was an increase of the HOMA-β in group NCO, a decrease of 1.08 kg in group NC50. There was an increase in energy expenditure in physical activity in the group subjects NC50	5
Hockney	2006	USA	R, DB, 16 PC	13	13	F/M	Total: 41.8	Met DSM-IV criteria for schizophrenia, mean age was 41.8 years (range, 21-67 years), mean	Schizophrenia	12	Chromium picolinate: 400 mg/d	No co-supplement	Body weight rose slightly in both groups over the period of the study, beneficial effects of	3

TABLE 1 (Continued)

Author	Year	Country	Design	No. of subjects in case	No. of controls	Gender	Age (mean)	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Iqbal	2009	USA	R, DB, PC	33	30	F/M	Intervention: 47.7; Control: 51.1	duration of illness was 28.8 years (range, 2-54 years) Waist circumference $\geq$ 102 cm for men and $\geq$ 89 cm for women and at least two of the following: systolic blood pressure $\geq$ 130 or diastolic blood pressure $\geq$ 85 mmHg or taking $\geq$ 1 antihypertensive agent; FBG $\geq$ 6.1 mmol/L, but $<$ 7 mmol/L; fasting TGs $\geq$ 1.68, but $\leq$ 8.96 mmol/L; HDL-C $\leq$ 1 mmol/L for males and $\leq$ 1.29 mmol/L for females.	Metabolic syndrome and obesity	15	Chromium picolinate: 500 mg/d	No co-supplement	CrPic increased acute insulin response to glucose, CrPic (1000 $\mu$ g/d) does not improve key features of the metabolic syndrome in obese nondiabetic patients.	4
Jo	2016	Norway	R, PC	8	2	F	Intervention: 34.7; Control: 40.5	Non-smoking individuals, BMI range of 26.0 to 39.6	Overweight and obesity	4	Combined calcium, iodine, magnesium and chromium: 50 mg/d	Magnesium, iodine, calcium	Reduction are seen both in body weight and BMI	2
Joseph	1999	USA	R, DB, PC	17	15	F/M	Intervention: 63; control: 60	Age, 54 to 71 years; BMI of 26 to 36 kg/m <sup>2</sup> , subjects do not have any metabolic or cardiac abnormalities.	Overweight	13	Chromium picolinate: 924 mg/d	No co-supplement	Decrease in the insulin AUC, RT decreases the insulin response following an oral glucose challenge in overweight men and women without affecting glucose tolerance, decrease in circulating insulin may result from an increase in insulin clearance	3

TABLE 1 (Continued)

Author	Year	Country	Design	DB, %	PC	No. of subjects in case	No. of controls	Gender	Age (mean)	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Kaats	1996	USA	R, DB, PC	33	55	F/M	Intervention: 45.9; control: 44.3	BMI $\geq 25$ kg/m <sup>2</sup>	Overweight	10	Chromium picolinate: 200 mg/d	No co-supplement	Significantly higher positive changes in body composition compared with placebo.	5		
Kaats	1997	USA	R, DB, PC	67	56	F/M	Intervention: 45.7; control: 44.4	BMI $\geq 25$ kg/m <sup>2</sup>	Overweight	11	Chromium picolinate: 400 mg/d	No co-supplement	Both the 200-pg and 400-pg groups had significantly higher positive changes in body composition improvement compared with placebo. A single-factor analysis of variance weighted linear trend was also highly significant	5		
Liu	2015	USA	R, DB, PC	26	26	F/M	NS	Subjects aged between 25 and 65 years, overweight (BMI $\geq 25$ kg/m <sup>2</sup> ), presenting a FPG level between 5.55 and 7 mmol/L	Overweight, obesity, pre diabetes	16	Dietary supplement containing cinnamon, chromium and carnosine: 20 mg/d	Cinnamon, carnosine	Decreased FPG compared to placebo, fat-free mass (%) increased with the dietary supplement compared to placebo	5		
Nussbaumerova	2017	Denmark	R, DB, PC	32	33	F/M	Intervention: 57; control: 58	Plasma glucose level in the second hour of oGTT $\geq 7.8$ and $\leq 11.0$ mmol/L, two or more following risk factors of metabolic syndrome	Type 2 diabetes	24	ChromoPrecise yeast: 300 mg/d	No co-supplement	Only resting heart rate was significantly reduced in patients treated by Cr yeast, reflecting reduced sympathetic activity	5		
Robati	2015	Iran	R, PC	42	44	F/M	Total: 35.65 years, BMI more than 25 kg/m <sup>2</sup>	Age range, 20_50 years, BMI more than 25 kg/m <sup>2</sup>	Overweight, obesity	16	Chromium picolinate: 924 mg/d	No co-supplement	Decrease in body weight, BMI, waist circumference.	2		

**TABLE 1** (Continued)

Author	Year	Country	Design	SB, n	PC, n	No. of subjects in case group	No. of controls	Gender	Age (mean)	Inclusion criteria	Clinical condition of subjects	Follow-up duration	Dosage	Co-supplements or other drugs	Significant outcome	Jadad score
Whitfield	2015	New Zealand	R, SB, PC	6	6	6	6	F/M	Total: 61.7	Participants with suboptimal glycaemic control (HbA1c > 8.0 mmol/mol or 9.5%) using sulphonylureas or insulin, taking supplements containing cinnamon, chromium or magnesium were not excluded	Type 2 diabetes	6	Cinnamon, chromium- and magnesium-formulated honey: 200 mg/d	Cinnamon, magnesium	There was a statistically significant reduction in total cholesterol, LDL cholesterol and weight. There was a trend towards increased HDL and reduced systolic blood pressure in the intervention treatment.	5
Yanni	2016	Greece	R, SB, PC	15	15	15	15	F/M	Intervention: 65.9; control: 64.8	Age within 40 to 65 years, BMI: 25 < BMI < 31 kg/m <sup>2</sup> , fasting plasma glucose > 125 mg/dL at screening and glycosylated haemoglobin (HbA1c) < 8.5% for the last 3 months before screening	Type 2 diabetes	12	Cr-enriched yeast bread: 400 mg/d	No co-supplement	Significant reduction in body weight and systolic blood pressure was observed, subjects of WWCrB group exerted lower levels of glucose, insulin and HbA1c and improved insulin resistance	4

Abbreviations: AUC, under the curve; BMI, body mass index; DB, double blind; PC, placebo; RT, resistance training.

1000 µg/d with the median of 400 µg/d. Mean age of participants in the intervention and control groups were in the range of 24 to 68 years.

Changes in BMI were reported in eight trials<sup>20,24,27,29,31-34</sup> and 19 trials reported changes in body weight.<sup>12,17-30,32,33</sup> The reported mean BMI of all included trials was over 25 kg/m<sup>2</sup>, therefore all included participants were considered as subjects with overweight/obesity. Of the 21 RCTs, 12 reported body fat percentage,<sup>17,18,20-25,29,34</sup> eight RCTs measured waist circumference<sup>19,20,25,28,29,31,33,34</sup> and only three studies specified the waist to hip ratio.<sup>20,25,32</sup> In terms of study quality, 13 trials were categorized as high-quality with Jadad score<sup>12</sup> of  $\geq 3$ <sup>17,19,22-26,28-32</sup>; and eight as low-quality studies with Jadad score of  $< 3$ <sup>12,18,20,21,27,33,34</sup> (Table 2).

### 3.3 | Effect of chromium supplementation on main outcomes

Of all 21 included trials, 19 trials reported the changes in body weight, in which seven reported a significant reduction after administration of chromium.<sup>20-22,25,27,33</sup> Eight trials reported changes in BMI, and two trials showed significant reductions following chromium supplementation<sup>27,33</sup>; two trials of 12 included trials which measured body fat percentage, reported a significant decrease after supplementation of chromium<sup>22</sup> and of the eight trials presenting waist circumference, only one showed a significant reduction following chromium supplementation.<sup>33</sup> As is shown in Figure 2, a forest plot of 19 trials showed significant weight loss following chromium supplementation (WMD: -0.75 kg, 95% CI, -1.04, -0.45,  $P < 0.001$ ) with the Hedges's  $g$

standardized mean difference of 0.56 which defines the magnitude of the effect size as medium.<sup>35</sup> The heterogeneity for the meta-analysis of body weight was 76%. The meta-analysis result showed significant reductions in BMI and body fat percentage in chromium groups compared with that of the control group (BMI WMD: -0.40, 95% CI, -0.66, -0.13,  $P = 0.003$ ; body fat percentage WMD: -0.68%, 95% CI, -1.17, -0.19,  $P = 0.007$ ). A low level of heterogeneity was observed for the analysis of body fat percentage ( $P = 0.23$ ,  $I^2 = 22$ ). A forest plot of included trials did not show a statistically significant reduction of waist circumference and waist to hip ratio in chromium supplementation groups over placebo groups. Moreover, a significant heterogeneity was observed in the meta-analysis of waist circumference.

### 3.4 | Subgroup and sensitivity analyses

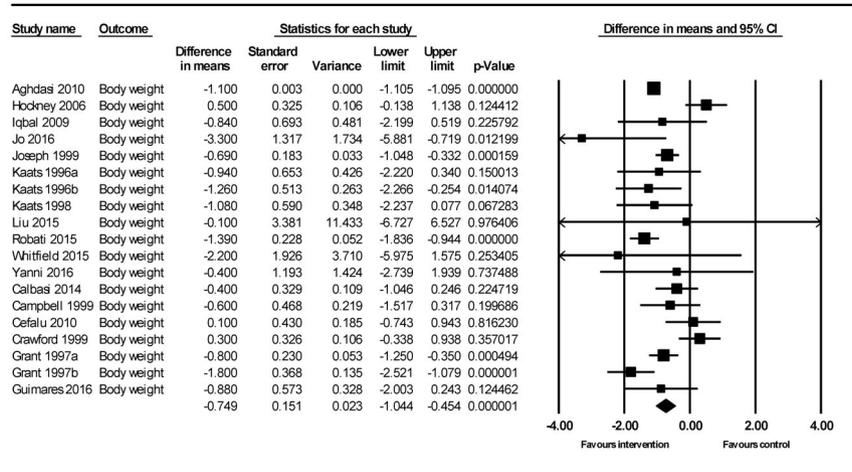
The results of subgroup analyses are presented in Table 3. Overall, there was a significant reduction in body weight, BMI and body fat percentage following supplementation among trials with duration of less than 12 weeks (body weight: -0.76 kg, 95% CI -1.26, -0.26; BMI: -1.14 kg/m<sup>2</sup>, 95% CI -1.93, -0.36 and body fat percent: -1.19%, 95% CI -1.72, -0.66). Longer term trials showed a significant reduction just in body weight by 0.91 kg (95% CI -1.22, -0.60,  $P < 0.001$ ). The subgroup analysis by dosage of chromium supplementation showed a significant difference in the mean change of body weight and body fat percentage in trials which administered the supplement in dose of less than 400 µg/d (WMD body weight: -1.08 kg, 95% CI -1.60, -0.55,  $P < 0.001$  and body fat percent: -0.94%, 95%

**TABLE 2** Quality of the 20 included trials based on the Jadad score. The studies with score of  $\geq 3$  categorized as high quality and  $< 3$  as low quality studies

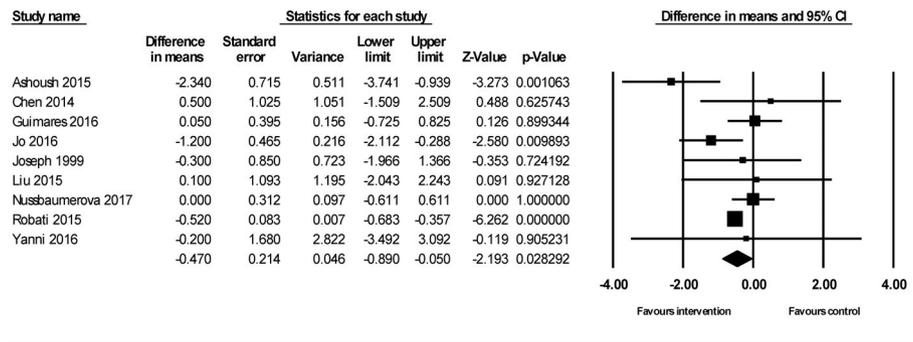
Study; year	Blinding	Randomization	Withdrawals and dropouts descriptions	Score
Aghdassi; 2010	1	2	1	4
Calbasi; 2014	2	2	1	5
Campbell; 1999	1	2	1	4
Cefalu; 2010	1	1	0	2
Chen; 2014	1	1	0	2
Crawford; 1999	1	2	1	4
Grant; 1997	0	1	0	1
Guimares; 2016	2	2	1	5
Hockney; 2006	1	1	0	2
Iqbal; 2009	1	2	1	4
Jo; 2016	0	1	1	2
Joseph; 1999	1	1	0	2
Kaats; 1996	2	2	1	5
Kaats; 1998	2	2	1	5
Liu; 2015	2	2	1	5
Nussbaumerova; 2017	2	2	1	5
Robati; 2015	0	1	1	2
Whitfield; 2015	2	2	1	5
Yanni; 2016	2	1	1	4

**FIGURE 2** A, Forest plot displaying the comparison of body weight between chromium supplementation and control groups. Random effects model was used to pool the standard mean differences of indicators. B, Forest plot displaying the comparison of BMI between chromium supplementation and control groups. Random effects model was used to pool the standard mean differences of indicators. C, Forest plot displaying the comparison of body fat percentage between chromium supplementation and control groups. Random effects model was used to pool the standard mean differences of indicators. D, Forest plot displaying the comparison of waist circumference between chromium supplementation and control groups. Random effects model was used to pool the standard mean differences of indicators. CI, confidence interval; I-squared inconsistency

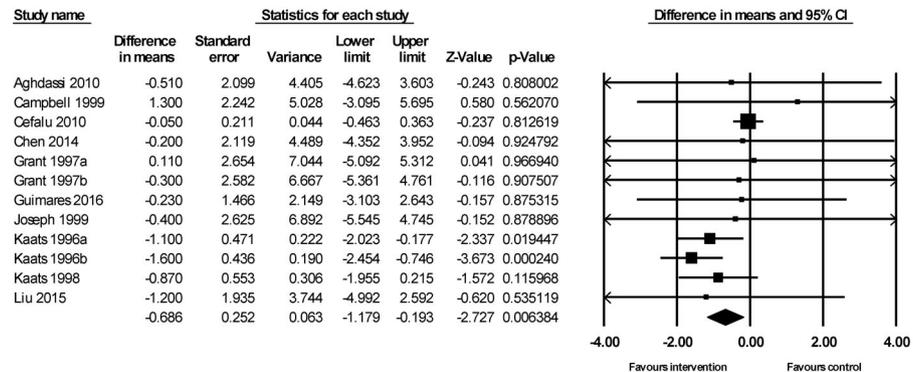
(A)



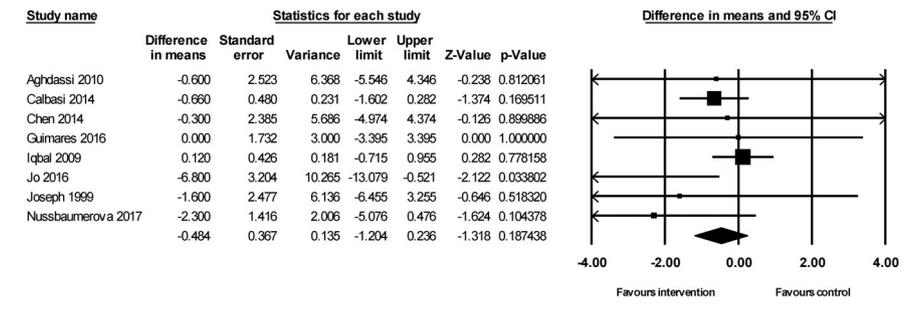
(B)



(C)



(D)



**TABLE 3** Stratified analysis based on four pre-specified subgroups: duration of supplementation, dosage of supplementation, clinical condition and quality of study

Sub group	Bodyweight			BMI			Body fat percentage			Waist circumference			Waist to hip ratio			Lean body mass		
	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect	WMD (95% CI)	Heterogeneity (I2, P)	Overall effect
Duration	≤ 12 weeks																	
	-0.76 (-1.26, -0.26)	69%, P = 0.0002	P = 0.003	-1.14 (-1.93, -0.36)	0%, P = 0.56	P = 0.004	-1.19 (-1.72, -0.66)	0%, P = 0.72	P < 0.0001	-3.48 (-9.48, 2.52)	91%, P = 0.001	P = 0.26	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
>12 weeks	Chromium dosage																	
	-0.91 (-1.22, -0.60)	62%, P = 0.02	P < 0.0001	-0.63 (-1.35, -0.08)	P = 0.05	P = 0.08	-0.07 (-0.47, 0.33)	P = 0.99	P = 0.72	-0.09 (-0.81, 0.63)	P = 0.67	P = 0.81	0.01 (-0.02, 0.03)	P = 0.69	P = 0.66	-0.57 (-2.92, 1.78)	0%, P = 0.78	P = 0.63
<400 mg/d	Clinical condition																	
	-1.08 (-1.60, -0.55)	47%, P = 0.07	P < 0.0001	-0.34 (-1.19, 0.52)	P = 0.11	P = 0.44	-0.94 (-1.77, -0.12)	P = 0.98	P = 0.02	-1.86 (-4.67, 0.96)	73%, P = 0.001	P = 0.20	Not applicable	Not applicable	Not applicable	-0.77 (-3.50, 1.96)	Not applicable	P = 0.58
≥400 mg/d	Diabetic subjects																	
	-0.60 (-0.99, -0.21)	83%, P < 0.00001	P = 0.003	-0.48 (-0.64, 0.33)	P = 0.45	P < 0.001	-0.68 (-1.54, 0.18)	P = 0.04	P = 0.12	-0.16 (-1.00, 0.67005D)	2%, P = 0.38	P = 0.71	0.01 (-0.02, 0.03)	P = 0.69	P = 0.66	0.00 (-4.61, 4.61)	Not applicable	P = 1.00
Non-diabetic subjects	Non-diabetic subjects																	
	-0.84 (-1.16, -0.51)	78%, P < 0.00001	P < 0.00001	-0.51 (-0.68, 0.35)	P = 0.83	P < 0.001	-1.17 (-1.69, -0.65)	P = 0.88	P < 0.0001	-2.14 (-5.69, 1.41)	79%, P = 0.003	P = 0.24	0.01 (-0.02, 0.03)	P = 0.69	P = 0.66	0.00 (-4.61, 4.61)	Not applicable	P = 1.00
High quality	High quality																	
	-0.80 (-1.12, -0.49)	30%, P = 0.15	P < 0.00001	0.02 (-0.45, 0.48)	P = 1.00	P = 0.94	-1.17 (-1.69, -0.65)	P = 0.80	P < 0.00001	-0.30 (-0.88, 0.28)	0%, P = 0.47	P = 0.31	-0.30 (-0.88, 0.28)	Not applicable	P = 0.55	-0.57 (-2.92, 1.78)	0%, P = 0.78	P = 0.63
Low quality	Low quality																	
	-0.83 (-1.40, -0.25)	85%, P < 0.00001	P = 0.005	-0.60 (-0.99, -0.20)	P = 0.29	P = 0.003	-0.60 (-0.99, -0.20)	P = 1.00	P = 0.79	-3.17 (-7.40, 1.06)	64%, P = 0.06	P = 0.14	0.00 (-0.04, 0.04)	P = 0.79	P = 1.00	Not applicable	Not applicable	Not applicable

Abbreviations: BMI, body mass index; CI, confidence interval; I2, percentage score for heterogeneity; WMD, weighted mean difference.

CI  $-1.77, -0.12, P = 0.02$ ). Higher dosage of chromium supplementation revealed the significant reduction in both body weight (WMD:  $-0.60$  kg, 95% CI  $-0.99, -0.21, P = 0.003$ ) and BMI (WMD:  $-0.48$  kg/m<sup>2</sup>, 95% CI  $-0.64, -0.33, P < 0.001$ ). In another subgroup analysis, the results of subjects with non-diabetes disorders revealed a significant reduction in mean difference of body weight, BMI and body fat percentage compared with control groups (body weight:  $-0.84$  kg, 95% CI  $-1.16, -0.51$ , BMI:  $-0.51$  kg/m<sup>2</sup>, 95% CI  $-0.68, -0.35$  and body fat percent:  $-1.17\%$ , 95% CI  $-1.69, -0.65$ ). However, unlike the subjects with non-diabetes disorders, the patients with diabetes did not show differences in mean difference of any anthropometric indices. In the subgroup analysis by quality of studies, the high-quality studies showed significant differences in the mean change of body weight and body fat percentage (body weight:  $-0.80$  kg, 95% CI  $-1.12, -0.49$  and body fat percent:  $-1.17\%$ , 95% CI  $-1.69, -0.65$ ).

Sensitivity analyses were carried out to test the robustness of the overall analysis. Therefore, we tested the effect of removing the data of each trial and monitored the direction of the result. In the sensitivity analyses, omitting the trials by Grant et al<sup>21</sup> and Hockney et al<sup>25</sup> resulted in a significant reduction of 0.67 kg (95% CI  $-0.98, -0.36$ ) and 0.84 mg/L (95% CI  $-1.11, -0.58$ ), as the lower and upper range of analysis, respectively (Figure 3). The findings demonstrate the absence of the differential effect of individual studies.

### 3.5 | Meta regression

Meta-regression analysis was carried out to evaluate the effect of potential moderators on the estimated effect size. The results suggested the positive association between body weight and measured moderators including chromium dosage and duration of supplementation (chromium dosage [slope: 0.00074; 95% CI: 0.00014, 0.00133;  $P = 0.01$ , Figure 4A] and duration of supplementation [slope: 0.04; 95% CI:  $-0.007, 0.10$ ;  $P = 0.08$ , Figure 4B]), which is compatible with the subgroup analysis.

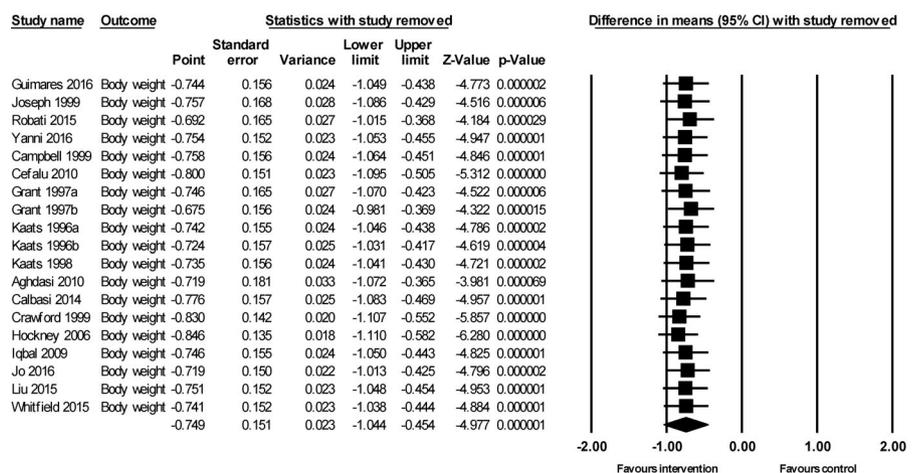
### 3.6 | Publication bias

The publication bias of this meta-analysis was performed using funnel plot, Egger's linear regression, and Begg's rank correlation. The symmetrical shape of distribution did not reveal any signs of publication bias (Figure 5). Based on Egger's linear regression test, no evidence of publication bias was observed (intercept: 0.12; SE: 0.84; 95% CI:  $-1.73, 1.97$ ;  $t = 0.14, df = 11$ ; two-tailed  $P = 0.88$ ). Moreover, the absence of publication bias was identified by Begg's rank correlation with even dispersion of mean differences around the pooled effect estimate (Kendall's Tau with continuity correction:  $-0.01$ ;  $z = 0.06$ ; two-tailed  $P = 0.95$ ).

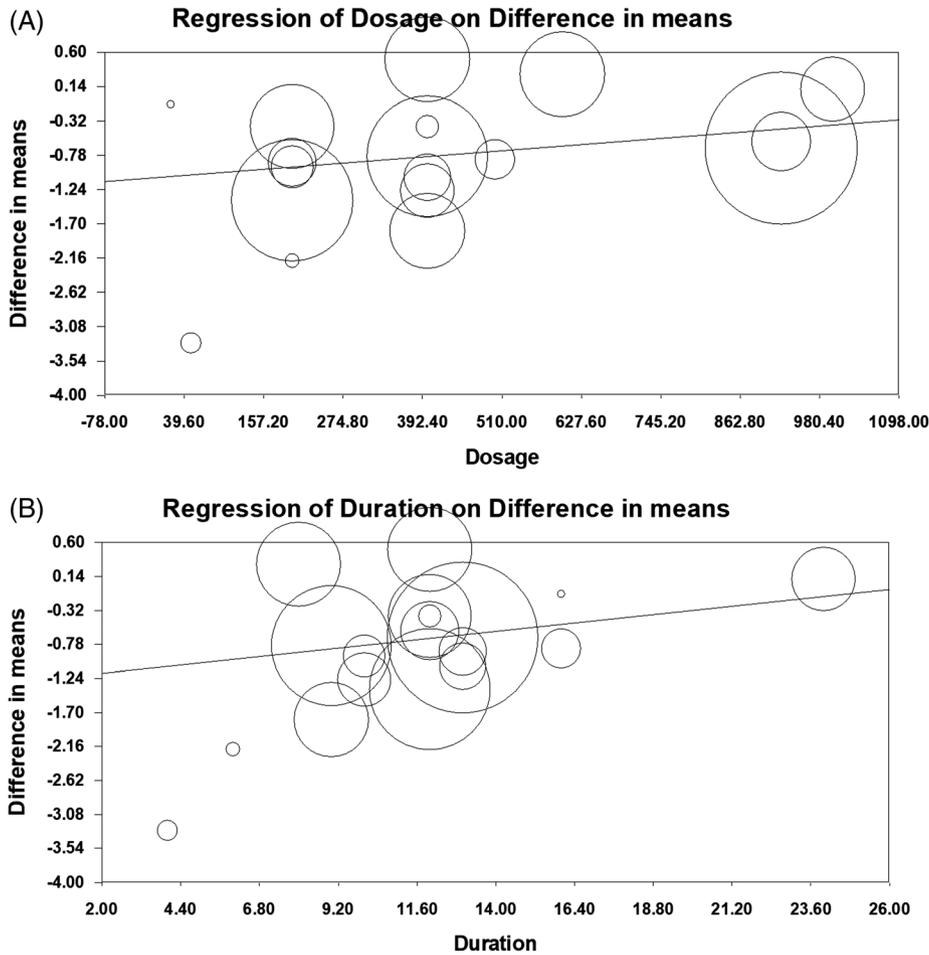
## 4 | DISCUSSION

To our knowledge, the present study is the most up to date and comprehensive analysis from trials on the efficacy of chromium supplementation on anthropometric indices in subjects with overweight and obesity. In particular, a previous meta-analysis of Onakpoya et al included 18 trials with 974 subjects.<sup>10</sup> The study of Tian et al<sup>36</sup> was performed in trials in which the picolinate form of chromium supplement was administered. However, it was more comprehensive compared with the one of Onakpoya. Moreover, the latter meta-analysis included nine RCTs involving a total of 622 participants while we included 21 trials with larger sample sizes enrolled 1316 participants. Therefore, our findings provide the most up to date evidence in this important area of research.

The findings from the present meta-analysis indicate that compared with placebo, chromium supplementation, as picolinate, nicotinate or chromium-enriched yeast, was associated with significant reductions in overall weight loss (WMD:  $-0.75$  kg, 95% CI,  $-1.04, -0.45, P < 0.001$ ), BMI (WMD:  $-0.40$ , 95% CI,  $-0.66, -0.13, P = 0.003$ ) and body fat percentage (WMD:  $-0.68\%$ , 95% CI,  $-1.32, -0.03, P = 0.04$ ) in individuals with overweight and obesity. Subgroup analysis confirmed significant reductions in maximal body weight, BMI and body fat percentage in trials with a duration of  $\leq 12$  weeks (body weight:  $-0.76$  kg, 95% CI  $-1.26, -0.26$ , BMI:



**FIGURE 3** Sensitivity analysis for the effect of chromium supplementation on body weight

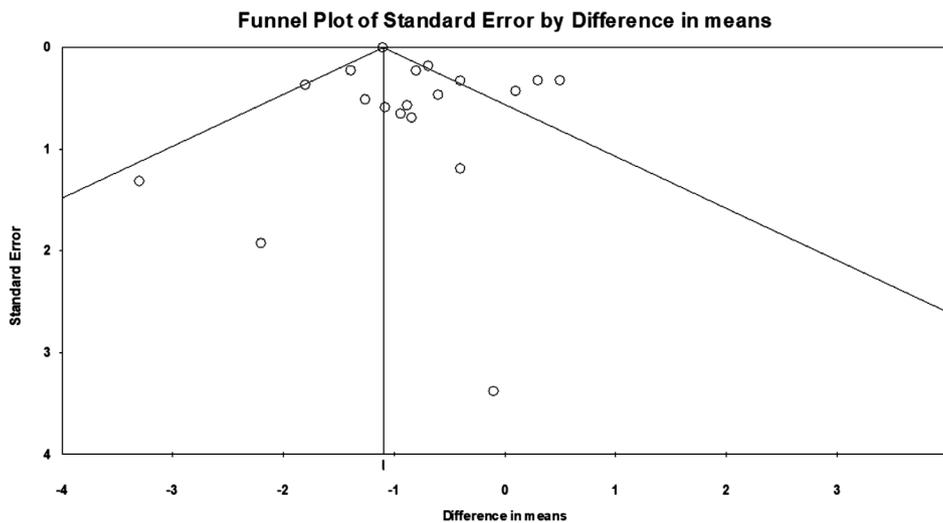


**FIGURE 4** A, Meta-regression plot of the association between mean differences of body weight after chromium supplementation with dosage of the treatment. B, Meta-regression plot of the association between mean differences of body weight after chromium supplementation with duration of supplementation

-1.14 kg/m<sup>2</sup>, 95% CI -1.93, -0.36, and body fat percent: -1.19%, 95% CI -1.72, -0.66), and with doses of ≤400 µg/d (bodyweight: -1.08 kg, 95% CI -1.60, -0.55 and body fat percent: -0.94%, 95% CI -1.77, -0.12).

Our findings contrast with the recommendations from a previous meta-analysis by Onakpoya et al suggesting that future clinical trials

supplement with chromium for at least 16 weeks. In their study, a maximal weight loss of 1 kg was reached at 16 weeks, and this seems to be the rationale for their recommendations. In accordance, we analysed RCT's with a study duration up to 24 weeks, and our data indicated a greater weight loss (ie, 0.76 kg) following sub-group analysis for study duration of ≤12 weeks. Nonetheless, only five trials



**FIGURE 5** Funnel plot for publication bias in included trials on the effect of chromium supplementation on body weight

supplemented chromium over 12 weeks.<sup>18-20,27,29</sup> Interestingly, in comparison with the previous meta-analysis, our study showed a moderate effect size of chromium supplementation on body weight and the finding increases our confidence that chromium supplementation may result in weight loss. However, conclusions cannot be easily drawn, and we recommend future studies clarify the effect of the duration of chromium supplementation on body composition.

The dosage of chromium supplemented ranged from 200 to 1000 µg/d with a median of 400 µg/d. Subgroup analysis by dosage showed significant improvement in the mean change of body weight and body fat percentage in trials which administered chromium at a dose of ≤400 µg/d. This optimal dose of ≤400 µg/d has also been described previously by Onakpoya et al, in terms of maximal weight loss achieved. It is noteworthy, that previous studies have reported concerns regarding the safety of chromium supplementation, particularly as picolinate. Some of these adverse effects have included renal and hepatic impairment and potential genotoxicity at moderate to high doses. However, conclusions from recent expert committees have found no evidence of genotoxicity with picolinate use, and it is generally considered not toxic to human health with oral doses up to 1000 mg/d. In our study, we did not find any evidence of specific adverse effects with chromium supplemented as picolinate, nicotinate or enriched yeast, with doses between 200 and 1000 µg/d.

Waist circumference is an index for visceral adiposity and is associated with the risk of cardiometabolic disease. In our study, we did not observe any significant reductions in waist circumference, or waist to hip ratio, following chromium supplementation as compared with placebo. Our findings are like those of Onakpoya et al, and it is unclear at this juncture whether these effects are clinically relevant or due to inconsistencies with measuring waist circumference and waist to hip ratio, as previously discussed.

Some evidence indicates lower blood concentrations of chromium in populations with diabetes and it has been postulated that chromium supplementation could potentiate the metabolic action of insulin and lower some of the risk factors associated with CVD, particularly in individuals with overweight. In our study, we included individuals with diabetes in our analysis. However, we did not observe any significant reductions or improvements for any of the anthropometric indices associated with body composition in this population. It is uncertain why we did not find any improvements, however, it is likely that it could be due to the limited number of trials conducted on patients with diabetes,<sup>18,28,29,32</sup> regarding changes in body composition. However, our finding is in agreement with the study of Ganguly et al who also reported no significant improvements between the control and chromium yeast groups for glycaemic status, blood pressure, lipid profile, body weight and body fat percentage in hyperglycaemic mice.

There were several limitations to our study, which included the low number of trials, particularly those of a high quality. We also did not consider lifestyle factors, including physical activity or dietary factors, which may have influenced the outcome of our meta-analysis. However, we used a robust search strategy and included individuals

with diabetes in our analyses, which has previously been recommended in earlier reviews.

## 5 | CONCLUSION

In conclusion, chromium supplementation was associated with some improvements in body composition, particularly body weight and body fat percentage, in participants with obesity and overweight. These effects were achieved in shorter durations than previous analyses. Although the effect size was medium, the clinical relevance of chromium as a weight loss aid remains uncertain. Further investigation from larger and better-designed studies are necessary to elucidate the potential benefits of chromium as a weight loss adjunct, especially in patients with diabetes.

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## CONFLICTS OF INTEREST

No conflict of interest was declared.

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# Chromium supplementation in overweight and obesity: a systematic review and meta-analysis of randomized clinical trials

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## Abstract

The increased prevalence of obesity has made the use of dietary supplements as weight reducing agents highly popular, but their efficacy has not been proven. One such supplement is chromium. The purpose of this review was to evaluate the evidence for or against the efficacy of chromium supplementation in overweight and obese individuals. Electronic searches were conducted in Medline, Embase, Amed and The Cochrane Library. The bibliographies of located articles were also searched. No age, gender or language restrictions were imposed. The reporting quality of identified randomized clinical trials (RCTs) was assessed using a methodological checklist adapted from the Consolidated Standard of Reporting Trials Statement and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Thirty-nine trials were identified and 20 were included. There were variations in reporting quality of included studies. A meta-analysis of 11 studies showed a statistically significant difference in weight loss favouring chromium over placebo (mean difference (MD): -0.50 kg; 95% confidence interval (CI): -0.97, -0.03). There was a high statistical heterogeneity. Adverse events included watery stools, vertigo, headaches and urticaria. The evidence from available RCTs shows that chromium

supplementation generates statistically significant reductions in body weight. The magnitude of the effect is small, and the clinical relevance is uncertain. Future trials should last at least 16 weeks and greater uniformity in the measuring and assessment tools for body composition is recommended.



## Chromium Supplementation and the Effects on Metabolic Status in Women with Polycystic Ovary Syndrome

### Abstract

**Background:** The aim of the present study was to evaluate the beneficial effects of chromium intake on markers of insulin metabolism and lipid profiles in women with polycystic ovary syndrome (PCOS). **Methods:** In a prospective, randomized, double-blind, placebo-controlled trial, 64 women with PCOS were randomized to receive 200 µg chromium picolinate supplements (n = 32) or placebo (n = 32) for 8 weeks. Fasting blood samples were obtained at baseline and 8 weeks after the intervention to quantify markers of insulin metabolism and lipid concentrations. **Results:** Chromium supplementation in women with PCOS resulted in significant decreases in serum insulin levels ( $-3.6 \pm 7.4$  vs.  $+3.6 \pm 6.2$  µIU/ml,  $p < 0.001$ ), homeostasis model of assessment-insulin resistance (HOMA-IR;  $-0.8 \pm 1.6$  vs.  $+0.9 \pm 1.5$ ,  $p < 0.001$ ), homeostatic model assessment-beta cell function (HOMA-B;  $-15.5 \pm 32.3$  vs.  $+13.6 \pm 23.1$ ,  $p < 0.001$ ), and a significant increase in quantitative insulin sensitivity check index (QUICKI) score ( $+0.02 \pm 0.03$  vs.  $-0.008 \pm 0.02$ ,  $p = 0.001$ ) compared with the placebo. In addition, a trend toward a significant effect of chromium supplementation on decreasing serum triglycerides ( $-12.4 \pm 74.4$  vs.  $+15.2 \pm 32.4$  mg/dl,  $p = 0.05$ ), very low-density lipoprotein-cholesterol ( $-2.5 \pm 14.9$  vs.  $+3.0 \pm 6.5$  mg/dl,  $p = 0.05$ ), and cholesterol concentrations ( $-8.6 \pm 21.9$  vs.  $+0.7 \pm 22.4$  mg/dl,  $p = 0.09$ ) was seen. **Conclusions:** Eight weeks of chromium supplementation among PCOS women had favorable effects on markers of insulin metabolism.