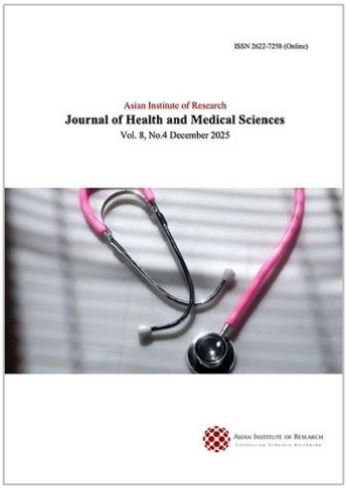

Journal of Health and Medical Sciences

Fatahi, M., Aghajani, S., Javaheri, H., & Toqroljerdi, M. H. F. (2025), The Effect of Chromium Supplements on Insulin Resistance: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Journal of Health and Medical Sciences*, 8(4), 13-42.

ISSN 2622-7258

DOI: 10.31014/aior.1994.08.04.245

The online version of this article can be found at:
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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.8, No.4, 2025: 13-42
ISSN 2622-7258

DOI: 10.31014/aior.1994.08.04.245

The Effect of Chromium Supplements on Insulin Resistance: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: With diabetes rising as a major health issue in developed nations, insulin resistance is gaining more attention. Understanding insulin's role and treatment options for insulin resistance is critical for preventing chronic diseases. We planned to evaluate the impact of chromium on insulin resistance. Method: A comprehensive search was performed using PubMed, Scopus, Embase, and Web of Science databases to assess the effectiveness of chromium trace element on insulin resistance and glucose profile. This review focused solely on randomized controlled trials that were published in English. Results: Our search yielded 2,363 articles. After removing duplicates and conducting thorough title and abstract screening, 45 articles were chosen for full-text evaluation. Among these, 35 articles were included in our systematic review. Finally, 20 studies with 1147 cases focused on patients with type 2 diabetes mellitus, prediabetic, and individuals with confirmed insulin resistance were selected for meta-analysis. The results demonstrated a significant reduction in the HOMA-IR index (pooled MD= -1.29; 95%CI (-1.84 to -0.73), PV= 0.00, I2= 94.7%). Additionally, a significant reduction in the FBS values (pooled MD= - 13.71; 95%CI (-26.29 to -1.12), PV= 0.03, I2= 97.74%) was observed. Regarding the efficacy of chromium on the HbA1C levels, no significant changes were detected (pooled MD= - 0.17; 95%CI (-0.63 to 0.29), PV= 0.42, I2= 96.03%). Conclusion: According to the available evidence, chromium improves insulin resistance in individuals with diabetes or those experiencing insulin resistance. Nevertheless, Additional well-structured and high-quality clinical trials are needed to thoroughly clarify the impact of chromium supplementation on insulin resistance in other situations, like women with PCOS or prediabetic populations.

Keywords: Chromium, Insulin Resistance, Insulin Sensitivity

1. Introduction

The insulin hormone interacts with receptors on target cells and triggers an anabolic response (Petersen et al., 2017). Primarily, insulin in skeletal muscles and the liver increases glucose consumption through glycogen synthesis while suppressing lipolysis in white adipose tissue. The substance indirectly inhibits hepatic gluconeogenesis by reducing hepatic acetyl-CoA levels and diminishing pyruvate carboxylase activity (Schinner et al., 2005). Insulin resistance (IR) is marked by reduced responses of target cells accompanied by compensatory hyperinsulinemia. Potential contributing factors could include the down-regulation of insulin receptors, or genetic variations affecting tyrosine phosphorylation of these receptors, or may involve abnormalities of GLUT 4 (Glucose transporter proteins) function (Wilcox et al., 2005).

IR is associated with overweight, hypertension (HTN), type 2 diabetes mellitus (T2DM), and hyperlipidemia; however, some mechanisms remain unclear (Rao et al., 2006). Diminished muscle glucose metabolism in response to insulin may cause hepatic steatosis and, along with a reduction in substrate oxidation, may be linked to mitochondrial dysfunction (Petersen et al., 2006). There may be a connection between polycystic ovary syndrome (PCOS) and IR, but the importance of this relationship remains complex and not fully understood (Moghetti et al., 2021). Ongoing research suggests that IR may be a contributing element in the development of cancer by mechanisms that include hyperinsulinemia, which provokes increasing levels of insulin-like growth factor 1 (IGF-1), potentially influencing the initiation and progression of tumors in individuals with IR. Moreover, there is frequently an excessive generation of reactive oxygen species that can be harmful to DNA and potentially contribute to the onset of cancer. (Arcidiacono et al., 2012). Interestingly, brain neurons possess insulin receptors, and insulin is integral to neuronal growth, synaptic development, and mitogenesis. Various preclinical studies have shown impaired insulin signaling to be associated with neurodegenerative diseases of the brain (Cholerton et al., 2011. Hölscher et al., 2020). Insulin resistance exerts a multifaceted influence on the body, potentially leading to long-term complications. Therefore, multiple strategies have been proposed to mitigate insulin resistance. These strategies include using antidiabetic agents, anti-inflammatory medications, and the supplementation of vitamins and minerals, among others (Lebovitz et al., 2004. McDonald et al., 2007. Tong et al., 2022. Zhao et al., 2023). Chromium is one of the medications that has been used for reducing insulin resistance (Nishimura et al., 2021). The exact mechanism by which chromium affects insulin metabolism is not entirely understood. It has been suggested that trivalent chromium improves insulin function in peripheral tissues (Lipko et al., 2018). In vitro research suggests that chromium may enhance insulin sensitivity by stimulating the function of insulin receptors (Sahin et al., 2007). It has been demonstrated that chromium enhances insulin receptor β activity. Additionally, chromium promotes the movement of Glut4, a protein that helps cells take glucose to the cell surface. Chromium reduces the activity of PTP-1B (protein tyrosine phosphatase-1B), which normally slows down insulin signaling. It also helps reduce stress within cells and helps move cholesterol out of cell membranes, which supports the movement of Glut4 and increases glucose uptake (Hua et al., 2011).

Animal studies have shown an increase in chromium losses in diabetic rats (Clodfelder et al., 2017) and have expressed the positive impact of chromium in decreasing insulin resistance in obese mice (Wang et al., 2006. Sreejayan et al., 2008. Król et al., 2010). Clinical trials have examined the effects of chromium, either alone or in combination with other interventions, on glucose metabolism (Lai et al., 2008. Dou et al., 2016. Saiyed et al., 2016. Yao et al., 2021). In addition, some meta-analyses have demonstrated the effects of chromium on reducing insulin resistance in T2DM (Balk et al., 2007. Heshmati et al., 2018.), and some showed a decrease in fasting glucose (Abdollahi et al., 2017. Zhao et al., 2022). While the majority of current research investigates the impact of supplementation on insulin and glucose profiles, in this review, we aimed to explore and compare the impact of chromium on insulin resistance, evaluating its effects across different populations.

2. Method

The protocol for the study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), and it is assigned the registration number CRD420250655755. The research adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

2.1. Search Strategy

An extensive search was performed across PubMed, Web of Science, Scopus, and Embase databases in January 2025. The objective was to identify randomized controlled trials assessing the impact of chromium supplementation on insulin sensitivity and resistance. We included a diverse population rather than narrowing it down to a particular group. The search utilized MeSH terms, synonyms, and related keywords for chromium, insulin resistance, and metabolic syndrome. In addition, a comprehensive manual search was conducted utilizing Google Scholar alongside an exploration of gray literature sources. The full search strategy on different databases is provided in Appendix 1.

Two independent reviewers examined and evaluated all identified articles to determine their eligibility according to the established inclusion and exclusion criteria. To guarantee the correctness of the chosen studies, any conflicts were addressed through discussions with a third reviewer.

2.2. Inclusion and Exclusion Criteria

We employed the PICO framework to assess the population, intervention, comparison, and outcome as a guiding structure to clearly define the eligibility criteria (Table 1). We considered all randomized controlled trials (RCTs) published in English in peer-reviewed journals up to January 2025. These studies focused on the impact of chromium supplementation on insulin and glucose levels.

We excluded non-RCTs, observational studies, case reports, and review articles to ensure a focused analysis. Additionally, we excluded articles that did not report relevant outcomes.

Table 1: The population, intervention, comparison, outcome study design (PICO)

Domain	Criteria selection
Participants	Individuals assessed for insulin resistance (no specific population restriction)
Intervention group	Chromium supplementation
Comparison group	Placebo
Outcomes	Insulin level, Glucose profile, Insulin resistance, Insulin sensitivity

2.3. Data Extraction

Two reviewers were tasked with extracting data, with a clear focus on enhancing the quality of our work. An Excel spreadsheet was used to systematically gather study characteristics, including the lead author's name, year of publication, sample size, and participant demographics. Information related to the intervention, such as the type of supplement, dosage, and treatment duration, was also recorded. The outcome results on fasting blood sugar levels (FBS), glucose tolerance test (GTT), HbA1C, insulin, values for insulin resistance, the methods used to determine insulin resistance, or insulin sensitivity. Furthermore, Additional outcomes, such as body mass index (BMI), blood pressure (BP), and lipid profiles, were recorded when accessible. Any discrepancies in the results were addressed by a third reviewer.

2.4. Quality Assessment

The quality of articles was assessed using the updated Cochrane Risk of Bias (RoB-2) tool. Each research study was categorized as having either a low or high risk of bias or exhibiting concerns in different areas. These key areas included the intriguing dynamics of random sequence generation, the essential practice of allocation

concealment, the critical aspect of selective reporting, the various methods of blinding, and the exploration of potential biases (Sterne et al. 2019).

2.5. Data Analysis

The mean change and SD (standard deviation) between the baseline and after intervention HOMA-IR were drawn out. The standardized mean difference (SMD) and 95% confidence interval (CI) were used to compare the effect size. For the studies that provided fasting insulin and glucose values, without stating HOMA-IR, we calculated it by using the following formula:

fasting insulin (mIU/L) ×fasting glucose (mg/dL)/405. For analysis, we included only the studies that were conducted among diabetes, prediabetes, and individuals with documented IR. Our main goal was to assess the efficacy of chromium on the HOMA-IR level. For primary analysis, we excluded the studies among healthy populations and overweight individuals. Then, we assessed the effectiveness of chromium on glycemic variables among women with PCOS as a separate group due to the sufficient included articles to conduct a meta-analysis. Regarding healthy and overweight groups, we did not have enough articles assessing the HOMA-IR index, so we did not include them in the analysis.

We employed a random-effect model using restricted maximum likelihood estimation. The between-study heterogeneity was assessed using Cochrane's Q statistic and Hedges 'g I^2 estimation. I^2 values of 25-50% served as low, values of 50-75% medium, and more than 75% meant substantial heterogeneity. Sensitivity analyses (small study effect) were investigated by the leave-one-out method, and subgroup analysis was conducted by the overall ROB result, age, intervention dose, and duration. Publication bias was studied using standard and contoured funnel plots, Egger's test, and the non-parametric trim-and-fill test. The Grading Quality of Evidence and Strength of Recommendations for diagnostic tests and strategies (GRADE) checklist was used to determine the certainty of evidence. STATA version 17.0.0. Statistical software was used for all analyses.

3. Results

3.1. Study Selection

We initially discovered 2,363 articles, including 351 from PubMed, 484 from Scopus, 792 from the Web of Science, and 736 from Embase. After eliminating duplicate entries, 1,198 articles were screened. The first screening focused on titles, resulting in 155 articles. After reviewing the abstracts, 45 articles were chosen for full-text evaluation, ultimately bringing about the inclusion of 35 articles as shown in Figure 1.

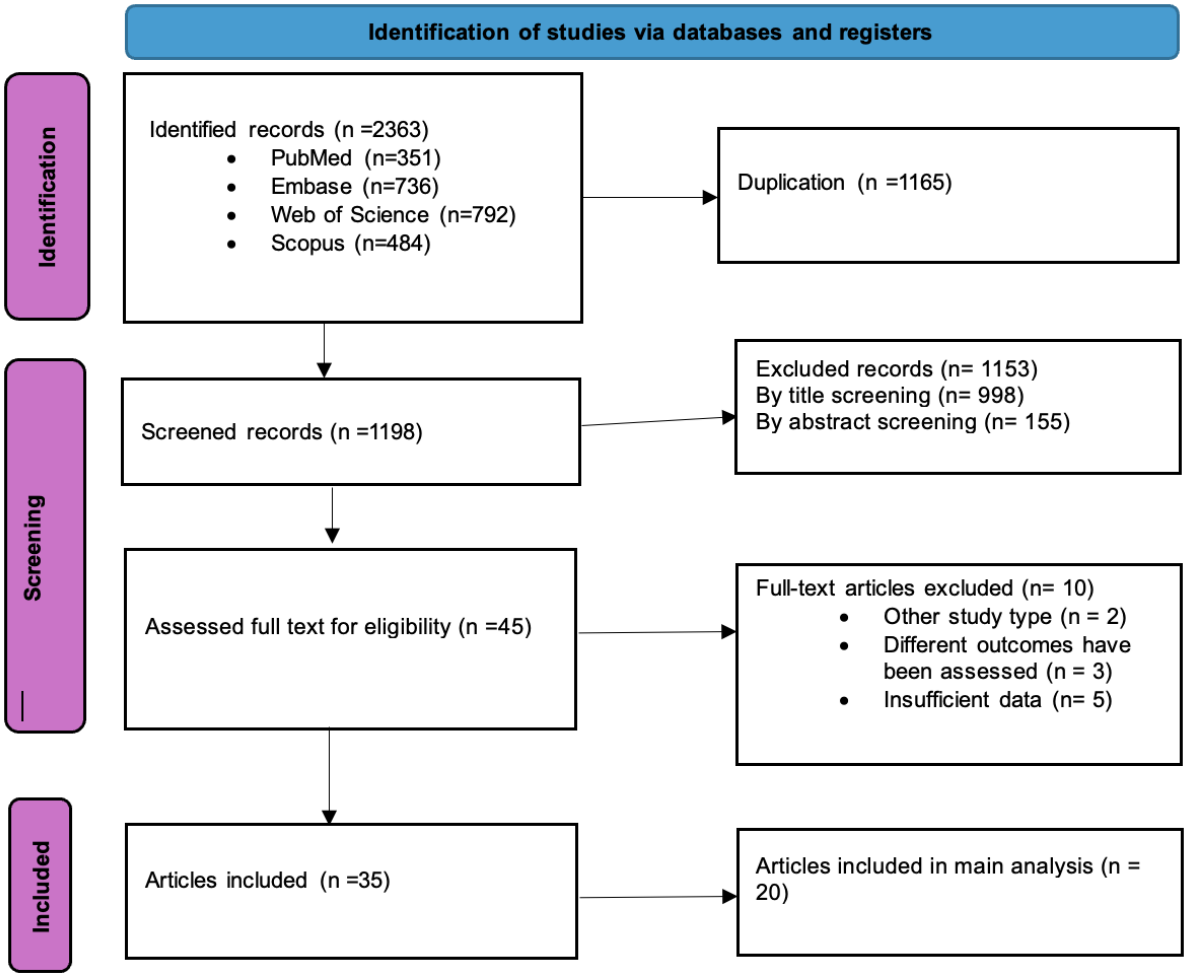

Figure 1: PRISMA diagram for included articles

The RCTs included in our study were published between 1981 and 2024. A total of 35 studies assessing glucose profile and insulin levels were examined. Of these, 14 studies focused on patients with T2DM, three studies on individuals with glucose intolerance, two studies among those with IR, two investigations on HIV-positive cases with IR, and four studies targeted women with PCOS. While four studies involved healthy individuals, five studies involved overweight individuals, and one on non-alcoholic fatty liver patients. Three studies included more than one chromium supplementation arm. These arms were pooled into a single intervention group, as recommended in the Cochrane Handbook, to ensure a single independent comparison with the control group in each study. The interventions lasted 6 to 38 weeks, and the prescribed dosages of chromium supplementation varied from 50µg to 1000µg. The most used form of chromium was chromium picolinate. The trial by Silpa et al. (2024) enrolled 60 participants but did not report group sizes; therefore, an equal allocation of 30 patients in each group was assumed based on the total sample size and comparable baseline variables. Table 2 demonstrates the included studies. Tables 3-5 outline the main findings of these studies based on the population.

Table 2: The characteristics of included studies.

Studies	Population	Sample size(I/P)	Age (I/P)	Male (I/P)	Intervention dose and type	Duration
Silpa et al./ 2024	T2DM	60	50.6+/-4.5 vs 51.9+/-5.5	NS	NS	8w
Talab et al./ 2020	T2DM	52 (26 vs 26)	50.4+/-6.0 vs 51.4+/-6.0	7 / 11	400µg CrP	8w
Farrokhian et al./ 2019	T2DM	64 (32 vs 32)	58.0+/-8.0 vs 60.9+/-7.7	15 / 17	200µg CrP	12w

Imanparast et al./ 2019	T2DM	46 (23 vs 23)	50.4+/-8.5 vs 51.7+/-9.1	10 / 13	500µg CrP	16w
Yanni et al./ 2018	T2DM	30 (15 vs 15)	NS	9 / 9	NS dose CY bread	12w
Chen et al./ 2014	T2DM	66 (38 vs 28)	53.3 ± 10.1 vs 54.2 ± 8.5	22 / 21	400µg CCl (milk)	16w
Guimarães et al./ 2013	T2DM	42	51.35 (200µg) 50.75 (50µg) 50.47 (p)	5 (200µg) 3 (50µg) 4 (p)	(23): 200µg (18): 50µg CrN	12w
Jain et al./ 2012	T2DM	83 28 (CDNC) 28 (CrP) 27 (P)	48.79 (CDNC) 51.12 (CrP) 48.64 (P)	14 (CDNC) 10 (CrP) 4 (P)	400µg	12w
Lai et al./ 2008	T2DM	20 (10 vs 10)	53.2+/-2.0 vs 50.05+/-1.9	4 / 5	1000µg CY	24w
Kleefstra et al. / 2007	T2DM	56 (28 vs 28)	68+/-8.2 vs 66+/-8.6	18 / 17	400µg CY	4w
Pei et al./ 2006	T2DM	60 (30 vs 30)	54.2+/-7.1 vs 55.6/-8.2	16 / 17	200µg Chromium enriched milk	16w
Martin et al./ 2006	T2DM	29 (17 vs 12)	NS	NS	1000µg CrP	12w
Racek et al./ 2005	T2DM	36 (19 vs 17)	61.8 vs 60.8	5 / 4	400µg CrY	12w
Ghosh et al./ 2002	T2DM	100 (50 vs 50)	NS	NS	400µg Trivalent	12w
Nussbaumerova et al./ 2017	prediabetic	70 (35 vs 35)	57+/-10 vs 58+/-9	12 / 13	300µg CY	24w
Ali et al./ 2012	prediabetic	60 (30 vs 30) 58 (29 vs 29)	NS	NS	500µg (15) 1000µg (15) CrP	24w
Gunton et al./ 2005	prediabetic	40 (20 vs 20)	NS	NS	800µg CrP	12w
Zhao et al./ 2024	IR individuals	60 (30 vs 30)	53.87+/-8.73 vs 50.89+/-8.06	18 / 12	160µg CY	12w
Dou et al./ 2016	IR individuals	60 (30 vs 30)	55.3+/-3.3 vs 55.6+/-3.36	NS	160µg CY	12w
Stein/ et al./ 2013	HIV with glucose intolerance	39 (20 vs 19)	47.6+/-1.7 vs 47.3+/-1.7	13 / 13	1000µg CrP	8w
Aghdassi et al./ 2010	HIV with IR	52 (26 vs 26)	46.8+/-1.5 vs 50.2+/-1.4	25 / 25	400µg CrN	16w
Jamilian et al./ 2018	PCOS	40 (20 vs 20)	30.3+/-4.6 vs 32.3+/-3.0	none	200µg CrP	8w
Ashoush et al./ 2016	PCOS	85 (44 vs 41)	24.7+/-3.7 vs 24.6+/-4	none	1000µg CrP	24w
Jamilian et al./ 2015	PCOS	64 (32 vs 32)	24.9+/-5.0 vs 24.4+/-4.4	none	200µg CrP	8w
Lucidi et al./ 2005	PCOS	10 (6 vs 4)	NS	none	200µg CrP	16w

Masharani et al./ 2012	Healthy	31 (16 vs 15)	35.9+/-11.5 vs 38.6+/-10.5	9 / 8	1000µg CrP	16w
Amato et al./ 2000	Healthy	52 (26 vs 26)	69.3+/-1.4	25 / 25	400µg CrP	16w
Riales et al./ 1981	Healthy	23 (12 vs 11)	46+/-9 vs 49+/-9	12 / 11	200µg trivalent	12w
Wilson et al./ 1995	Healthy	26 (15 vs 11)	36.7+/-1.82 vs 35.5+/-1.89	5 / 6	220µg CrP	12w
Sala et al./ 2017	Overweight	24 (8 vs 9 vs 7)	36.6	16.2%	8: 1000µg 9:600µg CrP	12w 24w
Yazaki et al./ 2010	Overweight	80 (40 vs 40)	NS	NS	1000µg CrP	12w 24w
Kim et al./ 2010	Overweight children	25 (12 vs 13)	10.7+/-0.2 vs 10.38+/-0.3	4 / 8	200µg CrCl	6w
Iqbal et al./ 2009	Overweight with Metabolic syndrome	63 (33 vs 30)	47.7+/-10 vs 51.1+/-13	13 / 18	1000µg CrP	16w
Cefalu et al./ 1999	Overweight	29 (15 vs 14)	45+/-3 vs 49+/-4	5 / 6	1000µg CrP	38w
Moradi et al./ 2021	Fatty liver disease	46 (23 vs 23)	38.9+/-7.3 vs 40.3+/-6.7	14 / 12	400µg CrP	12w

T2DM: type 2 diabetes mellitus, IR: insulin resistance, PCOS: polycystic ovary syndrome, HIV: human immunodeficiency virus, NS: non-specified, CrPic: chromium picolinate, CrN: chromium nicotinate, CrCl: chromium chloride, CDNC: chromium dinicocysteinate, CY: chromium-enriched yeast

Table 3: The effects of chromium on the outcomes in those with diabetes, prediabetic conditions, or known insulin resistance

Study	Assessment method	Primary outcome	Other findings
Silpa et al. (2024)	Fasting insulin	-The endpoint means insulin levels in groups differed significantly ($P < 0.05$). - No significant difference in FBS	- No significant difference in lipid profiles
Zhao et al. (2024)	HOMA-IR	-No significant decreases from the baseline values of FBS and HOMA-IR were observed in both groups.	NS
Talab et al. (2020)	HOMA-IR	- Changes in HOMA-IR between groups were significant ($P < 0.001$). - No significant changes in FBS and insulin levels were reported.	- Significant improvement in total cholesterol and LDL in the intervention group.
Farrokhian et al. (2019)	HOMA-IR Insulin sensitivity (QUICKI)	- Cr significantly reduced FBS ($P = 0.007$), insulin, and HOMA-IR ($P < 0.001$).	- Cr decreased body weight ($P = 0.001$) and BMI ($P = 0.002$). - Cr significantly reduced diastolic blood pressure ($P = 0.01$).
Imanparast et al. (2019)	HOMA-IR	- An increase in the HOMA-IR in the placebo group was reported.	- No changes in the lipid profile were observed.

		- FBS and HbA1c did not change significantly.	
Yanni et al. (2018)	HOMA-IR	- Cr significantly decreased FBS and HbA1C ($P < 0.05$). - Serum insulin and HOMA-IR were lower in the Cr intervention group ($P < 0.05$).	-No difference in lipid profile was observed.
Nussbaumerova et al. (2017)	HOMA-IR	- There were no significant changes in FBS, HbA1C, and HOMA-IR, a slight decrease in insulin levels in the second hour of GTT in the Cr group.	- Fasting lipids, CRP, and oxidative stress markers did not change during the study.
Dou et al. (2016)	HOMA-IR	- No significant decreases from the baseline values were documented in both groups.	NS
Chen et al. (2014)	Insulin sensitivity	-SI was improved in the Cr group notably. - FBS significantly decreases in the Cr group.	-No substantial changes were observed in the TG, total cholesterol, LDL, and HDL. - Waist circumference and ALT decreased significantly in the Cr group.
Stein et al. (2013)	HOMA-IR	- No statistically significant differences were observed in the responses of FBS and HOMA-IR in the Cr group.	- There was a significant improvement in serum HDL in the group supplemented with Cr**.**
Guimarães et al. (2013)	HOMA-IR	- No marked difference between groups in FBS, HbA1C, and HOMA-IR. - HOMA-β increased in the placebo group.	- No marked difference between groups in total cholesterol and LDL. - HDL increased in the placebo group.
Jain et al. (2012)	HOMA-IR	- No differences in glycemic profile after supplementation were observed. - Significant reduction in the insulin level and insulin resistance after supplementation with Cr.	NS
Ali et al. (2012)	HOMA-IR	- The groups had no significant differences in insulin, HOMA-IR, or glucose profile.	- No significant differences on lipid profile or blood pressure were observed.
Aghdassi et al. (2010)	HOMA-IR	- Cr caused a significant drop in HOMA-IR and blood insulin levels. - Baseline IR significantly affected the response to Cr, with a strong link between initial insulin levels and the reduction in	- TG was reduced after Cr supplementation. - There was no change in FBS, Hb A1c, HDL or CD4 cell count between groups.

		blood insulin post-supplementation ($p = 0.0001$).	
Lai et al. (2008)	HOMA-IR	- In the Cr group, there was a significant reduction in FBS, HbA1c, and the insulin resistance index ($p<0.05$).	- The glutathione peroxidase activity showed a notable increase ($p<0.05$).
Kleefstra et al. (2007)	HOMA-IR	- No meaningful differences were found between groups for FBS, HbA1C, and insulin resistance.	- No marked difference in blood pressure, body fat, body weight, or serum lipids was found.
Pei et al. (2006)	HOMA-IR	- The Cr group demonstrated a lower FBS, fasting insulin, and HbA1C, especially in male patients ($p<0.05$). - A marked improvement in HOMA-IR ($p<0.05$) was documented.	- No marked changes in lipid profiles were stated.
Martin et al. (2006)	Insulin sensitivity	- Participants given sulfonylurea/Cr showed significantly lower fasting blood sugar, glucose AUC, and improved insulin sensitivity compared to those on sulfonylurea/placebo.	- Those on sulfonylurea/placebo showed notable increases in body weight and body fat percentage.
Racek et al. (2005)	Fasting insulin	- The changes in the FBS in the Cr group were notably different ($p < 0.01$). - A slight but not statistically significant reduction in insulin levels was found in the intervention group.	- No considerable differences in TG, total cholesterol, HDL, and LDL were documented.
Gunton et al. (2005)	HOMA-IR	- The two groups had no significant differences in insulin and HOMA-IR.	- There was a minor deterioration in total cholesterol in the placebo intervention.
Ghosh et al. (2002)	Fasting insulin	-Significant improvement in FBS and HbA1C with Cr supplementation. - Significant reduction in serum insulin was documented in the Cr group.	- No marked changes in lipid profile documented.

Cr: chromium, ISI: insulin sensitivity index, FSIVGTT: frequently sampled intravenous glucose tolerance test, QUICKI: quantitative insulin sensitivity check index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TG: triglyceride, FBS: fasting blood sugar, HbA1C: Hemoglobin A1c, AUC: area under the curve, P: P value

Table 4: The effects of chromium on the outcomes in overweight or healthy individuals.

Study	Assessment method	Primary outcome	Other findings
Moradi et al. (2021)	HOMA-IR Insulin sensitivity	- Cr significantly decreased TG, insulin,	- No remarkable differences in total

	(QUICKI)	and HOMA-IR ($p < 0.05$). - There were no major differences in FBS and HbA1C ($P > 0.05$).	cholesterol, HDL, and LDL were noted ($P > 0.05$).
Sala et al. (2017)	Insulin sensitivity (ISI)	- The AUC showed a significant increase in the placebo group ($p < 0.02$), while there was a notable decrease in the group that received 600mg of CrP ($p < 0.03$). -Insulin AUC increased significantly, whereas ISI dropped considerably ($p < 0.03$).	NS
Masharani et al. (2012)	Insulin sensitivity (euglycemic hyperinsulinemic clamp)	- Cr caused no major changes in the IS value ($p=0.83$).	NS
Yazaki et al. (2010)	Fasting insulin	- There was no difference in fasting glucose and insulin levels compared to the baseline.	- No changes in lipid profile observed between groups. - No changes were documented in BMI between groups.
Kim et al. (2010)	HOMA-IR	- Cr significantly dropped HOMA-IR, while placebo rose it. - No considerable changes in FBS were found.	-The decrease in body fat percentage was more significant in the Cr group compared to the placebo group ($P= 0.04$). - No treatment effects were observed for BMI, waist circumference, blood pressure, total cholesterol, TG, and HDL.
Iqbal et al. (2009)	Insulin/ glucose ratio	- After Cr treatment, there were no marked changes in SI and glucose effectiveness index.	- A small, non-significant decrease in LDL levels was noted in the Cr group, while the placebo group experienced an increase.
Amato et al. (2000)	Insulin Sensitivity Assessment (FSIVGTT)	- Insulin sensitivity and glucose effectiveness showed remarkable changes with chromium.	- No significant changes in lipids, or body composition were documented.
Cefalu et al. (1999)	Insulin Sensitivity Assessment (FSIVGTT)	- Those in the Cr group had a significant rise in insulin sensitivity at the midpoint ($P < .05$) and end of the study ($P < .005$). - No changes in glucose effectiveness were noted between groups.	NS
Wilson et al. (1995)	Insulin sensitivity (ISI)	-Participants with high initial insulin resistance showed a significant ($P < 0.03$) decrease after Cr.	NS

		- No significant changes in FBS after Cr was documented.	
Riales et al. (1981)	Insulin/ glucose ratio	- In the Cr group, mean plasma glucose levels were lower at 6 weeks than at baseline, but only the FBS was lower at 12 weeks. - A decrease in the I/G ratio that indicates increased insulin sensitivity.	- A borderline drop in TG was found in the Cr group.

Cr: chromium, ISI: insulin sensitivity index, FSIVGTT: frequently sampled intravenous glucose tolerance test, QUICKI: quantitative insulin sensitivity check index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TG: triglyceride, FBS: fasting blood sugar, HbA1C: Hemoglobin A1c, AUC: area under the curve, P: P value

Table 5: The effects of chromium on the outcomes in women with polycystic ovary syndrome.

Study	Assessment method	Primary outcome	Other findings
Jamilian et al. (2018)	HOMA-IR Insulin sensitivity (QUICKI)	- Cr resulted in significant reductions in FBS (P = 0.03), serum insulin levels (P = 0.004), HOMA-IR (P = 0.005).	- Cr significantly decreased serum TG (P = 0.004), VLDL (P = 0.004) and total cholesterol values (P = 0.03).
Ashoush et al. (2016)	Glucose/ insulin ratio	- Treatment with Cr did not significantly change FBS in the groups (P = 0.594 and 0.32). - Women in the Cr group had a remarkable decrease in fasting insulin (P = 0.007) along with a major rise in the FGIR (P= 0.047).	- Women in the Cr group had a marked drop in BMI (P< 0.001).
Jamilian et al. (2015)	HOMA-IR, HOMA-B Insulin sensitivity (QUICKI)	- Cr resulted in significant decreases in insulin (p < 0.001), HOMA-IR (p < 0.001), and HOMA-B (p < 0.001) values.	- Cr decreased TG (p = 0.05), VLDL (p = 0.05), and cholesterol concentrations (p = 0.09).
Lucidi et al. (2005)	Insulin sensitivity	- Slight but not significant decrease in insulin sensitivity from baseline in Cr group was observed. - Cr resulted in significant improvement in glucose tolerance tests. -The FBS did not change markedly from baseline after treatment.	NS

Cr: chromium, ISI: insulin sensitivity index, FSIVGTT: frequently sampled intravenous glucose tolerance test, QUICKI: quantitative insulin sensitivity check index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, TG: triglyceride, FBS: fasting blood sugar, HbA1C: Hemoglobin A1c, AUC: area under the curve, P: P value

3.3. Quality Assessment

Figure 2 illustrates the outcomes of the risk of bias assessment conducted on the selected articles. Out of the total articles reviewed, fifteen were identified as having a high risk of bias. Conversely, eleven articles were classified as having a low risk of bias, suggesting that they adhered to more rigorous research standards and produced reliable results. Additionally, eight articles were identified as having some concerns related to bias, highlighting specific areas where the research may be weakened or questioned.

study	D1	D2	D3	D4	D5	Overall
Aghdassi/2010	+	+	+	+	+	+
Amato/2000	+	+	+	+	+	+
Ashoush/2016	+	+	+	+	!	!
Kim/2010	!	+	+	!	!	-
Lai/2008	!	!	+	+	!	-
Cefalu/1999	!	+	+	!	!	!
Dou/2016	!	+	+	+	+	!
Farrokhian/2019	!	+	+	+	+	+
Lucidi/2005	-	+	+	+	+	-
Guimaraes/2013	+	!	+	!	!	!
Gunton/2005	!	+	+	+	+	!
Iqbal/2009	+	+	+	+	+	+
Jain/2012	+	+	+	+	+	+
Martin/2006	!	-	+	+	+	-
Jamilian/2015	+	+	+	+	+	+
Jamilian/2018	+	+	+	+	+	+
Masharani/2012	-	+	-	+	+	-
Moradi/2021	!	-	+	+	+	-
Kleefstra/2007	+	+	+	+	+	+
Riales/1981	!	-	+	+	-	-
Racek/2005	!	-	+	+	+	-
Nussbaumerova/ 2017	+	!	+	+	+	!
Pei/2006	!	-	+	+	+	-
Sala/2017	!	-	+	+	+	-
Silpa/2014	!	-	+	+	+	-
Stein/2013	!	!	+	+	+	!
Ghosh/2002	+	+	+	+	+	+
Talab/2020	!	-	+	+	+	-

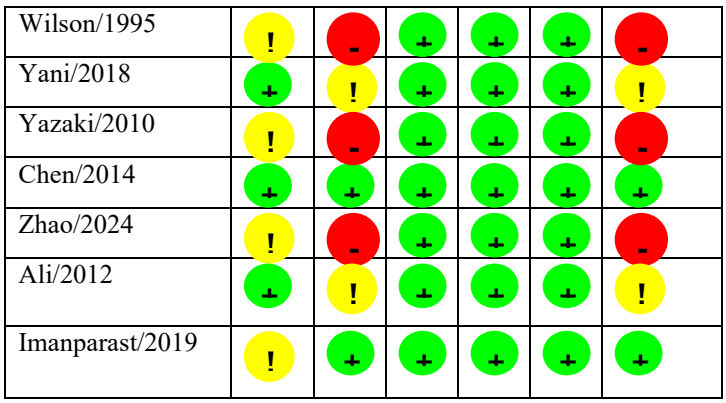

Figure 2: Cochrane Risk of Bias (RoB 2 Tool) Summary

3.4. Effects of chromium supplementation on HOMA-IR

Twenty studies with 1147 participants compared chromium and placebo on the HOMA-IR index among diabetic and prediabetic individuals. Meta-analysis of these studies demonstrated (Figure 3) that chromium significantly reduced the HOMA-IR index (pooled MD= -1.29; 95%CI (-1.84 to -0.73), P_V= 0.00), but this analysis had a high level of heterogeneity (I^2= 94.7%).

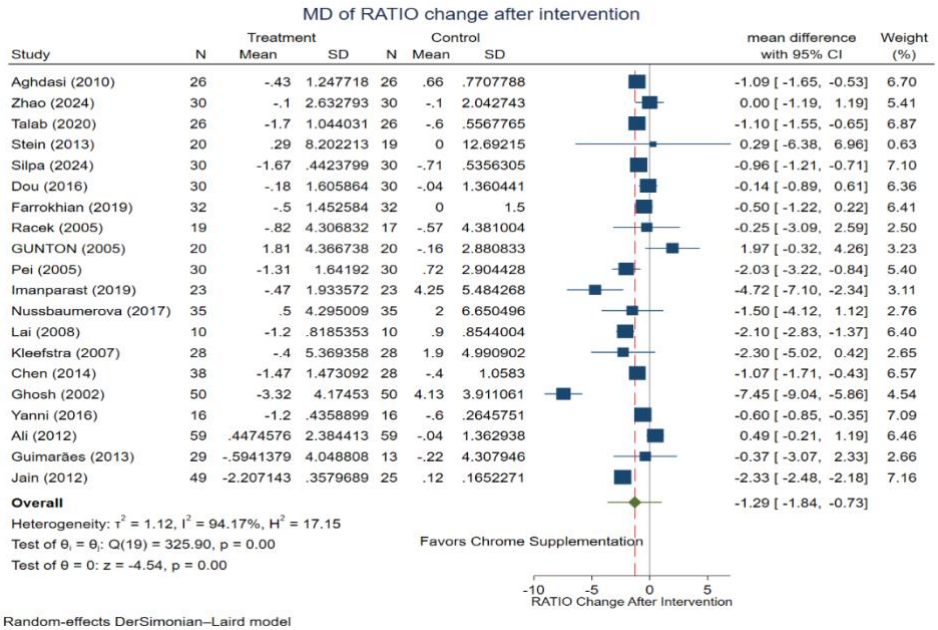

Figure 3: Forest plot for meta-analysis of HOMA-IR mean changes in the chromium group versus the control group

3.5. Effects of chromium supplementation on FBS and HbA1C

Seventeen studies evaluated the efficacy of the intervention on FBS levels and showed (Figure 4) a significant reduction in the FBS values (pooled MD= - 13.71; 95%CI (-26.29 to -1.12), P_V= 0.03, I^2= 97.74%). Regarding the efficacy of chromium on the HbA1C levels, no significant changes were detected (pooled MD= - 0.17; 95%CI (-0.63 to 0.29), P_V= 0.42, I^2= 96.03%) (Figure 5).

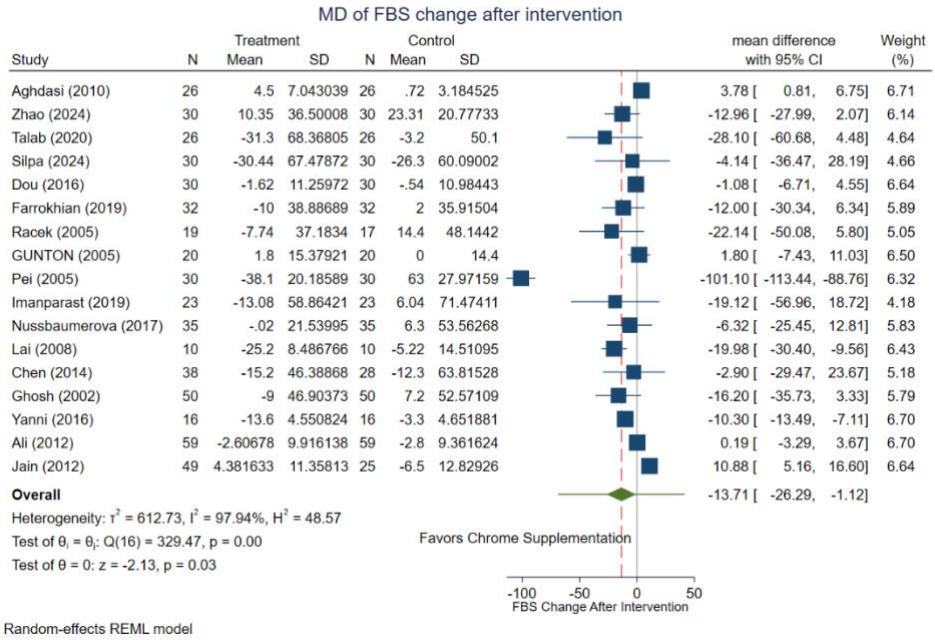

Figure 4: Forest plot for meta-analysis of FBS mean changes in the chromium group versus the control group

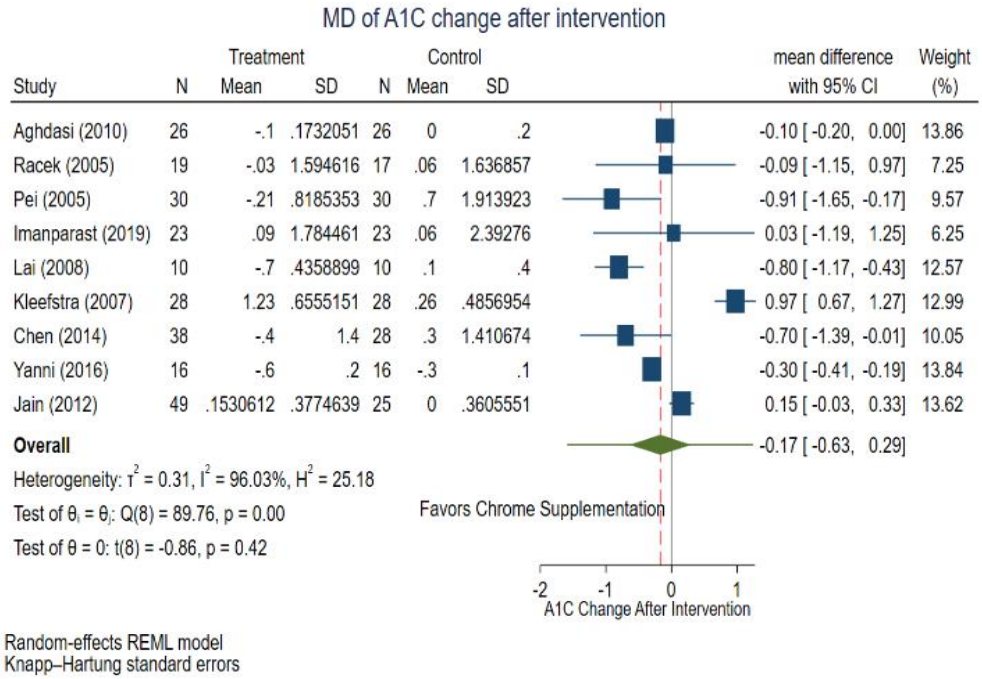

Figure 5: Forest plot for meta-analysis of HbA1C mean changes in the chromium group versus the control group

3.6. Effects of chromium supplementation on HOMA-IR and FBS among PCOS individuals

Four studies with 199 cases assessed the efficacy of chromium on fasting insulin and glucose among women with PCOS. No significant pooled reduction reported (HOMA-IR: (pooled MD= - 0.81; 95%CI (-4.01 to 2.38), P_V= 0.88, I^2= 2.10%), FBS: (pooled MD= - 0.12; 95%CI (-2.46 to 2.22), P_V= 0.48, I^2= 0.00%)) (Figure 6).

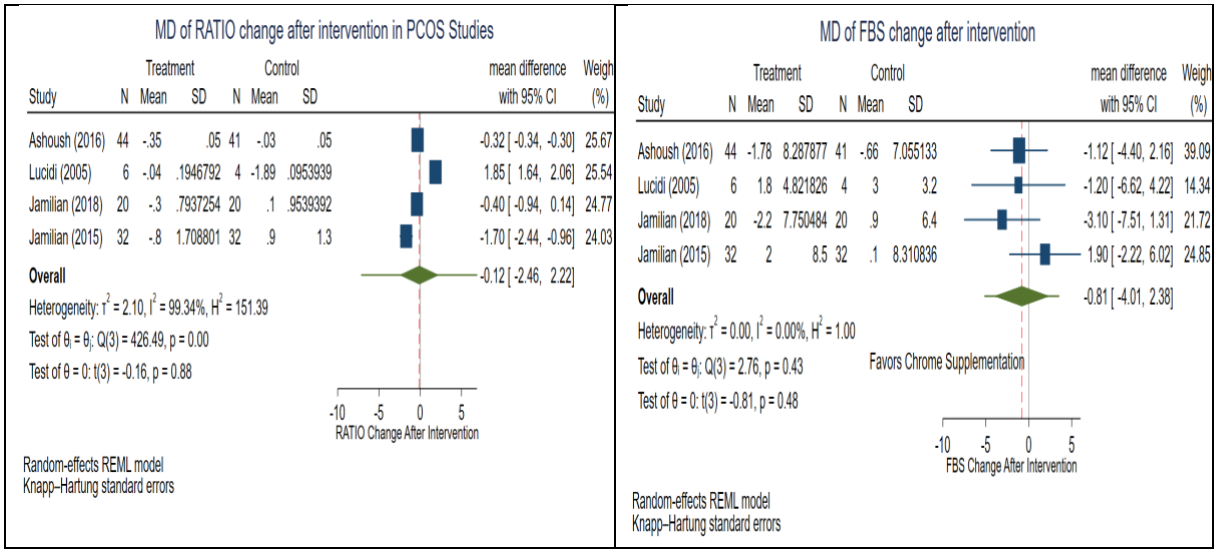

Figure 6: Forest plot for meta-analysis of HOMA-IR and FBS mean changes after intervention in women with PCOS

3.7. Subgroup analysis

Subgroup analysis didn't reveal a significant difference in SMD for HOMA-IR changes based on the patient age, chromium type, chromium dose, or duration of supplementation. The graphs for the subgroup analyses are available in Appendix 2-5. Additionally, the subgroup analysis based on the underlying condition did not show any significant differences in the HOMA-IR SMD (Appendix 6). However, the results of subgroup analysis based on the quality of the included articles partially explained heterogeneity and showed that the quality of the studies is a significant moderator of the effects of chromium on HOMA-IR ratio (Appendix 7).

3.8. Sensitivity analysis

Leve one out sensitivity analyses on HOMA-IR confirmed the robustness of the outcome, as the removal of any study didn't alter the pooled SMD. In contrast, the results for FBS change showed a weaker and less consistent negative effect (Appendix 8,9).

3.9. Publication bias

The standard and counter-enhanced funnel plot inspection demonstrated an asymmetric distribution (Appendix 10). However, several studies were located outside the contour for p > 10%, which suggests that the asymmetry may not be solely due to publication bias, but possibly other factors such as small-study effects. To statistically investigate the asymmetry, Egger's regression test for small-study effects was conducted. The results of the test showed a statistically significant asymmetry (beta1 = -11.43, SE = 1.887, z = -6.06, p < 0.0001). A nonparametric trim-and-fill analysis was performed to estimate the impact of publication bias on the overall effect size by imputing missing studies (Appendix 11). The analysis identified no missing studies (observed = 20, imputed = 0). The pooled Hedges's g for both observed studies and the combination of observed and imputed studies was the same (-0.624, 95% CI [-0.748, -0.500]).

3.10. GRADE

The GRADE checklist was applied for three outcomes, including HOMA-IR, FBS, and HbA1C changes. The final level of certainty for these outcomes was moderate, low, and moderate, respectively. The GRADE table is available at https://1drv.ms/x/c/7234bfd3278bfcf9/EaYLYCShZrZMnOqp7S0Hf4kB1TOba-i4QMSzzgcj7B6Kpw?e=HPR00O.

4. Discussion

This meta-analysis demonstrated that chromium supplementation significantly decreased IR in populations with diabetes and those experiencing IR. Furthermore, a significant reduction in FBS was observed. However, the analysis did not detect a significant change in HbA1c levels, suggesting that while chromium may have an acute effect on insulin resistance and fasting glucose, its long-term impact on overall glycemic control, as measured by HbA1c, remains inconclusive. The results of the analysis are consistent with several previous studies and reviews that have supported the beneficial role of chromium in managing insulin resistance (Balk et al., 2007. Abdollahi et al., 2013. Asbaghi et al., 2020). Accordingly, Balk et al. (2007) meta-analysis stated that chromium decreased glycemic indices in diabetics without any effect on glucose metabolism in those with normal blood glucose. Although our results contrast with the Zhao et al. (2022) meta-analysis, which stated that the only glycemic index significantly affected by chromium is HbA1c. This discrepancy may be attributed to differences in the inclusion criteria of the studies, the specific patient populations analyzed, or the high degree of heterogeneity noted in our analysis, which could mask an effect on HbA1c.

While chromium supplementation did not show any significant effect on the HOMA-IR index or FBS in women with PCOS, a non-significant reduction in this population may suggest the benefits of chromium may extend beyond individuals with diabetes and prediabetes, offering a potential therapeutic avenue for improving metabolic health in PCOS patients. Two previous meta-analyses stated the significant effect of chromium on HOMA-IR, with fewer included articles (Tang et al., 2018. Heshmati et al., 2018). Additionally, Fazelian et al. (2017) showed improvement in insulin sensitivity after chromium treatment in women with PCOS. Based on our results, it appears that the statistical significance of this finding diminished as more RCTs were included in the analysis.

A subgroup analysis by intervention duration suggested that the beneficial effects of chromium on IR may be more pronounced at 12 weeks, with no meaningful effects observed at 8 or 24-week durations. These results align with Asbaghi et al. (2020) on the duration of supplementation. Chromium doses up to 500µg were associated with a greater improvement in HOMA-IR levels.

The bioavailability of chromium might be affected by different variables. Certain elements have been demonstrated to affect chromium absorption, as a diet rich in phytate and simple sugars may reduce it (Anderson et al., 2003). Some studies have confirmed that additional trace elements can enhance the beneficial effects of chromium on metabolic health. Zhao et al. (2024) noted that the combined supplementation of chromium and magnesium enhances glucose and lipid levels while decreasing inflammation and oxidative stress markers. Imanparast et al. (2020) showed that co-supplementation of chromium and vitamin D3 significantly decreases HOMA-IR. Lai et al. (2008) demonstrated that combining vitamin C or vitamin E with chromium is as effective as chromium supplementation in improving insulin resistance. Chromium's bioavailability varies by form, with picolinate seeming to be the most stable and bioavailable (Anderson et al., 2008); however, our subgroup analysis did not find any significant differences based on the form of supplementation. Furthermore, given the natural decline in chromium levels with aging, supplementation needs may vary from person to person (Schinner et al., 2005). This is supported by our finding of a non-statistically significant reduction in HOMA-IR in those older than 60, indicating that further research is needed to determine the optimal dosage and duration for this specific population.

5. Limitations

Our results showed that despite a significant pooled reduction in HOMA-IR and FBS with chromium supplementation, the wide 95% prediction interval (PrI) suggests limited generalizability to new populations or settings. Furthermore, there were an insufficient number of studies reporting IR to perform a subgroup analysis in overweight and healthy populations. Further investigation through well-structured RCTs, which modify a range of variables, may be instrumental in accurately assessing chromium's efficacy across diverse populations.

6. Conclusion

Chromium supplementation has been demonstrated to reduce insulin resistance in patients with T2DM and those who already exhibit significant insulin resistance. However, individuals without established insulin resistance may not experience benefits from chromium.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Ethical Approval: As this article is a review of previously published articles, an ethics approval statement is not applicable.

Declaration of Generative AI and AI-assisted Technologies: This study has not used any generative AI tools or technologies in the preparation of this manuscript.

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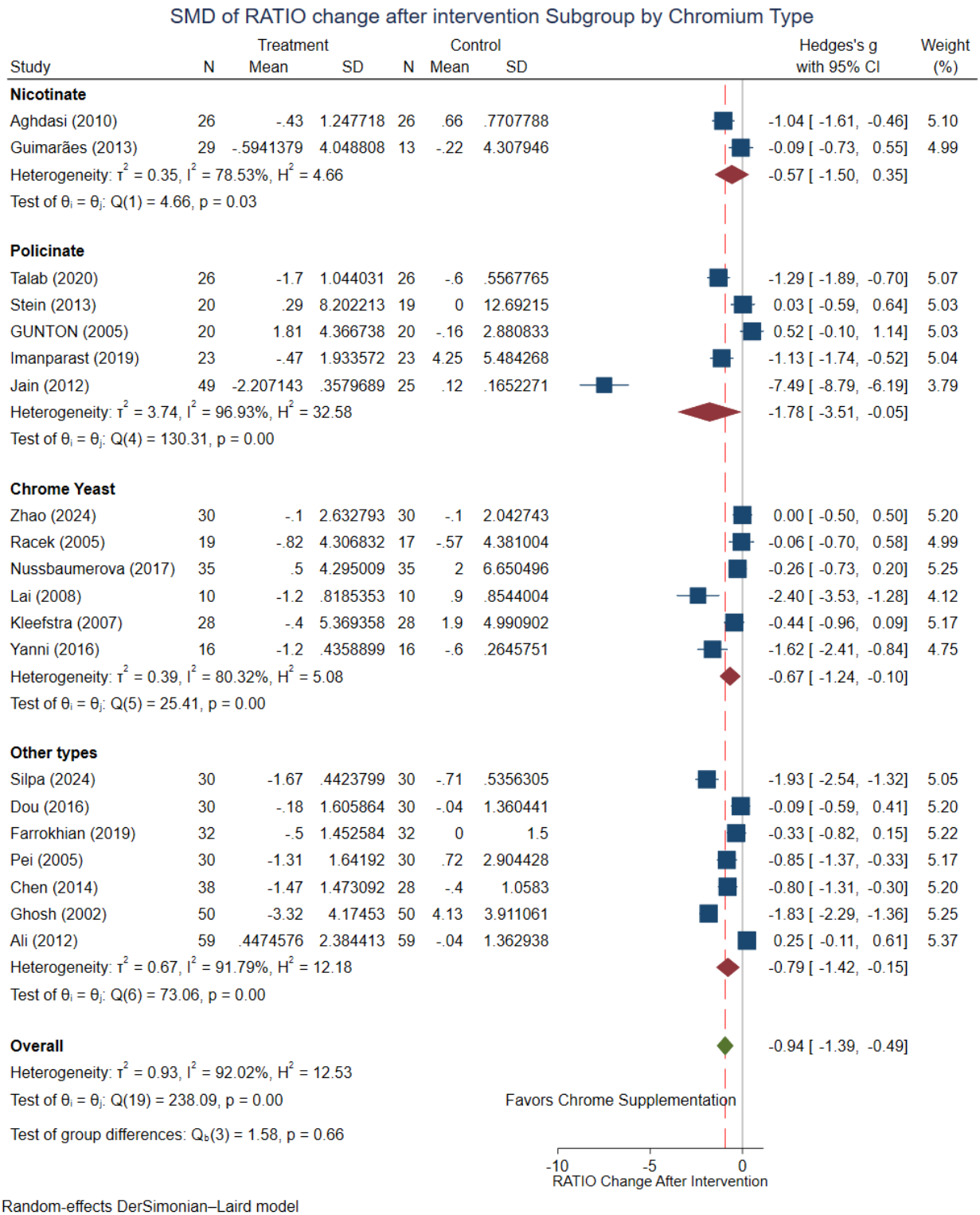
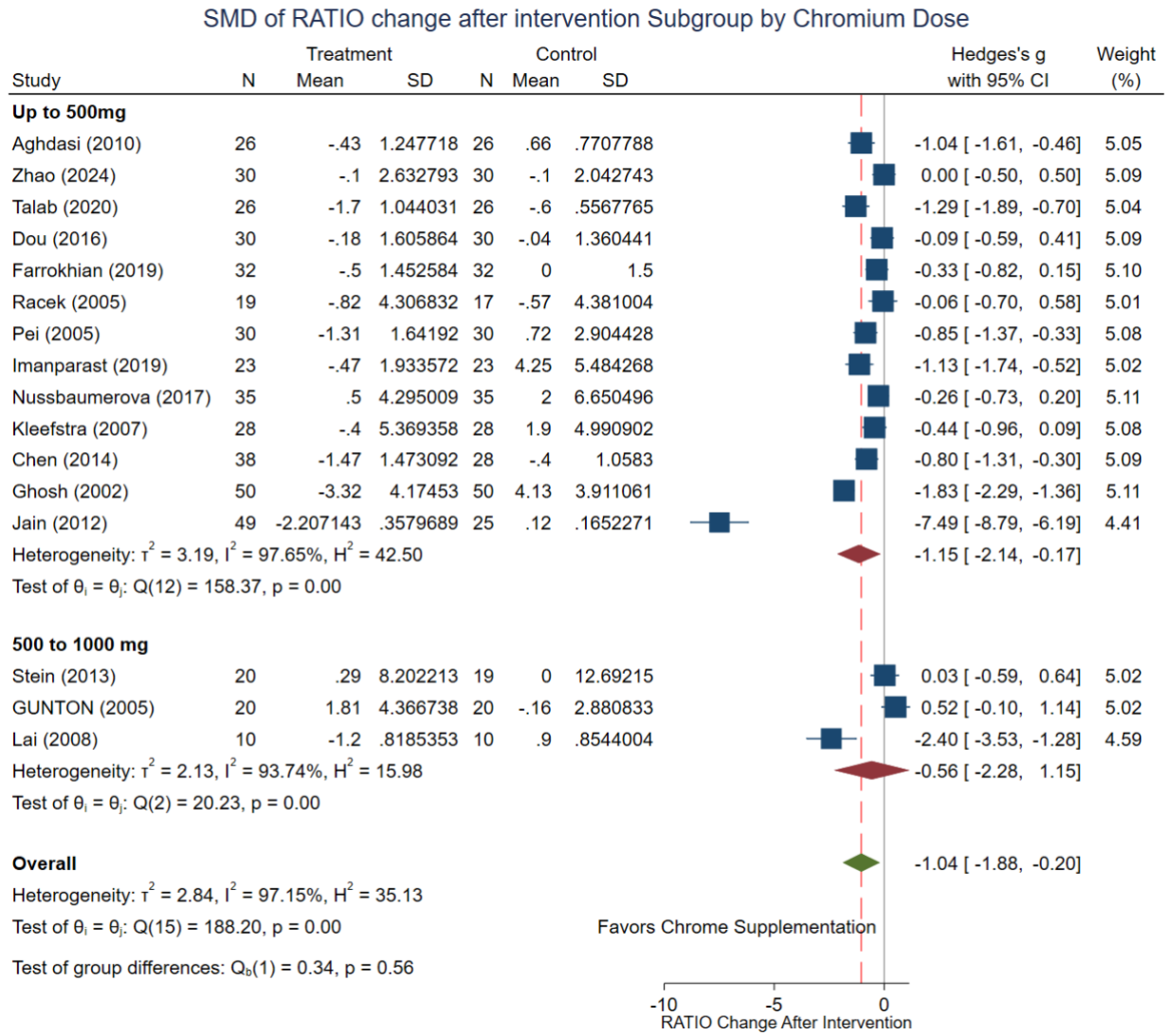
Appendix

PubMed Search Strategy **Results: 351**	(“chromium”[mesh] OR chromium[tiab] OR chrome[tiab]) AND (“Insulin resistance”[mesh] OR Metabolic syndrome[mesh] OR Insulin resistance[tiab] OR Metabolic syndrome[tiab] OR Reaven syndrome[tiab] OR Insulin resistance[tiab] OR Metabolic X[tiab])
Embase Search Strategy **Results: 736**	(‘chromium’/exp OR ‘chromium’:ti,ab OR ‘chrome’:ti,ab) AND (‘Insulin resistance’/exp OR ‘Metabolic syndrome’/exp OR ‘Insulin resistance’:ti,ab OR ‘Metabolic syndrome’:ti,ab OR ‘Reaven syndrome’:ti,ab OR ‘Insulin sensitivity’:ti,ab OR ‘Metabolic X’:ti,ab)
SCOPUS Search Strategy **Results: 484**	(TITLE-ABS(“Chromium” OR “Chrome”)) AND (TITLE-ABS(“Insulin resistance” OR “Metabolic syndrome” OR “Reaven syndrome” OR “Insulin sensitivity” OR “Metabolic X”))
Web of Sciences Search Strategy **Results: 792**	(TS= (“chromium” OR “Chrome”)) AND (TS= (“Insulin resistance” OR “Metabolic syndrome” OR “Reaven syndrome” OR “Insulin sensitivity” OR “Metabolic X”))

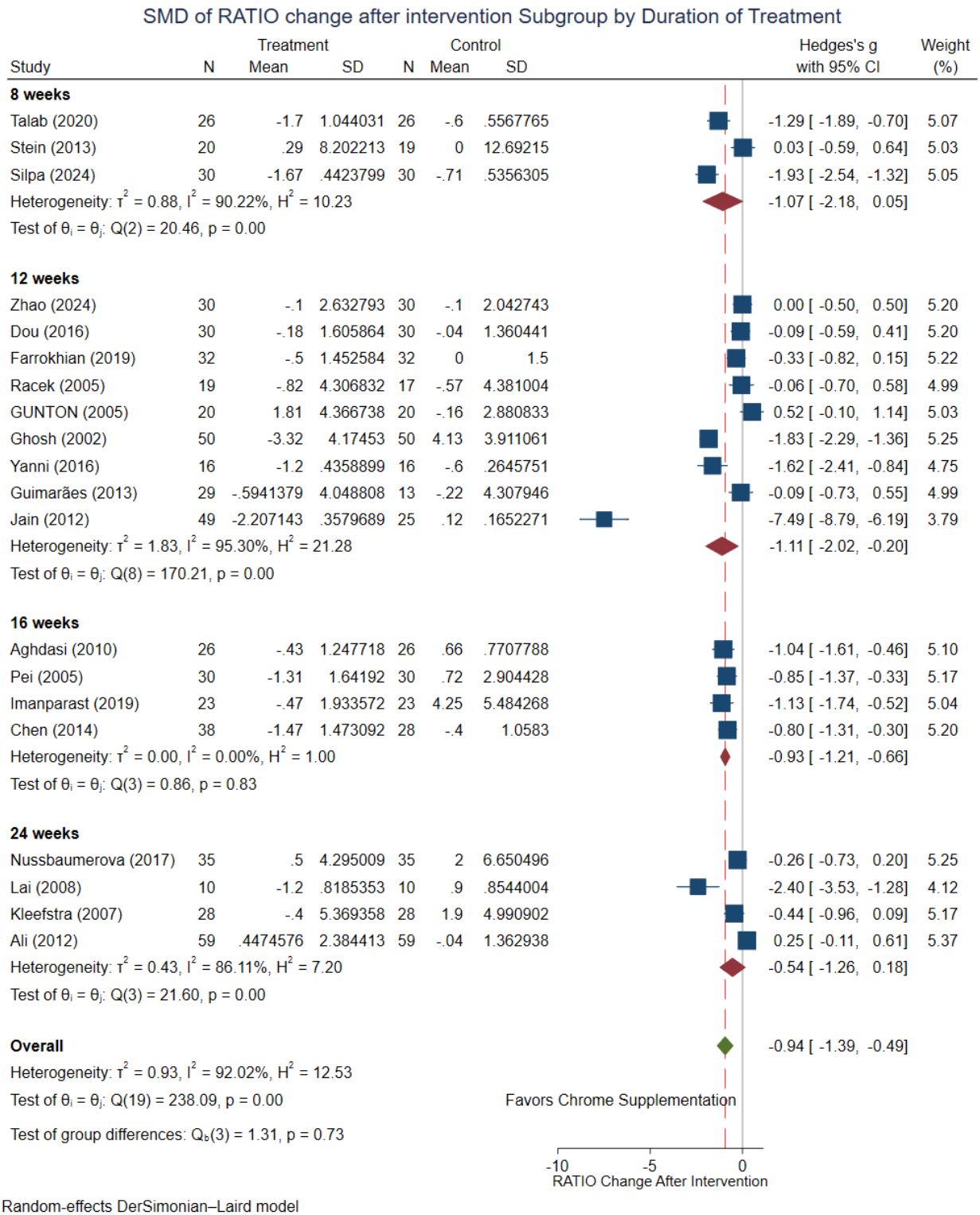
Appendix 2: Search strategy



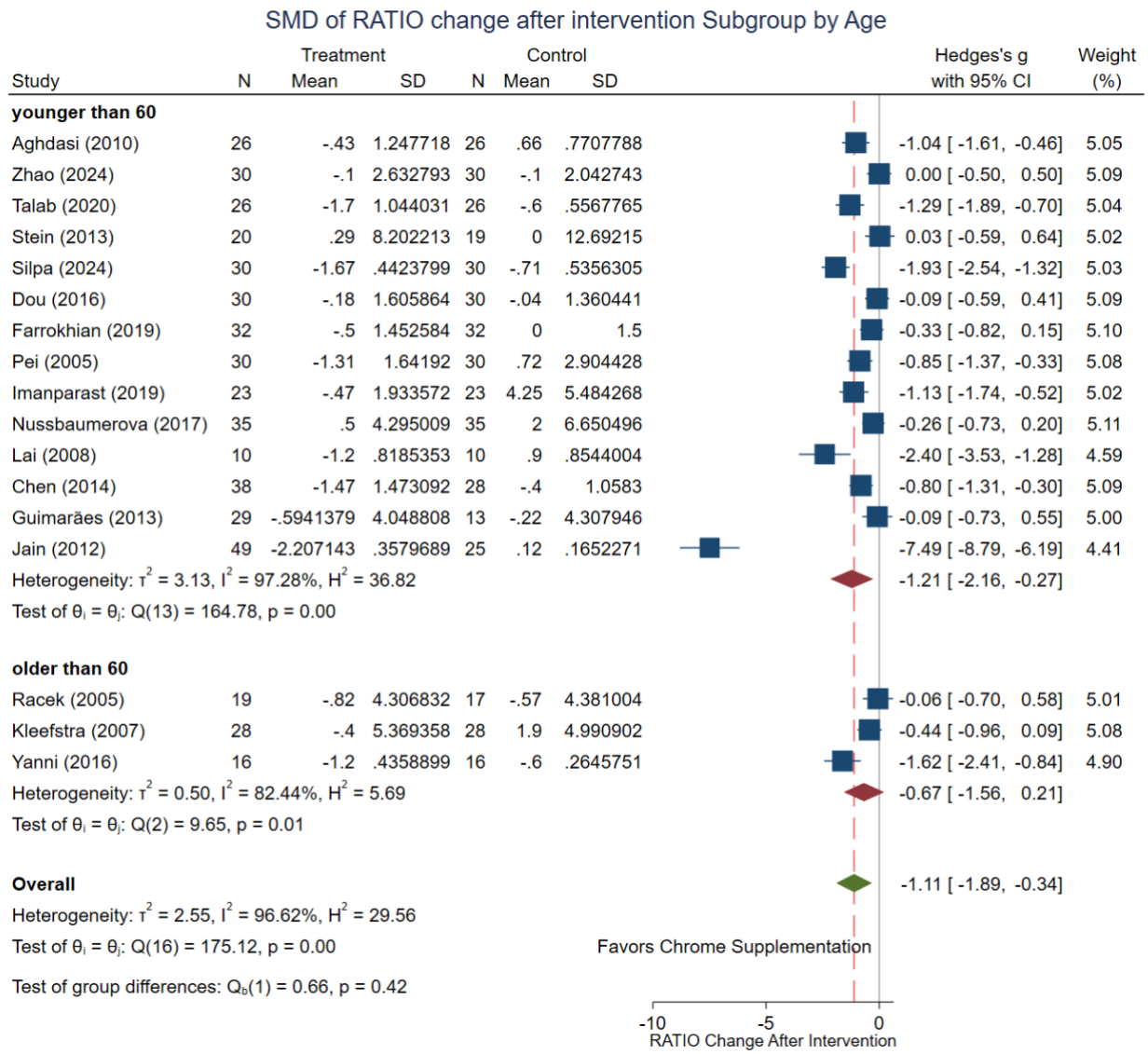
Appendix 2: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the chromium type



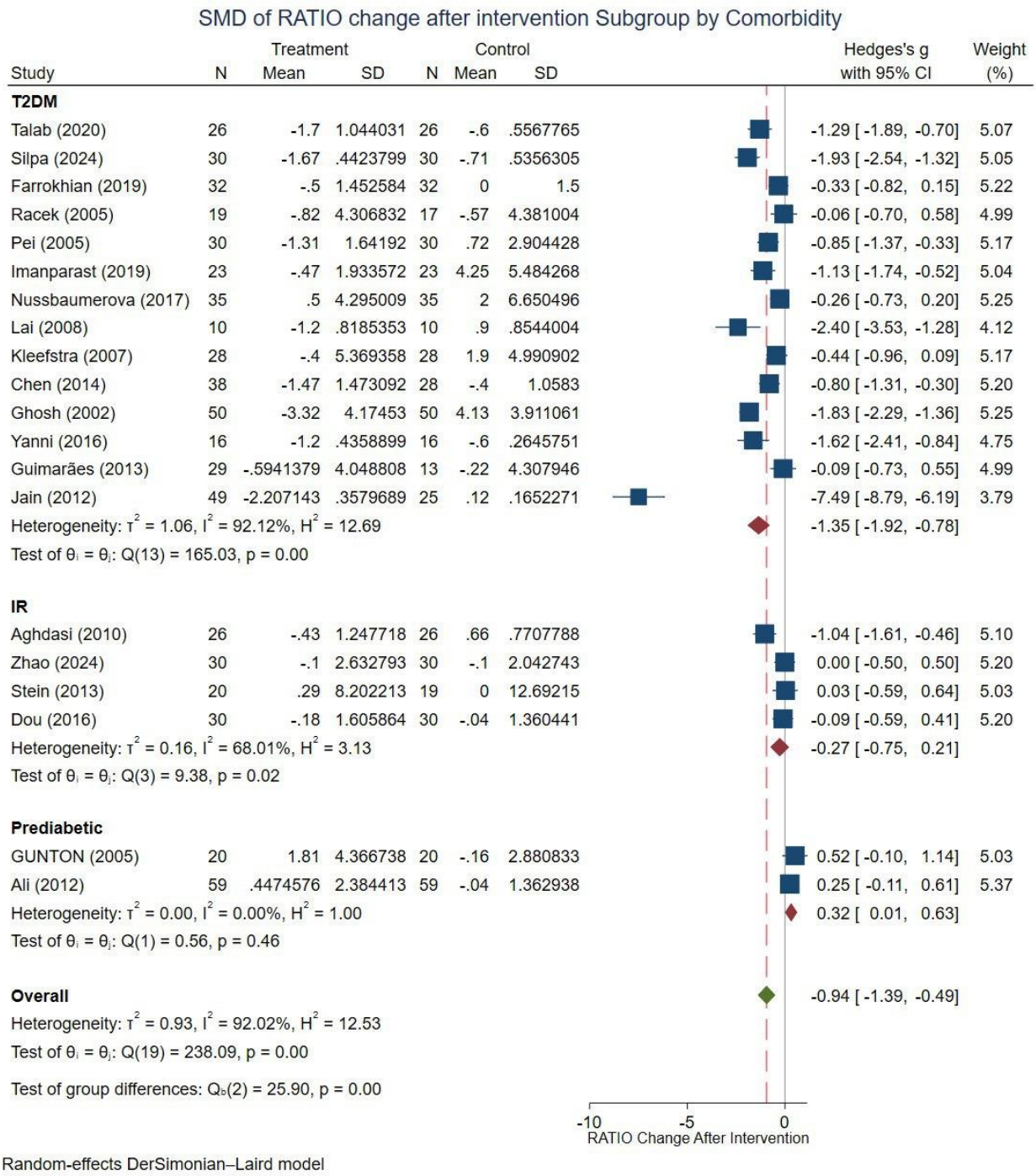
Appendix 3: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the chromium dose



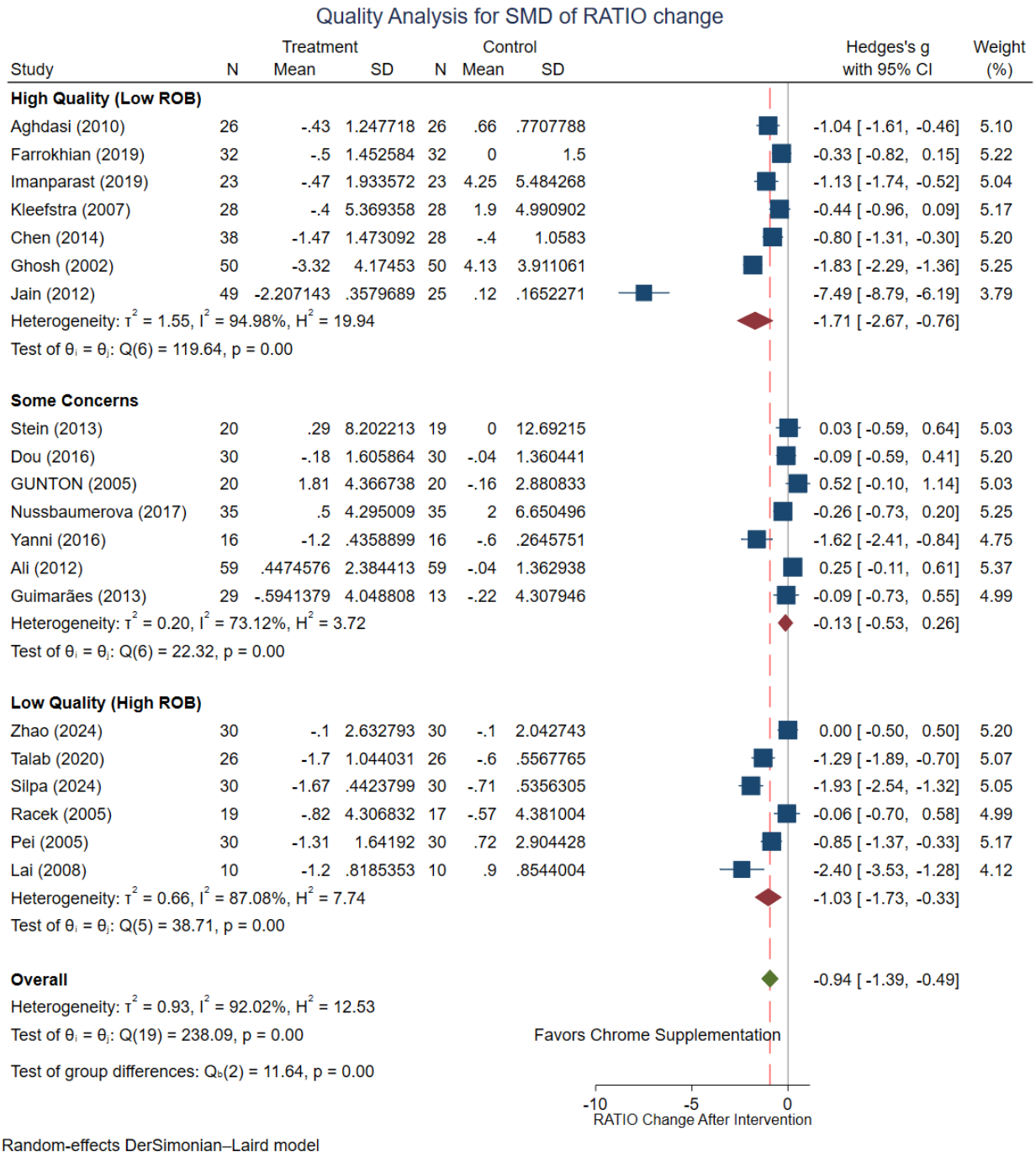
Appendix 4: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the duration of intervention



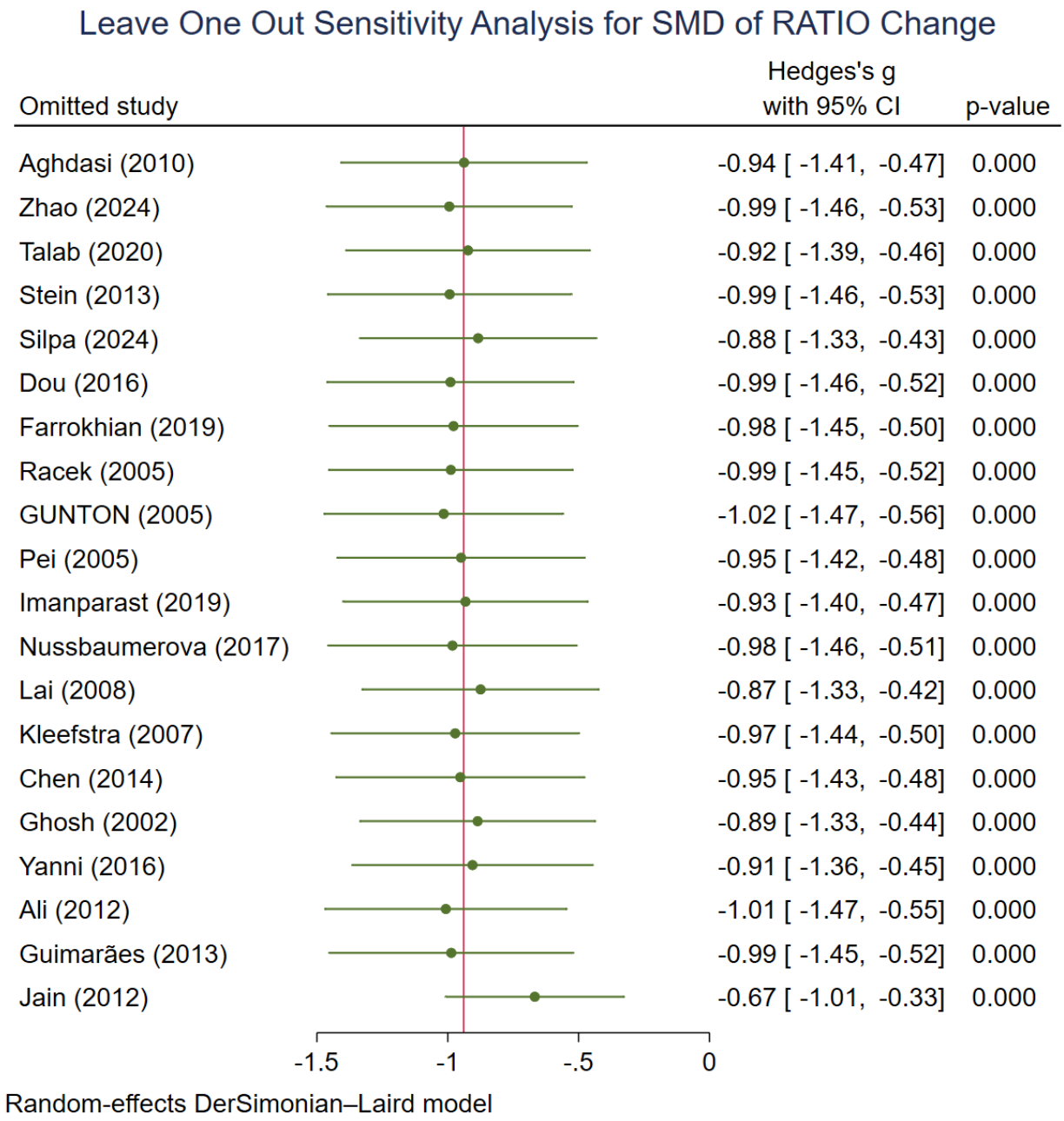
Appendix 5: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the population age



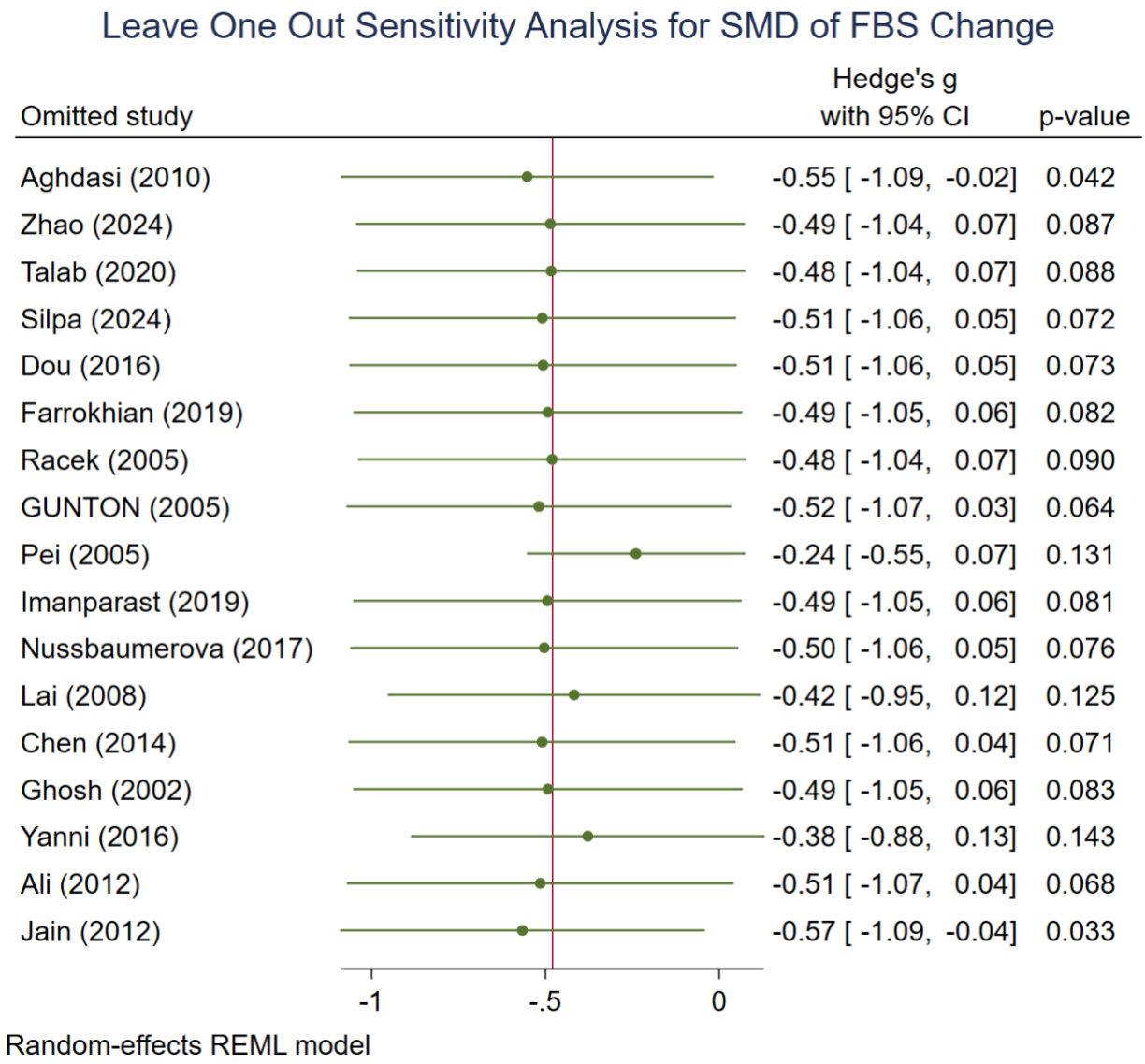
Appendix 6: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the underlying condition



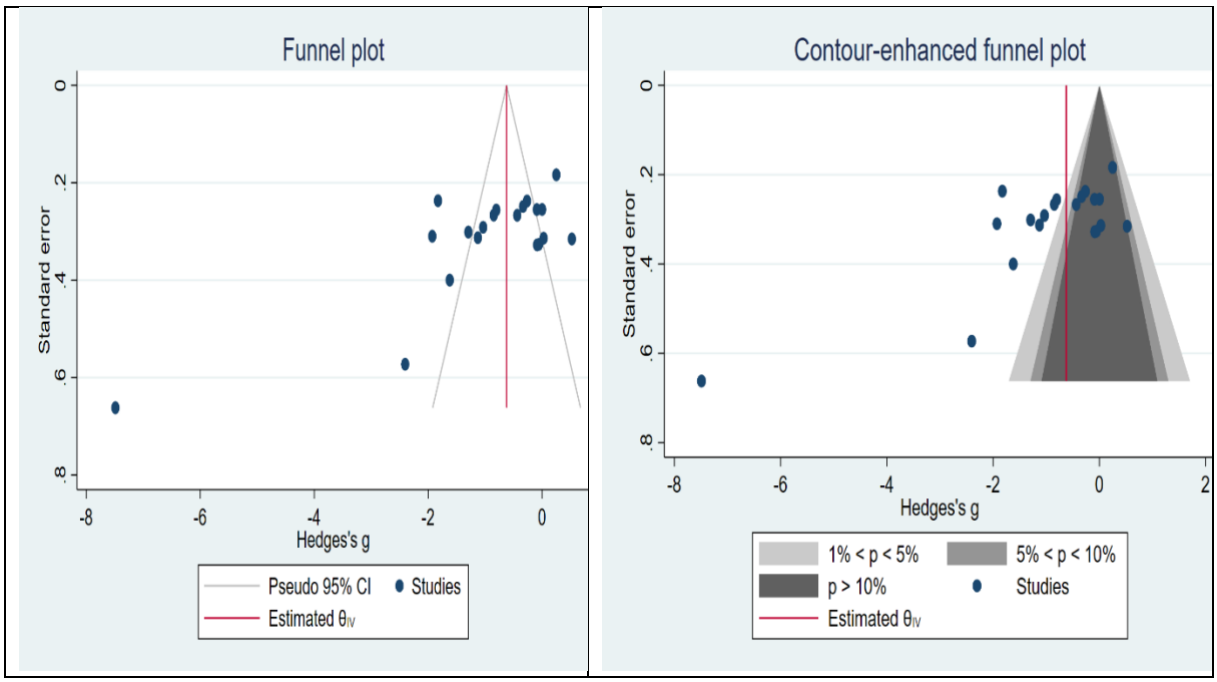
Appendix 7: Forest plot for subgroup analysis on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio based on the quality of the studies



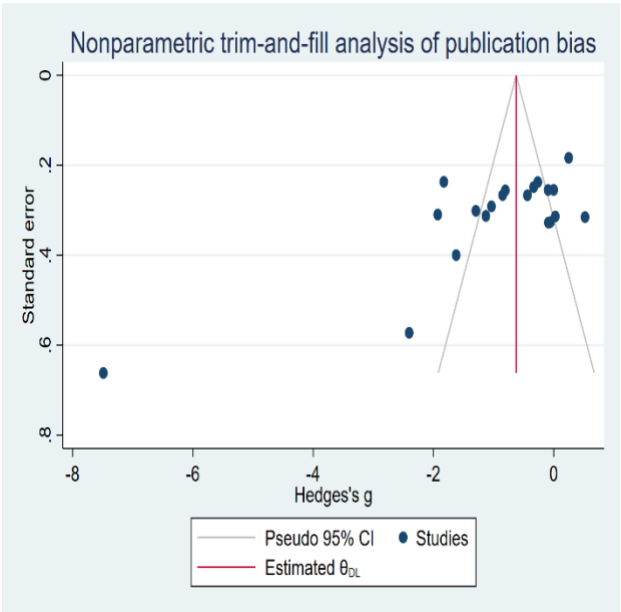
Appendix 8: Forest plot for sensitivity analysis based on the leave-one-out method of HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio



Appendix 9: Forest plot for sensitivity analysis based on the leave-one-out method of FBS (fasting blood sugar)



Appendix 10: Funnel plot for risk of publication bias assessment of the SMD of HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio



Appendix 11: Funnel plot for risk of publication bias assessment based on the trim and fill method of the SMD of HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) ratio