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Letters

RESEARCH LETTER

Chromium Supplementation to Reduce Cardiometabolic Risk Factors

A Novel Dose-Response Meta-Analysis of Randomized Clinical Trials

Trivalent chromium is an essential micronutrient that participates in the regulation of insulin receptor signal transduction as well as carbohydrate and lipid metabolism.[1] Circulating levels of chromium decrease with age,[2] and in patients with insulin resistance and type 2 diabetes (T2D).[3] Previous studies have shown that intravenous chromium infusion can reduce insulin requirement and improve hyperglycemia in patients with severe insulin resistance.[4] However, findings from randomized controlled trials (RCTs) investigating the efficacy of oral chromium supplementation in reducing cardiometabolic risk factors have been inconsistent. To reconcile the inconsistencies in the literature regarding the role of chromium in the development of health outcomes and the contradictory recommendations for the optimal intake of chromium, we conducted a systematic review and meta-analysis of relevant RCTs via a novel dose-response approach to investigate and clarify the impact and sources of heterogeneities in relation to chromium supplementation on cardiometabolic risk factors.

The study protocol was registered in PROSPERO database (CRD42022363706), and RCTs included in this meta-analysis had ethics approval from their respective institutional review boards. The PubMed, Web of Science, and the Cochrane databases were searched for RCTs through October 10th, 2022. RCTs that investigated the effect of oral chromium supplementation rather than intravenous injection chromium on measures of glycemic control (fasting blood glucose [FBG], hemoglobin A1c [A1C], and fasting blood insulin [FBI]), blood lipids (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], and triglyceride [TG]), or blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) were included.

Weighted mean differences of specific cardiometabolic risk factors between intervention and control groups and the standard deviations were used as the basis for each trial comparison. A random-effects model was used to calculate summary weighted mean differences and 95% CIs. In addition, when 10 or more comparison groups were available, we employed a novel 1-stage random-effects dose-response model to evaluate the dose-response relationship between chromium supplementation and changes in cardiometabolic paraments, where chromium supplementation was included as a continuous variable. Restricted cubic splines were used to pool the data from included studies into continuous dose-response curves. RevMan (version 5.4) and Stata/SE (version 17.0) were used to conduct all analyses, including the 1-stage approach for dose-response meta-analysis, based on the *drmeta* module of Stata/SE.[5]

A total of 64 studies consisting of 3,004 participants aged 18 to 90 years (median 54.2 years) were included, of which 34 RCTs were done in T2D patients and 30 in participants without T2D. There were 40 RCTs from Western countries and 24 from non-Western countries. The chromium intervention dose ranged from 7 to 1,000 μg/d (median 200 μg/d) with the median intervention duration was 12 weeks (ranged from 8 to 32 weeks).

Chromium supplementation lowered all the glycemic parameters (FBG, A1C, and FBI), all blood lipid parameters (LDL-C, HDL-C, TC, and TG), and SBP in the total population (**Figure 1A**). When subdivided according to T2D status, chromium improved all glycemic markers, HDL-C and TG in T2D participants. In non-T2D participants, chromium improved FBG and all blood lipid parameters except LDL-C. In the subgroup analysis divided by geographic/cultural background, chromium lowered all glycemic markers in Westerners and non-Westerners, except for FBG in non-Western participants. TC and TG were significantly reduced in non-Westerners, while only HDL-C was significantly improved in Westerners. SBP was significantly reduced in Westerners, while no significant effect was observed for both SBP and DBP in those non-Westerners. Chromium supplementation

FIGURE 1 **A Comprehensive Summary of Chromium Supplementation on Cardiometabolic Health**

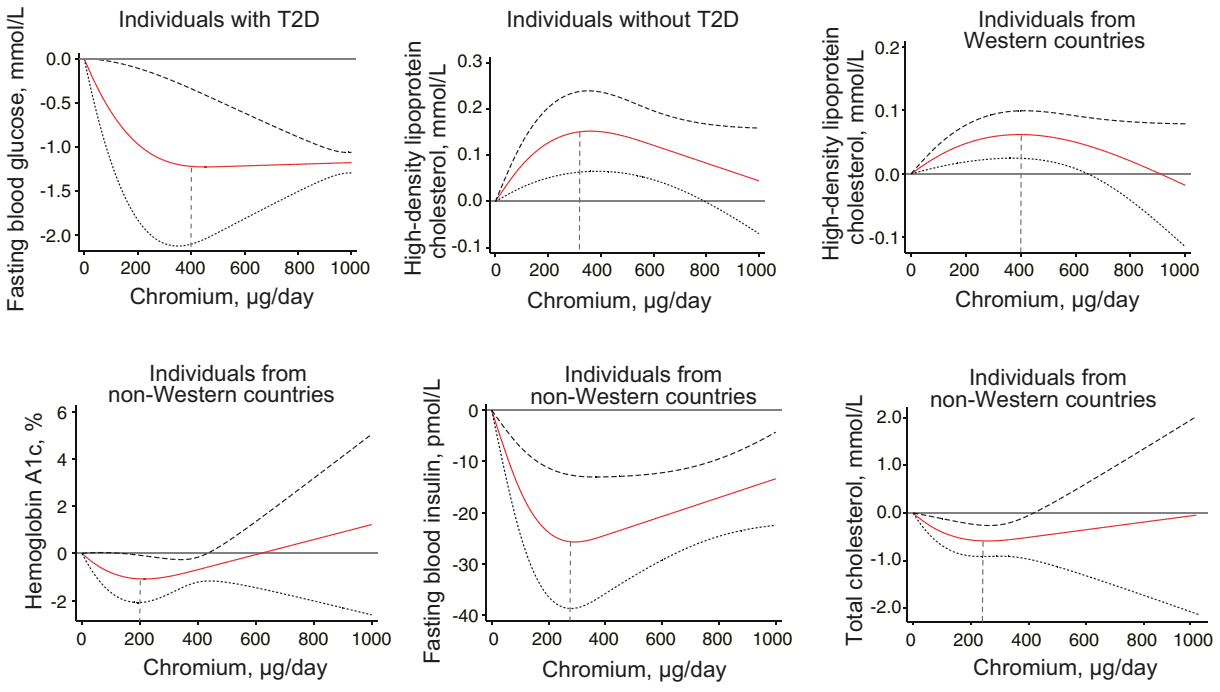
A Effect of chromium supplementation on cardiometabolic risk factors

Cardiometabolic risk factor		Total population	Individuals with type 2 diabetes	Individuals without type 2 diabetes	Individuals from Western countries	Individuals from non-Western countries
Blood glucose	Fasting blood glucose	-0.53 [-0.88, -0.18]	-0.89 [-1.70, -0.08]	-0.14 [-0.25, -0.03]	-0.21 [-0.39, -0.02]	-1.06 [-2.17, 0.04]
	Hemoglobin A1c	-0.43 [-0.68, -0.19]	-0.48 [-0.77, -0.20]	-0.16 [-0.36, 0.04]	-0.24 [-0.47, -0.02]	-0.67 [-1.17, -0.16]
	Fasting blood insulin	-14.46 [-21.32, -7.60]	-23.86 [-33.02, -14.68]	-4.39 [-10.44, 1.66]	-8.42 [-16.77, -0.08]	-21.35 [-30.57, -12.12]
Blood lipid	Low-density lipoprotein cholesterol	-0.16 [-0.30, -0.02]	-0.15 [-0.38, 0.08]	-0.15 [-0.31, 0.01]	-0.11 [-0.25, 0.03]	-0.23 [-0.52, 0.06]
	High-density lipoprotein cholesterol	0.06 [0.02, 0.09]	0.05 [-0.00, 0.11]	0.05 [0.02, 0.08]	0.05 [0.02, 0.07]	0.08 [-0.01, 0.17]
	Total cholesterol	-0.13 [-0.25, -0.02]	-0.13 [-0.31, 0.05]	-0.16 [-0.31, -0.00]	-0.03 [-0.16, 0.10]	-0.38 [-0.57, -0.19]
	Triglyceride	-0.26 [-0.45, -0.07]	-0.31 [-0.60, -0.02]	-0.25 [-0.48, -0.01]	-0.06 [-0.25, 0.13]	-0.72 [-1.14, -0.30]
Blood pressure	Systolic blood pressure	-3.33 [-6.49, -0.17]	-3.81 [-7.74, 0.13]	-1.84 [-5.72, 2.03]	-2.80 [-5.31, -0.29]	-5.46 [-11.75, 0.83]
	Diastolic blood pressure	-0.49 [-1.85, 0.86]	-0.87 [-2.90, 1.16]	0.54 [-0.93, 2.00]	-0.02 [-0.98, 0.94]	-1.04 [-4.48, 2.40]

Benefit | Neutral

GRADE High | Moderate | Low | Very low

B Dose-response meta-analysis of changes in cardiometabolic risk factors



(A) An evidence map summarizing chromium supplementation on cardiometabolic risk factors. Results were presented as weighted mean difference and 95% CIs. (B) Dose-response meta-analysis of chromium supplementation on cardiometabolic risk factors in diverse populations. Marginal average dose-response curve (solid red line) with 95% CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 μg/d as the referent (solid gray horizontal line).

displayed no effect on DBP in the total population or in any subgroup.

To explore if any dose-response effect existed between chromium and cardiometabolic risk factors, dose-response meta-analyses were performed in different subgroups (Figure 1B). A chromium dose of 400 μg/d or higher appears to be appropriate for FBG reduction in participants with T2D. In participants without T2D, an inverted U-shaped chromium-HDL-C association was detected, with a threshold of

300 μg/d of chromium showing an appropriate dose. In participants from Western countries, only a significantly inverted U-shaped chromium-HDL-C relationship was detected, with an appropriate chromium dose of 400 μg/d. In participants from non-Western countries, nonlinear J-shaped dose-response relationships were observed in chromium-A1C, chromium-FBI, and chromium-TC associations. A chromium dose of 200 μg/d appeared to be an appropriate dose for lowering these glycemic and blood lipid parameters.

These findings indicated that chromium supplementation improved cardiometabolic risk factors, although pre-existing cardiometabolic disorders and study location were the sources of heterogeneity that influenced the effects of chromium supplementation on cardiometabolic health. For the first time, we identified appropriate doses of chromium supplementation to improve blood glucose in T2D participants, which were not reported in previous studies.

Based on a novel method—the 1-stage restricted cubic splines—to assess dose-response relationships between chromium supplementation and cardiometabolic risk factors, this study shows the importance of adequate and different chromium intakes for cardiometabolic health that appear to be dependent on T2D status and ethnicity. However, considering the heterogeneity and short-term nature of existing RCTs, additional large and high-quality RCTs with long-term prospective followup are still warranted to determine the optimal balance of benefits and risks associated with chromium supplementation in diverse populations.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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