

Review Article



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Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Soluble Fiber Effect on Human Serum Leptin and Adiponectin: A Systematic Review and Dose-Response Meta-Analysis

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ABSTRACT

Literature showed that soluble fiber has beneficial effects on cardiometabolic risk factors and leptin and adiponectin serum levels. Our aim in this meta-analysis was to determine the effect of soluble fiber supplementation on leptin and adiponectin serum levels. A systematic search was conducted using PubMed, Scopus, and ISI Web of Science for eligible trials up to December 2021. A random-effects model was used to pool calculated effect sizes. Our analysis showed that soluble fiber supplementation did not significantly affect adiponectin (standardized mean difference [SMD], -0.49 Hedges's, 95% confidence interval [CI], -1.20, 0.21, p value = 0.167; $I^2 = 95.4$, p value < 0.001) and leptin (SMD, -0.8 Hedges's, 95% CI, -1.70, 0.08, p value = 0.076; $I^2 = 94.6$, p value < 0.001) concentrations in comparison with placebo. However, in the subgroup, soluble fiber supplementation had a significant improvement in leptin concentration in overweight and obese patients (SMD, -0.22 Hedges's, 95% CI, -0.43, -0.01, p value = 0.048) and a non-significant beneficial effect in adiponectin level in female (SMD, 0.29 Hedges's, 95% CI, -0.13, 0.71, p value = 0.183) and diabetic patients (SMD, 0.32 Hedges's, 95% CI, -0.67, 1.32, p value = 0.526). A non-linear association between soluble fiber dosage and adiponectin ($p_{\text{non-linearity}} < 0.001$) was observed. Soluble fiber supplementation could not change the circulatory leptin and adiponectin levels. However, beneficial effects were seen in overweight and obese leptin, and increases in adiponectin may also be observed in female and diabetic patients. Further studies are needed to confirm this results.

Keywords: Adiponectin; Leptin; Cardiometabolic risk; Meta-analysis

INTRODUCTION

Adiponectin is a protein secreted by adipose tissue that makes up about 0.01% of total plasma proteins [1,2]. According to previous studies, adiponectin's beneficial effects can be attributed to multiple mechanisms, such as anti-inflammatory, antioxidant, anti-atherogenic, and antithrombotic. It also reduces insulin resistance and improves blood glucose control [3-5]. Literature also suggests that adiponectin may be a marker for lower cardiovascular disease, metabolic syndrome (MetS), and diabetes risk [6].

Author Contributions

Conceptualization: Ghaedi H; Data curation: Zeinabi A, Ghaedi H; Formal analysis: Zeinabi A, Hosseini SA; Investigation: Zeinabi A, Hosseini SA; Methodology: Ghaedi H; Writing - original draft: Zeinabi A, Ghaedi H, Hosseini SA; Writing - review & editing: Zeinabi A, Ghaedi H, Hosseini SA.

Researchers have studied dietary changes that can improve adipokines concentration in recent years. In this regard, dietary content has attracted a lot of attention. Dietary changes, especially soluble fiber intake and lifestyle modifications, seem to influence adiponectin concentration [7,8].

Leptin regulates various physiological mechanisms linked to obesity and cardiovascular disease, including energy balance, neuroendocrine function, and metabolic pathways [9,10]. Leptin concentrations are mainly related to fat tissue and energy balance [11]. Hypothalamic receptors are responsible for the leptin effect, activating several signal transduction pathways, such as Janus kinase/signal transducer and activator of transcription-3 (JAK-STAT3), which is involved in the regulation of energy homeostasis, and phosphatidylinositol 3-kinase, involved in the regulation of food intake and glucose homeostasis [12-14]. Leptin induces beneficial effects in the body.

Literature reported a variety of soluble fiber-containing foods, including fruits and vegetables, legumes, and especially whole-grain cereals, have been suggested to promote cardiometabolic risk factors and leptin and adiponectin levels [15-17]. In recent decades, numerous studies have examined the efficacy of soluble fiber supplementation on leptin and adiponectin concentration; however, results have often been contradictory and inconsistent despite similar methodology.

Previous studies report that soluble fiber could decrease leptin secretion via a decrease in fat mass [18]. Also, soluble fiber may improve adipokine levels by decreasing lipogenesis in the liver and adipose tissue. Besides, the soluble fiber may also decrease leptin levels by improvement of leptin resistance [19].

The effect of soluble fiber supplementation on leptin and adiponectin concentration is also considered in some trials [20-37]; however, the results are inconclusive. Studies reported controversial results in adiponectin [20,21,23,26-33,35,36] and leptin [20-22,25,26,32-35] following soluble fiber supplementation. These inconsistencies in clinical findings might be explained by the differences in study and/or subjects characteristics (dose and duration of supplementation, sex, mean body mass index [BMI], and health status).

Therefore, attempting to resolve the inconsistencies focusing on soluble fiber's beneficial effects, this study aimed to systematically review and meta-analyse to derive a more precise estimate of the findings of randomised controlled trials (RCTs) reporting the changes in serum leptin and adiponectin concentration following soluble fiber supplementation in adults.

MATERIALS AND METHODS

The standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed to improve the quality of the systematic review and meta-analysis. Our study protocol was not registered on any website; however, it is available from the authors upon request.

Search strategy

An internet literature search was performed in scientific databases: PubMed (<http://www.ncbi.nlm.nih.gov>), Scopus (<http://www.scopus.com>), ISI Web of Science (<http://www>

webofscience.com), with no language or time frame restriction up to December 2021. The search strategy was drawn up using the following keywords and Medical Subject Heading terms: “Dietary Fiber,” “soluble dietary fiber,” “soluble fiber,” “viscous fiber,” “plant mucilage,” “glucan,” “beta glucan,” “alginate,” “plant gum,” “gum,” “gellan gum,” “gum arabic,” “acacia gum,” “guar gum,” “resistant starch,” “psyllium,” “inulin,” “resistant maltodextrin,” “wheat dextrin,” “polydextrose.” “prebiotic,” “prebiotic fiber,” “fermentable fiber,” “galactomannan,” “konjac,” “soluble corn fiber,” “fructooligosaccharide,” “oligofructose,” “galactooligosaccharide,” “pectin,” “oat,” “barley,” “randomized controlled trial,” “controlled clinical trial,” “clinical trial,” “controlled trial,” “randomized,” “placebo,” “intervention studies,” “intervention,” “random,” “randomly,” “blind,” “trial,” Boolean operators (“AND” and “OR”) were used to connect the terms listed above. Finally, electronic searches were supplemented by a hand search of the reference sections and citations of pertinent review articles and studies that met the inclusion criteria.

Study selection

First, irrelevant articles were excluded by scanning the titles and/or abstracts. Second, full-text versions of the remaining studies were obtained and carefully assessed for the following items: study design, participants; interventions; and reported outcome. Then, RCTs that investigated the efficacy of soluble fiber (as a supplement) on adults were included. At the end of the selection process, studies involving soluble fiber as part of a combination intervention, treatment duration of fewer than 2 weeks, were conducted on children/adolescents (< 18 years old) and pregnant female. A lack of a control group, means, and standard deviations (SDs) for targeted variables went unreported, and grey literature such as conference papers, dissertations, and patents were excluded from the systematic review and meta-analysis. To ensure accuracy, all steps of the study selection process were performed separately by at least 2 authors (A.Z. and H.G.). Any discrepancies were resolved by consensus. The participants, intervention/exposure, comparison, outcomes, and study design (PICOS) criteria used to describe the research question are presented in **Table 1**.

Data extraction

Each RCT was validated independently by 2 reviewers who were blinded to the authors or results, or all reviewers independently performed the screening of studies, selection, validation, data extraction and the assessment of methodological quality. Disagreements in the assessment of data were resolved by discussion and consensus was reached in all cases.

For each article included, pertinent information was extracted by 2 scholars independently and in duplicate, using a data abstraction form. Disagreements were settled through consultation. Data regarding the study characteristics (first author’s name, publication year, location, population), subject characteristics (mean age, gender, mean BMI), intervention details (type and dosage of soluble fiber, type of placebo or control groups, treatment duration, and background diet), trial design (cross-over or parallel, blinding, funding).

Table 1. Participants, intervention/exposure, comparison, outcomes, and study design criteria for inclusion and exclusion of studies

Parameters	Descriptions
Participants	Adults
Intervention	Soluble fiber (as supplement)
Comparison	Any comparator/control that incorporated a non-intervention group
Outcomes	Serum leptin and adiponectin concentration
Setting	Randomized controlled trials

Risk of bias assessment

Cochrane Collaboration tool was used to evaluate the risk of bias assessment among the studies included [38]. This validated tool explores the risk of bias in the following categories: random sequence generation, allocation concealment, blinding (participants and investigators), incomplete outcome data, selective outcome reporting, and other sources of bias. Each category was judged as high risk of bias (H), unclear risk of bias (U), or low risk of bias (L), based on the available information presented in the studies included. Studies were considered poor studies when they received (H) in ≥ 2 or (U) in ≥ 3 criteria. The risk of bias assessment was also undertaken by 2 authors separately. The difference in the overall quality score of the studies was resolved by discussion.

Statistical analysis

The whole process of statistical analysis was carried out using the STATA software version 17.0 (Stata Corporation, College Station, TX, USA). All data were collected as means \pm SD for each variable to estimate the pooled effects. In those studies, mean changes were not directly reported in the intervention and control groups, this was calculated by subtracting post-intervention data from the baseline values. SD was estimated by:

$$SD = \text{Standard Error of the Mean (SEM)} \times \text{sqrt}(n)$$

where n = number of subjects, SEM was reported.

SD of mean change was calculated according to the following formula [39]:

$$SD = \text{Square Root} ([SD \text{ Pre-Treatment}]^2 + [SD \text{ Post-Treatment}]^2 - [2R \times SD \text{ Pre-Treatment} \times SD \text{ Post-Treatment}])$$

assuming a correlation coefficient (R) = 0.75

Due to leptin and adiponectin reported in different units of measure, standardized mean difference (SMD) with 95% confidence interval (CI) was used for analysis. A random-effects model was applied to the meta-analysis to compensate for potential heterogeneity among included studies [40]. Heterogeneity among RCTs was assessed by the p value and I^2 statistic. In all analyses, a p value of 0.05 was considered statistically significant. Random-effects meta-regression was used to detect the potential associations between changes in leptin and adiponectin outcomes and putative moderators, including dose (≤ 10 g/day, > 10 g/day), duration (≥ 8 weeks, < 8 weeks) of supplementation, gender (female, both [male and female]), mean BMI (≥ 30 kg/m² and < 30 kg/m²) and study population (overweight-obese, MetS, type 2 diabetes [T2DM], healthy).

Sensitivity analysis was conducted to explore the contribution of each study to the reliability of the pooled effect sizes. Publication bias was assessed by Egger's regression and Begg's test [41]. Fractional polynomials modelling was executed to examine potential non-linear effects of soluble fiber dose (g/d) on targeted outcomes. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 10,150 potentially relevant studies were identified through electronic search. After removing duplicate records ($n = 8,476$), 2,209 articles remained after the title and abstract screening; and 54 studies of them were selected for the full-text evaluation. Among the remained articles, 36 were excluded for the following reasons: irrelevant articles ($n = 14$), insufficient data ($n = 9$), duplicated publication ($n = 5$), other languages ($n = 4$), and examined foods containing fibers ($n = 4$). Therefore, 18 studies [20-37] met the eligibility criteria and were included in a systematic review and meta-analysis. A flow chart of the systematic search and study selection process is presented in **Figure 1**.

Study characteristics

The characteristics of the eligible studies are presented in **Table 2**. Three studies were conducted in the USA [25,29,36], 6 in Japan [21,26,27,30,33,34], 2 in Canada [31,32], one in Germany [24], one in Hungary [20], one in Australia [22], one in China [28], one in Belgium [23], one in the Netherlands [37] and one in Poland [35]. All studies were published between the years 2006–2020. All studies were controlled clinical trials. Most studies were performed on both sexes, while 3 were conducted only on females [20,22,23], and 2 were conducted only on males [27,28]. Three studies were cross-over designs [24,36,37]. The results of the quality assessment of the eligible studies are presented in **Table 3**. Seven studies have good quality [24-26,28,31,32,34], 5 studies have fair quality [21-23,29,35], and 6 studies have poor quality [20,27,30,33,36,37].

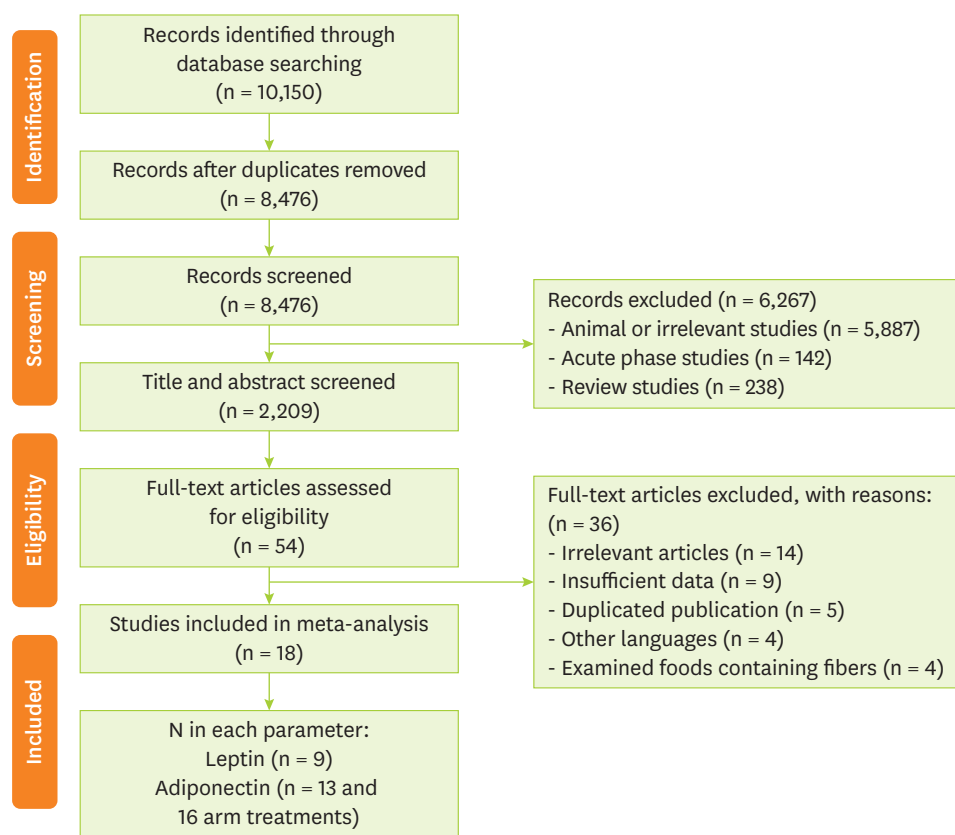


Figure 1. Flow chart of the process of the study selection.

Table 2. Demographic characteristics of the included studies

Study	Participants characteristic			Study characteristic			Intervention/Control characteristic			Background diet		
	Population	Sex (M/F)	Mean age (yr)	Location	Design	Duration (wk)	Funding	Type of fiber	Dose (g/d)		Form of administration	Comparator
Garcia et al. (2006) [24]	IGT	11 (4/7)	30.1 ± 5.7	Germany	C	6	S A	AX	15	Two bread rolls, each containing 5 g AX concentrate	Isocaloric bread rolls	Usual
Antal et al. (2010) [20]	Obese	23 (0/23)	28.7 ± 4.29	Hungary	P	12	NR A	Oligofructose	14	Jerusalem artichoke-concentrate products	Jerusalem artichoke-free products	LCD
Beck et al. (2010) [22]	Overweight	66 (0/66)	29.2 ± 2.2	Australia	P	12	NR A	Oat β-glucan	5–9	Products with oat β-glucan	High fiber products with no oat β-glucan	ERD
Li et al. (2010) [28]	Overweight	120 (120/0)	24.5 ± 0.2	China	P	12	D I	Glucose polysaccharide	34	250 mL of fruit juice that contained NUTRIOSE	Maltodextrin	Usual
Dewulf et al. (2012) [23]	Obese	30 (0/30)	35.85 ± 3.7	Belgium	P	12	D A	Inulin/oligofructose	16	Powder added to warm drinks	Maltodextrin	Usual
Hashizume et al. (2012) [26]	Mets	30 (20/10)	27.45 ± 2.6	Japan	P	12	D A	Resistant maltodextrin	9	Tea containing resistant maltodextrin	Tea without resistant maltodextrin	Usual
Maki et al. (2012) [29]	Obese	33 (11/22)	30.6 ± 0.5	USA	P	4	D A	High-amylose maize RS2	15 or 30	Mixed into cold or room-temperature beverages or foods	Starch	Usual
Reimer et al. (2013) [33]	Obesity	64 (28/36)	26.95 ± 2.6	Japan	P	14	D A	PGX	15	Powder	Rice flour	Usual
Wanders et al. (2013) [37]	Healthy	32 (8/24)	21.8 ± 1.9	Netherlands	C	15 days	D A	Pectin	5	Pectin containing foods	Isocaloric	Usual
Kobayakawa et al. (2013) [27]	Obesity	30 (30/0)	27.7 ± 0.8	Japan	P	12	D I	Galactomannan, inulin, β-glucan, alginate acid, cellulose, hemicelluloses	7.5	The adding the test food to the daily average diet	Blend of starch, colorant, and flavor	Usual
Geliebter et al. (2014) [25]	Overweight	36 (18/18)	32.2 ± 3.4	USA	P	4	NR A	Oat fibre	NR	Oat porridge breakfast	No-breakfast control	Usual
Nishimura et al. (2015) [30]	Healthy	47 (8/39)	21.9 ± 3.12	Japan	P	4	D A	Inulin-type fructans	0.9	Chicory root extract	Non-chicory root extract	Usual
Upadhyaya et al. (2015) [36]	Met	20 (8/39)	32.8 ± 1.1	USA	C	26	D A	RS4	NR	Flour containing 30% resistant starch type 4	Control flour	Usual
Aoe et al. (2017) [21]	Healthy	100 (NR)	27.5 ± 2.7	Japan	P	12	D A	β-glucan	4.4	High-β-glucan barley	β-glucan-free barley	Usual
Parnell et al. (2017) [31]	Obesity	20 (8/39)	29.9	Canada	P	12	D A	Oligofructose	21	Powder	Maltodextrin	Usual
Strączkowski et al. (2018) [35]	Obesity	52 (27/25)	27.4 ± 2.6	Poland	P	12	NR A	β-glucan	500 mg	NR	NR	LCD
Sakai et al. (2019) [34]	T2DM	30 (22/8)	25.1 ± 3.8	Japan	P	12	D A	Fucoidan	1,620 mg	Beverage containing fucoidan	Fucoidan-free beverage	Usual
Reimer et al. (2020) [32]	T2DM	290 (83/207)	40.0 ± 6.8	Canada	P	52	D I	PGX	15–20	Supplement packets	Rice flour	Usual

A, agency; AX, arabinoxylan; BMI, body mass index; C, cross-over; D, double; ERD, energy-restricted diet; IGT, impaired glucose tolerance; I, industry; LCD, low calorie diet; Mets, metabolic syndrome; NR, not-reported; P, parallel; PGX, PolyGlycoPLEX; RS2, type 2 resistant starch; S, single; T2DM, type 2 diabetes.

Table 3. The summary of review authors' judgments about each risk of bias item for included studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias	Overall
Garcia et al. (2006) [24]	L	L	L	L	L	U	Good
Antal et al. (2010) [20]	H	L	U	L	L	U	Poor
Beck et al. (2010) [22]	L	U	L	U	L	U	Fair
Li et al. (2010) [28]	L	L	L	L	L	U	Good
Dewulf et al. (2012) [23]	U	L	L	H	L	U	Fair
Hashizume et al. (2012) [26]	L	L	L	L	L	U	Good
Maki et al. (2012) [29]	L	U	L	H	L	U	Fair
Reimer et al. (2013) [33]	U	U	L	U	L	U	Poor
Wanders et al. (2013) [37]	L	U	L	U	L	U	Poor
Kobayakawa et al. (2013) [27]	U	U	L	U	L	U	Poor
Geliebter et al. (2014) [25]	L	L	L	L	L	U	Good
Nishimura et al. (2015) [30]	L	U	U	U	L	U	Poor
Upadhyaya et al. (2015) [36]	L	U	U	H	L	U	Poor
Aoe et al. (2017) [21]	L	L	U	U	L	U	Fair
Parnell et al. (2017) [31]	U	L	L	L	L	U	Good
Strączkowski et al. (2018) [35]	L	L	U	U	L	U	Fair
Sakai et al. (2019) [34]	U	L	U	L	L	U	Good
Reimer et al. (2020) [32]	L	U	L	L	L	U	Good

H, high risk of bias; L, low risk of bias; U, unclear or unrevealed risk of bias.

Meta-analysis results

The influence of soluble fiber on leptin levels

Nine studies [20-22,25,26,32-35] containing a total of 470 individuals (intervention = 241, control = 229) reported changes in serum leptin concentrations as an outcome measure. Pooled results using the random-effects model demonstrated an overall non-significant decline in leptin levels following soluble fiber interventions (SMD, -0.8 Hedges's, 95% CI, $-1.70, 0.08$, p value = 0.076 ; **Figure 2**). However, a significant degree of heterogeneity was observed among the studies ($p < 0.001$, $I^2 = 94.6\%$).

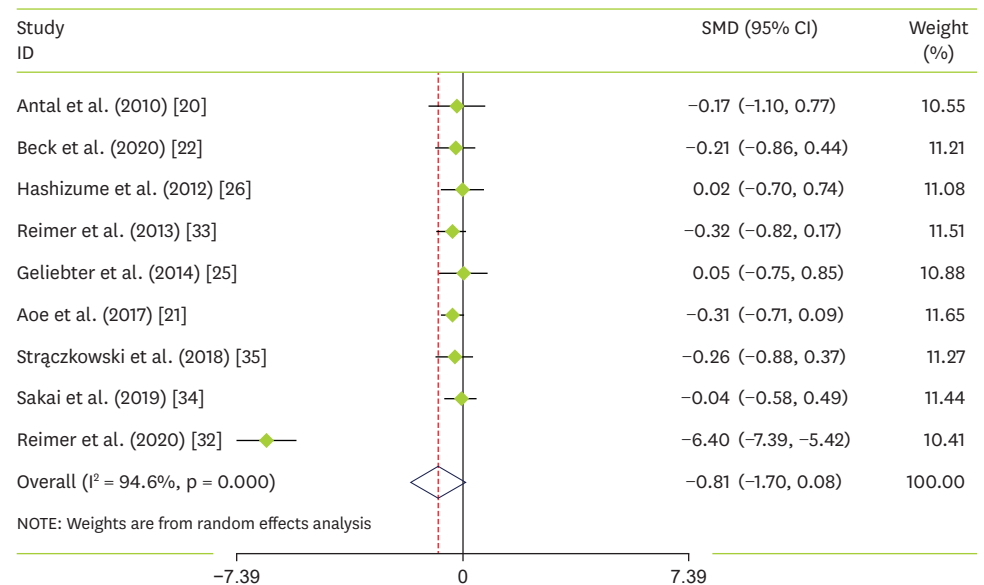


Figure 2. Forest plot of the effect of soluble fiber supplementation on leptin levels. SMD, standardized mean difference; CI, confidence interval.

To identify the source of this heterogeneity, we further sub-grouped based on duration (≥ 8 weeks and < 8 weeks), dose (≤ 10 g/day and >10 g/day), gender (female and both), baseline BMI (≥ 30 kg/m² and < 30 kg/m²) and study population (overweight-obese, MetS, T2DM and healthy). The results showed that subgroup analysis based on dose and baseline BMI could explain this heterogeneity. Sub-group analysis showed that soluble fiber could more decrease in leptin levels in participant with BMI ≥ 30 kg/m² (SMD, -3.17 Hedges's, 95% CI, -9.49, 3.15, p value = 0.326; I² = 99.0%, p < 0.001) and overweight and obese patients (SMD, -0.22 Hedges's, 95% CI, -0.43, -0.01, p value = 0.048; I² = 0.0%, p = 0.975) (Table 4).

No evidence of publication bias was found for leptin (p value = 0.229, Begg's test and p value = 0.466, Egger's test). Also, the sensitivity analysis showed that the overall estimate was not affected by the elimination of any study.

Table 4. Result of subgroup analysis of included studies in meta-analysis

Sub-grouped by	No. of trials	Effect size*	95% CI, p value	I ² (%)	p for heterogeneity	p for between subgroup heterogeneity
Leptin	9	-0.80	(-1.70, 0.08), 0.076	94.6	< 0.001	
Duration (wk)						0.199
< 8	1	0.05	(-0.75, 0.85), 0.903	-	-	
≥ 8	8	-0.92	(-1.90, 0.07), 0.068	95.2	< 0.001	
Dose (g/d)						< 0.001
≤ 10	4	-0.19	(-0.45, 0.08), 0.162	0.0	0.803	
> 10	3	-2.28	(-5.86, 1.29), 0.211	98.4	< 0.001	
Sex						0.302
Female	2	-0.20	(-0.73, 0.34), 0.470	0.0	0.937	
Both	7	-0.99	(-2.10, 0.12), 0.081	95.9	< 0.001	
Baseline BMI (kg/m ²)						< 0.001
< 30	7	-0.22	(-0.43, -0.01), 0.048	0.0	0.975	
≥ 30	2	-3.17	(-9.49, 3.15), 0.326	99.0	< 0.001	
Study population						< 0.001
Overweight–Obese	5	-0.22	(-0.51, 0.07), 0.137	0.0	0.959	
MetS	1	0.02	(-0.70, 0.74), 0.958	-	-	
T2DM	2	-3.21	(-9.44, 3.02), 0.313	99.2	< 0.001	
Healthy	1	-0.31	(-0.71, 0.09), 0.131	-	-	
Adiponectin	16	-0.49	(-1.20, 0.21), 0.167	95.4	< 0.001	
Duration (wk)						0.079
< 8	5	-0.16	(-0.65, 0.33), 0.534	61.3	0.035	
≥ 8	11	-0.83	(-1.82, 0.16), 0.102	96.8	< 0.001	
Dose (g/d)						0.001
≤ 10	5	-0.38	(-0.87, 0.10), 0.123	69.1	0.012	
> 10	10	-0.94	(-2.10, 0.22), 0.114	97.0	< 0.001	
Sex						0.127
Male	4	-9.69	(-14.28, -5.11), < 0.001	98.7	< 0.001	
Female	4	0.29	(-0.13, 0.71), 0.183	30.9	0.229	
Both	8	-0.35	(-0.97, 0.26), 0.264	91.9	< 0.001	
Baseline BMI (kg/m ²)						< 0.001
< 30	9	-1.59	(-2.93, -0.25), 0.020	97.0	< 0.001	
≥ 30	7	0.18	(-0.19, 0.55), 0.344	65.4	0.008	
Study population						< 0.001
Overweight–Obese	10	-1.16	(-2.38, 0.06), 0.062	96.7	< 0.001	
MetS	2	-0.05	(-0.52, 0.42), 0.833	0.0	0.647	
T2DM	2	0.32	(-0.67, 1.32), 0.526	85.8	0.008	
Healthy	2	-0.68	(-1.32, -0.05), 0.034	50.0	0.155	

The p value < 0.05 was considered statistically significant.

MetS, metabolic syndrome; T2DM, type 2 diabetes; CI, confidence interval.

*Calculated by random-effects model.

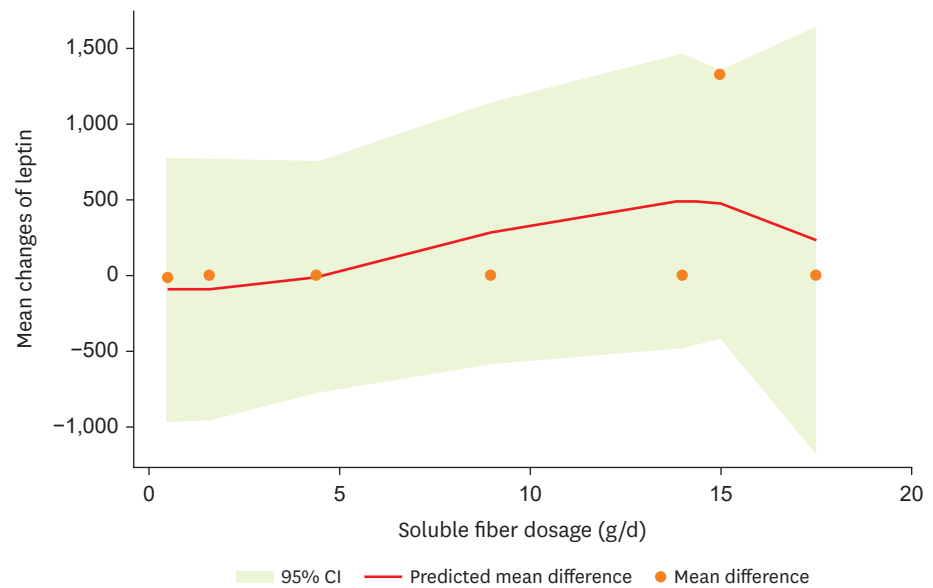


Figure 3. Non-linear dose-response effects of soluble fiber supplementation on leptin levels. CI, confidence interval.

A non-significant non-linear association between soluble fiber dosage and leptin ($p_{\text{non-linearity}} = 0.364$; **Figure 3**) was noted in the non-linear dose-response analysis.

The influence of soluble fiber on adiponectin levels

Thirteen studies [20,21,23,27-33,35,36] containing 16 treatment arms with a total of 980 individuals (intervention = 498, control = 482) reported changes in serum adiponectin concentrations as an outcome measure. Pooled results using the random-effects model demonstrated an overall non-significant effect in serum adiponectin following soluble fiber supplementation (SMD, -0.49 Hedges's, 95% CI, -1.20, 0.21, p value = 0.167; **Figure 4**). However, a significant degree of heterogeneity was observed among the studies (p value < 0.001, $I^2 = 95.4\%$).

Subgroup analysis based on the study population could explain the source of heterogeneity. Also, soluble fiber supplementation had a non-significant increase in adiponectin level in female (SMD, 0.29 Hedges's, 95% CI, -0.13, 0.71, $p = 0.183$) and T2DM (SMD, 0.32 Hedges's, 95% CI, -0.67, 1.32, p value = 0.526) (**Table 4**).

To discover the impact of every single study on the combined effect size, we removed each trial, one at a time, from the analysis and accounted for their individuality. We observed no significant effects of any individual study on the combined effect sizes.

The Egger's tests did not find a significant publication bias among the studies (p value = 0.499, Begg's test and p value = 0.003, Egger's test). The trim-and-fill method to detect sources of bias resulted in different results (SMD, -2.035 Hedges's, 95% CI, -3.056, -1.013).

After non-linear dose-response analysis, a significant non-linear association between dosage and adiponectin ($p_{\text{non-linearity}} < 0.001$; **Figure 5**) was observed.

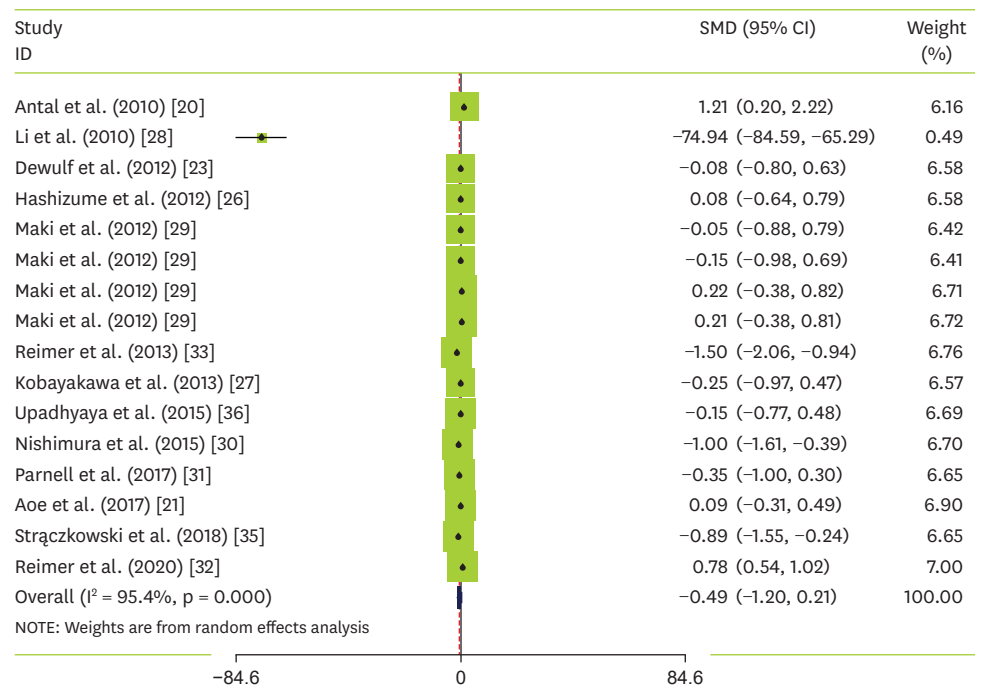


Figure 4. Forest plot of the effect of soluble fiber supplementation on adiponectin levels. SMD, standardized mean difference; CI, confidence interval.

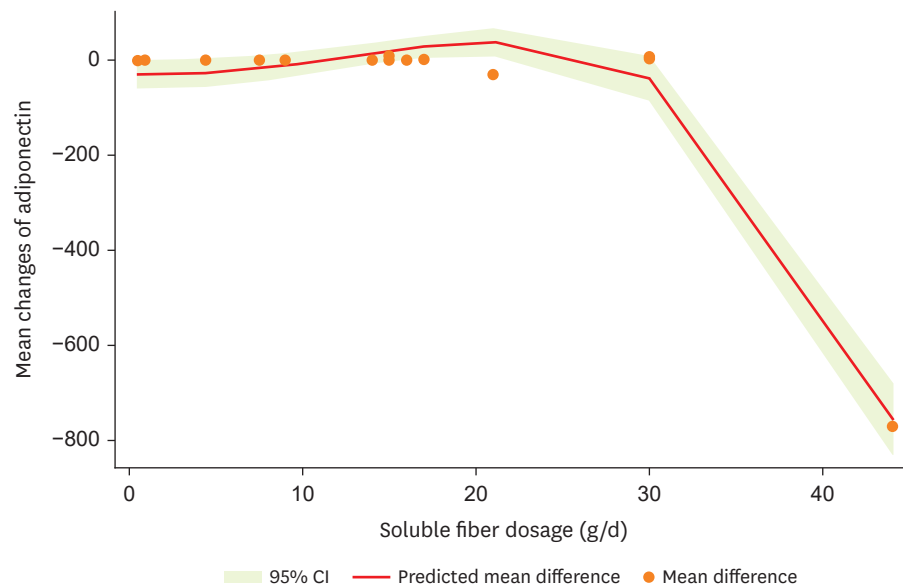


Figure 5. Non-linear dose-response effects of soluble fiber supplementation on adiponectin levels. CI, confidence interval.

DISCUSSION

This systematic review and dose-response meta-analysis aimed to evaluate the effects of soluble fiber supplementation on serum leptin and adiponectin concentrations. Our findings indicate that soluble fiber supplementation did not lead to significant changes in serum

leptin or adiponectin levels overall. However, subgroup analyses provided valuable insights, revealing that soluble fiber supplementation was associated with a significant reduction in leptin concentrations among overweight and obese individuals. Additionally, a non-linear dose-response relationship was observed between soluble fiber dosage and adiponectin levels.

The observed reduction in leptin concentrations among overweight and obese participants is of particular interest. Leptin, a hormone mainly produced by adipose tissue, has important acts in regulating weight management, food intake, energy homeostasis, glucose homeostasis, angiogenesis, immune responses, lipolysis, and fertility [42,43]. Serum leptin concentrations positively correlate with adiposity [44,45]. Therefore, overweight or obese individuals with hyperleptinemia development of leptin resistance usually cannot exert anorexigenic effects [44,45]. Recently, novel approaches have been introduced to attenuate the leptin levels in adiposity [45]. Applying soluble fiber supplementation as one of the dietary strategies has been suggested to improve adipokine levels [46]. Our findings suggest that soluble fiber supplementation might contribute to alleviating hyperleptinemia in these individuals. Mechanistically, soluble fiber could potentially impact leptin levels through various pathways. By reducing fat mass and influencing gut hormone release, soluble fiber might indirectly decrease leptin secretion [18]. Furthermore, soluble fiber's potential to improve adipokine levels by affecting lipogenesis, adenosine monophosphate-activated protein (AMP)-activated protein kinase (AMPK) activity, and leptin resistance warrants further investigation.

Previous studies have documented that soluble fiber administration may help to decrease fat mass and may consequently improve adipokines levels through slowing gastric emptying, declining glycemic index, and a load of meals, influencing gut hormone release, taking further time to be chewed, and decreasing calorie absorption of foods [47,48]. In addition, some studies indicated that soluble fiber might improve adipokine levels by decreasing lipogenesis in liver and adipose tissue, activating the AMPK, decreasing phosphoenolpyruvate carboxykinase expression in the liver, and increased expression of carnitine palmitoyltransferase-1 β in skeletal muscle [49,50]. The soluble fiber also may decrease leptin levels by improvement of leptin resistance. Zhang et al. [19], in an animal study, revealed that soluble fiber supplementation enhanced leptin activity by augmenting the expression of leptin receptors in white fat mass, increasing the leptin signaling pathway by improving JAK2/STAT3 and decreasing suppressor of cytokine signaling 3 expression [19]. Also, garlic administration as an important source of dietary soluble fiber may affect adiponectin and leptin levels.

The previous documents have revealed that garlic may affect adipokines through antioxidant properties. For example, garlic increases the nitric oxide bioavailability via advancing the cellular antioxidant capacity by providing cellular thiol antioxidants like cysteine and diminished glutathione, maintaining the functionally appropriate concentration of tetrahydrobiopterin and controlling oxidative inactivation of tetrahydrobiopterin [51,52]. Thus, according to the mentioned mechanisms, the consumption of soluble fiber can be suggested to manage leptin levels and resistance among overweight or obese subjects. Another important finding showed a non-linear association between soluble fiber dosage and adiponectin levels. Adiponectin has several physiological benefits, including anti-inflammation, anticancer, cardioprotective, decreasing hepatic steatosis, sensitizing tissues to insulin, hypolipidemic, and increasing high-density lipoprotein in the serum [53]. Given adiponectin's positive metabolic and physiological function, interventions that increase

adiponectin levels can help improve health status. It seems that soluble fiber, as one of the contents of functional foods through their properties, improves anthropometric and metabolic outcomes [54], consequently positively affecting adiponectin concentrations [55]. A further potential mechanism that can be considered in this context is the role of soluble fiber in adiponectin-mediated insulin resistance. Adiponectin is associated well with whole-body insulin sensitivity and is reduced in T2DM patients [56,57]. Brockman et al. [54], in an animal study on the Zucker Diabetic Fatty rats model, the high viscous soluble fiber group had the highest levels of adiponectin and the most significant insulin sensitivity. They suggested that adiponectin inhibits hepatic gluconeogenesis and enhances fatty acid oxidation in the muscle via advanced AMP kinase and peroxisome proliferator-activated receptor alpha activity, as a result, led to improved insulin sensitivity [58]. Future prospective randomized clinical trials with more extended supplementation period are required to obtain a more exact conclusion.

Our investigation has strengths, including completing a comprehensive search of published literature without limitations and adherence to the PRISMA criteria for writing our study. Additionally, most of the studies included in our investigation had high quality. We also used conservative statistical methods and sub-group analyses to detect any effect of study duration, dose, gender, baseline BMI, and study population on the overall effect examinations.

This study also has some limitations that need to be noted. Firstly, there was significant statistical heterogeneity in the selected studies. However, sub-groups analysis and sensitivity analyses were conducted. Secondly, the influence of the confounding variables, namely the genetic variants, lifestyle factors, race, and ethnicity, on evaluating the efficacy of soluble fiber administration on leptin and adiponectin serum concentrations was disregarded. Thus, our outcomes should be interpreted with caution.

The results of the present study also showed a beneficial effect of soluble fiber supplementation on decreasing serum leptin concentration among overweight and obese individuals.

In future studies, confounding factors such as genetic background, differences in lifestyle, race, and ethnicity on this efficacy should be assessed. A further controlled clinical trial with a good study design, long follow-up duration, and adequate power is warranted to verify the potential effect of soluble fiber supplementation on serum adipokines levels, notably among overweight and obese patients.

In conclusion, our findings contribute to the growing body of knowledge on the potential metabolic effects of soluble fiber supplementation. While the overall impact on serum leptin and adiponectin concentrations may be subtle, the specific reduction in leptin levels among overweight and obese individuals suggests a targeted benefit in this population. As we continue to uncover the intricate connections between dietary interventions and metabolic health, further research is warranted to fully harness the potential of soluble fiber as a component of effective strategies for weight management and metabolic improvement.

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