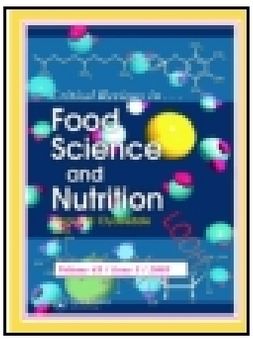

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Jamal Halajzadeh, Alireza Milajerdi, Željko Reiner, Elaheh Amirani, Fariba Kolahdooz, Maryam Barekat, Hamed Mirzaei, Seyyed Mehdi Mirhashemi & Zatollah Asemi (2019): Effects of resistant starch on glycemic control, serum lipoproteins and systemic inflammation in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled clinical trials, Critical Reviews in Food Science and Nutrition

To link to this article: https://doi.org/10.1080/10408398.2019.1680950

Published online: 29 Oct 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2019.1680950

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REVIEW

Effects of resistant starch on glycemic control, serum lipoproteins and systemic inflammation in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

The aim of this systematic review and meta-analysis was to evaluate the effects of resistant starch (RS) on glycemic status, serum lipoproteins and inflammatory markers in patients with metabolic syndrome (MetS) and related disorders. Two independent authors systematically searched online database including EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science from inception until 30 April 2019. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. The heterogeneity among the included studies was assessed using Cochrane's Q test and I-square (I^2) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size. Nineteen trials were included in this meta-analysis. Administration of RS resulted in significant reduction in fasting plasma glucose (FPG) (14 studies) (WMD: −4.28; 95% CI: −7.01, −1.55), insulin (12 studies) (WMD: −1.95; 95% CI: −3.22, −0.68), and HbA1C (8 studies) (WMD: −0.60; 95% CI: −0.95, −0.24). When pooling data from 13 studies, a significant reduction in total cholesterol levels (WMD: −8.19; 95% CI: −15.38, −1.00) and LDL-cholesterol (WMD: −8.57; 95% CI: −13.48, −3.66) were found as well. Finally, RS administration was associated with a significant decrease in tumor necrosis factor alpha (TNF-α) (WMD: −2.02; 95% CI: −3.14, −0.90). This meta-analysis showed beneficial effects of RS on improving FPG, insulin, HbA1c, total cholesterol, LDL-cholesterol and TNF-α levels in patients with MetS and related disorders, but it did not affect HOMA-IR, triglycerides, HDL-cholesterol, CRP and IL-6 levels.

KEYWORDS

Resistant starch; insulin resistance; metabolic syndrome; LDL-cholesterol; HDL-cholesterol; meta-analysis

Introduction

Currently, growing evidence suggests that intestinal microflora plays as important role in the development of metabolic disorders such as dyslipidemia, insulin resistance and inflammation (Panwar et al. 2013; Shen, Obin, and Zhao 2013). Microflora is defined as microorganisms that live within the human bodies (more than 2000 species of commensal bacterial organisms) (Neish 2009). Digestive tract is the most important part of the body where these microorganisms, especially bacteria, live. Many microorganisms, mostly gut microflora, have an influence on the function of human body by different mechanisms such as immunomodulation, protection by formation of physical barriers, anti-inflammatory by production of short chain fatty acids (SCFA), and production of bacteriocins (Montalto et al. 2009). Changes in composition of gut microflora can have beneficial or unfavorable effects on the health of the host organism. Diet is one of many factors that can cause persistence of a specific bacteria in the digestive tract (Panwar et al. 2013; Sekirov et al. 2010).

Resistant starch (RS) is defined as "selectively fermented ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits upon host health" (Gibson et al. 2010). RS is a fraction of starch which is resistant to digestive enzymes in small intestine and is delivered intact to colon to be fermented by bacteria. RS divided into five subtypes (RS1-RS5) based on their structure and sources (Homayouni et al.

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2014). Some of them are natural ingredients of some food and the others are produced or changed and added to some food products. RS1 is unreachable to amylases because it is trapped within the protein matrix and cell wall of grains or seeds. RS2 is ingredient of uncooked starch like raw potato and green banana which is resistant to digestive enzymes. RS3 occurs as a result of retrogradation. Eventually, RS4 is chemically modified starch while RS5 is the amylose-lipid complex starch.

RS increases saccharolytic fermentation and production of gases such as methane, hydrogen, carbon dioxide but also substances such as SCFA, mainly butyrate, propionate and acetate by a specific group of bacteria like Bifidobacterium and Lactobacillus in the proximal part of the large intestine (Roberfroid et al. 2010). SCFA with acidification of intestinal lumen inhibit the growth of pathogens (Blaut 2002) and modulate gut movements (Dass et al. 2007).They also contribute as an energy source. Recently, prebiotics such as RS have been considered as biotherapeutics and low-cost strategies for management of metabolic disorders and reduction of adverse outcomes of these disorders. Until now, the results of different studies analyzing the impact of different amounts and types of RS administration on metabolic outcomes have been controversial. The aim of this systematic review and meta-analysis was to summarize recent data on the effects of RS on metabolic parameters such as glycemic control, serum lipoproteins and low-grade chronic systemic inflammation in patients with metabolic syndrome (MetS) and related disorders such as obesity, diabetes mellitus and polycystic ovary syndrome.

Materials and methods

Search and studies selection strategies

International databases, including Cochrane Library, EMBASE, PubMed, and Web of Science were searched for relevant studies published from incent until 30 April 2019. A search strategy was developed using the following MeSH and text keywords; disease ["metabolic syndrome" OR "MetS" OR "disorders related to MetS" OR "Type 1 diabetes mellitus (T1DM)" OR "Type 2 diabetes mellitus (T2DM)" OR "diabetes" OR "obese" OR "overweight" OR "coronary artery disease (CAD)" OR "diabetic nephropathy" OR "hypertension" OR "blood pressure (BP)" OR "dyslipidemia" OR "cardiovascular disease"] AND intervention ("resistant starch", "RS" AND "supplementation" OR "intake" OR "administration"), and outcomes parameters ("fasting glucose" OR "fasting plasma glucose (FPG)" OR "insulin" OR "homeostasis model assessment of insulin resistance (HOMA-IR)" OR "HbA1c" AND "total cholesterol (TC)" "triglycerides (TG)" OR "low-density lipoprotein (LDL-cholesterol)" OR "LDL-C" OR "high-density lipoprotein (HDL-cholesterol)" OR "HDL-C" OR "C-reactive protein (CRP)" OR "interleukin-6 (IL-6)" OR "tumor necrosis factor-α (TNF-α)").

Inclusion and exclusion criteria

RCTs fulfilling following criteria were included in meta-analysis: human trials with either cross-over design or parallel, RCTs with data on the effect of RS (in form of supplements or dietary interventions) compared with a control including the intake of digestible starches or other carbohydrates or other fibers on glycemic status, serum lipoproteins and inflammatory markers with standard deviation (SD) and related 95% confidence interval (CI) for both intervention and control groups. Other studies such as animal experiments, *in vitro* studies, case reports, observational studies, trials without a control group, studies with 2 weeks or less duration time, and studies that did not achieve the least quality score were excluded from this meta-analysis.

Data extraction and quality assessment

Two independent authors (JH and EA) screened the articles based on the eligibility criteria. As the first step the title and abstract of studies were reviewed. Then, the full-text of relevant studies was assessed to ascertain the suitability of a study for the meta-analysis. Any disagreement was resolved by the judgment of the third author (ZA).

The following data were taken from selected studies: the first authors' name, year of publication, study location, sample size, study design, dosage of RS, type of disease, duration of the study, the mean and SD for glycemic status, serum lipoproteins and inflammatory markers in each intervention group. The quality of the selected RCTs was assessed by same independent authors using the Cochrane Collaboration risk of bias tool based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, and other sources of bias."

Data synthesis and statistical analysis

The effects of RS on the changes of the outcome parameters were calculated. Weighted mean difference (WMD) with 95% CI was used for pooling data to determine effect sizes. The change score approach was used to calculate the effect size of RS on the identified outcome. The random-effect model was used to report the pooled effect sizes using 95% CI.

Heterogeneity and publication bias

Heterogeneity of included studies was evaluated using Cochrane's Q test (with significant P-value <0.1) and I-square test (I^2 greater than 50 percent showing significant heterogeneity). The funnel plot, as well as the Beggs's and Egger's regression tests was used to evaluate the publication bias. Both STATA 11.0 (Stata Corp., College Station, TX) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) were applied for data analysis.

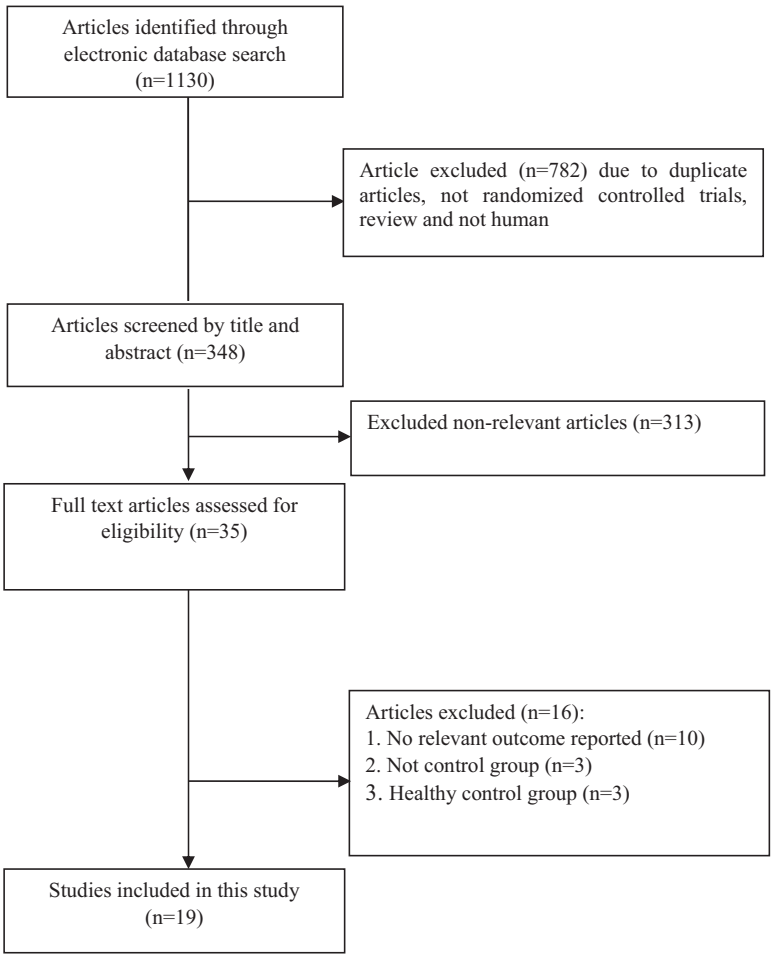


Figure 1. Literature search and review flowchart for selection of studies.

Results

Characteristics of included studies

19 studies which were published between 2004 and 2019 were included in the current this systematic review and meta-analysis. Flow-diagram for study selection is shown in Figure 1. Around 1014 subjects, 495 in intervention and 519 in control groups, were enrolled in included studies. Characteristics of included studies are summarized in Table 1. These studies were done in Korea, USA, Australia, Mexico, Iran, Canada, Serbia, Brazil, Denmark, and China. Participants were at risk of chronic diseases in some studies, while they had chronic diseases in other studies. Some studies used maize-derived resistance starch as the intervention substance, while the others extracted it from other dietary sources. The intervention period varied from 21 days to 12 months.

The effects of RS on glycemic control

Administration of RS resulted in a significant reduction in FPG (14 studies) (WMD: −4.28; 95% CI: −7.01, −1.55) (Table 2 and Figure 2a), insulin (12 studies) (WMD: −1.95; 95% CI: −3.22, −0.68) (Table 2 and Figure 2b), and HbA1c (8 studies) (WMD: −0.60; 95% CI: −0.95, −0.24) (Table 2 and Figure 2d), but it had no significant effect on HOMA-IR (10 studies) (WMD: −0.35; 95% CI: −0.85, 0.15) (Table 2 and Figure 2c). These findings remained unchanged in all subgroups. However, RS had no significant effect on FPG in studies done on subjects at risk of chronic diseases (WMD: −0.52; 95% CI: −2.07, 1.03) or those aged <50 years (WMD: −1.43; 95% CI: −1.53, 4.39), studies used maize as the source of RS (WMD: −0.23; 95% CI: −1.76, 1.29), and studies with a sample size of <50 participants (WMD: −0.60; 95% CI: −2.14, 0.94). In addition, a significant reduction was seen in HOMA-IR following RS supplementation among these subgroups: studies in both <50 (WMD: −1.24; 95% CI: −1.75, −0.73) or ≥50 (WMD: −0.21; 95% CI: −0.43, −0.01) years old subjects, parallel RCTs (WMD: −0.49; 95% CI: −0.70, −0.27), studies on patients with chronic diseases (WMD: −0.57; 95% CI: −0.85, −0.30), studies done among Eastern nations (WMD: −0.60; 95% CI: −0.84, −0.36), studies used both maize (WMD: −0.32; 95% CI: −0.62, −0.02) or other sources of RSs (WMD: −0.40; 95% CI: −0.66, −0.14), and those with a duration of ≥8 weeks (WMD: −0.70; 95% CI: −0.97, −0.44) or a sample size of ≥50 (WMD: −0.36; 95% CI: −0.57, −0.15) (Table 3).

The effects of RS on serum lipoproteins

Pooling data from 12 studies with 13 effect sizes, we found a significant reduction in total cholesterol levels following

Table 1. Characteristics of included studies.

References	Publication year	Sample size (control/intervention)	Country/population	Intervention (name and daily dose)	Duration	Age (y) (control, intervention)	Presented data
Park et al. (2004)	2004	13/12	Korea/overweight subjects	24 g/day resistant starch in form of supplement	21 days	43.6 ± 10.09, 42.3 ± 10.7	FPG, insulin, TG, TC, HDL-C, LDL-C
Larkin, Astheimer, and Price (2009)	2009	9/9	Australia/mildly hypercholesterolaemic subjects	16–20 g/day resistant starch in form of bread+ 250 ml/day soy milk and 45 g/day soy cereal	14 weeks	58.6 ± 7.7	TG, TC, HDL-C, LDL-C
Larkin, Astheimer, and Price (2009)	2009	12/12	Australia/mildly hypercholesterolaemic subjects	16–20 g/day resistant starch in form of bread+ 250 ml/day soy milk and 45 g/day soy cereal	14 weeks	58.6 ± 7.7	TG, TC, HDL-C, LDL-C
Penn-Marshall, Holtzman, and Barbeau (2010)	2010	15/15	USA/at risk forT2DM	12 g/day high-maize 260 (RS2) in form of bread	6 weeks	36.6 ± 8.4	FPG, insulin, HOMA-IR, CRP
Ble-Castillo et al. (2010)	2010	28/28	Mexico/T2DM	24 g/day native banana starch dissolved in 240 mL of water	4 weeks	51.7 ± 5.6	FPG, insulin, HbA1c, HOMA-IR, TG, TC, HDL-C
Kwak et al. (2012)	2012	44/41	Korea/patients with prediabetes or newly diagnosed T2DM	6.51 g resistant starch/refined rice pack	4 weeks	49.4 ± 11.5, 51.7 ± 12.99	FPG, insulin, HOMA-IR
Gargari et al. (2015)	2015	32/28	Iran/T2DM	10 g/day high-maize TM 260 (RS2) in form of packages	8 weeks	49.6 ± 8.4, 49.5 ± 8.0	FPG, HbA1c, TG, TC, HDL-C, LDL-C, CRP, TNF-α, IL-6
Aliasgharzadeh et al. (2015)	2015	25/30	Iran/women with T2DM	10 g/day resistant dextrin in form of supplement NUTRIOSEw06FM	8 weeks	49.6 ± 8·4, 49.2 ± 9·60	FPG, insulin, HbA1c, HOMA-IR, CRP, TNF-α, IL-6
Dainty et al. (2016)	2016	24/23	Canada/adults at risk of T2DM	1 bagel containing 25 g/day HAM-(RS2)	57 days	55.3 ± 7.78	FPG, Insulin, HOMA-IR
Karimi et al. (2016)	2016	28/28	Iran/women with T2DM	10 g/day RS2	8 weeks	48.6 ± 7.9, 49.5 ± 8.0	FPG, insulin, HbA1c, HOMA-IR, CRP
Dodevska et al. (2016)	2016	25/22	Serbia/obese prediabetic adults	lifestyle and dietary intervention with low-fat and high-fiber + dietary advices aimed at increasing total resistant starch intake	12 months	56.96 ± 6.13, 58.36 ± 6.12	FPG, insulin, HOMA-IR, TG, TC, HDL-C, LDL-C
Ribeiro Vieira et al. (2017)	2017	14/11	Brazil/overweight women with abdominal obesity	30 g/day resistant starch in form of unripe banana flour + cocoa beverage	6 weeks	32.7 ± 8.4, 37.7 ± 8.57	TNF-α, IL-6
Peterson et al. (2018)	2018	30/29	USA/adults with prediabetes	45 g/day high-amylose maize resistant starch (RS2)	12 weeks	55 ± 10, 54 ± 10	FPG, HbA1c, Insulin, TG, TC, HDL-C, LDL-C, CRP, TNF-α
Schioldan et al. (2018)	2018	19/16	Denmark/MetS	21 g/day resistant starch in form of food provided with heat-resistant high-amylose maize starch and raw potato-starch	4 weeks	58 ± 11	FPG, insulin, HOMA-IR, TG, TC, HDL-C, LDL-C
Cai et al. (2018)	2018	49/50	China/elderly with T2DM	8–34 g/day resistant dextrin + 10–30 g/inulin and 45 g/day milk powder in 240 mL warm water	12 weeks	60.16 ± 5.84, 60.94 ± 5.35	FPG, HbA1c, Insulin, HOMA-IR, TG, TC, HDL-C, LDL-C, CRP, TNF-α
Esgalhado et al. (2018)	2018	16/15	Brazil/hemodialysis patients	16 g/day resistant starch Hi-Maize® 260 (RS2) in form of cookies on dialysis days and powder in a sachet on non-dialysis days	4 weeks	53.5 ± 11.5, 56.0 ± 7.5	CRP, IL-6
Tayebi Khosroshahi et al. (2018)	2018	22/22	Iran/hemodialysis patients	20 g/day HAM-RS2 during the first 4 weeks and 25 g/day in the next 4 weeks	8 weeks	60 ± 14, 52 ± 11	TG, TC, HDL-C, CRP
Khosroshahi et al. (2019)	2019	21/23	Iran/hemodialysis patients		8 weeks	57.9 ± 13.34, 53.17 ± 10.15	TG, TC, HDL-C, CRP

				20 or 25 g/day of 60% resistant starch HAM-RS2 in form of crackers				
Meng et al. (2019)	2019	36/34	China/type 2 diabetic nephropathy	50 g of high-resistant starch, low-protein flour instead of a common staple of equal quality at lunch and dinner each day	12 weeks	61 ± 9.5, 62.85 ± 9.3		TG, TC, HDL-C, LDL-C, TNF-a, Il-6
Costa et al. (2019)	2019	51/62	Brazil/patients with prediabetes and T2DM	4.5 g/day resistant starch in form of green banana biomass + dietary intervention	6 months		18–85	FPG, HbA1c, Insulin, HOMA-IR, TG, TC, HDL-C, LDL-C

HOMA IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol, HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

the administration of RS (WMD: −8.57; 95% CI: −13.48, −3.66) (Table 2 and Figure 2f). However, no significant effects of RS on serum levels of TC was found in studies done in subjects aged ≥50 years (WMD: −0.26; 95% CI: −1.25, 0.74), cross-over RCTs (WMD: −0.02; 95% CI: −1.06, 1.03), studies done among those with chronic diseases (WMD: −0.13; 95% CI: −1.17, 0.91), studies done in both Eastern (WMD: −3.50; 95% CI: −7.35, 0.35) or Western (WMD: −0.41; 95% CI: −1.43, 0.62) countries, studies used maize (WMD: −3.09; 95% CI: −7.75, 1.56) or other sources of RSs (WMD: −0.49; 95% CI: −1.51, 0.52), and those with a duration of <8 weeks (WMD: −0.32; 95% CI: −1.36, 0.72) or a sample size of ≥50 (WMD: −0.07; 95% CI: −1.10, 0.96). Moreover, a significant increase of total cholesterol concentrations following intake of RS was found in studies which recruited patients with renal diseases (WMD: 14.55; 95% CI: 7.79, 21.31) (Table 3). RS had no significant effect on triglycerides (WMD: −0.58; 95% CI: −24.68, 23.52) (Table 2 and Figure 2e), and HDL-cholesterol (WMD: −0.22; 95% CI: −1.66, 1.22) (Table 2 and Figure 2h), when we combined data from 12 with 13 effect sizes, respectively. However, a significant reduction was seen in LDL-cholesterol following the intervention (WMD: −8.57; 95% CI: −13.48, −3.66) (Table 2 and Figure 2g). The same findings were also reached in some subgroups. However, RS significantly decreased triglycerides in studies performed on participants aged <50 years (WMD: −34.08; 95% CI: −54.22, −19.93). RS increased triglycerides concentrations in studies on patients aged ≥50 years (WMD: 28.06; 95% CI: 22.24, 33.87), cross-over RCTs (WMD: 52.10; 95% CI: 44.09, 60.11), studies done on patients with chronic diseases (WMD: 36.76; 95% CI: 29.79, 43.73), studies done in Western countries (WMD: 44.50; 95% CI: 37.09, 51.91), those which used other sources of RS than maize (WMD: 36.13; 95% CI: 29.38, 42.88), and studies with a duration of <8 weeks (WMD: 51.39; 95% CI: 43.44, 59.35) or a sample size of ≥50 (WMD: 30.09; 95% CI: 23.61, 36.56). RS intake did not change LDL-cholesterol concentrations in following studies: cross-over RCTs (WMD: −4.34; 95% CI: −9.48, 0.80). RS also increased HDL-cholesterol levels in studies on participants aged <50 (WMD: 2.68; 95% CI: 0.56, 4.81), studies used RS from maize (WMD: 1.44; 95% CI: 0.23, 2.56). However, reduction of HDL-cholesterol concentrations following intake of RS was seen in studies on patients aged ≥50 (WMD: −1.93; 95% CI: −2.08, −1.78), cross-over RCTs (WMD: −1.99; 95% CI: −2.14, −1.84), studies on those with chronic diseases (WMD: −1.93; 95% CI: −2.08, −1.78) or at risk for these diseases (WMD: −1.45; 95% CI: −2.68, −0.212), studies done in Western countries (WMD: −2.00; 95% CI: −2.15, −1.85), studies which used other sources of RS than maize (WMD: −1.96; 95% CI: −2.11, −1.81), and studies lasting <8 weeks of intervention (WMD: −1.98; 95% CI: −2.14, −1.83) or ≥50 participants (WMD: −1.93; 95% CI: −2.08, −1.78) (Table 3).

The effects of RS on inflammatory markers

Combining data from 8 studies for the effects of RS on CRP and from 5 studies for IL-6 and TNF-α, no significant changes in CRP levels (WMD: −0.40; 95% Confidence

Table 2. The effects of resistance starch on metabolic profiles.

				Heterogeneity	
Variables	Number of effect sizes	Weighted mean difference	CI 95%	I^2 (%)	p-value heterogeneity
FPG	14	−4.28	−7.01, −1.55	82.6	<0.001
Insulin	12	−1.95	−3.22, −0.68	84.4	<0.001
HOMA-IR	10	−0.35	−0.85, 0.15	79.6	<0.001
HbA1C	8	−0.60	−0.95, −0.24	91.9	<0.001
TG	13	−0.58	−24.68, 23.52	92.8	<0.001
TC	13	−8.19	−15.38, −1.00	92.7	<0.001
LDL-C	10	−8.57	−13.48, −3.66	68.5	<0.01
HDL-C	13	−0.22	−1.66, 1.22	85.3	<0.001
CRP	8	−0.40	−1.56, 0.77	78.9	<0.001
TNF-α	5	−2.02	−3.14, −0.90	55.9	0.06
IL-6	5	−0.93	−2.11, 0.26	85.9	<0.001

CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1C, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.

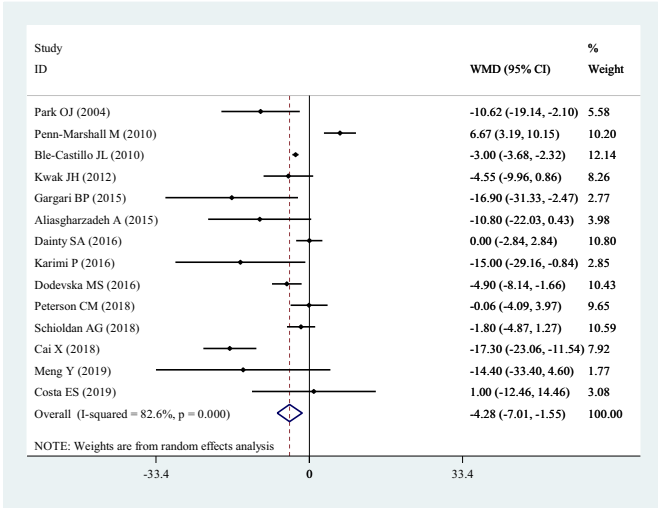
Interval (CI): −1.56, 0.77) (Table 2 and Figure 2i) and IL-6 levels (WMD: −0.93; 95% CI: −2.11, 0.26) were shown (Table 2 and Figure 2k), while a significant reduction in TNF-α (WMD: −2.02; 95% CI: −3.14, −0.90) (Table 2 and Figure 2j) was seen following intake of RS. Subgroup analysis showed a significant reduction of CRP levels following RS intake in studies done on patients aged <50 years (WMD: −1.48; 95% CI: −2.09, −0.85) and those with chronic diseases (WMD: −1.50; 95% CI: −2.13, −0.88) as well as studies performed in both Eastern (WMD: −0.88; 95% CI: −1.46, −0.31) and Western (WMD: −0.99; 95% CI: −1.74, −0.24) countries, with duration of both <8 weeks (WMD: −1.10; 95% CI: −1.89, −0.31) and ≥8 weeks (WMD: −0.84; 95% CI: −1.39, −0.28), and studies with a sample size of ≥50 participants (WMD: −1.41; 95% CI: −2.01, −0.80). A significant reduction was also seen in IL-6 concentrations following RS supplementation in studies which recruited patients aged <50 years (WMD: −1.01; 95% CI: −1.41, −0.62), studies done in Eastern countries (WMD: −1.11; 95% CI: −1.59, −0.64), studies used maize (WMD: −1.24; 95% CI: −1.97, −0.52) or other sources of RSs (WMD: −0.75; 95% CI: −1.20, −0.31), and studies with ≥8 weeks' duration or a sample size of ≥50 (WMD: −1.11; 95% CI: −1.59, −0.64). The findings of the effects of RS on markers of Inflammation did not change in other subgroups (Table 3).

Discussion

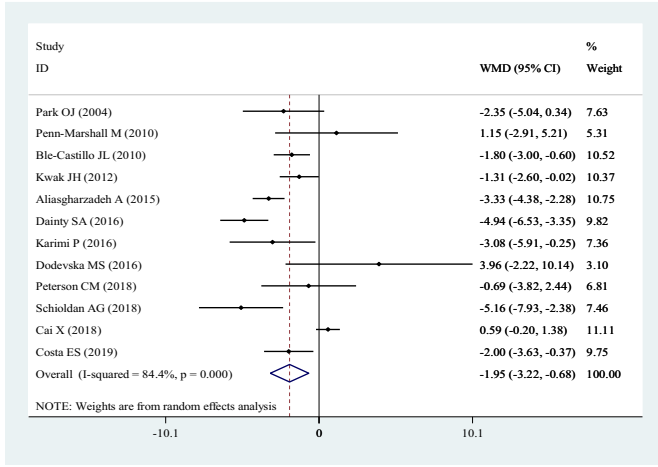
This meta-analysis showed beneficial effects of RS on FPG, insulin, HOMA-IR, HbA1c, total cholesterol, TNF-α and IL-6 levels in patients with MetS and related disorders, although it did not affect triglycerides, LDL-cholesterol and HDL-cholesterol levels. Prebiotics are indigestible material that escapes small intestine enzymes and is fermented in colon by bacteria. So far many reports have showed that intestine microbiota is associated with multiple risk factors for metabolic diseases. Prebiotics can influence metabolic complications such as altered blood glucose homeostasis, dyslipidemia and inflammation.

RS and glucose metabolism

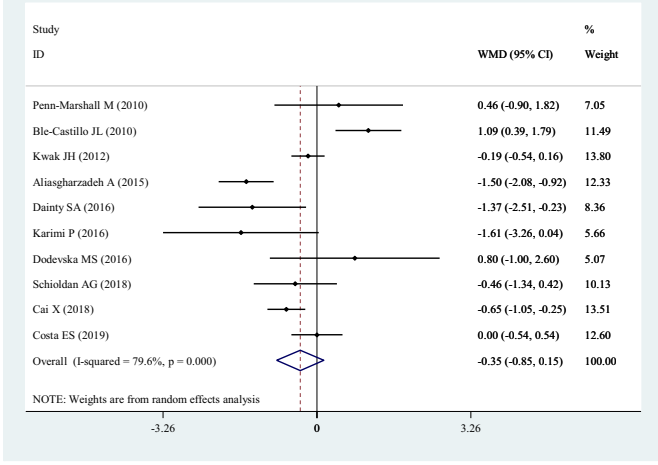
Increased FPG levels are a risk factor of cardiovascular diseases connected with different metabolic disorders such as diabetes and metabolic syndrome. Insulin resistance is a pathological situation in which cells fail to respond normally to insulin and can result in elevated FPG (Grundy et al. 2005). Insulin resistance is the basic change in metabolic syndrome (Grundy et al. 2005). Both increased FPG and insulin resistance stimulate insulin production in pancreatic β cells and accordingly elevate fasting insulin levels (Patel et al. 2016). Gut microflora is associated with various metabolic processes. Alterations in the diversity of gut microflora or decreased levels of bacteria species with beneficial effects directly affect the host's health (Kasubuchi et al. 2015; Shen, Obin, and Zhao 2013) and can be related to certain diseases, such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), obesity and cancer. Decreased number of useful bacteria in the gut promote a pro-inflammatory process (Panwar et al. 2013). Increased pro-inflammatory substances in the blood change the function of β-cells, which can cause an increase in FPG and insulin levels (Erejuwa, Sulaiman, and Wahab 2014; Shen, Obin, and Zhao 2013). Decreased number of useful bacteria such as Bifidobacteria in colon is associated with the incidence of T2DM (Erejuwa, Sulaiman, and Wahab 2014; Shen, Obin, and Zhao 2013). It seems that prebiotics such as RS can shift the gut microflora towards beneficial bacteria population and can improve glucose metabolism by suppressing metabolic endotoxemia (Cani and Delzenne 2009). The results of the studies on the effects of different types of RS on glucose metabolism have been contradictory in healthy individuals and patients with metabolic disorders. Maki et al. (Maki et al. 2012) showed that supplementation of 15 and 30 g/day high-amylose maize-RS2 did not alter FPG, but improved insulin sensitivity in overweight and obese men after 4 weeks. In a study by Castillo et al. (Ble-Castillo et al. 2010), consumption of 24 g/day of native banana starch for 4 weeks in obese T2DM patients did not change HbA1c, FPG and insulin resistance. In an another study, intake of 10 g/day of RS2 during 8 weeks significantly improved HbA1c, insulin levels and insulin resistance, but did not improve FPG in patients with diabetes (Karimi et al. 2016). Lobley et al. (2013) showed that consumption of 25 g/day RS after 3 weeks did not alter FPG in obese men, but did improve insulin levels and insulin resistance. Treatment with rice containing 6.51 g of RS daily for 4 weeks, caused an improvement in fasting insulin levels and insulin resistance in subjects with impaired FPG levels or newly diagnosed T2DM (Kwak et al. 2012). Prebiotics can



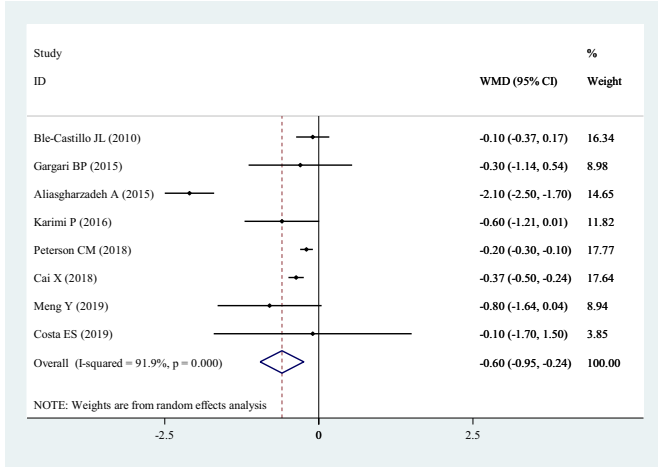
A: FPG



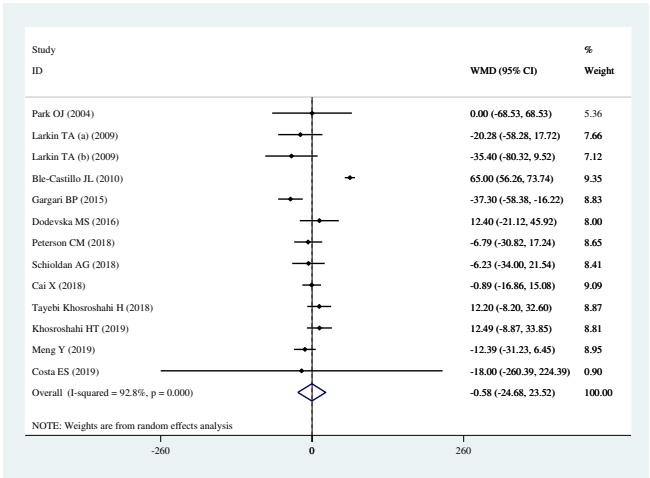
B: Insulin



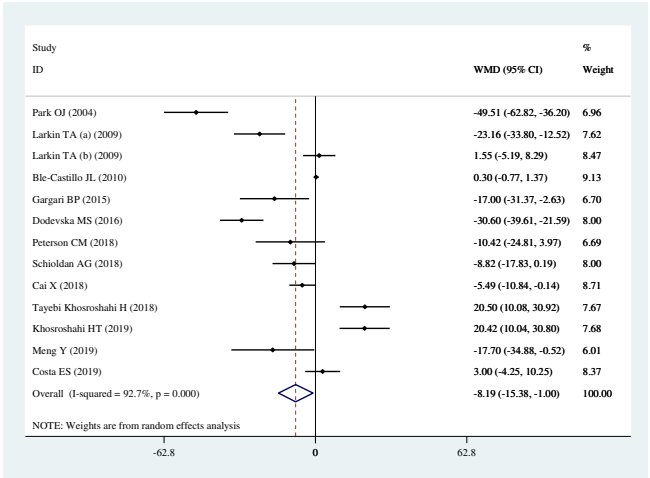
C: HOMA-IR



D: HbA1c



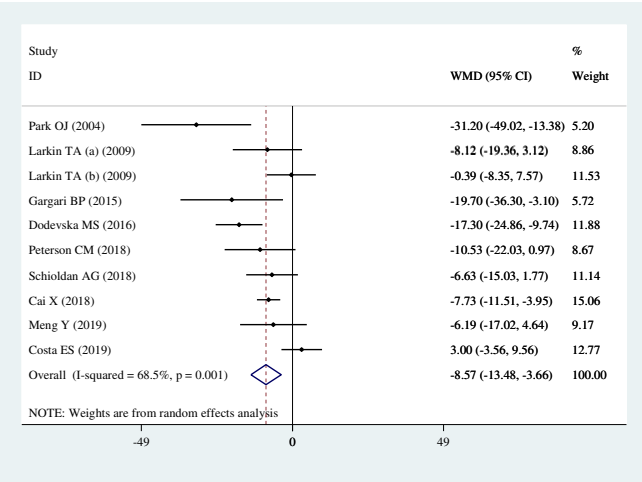
E: TG



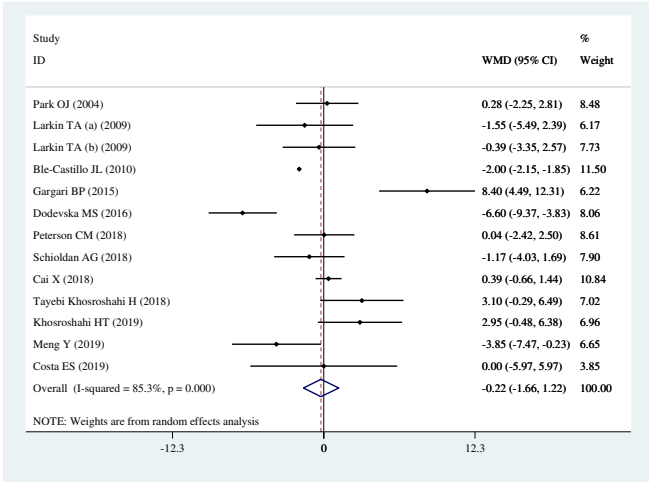
F: Total cholesterol

Figure 2. Meta-analysis glycemic control, serum lipids and inflammatory markers weighted mean difference estimates for a) FPG, b) insulin, c) HOMA-IR, d) HbA1c, e) triglycerides, f) total cholesterol, g) LDL-cholesterol, h) HDL-cholesterol, i) CRP, j) TNF-α, and k) IL-6 levels in the resistance starch and placebo groups (CI = 95%).

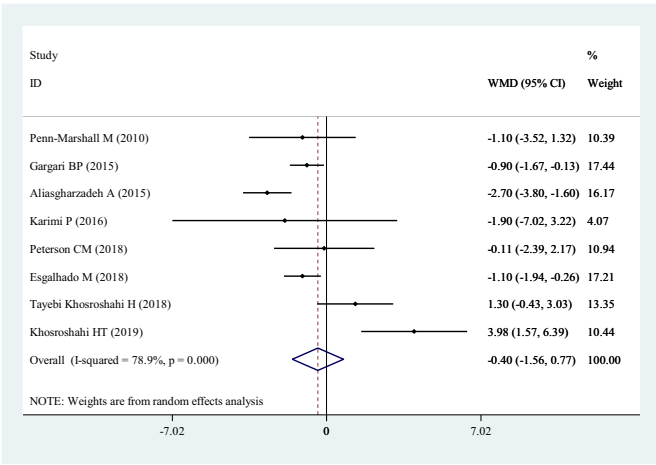
improve glycemic status most probably by different mechanisms. Effects on metabolic endotoxemia (Dewulf et al. 2013), oxidative stress (Kellow et al. 2014) and inflammation (Gargari et al. 2015), downregulation of expression of transcription factors that are involved in fatty acid oxidation and lipogenesis (Aziz et al. 2009), reduction of free fatty acids levels in blood (Higgins et al. 2004), slowdown of emptying the stomach content, reduction of glucose



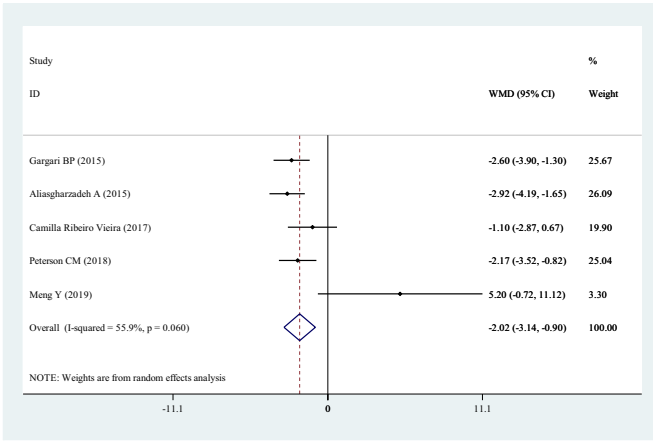
G: LDL-cholesterol



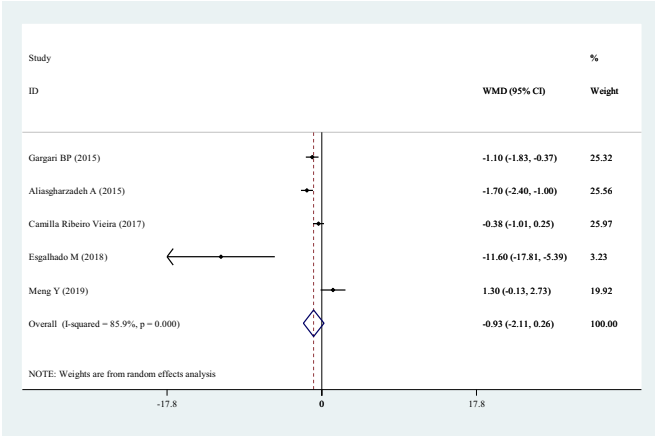
H: HDL-cholesterol



I: CRP



J: TNF-α



K: IL-6

Figure 2. Continued

absorption, increasing of glucagon-like peptide-1 production (Panwar et al. 2013; Roberfroid et al. 2010) – all these may improve glycemic control.

RS and serum lipoproteins

Prevalence of CVD is high in atherogenic dyslipidemia which is characterized by elevated triglycerides, VLDL-cholesterol and moderately elevated LDL-cholesterol levels as well as decreased HDL-cholesterol levels (Aguiar et al. 2015; Chapman et al. 2011; Fruchart et al. 2008). Metabolic endotoxemia as result of changing of gut microflora composition can be involved in the incidence of atherosclerosis and CVD (Creely et al. 2007) primarily due to increased total cholesterol and decreased HDL-cholesterol levels (Pussinen et al. 2007). Prebiotics might influence CVD by

Table 3. Subgroup analyses for the effects of resistance starch on metabolic profiles

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	Between-study I^2 (%)
FPG	Participants' age	<50 year	5	1.43	−1.53, 4.39	87.6	<0.01
		≥50 year	9	−3.00	−3.61, -2.38	76.4	
	Study design	Parallel	10	−6.02	−7.98, -4.06	71.2	<0.01
		Cross-over	4	−2.48	−3.11, -1.85	90.6	
	Participants' disease	At risk of chronic diseases	6	−0.52	−2.07, 1.03	80.8	<0.01
		Chronic diseases	7	−3.21	−3.86, -2.56	84.4	
		Renal diseases	1	−14.40	−33.40, 4.60	–	
	Country	Eastern	7	−11.21	−14.39, -8.02	46.1	<0.001
		Western	7	−2.50	−3.12, -1.89	83.2	
	Source of resistance starch	Maize	8	−0.23	−1.76, 1.29	79.2	<0.001
		Other sources	6	−3.29	−3.95, -2.64	82.0	
	Study duration	<8 weeks	5	−2.68	−3.33, -2.04	87.8	0.24
		≥8 weeks	9	−3.77	−5.49, -2.04	80.2	
	Study sample size	<50	5	−0.60	−2.14, 0.94	86.5	<0.01
		≥50	9	−3.21	−3.87, -2.56	77.5	
Insulin	Participants' age	<50 year	4	−2.97	−3.88, -2.07	35.0	<0.001
		≥50 year	8	−1.13	−1.63, -0.62	86.9	
	Study design	Parallel	8	−1.10	−1.61, -0.59	83.1	<0.001
		Cross-over	4	−2.97	−3.86, -2.09	81.1	
	Participants' disease	At risk of chronic diseases	6	−2.18	−2.95, -1.42	70.9	0.05
		Chronic diseases	6	−1.26	−1.80, -0.72	91.3	
	Country	Eastern	5	−1.05	−1.60, -0.51	89.4	<0.01
		Western	7	−2.53	−3.28, -1.79	73.7	
	Source of resistance starch	Maize	7	−2.65	−3.45, -1.85	70.4	<0.01
		Other sources	5	−1.10	−1.62, -0.57	90.0	
	Study duration	<8 weeks	5	−1.82	−2.61, -1.04	52.1	0.43
		≥8 weeks	7	−1.45	−1.98, -0.91	90.2	
	Study sample size	<50	5	−3.70	−4.85, -2.54	74.6	<0.001
		≥50	7	−1.20	−1.68, -0.73	84.7	
HOMA-IR	Participants' age	<50 year	3	−1.24	−1.75, -0.73	71.2	<0.001
		≥50 year	7	−0.21	−0.43, -0.01	75.0	
	Study design	Parallel	6	−0.49	−0.70, -0.27	77.1	0.01
		Cross-over	4	0.18	−0.28, 0.64	81.0	
	Participants' disease	At risk of chronic diseases	5	−0.16	−0.44, 0.12	39.2	0.03
		Chronic diseases	5	−0.57	−0.85, -0.30	88.0	
	Country	Eastern	4	−0.60	−0.84, -0.36	81.1	<0.01
		Western	6	0.13	−0.22, 0.48	69.9	
	Source of resistance starch	Maize	5	−0.32	−0.62, -0.02	46.6	0.69
		Other sources	5	−0.40	−0.66, -0.14	89.0	
	Study duration	<8 weeks	4	0.03	−0.26, 0.32	74.9	<0.001
		≥8 weeks	6	−0.70	−0.97, -0.44	73.5	
	Study sample size	<50	4	−0.40	−0.98, 0.19	50.3	0.91
		≥50	6	−0.36	−0.57, -0.15	86.9	
HbA1C	Participants' age	<50 year	3	−1.46	−1.77, -1.15	91.9	<0.001
		≥50 year	5	−0.26	−0.33, -0.18	44.9	
	Country	Eastern	5	−0.53	−0.64, -0.41	93.9	<0.001
		Western	3	−0.19	−0.28, -0.09	00.0	
	Source of resistance starch	Maize	3	−0.21	−0.31, -0.11	00.0	<0.01
		Other sources	5	−0.46	−0.57, -0.35	94.6	
TG	Participants' age	<50 year	2	−34.08	−54.22, -19.93	3.8	<0.001
		≥50 year	11	28.06	22.24, 33.87	92.4	
	Study design	Parallel	9	−4.06	−11.86, 3.74	50.6	<0.001
		Cross-over	4	52.10	44.09, 60.11	94.4	
	Participants' disease	At risk of chronic diseases	6	−8.07	−23.81, 7.66	00.0	<0.001
		Chronic diseases	4	36.76	29.79, 43.73	97.5	
		Renal diseases	3	2.94	−8.67, 14.56	51.3	
	Country	Eastern	6	−4.76	−13.27, 3.76	67.1	<0.001
		Western	7	44.50	37.09, 51.91	92.4	
	Source of resistance starch	Maize	6	−4.67	−14.62, 5.29	65.2	<0.001
		Other sources	7	36.13	29.38, 42.88	94.5	
	Study duration	<8 weeks	5	51.39	43.44, 59.35	92.9	<0.001
		≥8 weeks	8	−4.11	−11.96, 3.74	56.8	
	Study sample size	<50	7	3.43	−7.62, 14.49	7.9	<0.001
		≥50	6	30.09	23.61, 36.56	96.5	
TC	Participants' age	<50 year	2	−34.50	−44.27, -24.74	90.6	<0.001
		≥50 year	11	−0.26	−1.25, 0.74	90.7	
	Study design	Parallel	9	−5.86	−8.96, -2.75	93.8	<0.01
		Cross-over	4	−0.02	−1.06, 1.03	86.6	
	Participants' disease	At risk of chronic diseases	6	−11.29	−15.00, -7.58	94.0	<0.001
		Chronic diseases	4	−0.13	−1.17, 0.91	77.5	
		Renal diseases	3	14.55	7.79, 21.31	87.5	

(*continued*)

Table 3. Continued.

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	Between-study I^2 (%)
	Country	Eastern	6	−3.50	−7.35, 0.35	94.6	0.12
		Western	7	−0.41	−1.43, 0.62	91.3	
	Source of resistance starch	Maize	6	−3.09	−7.75, 1.56	94.6	0.28
		Other sources	7	−0.49	−1.51, 0.52	91.5	
	Study duration	<8 weeks	5	−0.32	−1.36, 0.72	94.7	0.07
		≥8 weeks	8	−3.34	−6.53, -0.14	91.9	
	Study sample size	<50	7	−7.00	−10.55, -3.46	95.5	<0.001
		≥50	6	−0.07	−1.10, 0.96	69.6	
LDL-C	Participants' age	<50 year	2	−25.04	−37.19, -12.90	00.0	<0.01
		≥50 year	8	−6.50	−8.97, -4.04	96.0	
	Study design	Parallel	7	−8.05	−10.79, -5.32	76.3	0.21
		Cross-over	3	−4.34	−9.48, 0.80	00.0	
	Participants' disease	At risk of chronic diseases	6	−6.40	−10.05, -2.75	80.8	0.79
		Chronic diseases	3	−8.05	−11.42, -4.65	1.4	
		Renal diseases	1	−6.19	−17.02, 4.64	–	
	Country	Eastern	4	−8.95	−12.37, -5.53	63.6	0.16
		Western	6	−5.53	−8.94, -2.13	72.8	
	Source of resistance starch	Maize	4	−12.04	−17.96, -6.12	56.6	0.08
		Other sources	6	−6.28	−8.92, -3.63	73.1	
	Study duration	<8 weeks	4	−6.40	−11.34, -1.46	69.1	0.70
		≥8 weeks	6	−7.50	−10.26, -4.73	73.3	
	Study sample size	<50	5	−9.66	−13.79, -5.52	73.9	0.15
		≥50	5	−5.98	−8.95, -3.00	64.4	
HDL-C	Participants' age	<50 year	2	2.68	0.56, 4.81	91.4	<0.001
		≥50 year	11	−1.93	−2.08, -1.78	80.8	
	Study design	Parallel	9	0.19	−0.58, 0.96	84.1	<0.001
		Cross-over	4	−1.99	−2.14, -1.84	00.0	
	Participants' disease	At risk of chronic diseases	6	−1.45	−2.68, -0.21	70.9	0.01
		Chronic diseases	4	−1.93	−2.08, -1.78	93.6	
		Renal diseases	3	0.92	−1.09, 2.92	79.2	
	Country	Eastern	6	0.86	0.00, 1.71	79.9	<0.001
		Western	7	−2.00	−2.15, -1.85	60.4	
	Source of resistance starch	Maize	6	1.44	0.23, 2.65	73.8	<0.001
		Other sources	7	−1.96	−2.11, -1.81	81.7	
	Study duration	<8 weeks	5	−1.98	−2.14, -1.83	12.8	<0.001
		≥8 weeks	8	0.18	−0.62, 0.99	86.1	
	Study sample size	<50	7	−0.76	−1.91, 0.38	78.2	0.04
		≥50	6	−1.93	−2.08, -1.78	90.1	
CRP	Participants' age	<50 year	4	−1.48	−2.09, -0.85	57.2	<0.01
		≥50 year	4	−0.22	−0.90, 0.47	84.1	
	Participants' disease	At risk of chronic diseases	2	−0.58	−2.24, 1.09	00.0	0.03
		Chronic diseases	3	−1.50	−2.13, -0.88	71.0	
		Renal diseases	3	−0.23	−0.95, 0.49	89.4	
	Country	Eastern	5	−0.88	−1.46, -0.31	87.7	0.82
		Western	3	−0.99	−1.74, -0.24	0.0	
	Study duration	<8 weeks	2	−1.10	−1.89, -0.31	0.0	0.59
		≥8 weeks	6	−0.84	−1.39, -0.28	84.8	
	Study sample size	<50	4	−0.30	−0.99,0.39	84.5	0.01
		≥50	4	−1.41	−2.01, -0.80	63.6	
TNF-α	Participants' age	<50 year	3	−2.42	−3.22, -1.61	28.8	0.44
		≥50 year	2	−1.81	−3.12, -0.49	82.3	
	Country	Eastern	3	−2.58	−3.48, -1.68	71.0	0.26
		Western	2	−1.78	−2.85, -0.70	0.0	
	Source of resistance starch	Maize	2	−2.39	−3.31, -1.46	0.0	0.65
		Other sources	3	−2.08	−3.10, -1.06	76.9	
IL-6	Participants' age	<50 year	3	−1.01	−1.41, -0.62	73.7	0.02
		≥50 year	2	0.65	−0.74, 2.04	93.7	
	Country	Eastern	3	−1.11	−1.59, -0.64	85.4	0.12
		Western	2	−0.50	−1.13, 0.13	91.9	
	Source of resistance starch	Maize	2	−1.24	−1.97, -0.52	90.8	0.26
		Other sources	3	−0.75	−1.20, -0.31	87.7	
	Study duration	<8 weeks	2	−0.50	−1.13, 0.13	91.9	0.12
		≥8 weeks	3	−1.11	−1.59, -0.64	85.4	
	Study sample size	<50	2	−0.50	−1.13, 0.13	91.9	0.12
		≥50	3	−1.11	−1.59, -0.64	85.4	

CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; FPG: Fasting plasma glucose; HOMA-IR: Homeostatic model assessment for insulin resistance; HbA1C: Hemoglobin A1c; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol

improving the gut microflora. Potential lipid-lowering effects of prebiotics can be caused by mechanisms such as enhanced excretion of cholesterol by feces as a result of reduced cholesterol absorption (Yoo and Kim 2016), modulation of metabolism of bile acids (Roberfroid et al. 2010), and increased production of SCFA via selective fermentation

in colon (Kim and Shin 1998). The effect of prebiotics in improving lipoproteins is controversial. Gargari et al. (2015) showed that intake of 10 g/day of RS2 for 8 weeks decreased triglycerides and increased HDL-cholesterol in patients with T2DM. Nichenametla et al.(Nichenametla et al. 2014) reported a decrease in total cholesterol in subjects with-MetS without it and reduced HDL-cholesterol in patients with-MetS after intake of RS4-flour for 12 weeks. In another study, 40 g/day of HAM-RS2 intake had no effect on fasting/postprandial triglycerides or total cholesterol levels for 8 weeks in patient's with-MetS (Robertson et al. 2012). Treatment with 1 bagel containing 25 g/day HAM-RS2 did not change total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides concentrations (Dainty et al. 2016). In a single-blind, randomized intervention crossover study, the effect of intake of 40 g/day of HAM-RS2 significantly elevated triglycerides levels, with no effect on total cholesterol levels after12 weeks in patients with (Bodinham et al. 2014). These conflicting results can be due to different prebiotic types, various dosages, different duration of intervention, and clinical characteristics of participants. The only meta-analysis which analyzed some of the parameters which we did was the one most recently published by Wang et al. (Dainty et al. 2016). They showed that RS supplementation can reduce LDL-cholesterol besides improving FPG, fasting insulin, insulin resistance and sensitivity, especially in patients with diabetes who were overweight or obese. Another meta-analysis published a year earlier showed that RS supplementation decreases total cholesterol levels but also LDL-cholesterol and that a higher dose (>20 g/day) RS can also decrease triglycerides levels (Yuan et al. 2018). These results are slightly different from ours but the authors of these papers have stated that their result should be carefully taken into account.

RS and inflammation

Chronic inflammation is characterized by abnormal production of inflammatory mediators and their concentrations in blood, including TNF-α, IL-6 and CRP. Clinical evidence shows that inflammation has a substantial role in the development of metabolic disorders such as MetS, T1DM and T2DM and complications of these diseases. The dysbiosis causes stimulation of inflammatory responses in the gut. Inflammation causes damage to intestinal epithelium barrier integrity by disruption of cell-to-cell junctions and increases its permeability. Increased permeability induces penetration of bacteria and toxins in the bloodstream, known as endotoxemia (Shen, Obin, and Zhao 2013) and the risk of sepsis. Bacterial toxins such as lipopolysaccharides (LPS) which are a component of gram negative bacteria, are the main factors that cause and sustain the low-grade chronic systemic inflammation. Bacterial LPS released into bloodstream can be detected by LPS-binding protein. LPS trigger releasing of inflammatory cytokines and chemokines from various circulatory host cells such as macrophages (Cohen 2002). Reduction of some anaerobic bacteria such as Bifidobacteria and *Aecalibacterium prausnitzii* can result in an increase of bacterial LPS in the blood. These anaerobic bacteria prevent penetration of other bacteria and their metabolites into the blood by modulating the endothelial barrier permeability (Cani and Delzenne 2009). Possible benefits of IR as prebiotic might be achieved by attenuating chronic systemic inflammation by shifting gut flora towards protective bacteria such as Bifidobacteria (Looijer–Van Langen and Dieleman 2008). RS can suppress colon inflammation by increasing generation of SCFA, mainly butyrate. Probable mechanism of anti-inflammatory effects of butyrate can be due to inhibition of nuclear factor kappa B (NF-κB) activation as well as down-regulating the generation of pro-inflammatory cytokines (Segain et al. 2000; Tedelind et al. 2007). Bodinham et al. (2014) showed a reduction in TNF-α levels but no effects on IL-6 with intake of 40 g/day of RS2 in patients with T2DM after 12 weeks. Also, the intake of barley-kernel bread (31% of bread) also decreased IL-6 levels in healthy individuals (Nilsson et al. 2010).

The current meta-analysis is among rare studies that have summarize findings from earlier studies on the effects of RS supplementation on metabolic panel and inflammation. Visual inspection of funnel plots and resulted in no evidence of publication bias among included studies. However, some limitations of this meta-analysis should be considered when interpreting the conclusions. Participants of these studies had different metabolic conditions from MetS to its related disorders, including T1DM, T2DM, diabetic nephropathy, obesity, arterial hypertension and dyslipidemia. Although these conditions are greatly similar in pathogenesis and symptoms, some differences between them should not be ignored. In addition, differences in sources of RS as well as various amounts of intake and duration of intervention are also other concenrns which could partially explain our heterogenous findings.

Conclusions

This meta-analysis demonstrated the beneficial effects of RS on FPG, insulin, HbA1c, total cholesterol, LDL-cholesterol and TNF-α levels in patients with MetS and related disorders. However, RS did not show any significant effect on HOMA-IR, triglycerides, HDL-cholesterol, CRP and IL-6 levels. Therefore, adherence to RS-rich dietary patterns will help to control metabolic complications among patients who suffering from chronic diseases. This might be done by reduction of serum lipids and glucose concentrations as well as modulation of low-grade inflammation through inhibition of some pro-inflammatory pathways.

Author contributions

ZA contributed in conception, design, statistical analysis and drafting of the manuscript. JH, AM, ZR, EA, FK, MB, HM and SMM contributed in data collection and manuscript drafting. All authors approved the final version for submission. ZA supervised the study.

Ethics approval and consent to participate

This study was considered exempt by the KAUMS Institutional Review Board.

Competing interests

The authors declare no conflict of interest.

Funding

The present study was founded by a grant from the Vice Chancellor for Research, Kashan University of Medical Sciences, in Iran.

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