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Angaben zur Veröffentlichung / Publication details:

Steckhan, Nico, Christoph-Daniel Hohmann, Christian Kessler, Gustav Dobos, Andreas Michalsen, and Holger Cramer. 2016. "Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: a systematic review and meta-analysis." *Nutrition* 32 (3): 338–48. https://doi.org/10.1016/j.nut.2015.09.010.

Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: A systematic review and meta-analysis

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Introduction

Metabolic syndrome (MetS) is a major health issue of Western and westernized modern societies [1]. Here, lifestyle is often characterized by stress, fast food, and little exercise. The World Health Organization states obesity and overweight as the fifth leading risk for global deaths [2]. MetS is defined by the simultaneous occurrence of at least three of the following criteria: central obesity, elevated blood pressure, elevated plasma glucose, and dyslipidemia [3]. Obesity is common among patients suffering from MetS, which is associated with serious comorbidities [3]; obesity is a critical risk factor for cardiovascular diseases, diabetes mellitus 2, and arterial diseases [4].

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These symptoms of MetS interact with and exacerbate each other.

The primary mediators of Mets may be excess accumulation of abdominal fats and mature adipocytes [5]. Insulin resistance correlates with a state of chronical subclinical inflammation and endothelial dysfunction. Furthermore, MetS is thought to be a low-grade inflammatory disease [5].

Adipose tissue itself can be seen as an endocrine organ that plays a critical role in the immune homeostasis. It produces and releases a variety of adipokines and cytokines, including leptin, adiponectin, resistin, and visfatin, as well as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and others [6,7]. Proinflammatory molecules produced by adipose tissue have been implicated as active participants in the development of metabolic disease [5]. Furthermore, adipose tissue macrophages are a prominent source of proinflammatory cytokines, which can block insulin action in adipose tissue, skeletal muscle, and liver autocrine/paracrine signaling and cause systemic insulin resistance via endocrine signaling, providing a potential link between inflammation and insulin resistance [6]. Dietary approaches are thought to positively influence the immune responses by decreasing its predominant proinflammatory milieu [8].

Several trials and reviews have documented the potential benefits of different dietary approaches on immune functions [5, 8–11]. However, just a few studies about different dietary approaches for patients with MetS were conducted.

A primary goal of low-carbohydrate diets is weight loss. Weight loss leads to reductions in inflammatory biomarkers in overweight men [12]. Experimental studies have provided evidence that, independent from weight gain, high intake levels of refined or simple carbohydrates are associated with proinflammatory effects [13].

Low-fat diets may simultaneously change macronutrient intake and quality that can increase intake of natural anti-inflammatory foods, such as fruits and vegetables, which may ultimately lower C-reactive protein (CRP) [14]. Another proposed mechanism involves low-fat foods limiting postprandial glucose response, thereby inhibiting cytokine release into the bloodstream [15] and subsequent CRP release from the endothelium [16].

Refined grains are able to induce short-term acute hyperglycemia and thus trigger proinflammatory cytokines. Switching to a diet rich in whole grains may decrease circulating levels of free radicals and proinflammatory cytokines, such as IL-6, IL-18, and TNF-α [8]. Intervention studies found a decrease in markers of inflammation in subjects with MetS who consume Mediterranean diets and/or adhere to national dietary guidelines [9]. By contrast, diets high in refined starches, sugars, and saturated and trans-fatty acids and poor in natural antioxidants and fiber from fruits, vegetables, and whole grains may cause an activation of the innate immune system. This is most likely caused by the excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines. Thus, it seems likely that dietary adjustments have the potential to mediate a major effect on different components of MetS.

This systematic review was conducted to assess whether dietary interventions can positively modulate the immune system in MetS and help to improve favorable conditions, thus reducing the severity of the metabolic disorders in MetS.

Methods

This review was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [17] and the recommendations of the Cochrane Collaboration [18].

Eligibility criteria

To be eligible, studies had to meet the following conditions:

1. Types of studies. Only randomized controlled trials (RCTs) and randomized crossover studies were eligible. Crossover studies were only eligible if data of the first active treatment phase were available. Studies were eligible only if they were published as full-text articles in peer-reviewed scientific journals. No language restrictions were applied.
2. Types of participants. Studies of adult (older than 18 y) patients with MetS were eligible. There are slightly different definitions of MetS, because 41.3% of the patients were Caucasians. In general, MetS was defined as the presence of at least three of five risk factors defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [19] and WHO-Asia Pacific (WHO Expert Consultation, 2004): increased waist circumference (>90 cm in men and >80 cm in women), hypertriglyceridemia (>150 mg/dL [1.7 mmol/L]), low levels of high-density lipoprotein cholesterol (HDL-C; <40 mg/dL [1 mmol/L] in men and <50 mg/dL [1.3 mmol/L] in women), elevated blood pressure (≥130/85 mm Hg or use of antihypertensive medication), and elevated fasting plasma glucose (≥110 mg/dL [6.105 mmol/L] or treatment for diabetes mellitus).
3. Types of interventions. Studies that compared interventions with main focus on diets with conventional diets or no treatment were eligible. Studies were excluded if they intervened only with supplements (multivitamins) such as certain nutritional or phytopharmacological drugs, such as n-3 fatty acids or antidiabetics. If studies supplemented beside a dietary regime, those studies were also eligible. Articles dealing only with postprandial effects of a dietary or meal intervention were excluded. No further restrictions were made regarding dietary approaches or length of the intervention. Multimodal interventions of diet combined with exercise and behavior training or other lifestyle interventions were also eligible.
4. Types of outcome measures. Studies were eligible if they assessed at least one immunologic and atherosclerotic outcome. Outcomes of interest were important immunologic factors such as CRP, IL-6, TNF-α, nuclear factor kappa B, interferon-gamma, and intercellular adhesion molecule 1, to name a few. (For more details, see search strategy, Supplementary File 1.) Secondary outcomes were body weight, blood pressure, HDL, low-density lipoprotein, triacylglycerols, insulin, glucose, and glycated hemoglobin.

Search strategy and study selection

Three electronic databases were searched: Medline/PubMed, Scopus, and the Cochrane Library. Searches were undertaken in September 2014. All articles published until September 2014 were considered for this review. References of included studies and key review and guideline reports were checked for additional studies.

The literature search was constructed around the search terms “diet” and “metabolic syndrome” with main focus on inflammatory markers. Search strategy was adapted for each database as necessary. The complete search strategy for PubMed can be found in Supplementary File 1.

Additionally, reference lists of identified original articles and reviews were searched manually. Abstracts of identified records were screened and the full articles of potentially eligible studies were retrieved.

Data extraction and management

C.-D.H. and N.S. independently extracted data on characteristics of the studies (e.g., trial design, randomization, and blinding), characteristics of the patient population (e.g., sample size, age, and diagnosis), characteristics of the intervention and control condition (e.g., type, program length, frequency, and duration), dropout rates, outcome measures, follow-ups, results, and safety. Discrepancies were rechecked with a third reviewer and consensus was achieved by discussion. Table 1 is organized by date.

Risk of bias in individual studies

Risk of bias was assessed by two authors independently using the Cochrane risk of bias tool. This tool assesses risk of bias on the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias [18]. Trial authors were contacted for further details if necessary. Studies with high risk of attrition bias were not excluded from meta-analyses.

Table 1
Characteristics of randomized controlled trials included for the systematic review investigating the effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome

Reference (origin of study)	Patients (n, diagnosis, comorbidities, mean age, female %, Caucasians %)	Co-interventions, medication	Treatment group (diet type, other interventions)	Control group (intervention)	Compliance	Longest follow-up	Outcome measures (inflammatory markers, other outcome)
Giacco et al. [25] (Finland, Italy)	n = 146, ATP III, 44.5% females		Whole-grain cereal foods 48% carbohydrate, 31% fat, 18.7% protein energy distribution ≈7950 kJ/d	Refined cereal foods 49% carbohydrate, 30.8% fat, 17.8% protein energy distribution ≈8222 kJ/d	16% T: 13% dropout C: 19% dropout	3 mo	hsCRP, IL-6, IL-1 ra, TNF-alpha
Rajaie et al. [59] (Iran)	n = 39, 42 y, 100% females		Low fat 58% carbohydrate, 28% fat, 14% protein energy distribution 7280 kJ/d	High fat 46% carbohydrate, 40% fat, 14% protein energy distribution 7238 kJ/d	23% T: 26% dropout C: 20% dropout	6 wk	E-selectin, hsCRP, hsTNF-alpha, IL-6, sICAM-1, sVCAM-1
Uusitupa et al. [31] (Finland)	n = 213, 55 y, 67% females		Nordic diet	Conventional diet	16% T: 4% dropout C: 27% dropout	6 mo	hsCRP, IL-6, IL-1
Heggen et al. [26] (Norway)	n = 181, 49 y, 58% females		Low fat 55% to 60% carbohydrate, <30% fat, 15% protein energy distribution −2000 kJ/d	Low glycemic 30% to 35% carbohydrate, 35% to 40% fat, 25% to 30% protein energy distribution −2000 kJ/d	10%	3 mo	TNF-alpha, IL-6, PAI-1, MCP-1, adiponectin
Camhi et al. [23] (United States), DEER study	n = 377, grade 3 NCEP ATP III, 33% females, 86% Caucasians	Exercise	Low fat diet, diet + physical activity, physical acivity	Usual lifestyle	27%	1 y	hsCRP
Oh et al. [28] (Korea)	n = 29, grade 3 NCEP ATP III, 66.5 y, 100% females	Exercise, education, pharmacotherapy	Therapeutic lifestyle modification, exercise, education, pharmacotherapy	Educational book, usual behavior	38.5% dropout in control group	4 wk	MCP-1, RBP-4
Petersson et al. [29], LIPGENE study	n = 486, 55 y, 58% females		Low fat 49.1% carbohydrate, 29.2% fat, 25% protein energy distribution 8.1 MJ	High fat 41.9% carbohydrate, 39.8% fat, 16% protein energy distribution 8.5 MJ	14%	3 mo	CRP
Brinkworth et al. [22] (Australia)	n = 118, obesity + one additional risk factor, 51 y, 43% females		Low-carb diet 8.9% carbohydrate, 54.9% fat, 32.3% protein energy distribution ≈6882 kJ/d	Low-fat diet 46.4% carbohydrate, 26.4% fat, 21.8% protein energy distribution ≈6800 kJ/d	41% T: 20% dropout C: 21% dropout	1 y	CRP, IL-6, TNF-alpha, PAI-1
Al-Sarraj et al. [21] (United Arab Emirates)	n = 39, grade 3 NCEP ATP III, 64% females, 18 to 50 y		Low-carb diet, 20% to 25% carbohydrate, 50% to 55% fat, 25% to 30% protein energy distribution ≈10 740 kJ/d	6 wk CRD + 6 wk AHA low-fat diet 55% carbohydrate, 25% to 30% fat, 15% to 20% protein ≈10 075 kJ/d	28%	3 mo CRD	CRP, TNF-alpha, IL-6, ICAM-1, MCP-1
Katcher et al. [27] (United States)	n = 50, 50 y, 50% females, 96% Caucasians		Whole-grain-enriched diet 54.6% carbohydrate, 27.8% fat, 19.1% protein energy distribution ≈6740 kJ/d	Avoid grain 49.9% carbohydrate, 30.5% fat, 20% protein energy distribution ≈6590 kJ/d	6%	3 mo	CRP, PAI-1, IL-6, TNF-alpha
Villareal et al. [32] (United States)	n = 27, 69 y, 9% females, 11% Caucasians	Exercise, multivitamin supplement, education/ behavioral therapy	Hypocalorie diet 50% carbohydrate, <30% fat, 20% protein energy distribution −3138 kJ/d	No therapy, maintain usual diet	11% T: 11% dropout C: 10% dropout	6 mo	CRP, IL-6
Esposito et al. [24] (Italy)	n = 180, grade 3 NCEP ATP III, 44 y, 27.7% females		Mediterranean diet 58% carbohydrate, 28% fat, 14% protein energy distribution ≈8640 kJ/d	Prudent diet 57% carbohydrate, 30% fat, 13.5% protein energy distribution ≈9139 kJ/d	9% 9% in each group	2 y	hsCRP, IL-6, IL-7, IL-18
Seshadri et al. [30] (United States)	n = 132, 52 y, 17 % females, 38% Caucasians		Low = carb diet 32% carbohydrate, 43% fat, 18% protein energy distribution 5924 kJ/d	Conventional diet 50% carbohydrate, 33% fat, 18% protein energy distribution 6615 kJ/d	41% T: 8% dropout C: 24% dropout	6 mo	hsCRP

AHA, American Heart Association; C, control; CRD, carbohydrate-restricted diet; *hsCRP*, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; PAI-1, plasminogen activator inhibitor 1; RBP-4, retinol binding protein 4; T, treatment; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion protein 1

Statistical analysis

A meta-analysis was performed for each dietary intervention with Revman 5 software (Cochrane Information Management System) if sufficient data were available for more than one trial. The random-effect inverse-variance model was used. Standardized mean differences (SMDs) of continuous outcomes and 95% confidence intervals (95% CIs) were calculated. Outcomes were extracted by comparing the longest follow-up mean change from baseline and the standard deviation of this change between intervention and control diets. If no mean change was reported, postintervention absolute values were used.

If no standard deviations were reported, they were calculated from standard errors or confidence intervals [18]. If none of these strategies was successful, standard deviations were imputed from other RCTs with comparable characteristics. If no means were reported, attempts were made to obtain the missing data from the trial authors by e-mail.

Assessment of heterogeneity

Statistical heterogeneity between studies was analyzed using the I^2 statistics, a measure of how much variance between studies can be attributed to differences between studies rather than chance. The magnitude of heterogeneity was categorized [12] as follows:

1. I^2 = 0% to 24%: low heterogeneity
2. I^2 = 25% to 49%: moderate heterogeneity
3. I^2 = 50% to 74%: substantial heterogeneity
4. I^2 = 75% to 100%: considerable heterogeneity

The $\div^2$ test was used to assess whether differences in results are compatible with chance alone. Given the low power of this test when only few studies or studies with low sample size are included in a meta-analysis, a $P \leq 0.10$ was regarded to indicate statistically significant heterogeneity [12].

Sensitivity analysis

To test the robustness of significant results, sensitivity analyses were conducted for studies with high versus low risk of bias at the domains selection bias, detection bias, and attrition bias. If statistical heterogeneity was present in the respective meta-analysis, sensitivity analyses were also used to explore possible reasons for heterogeneity.

Risk of publication bias

Risk of publication bias was assessed for each meta-analysis that included at least 10 studies. Funnel plots—scatter plots of the intervention effect estimates from individual studies against the studies' standard error—were generated using Review Manager 5 software [18,20]. As the precision of effect estimates normally increases with sample size, effect estimates from studies with larger standard errors will scatter more widely than those of studies with smaller standard errors. Unpublished smaller studies with non-significant results will therefore result in asymmetrical funnel plots [18,20]. Publication bias was assessed by visual analysis with roughly symmetrical funnel plots regarded to indicate low risk and asymmetrical funnel plots regarded to indicate high risk of publication bias [18,20].

Results

Literature search

Literature search retrieved 686 records; 194 of them were duplicates. We screened 492 abstracts, and 13 full-text articles [21–32,59] with a total of 2017 patients were assessed for eligibility and all of them were eligible for qualitative analysis (Fig. 1).

We had to exclude studies by abstracts when no NCEP ATP III criteria were used or the intervention involved no dietary pattern or if none of our primary outcome (see Supplementary File 1 for search terms on immune markers) was mentioned. Twenty-seven articles [33–58] had to be excluded because of the following reasons: Thirteen studies were excluded because inclusion criteria did not match the required NCEP ATP III criteria. Brinkworth et al. [22] included obese subjects with at least one additional metabolic risk factor. Four other studies did not fit into our definition of dietary patterns (e.g., supplementation only). Two studies did not report any immunologic outcome. Eight studies were excluded because of other reasons (e.g., measurement of postprandial effects).

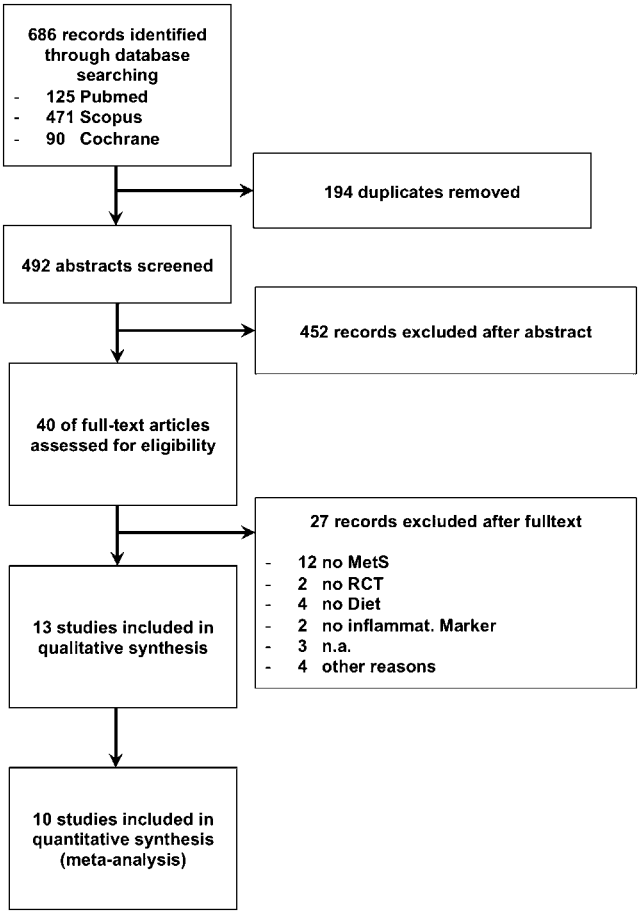

Fig. 1. Flowchart of the literature search.

We included 10 full-text articles with a total of 1585 participants in the analysis. The reference period was between 2004 and 2013.

Study characteristics

Characteristics of the study and patient population, intervention, control condition, outcome measures, follow-ups, and results are shown in Table 1.

Two studies were multicentric [25,29]. Patients were recruited from department outpatient services, universities and connected facilities, or by public advertisements.

Participants

None of the included trials reported any significant differences in sociodemographic characteristics of participants in the intervention or control treatment arm. The RCTs included a total of 2017 participants; sample size ranged from 27 to 486 with a median of 132. Participants' mean age ranged from 18 to 69 y, with a median of 52 y; four RCTs did not report mean age. Between 9% and 100% of participants were female (median 50%).

Only three RCTs reported the race of included participants; 41.3% participants were Caucasians.

Intervention characteristics

The 13 studies included in the qualitative analysis were RCTs with dietary interventions that ranged from 1 mo to 2 y, with a median of 3 mo [25–29,59]. Six studies had less than 6 mo duration.

Three studies compared a low-carbohydrate diet to a variety of control diets, including low-fat and conventional diets [21,22,30]. Four studies compared low-fat with low-carbohydrate, low-glycemic index, or high-fat diets [21,22,26,29]. Two studies compared whole-grain diets with refined-grain diets [25,27]. Three studies compared a multimodal intervention with no treatment (usual lifestyle) [23,28,32]. More details are given in Table 1. One study used a crossover design [59]. One of the multimodal studies reported comedication [28]. One study gave multivitamin supplements along with dietary advice [32]. Eight studies had isocaloric conditions. The study by Villareal et al. [32] compared a hypocaloric diet (−3138 kJ/d) with usual diet. All studies were conducted in clinical outpatient services, and all patients were examined and looked after by a physician.

Overall dropout rate was high across all studies (from 6% to 41% dropout with a median of 21.46%). Low-carbohydrate diet seems to have higher dropout rates than low-fat diets. D*iets enriched with whole grains* had the smallest dropout rate. Seven studies reported asymmetrical dropout rates.

Outcome measures

CRP was assessed in 10 RCTs (5 studies measured hsCRP), IL-6 in 7 RCTs, TNF-α in 4 RCTs, and MCP-1 in 3 RCTs. Further inflammatory markers (e.g., IL-1 R, IL-18, ICAM-1, and PAI-1) were reported only in a few RCTs and could not be analyzed. Outcomes were assessed immediately after the end of the intervention in most RCTs. Weight loss was assessed in all of the studies. Serum insulin was assessed in seven studies. Studies reported a weight reduction from 0.7 to 14 kg.

None of the studies reported safety-related complications and adverse events.

Risk of bias in individual studies

Risk of bias in individual studies is shown in Figure 2; risk of bias across all included studies is shown in Figure 3. Seven RCTs reported adequate random sequence generation [23–25,27,29,30,32] and allocation concealment [24,25], and five RCTs reported adequate blinding of outcome assessment [23–25,30,31]. No RCT reported adequate blinding of participants and personnel [24,25]. We did not exclude studies with high risk of bias. Excluding studies with high risk of bias may result in too few studies to be useful. In line with the recommendations of the Cochrane Collaboration, we have thus included all studies in the primary analysis but conducted sensitivity analyses that restricted the analysis to studies with low risk of bias.

Meta-analyses

C-reactive protein

Meta analyses revealed effects of low-fat diets compared with other diets (SMD: −0.98; 95% CI: −1.6 to −0.35; $P = 0.002$; $I^2 = 0\%$) (Fig. 4A).

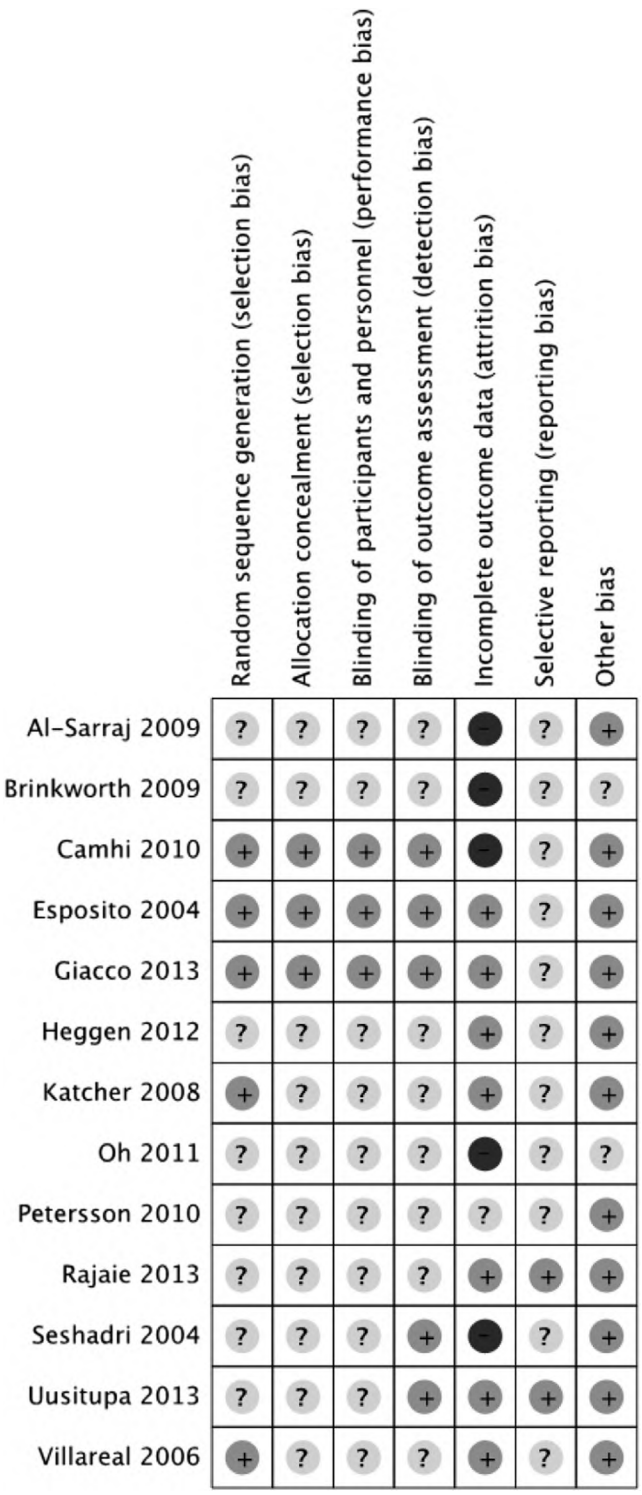

Fig. 2. Risk of bias for individual studies.

Meta analyses revealed no effects of whole grains compared with refined grains (SMD: −0.31; 95% CI: −0.81 to 0.2; $P = 0.23$; $I^2 = 57\%$) (Fig. 4A).

IL-6

Meta-analyses revealed no effects of whole grains compared with refined grains (SMD: 0.28; 95% CI: −0.32, 0.89; $P = 0.28$; $I^2 = 70\%$) (Fig. 4B).

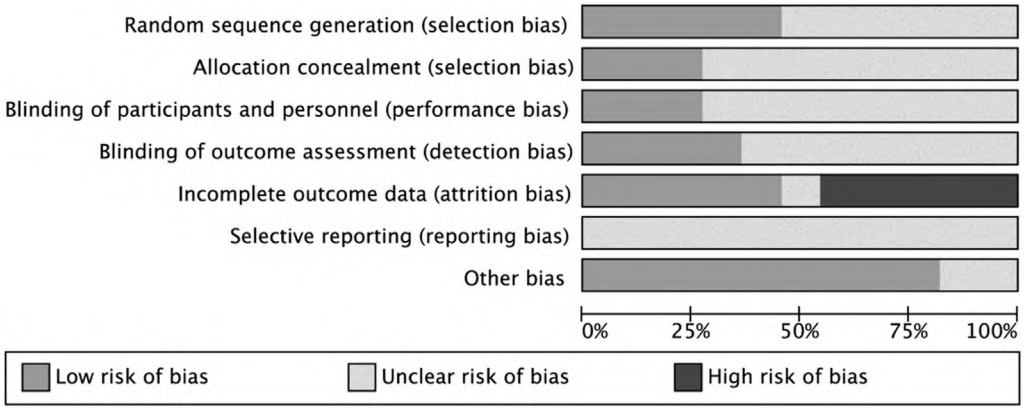

Fig. 3. Risk of bias for all included studies.

TNF-α

Meta-analyses revealed no effects of whole grains compared with refined grains (SMD: 0.01; 95% CI: −0.52 to 0.54; $P = 0.97$; $I^2 = 62\%$) (Fig. 4C).

Weight loss

Meta-analyses revealed that low-fat diets decreased weight less effectively compared with other diets (SMD: 1.08; 95% CI: −0.75 to 2.91; $P = 0.25$; $I^2 = 97\%$). Low-carbohydrate diets compared with other diets (SMD: −1.23; 95% CI: −2.08 to −0.38; $P = 0.0043$; $I^2 = 85\%$), whole-grain diets compared with refined-grain diets (SMD: 0.11; 95% CI: −0.20 to 0.42; $P = 0.49$; $I^2 = 7\%$), and multimodal interventions compared with usual lifestyle (SMD: −1.02; 95% CI: −1.97 to −0.07; $P = 0.04$; $I^2 = 56\%$) reduced weight (Fig. 5A).

Fasting insulin

Meta-analyses revealed no effects of low-fat diets compared with other diets (SMD: −0.01; 95% CI: −0.28, 0.26; $P = 0.95$; $I^2 = 0\%$), whole-grain diets compared with refined-grain diets (SMD: 0.15; 95% CI: −0.15 to 0.45; $P = 0.32$; $I^2 = 0\%$), or multimodal interventions compared with usual lifestyle (SMD: −2.25; 95% CI: −4.88 to 0.38; $P = 0.09$; $I^2 = 90\%$; Fig. 5B).

Meta-analyses did reveal effects of low-carbohydrate diets compared with other diets (SMD: −0.33; 95% CI: −0.63 to 0.03; $P = 0.03$; $I^2 = 5\%$) (Fig. 5B).

Sensitivity analyses

When only RCTs with adequate random sequence generation were considered, an effect for whole grain compared with refined grain was found for HDL (SMD: 5.37 mg/dL; 95% CI: 4.74, 6.00 mg/dL; $P < 0.01$; heterogeneity: $I^2 = 0.08\%$; $\chi^2 = 2.34$; $P = 0.23$). When excluding studies with unclear detection bias and unclear attrition bias, no meta-analysis was possible.

No effect for CRP was found when studies with significant between-group differences in weight reduction were excluded ($P = 0.70$). Also, no effect for fasting insulin was found after exclusion of studies with group difference in weight loss.

Sensitivity analysis was not possible after exclusion of studies showing between-group difference of weight reduction.

Publication bias

Funnel plot was asymmetrical for weight reduction (Fig. 6). Thus, publication bias could be expected.

Discussion

Summary of evidence

The meta-analysis of 10 RCTs provides small evidence that modifying dietary patterns can improve immunologic properties, serum insulin, and weight loss in people with MetS. Low-fat diets reduced levels of CRP significantly compared with control diets (SMD: −0.98; 95% CI: −1.6 to −0.35, $P = 0.002$). Low-fat diets restrict fat to less than 30% of daily energy intake. Because we found no between-group difference for CRP after sensitivity analyses, we assume that decrease of CRP was dependent on weight loss.

Low-carbohydrate diets were able to decrease insulin compared with other diets (SMD: −0.33; 95% CI: −0.63 to −0.03; $P = 0.03$). Again, no between-group difference for insulin was found after excluding studies with significant weight loss. Hence, insulin is dependent on weight loss. Low-carbohydrate diets were able to reduce weight (mean = −10.53 kg) compared with other diets (SMD: −1.23; 95% CI: −2.08 to −0.38; $P = 0.0043$; $I^2 = 85\%$).

Weight loss reduces plasma levels of immune factors such as CRP [60,61]. In general, weight loss has the ability to reduce several proinflammatory markers, such as CRP, IL-6, and TNF-α. None of the studies described safety-related complications.

Agreements with prior systematic reviews and studies

The results of this meta-analysis are partly in line with those of prior systematic reviews focusing on diabetes mellitus 2 and insulin sensitivity. Ajala et al. [62] concluded that low-carbohydrate, low-glycemic index (GI), Mediterranean, and high-protein diets may be effective in improving various markers of cardiovascular risk in people with diabetes. The Mediterranean diet seems to be a promising dietary pattern reducing risk factors of MetS [63], and incorporating beneficial fatty acids and phytonutrient-rich foods exerts therapeutic benefits under both weight-stable and weight-loss conditions [64].

Combining diet, exercise, and behavioral training into a multimodal intervention is of course the most effective treatment for MetS. The systematic review and meta-analysis of Yamaoka and Tango [65] reported that complex lifestyle modification interventions reduce MetS-related abnormalities. Esposito et al. [24] reported that a whole dietary pattern such as the Mediterranean dietary pattern is able to improve several disease-related outcomes in patients with MetS. Combining a

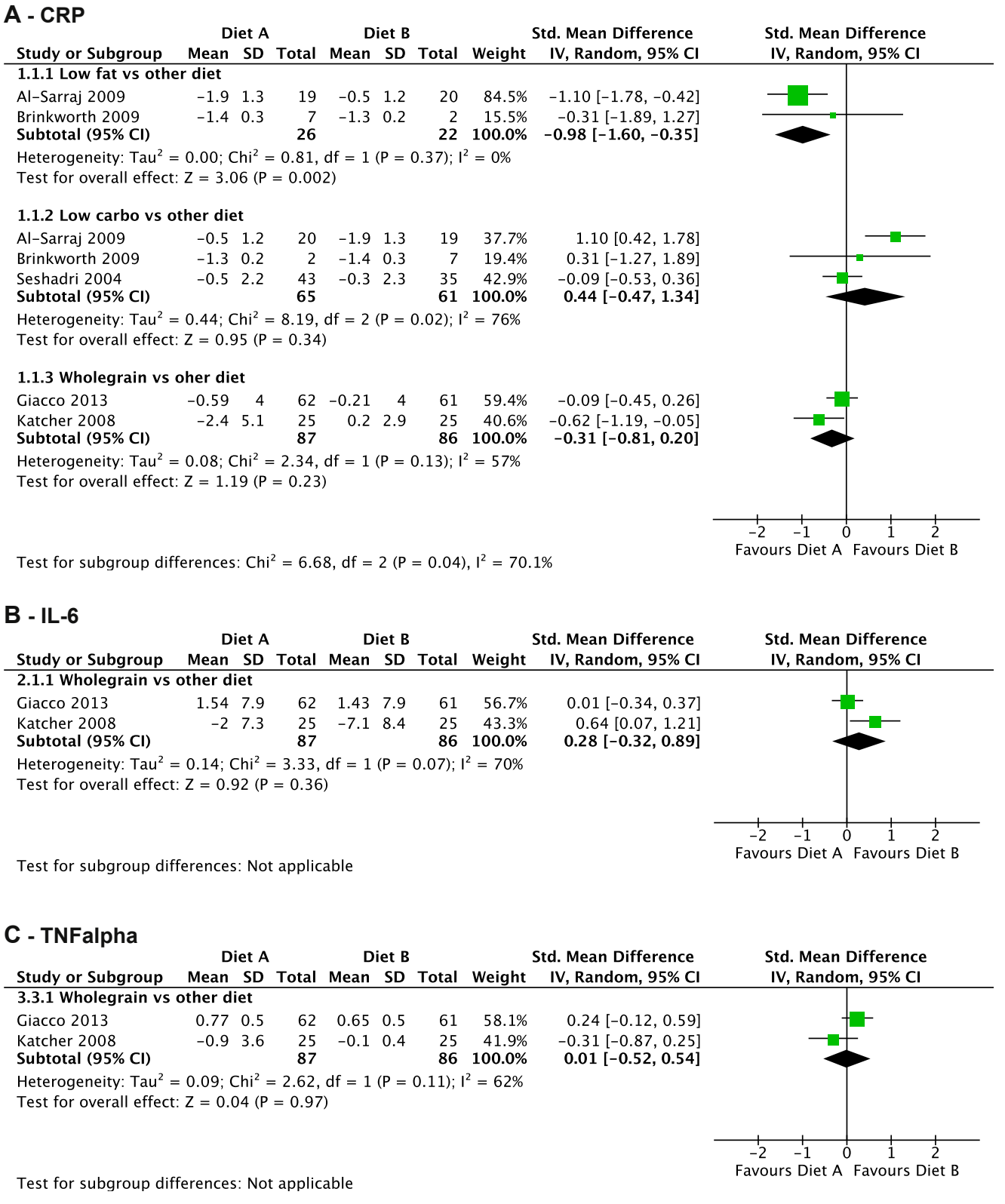

Fig. 4. Forest plots summarizing the effects of different dietary approaches on immune markers.

healthy dietary pattern with exercise in a multimodal intervention will protect patients from metabolic problems and cardiovascular events [28,32].

A number of epidemiologic studies have documented a link between various dietary patterns and markers of inflammation. In the Multi-Ethnic Study of Atherosclerosis, a healthy dietary

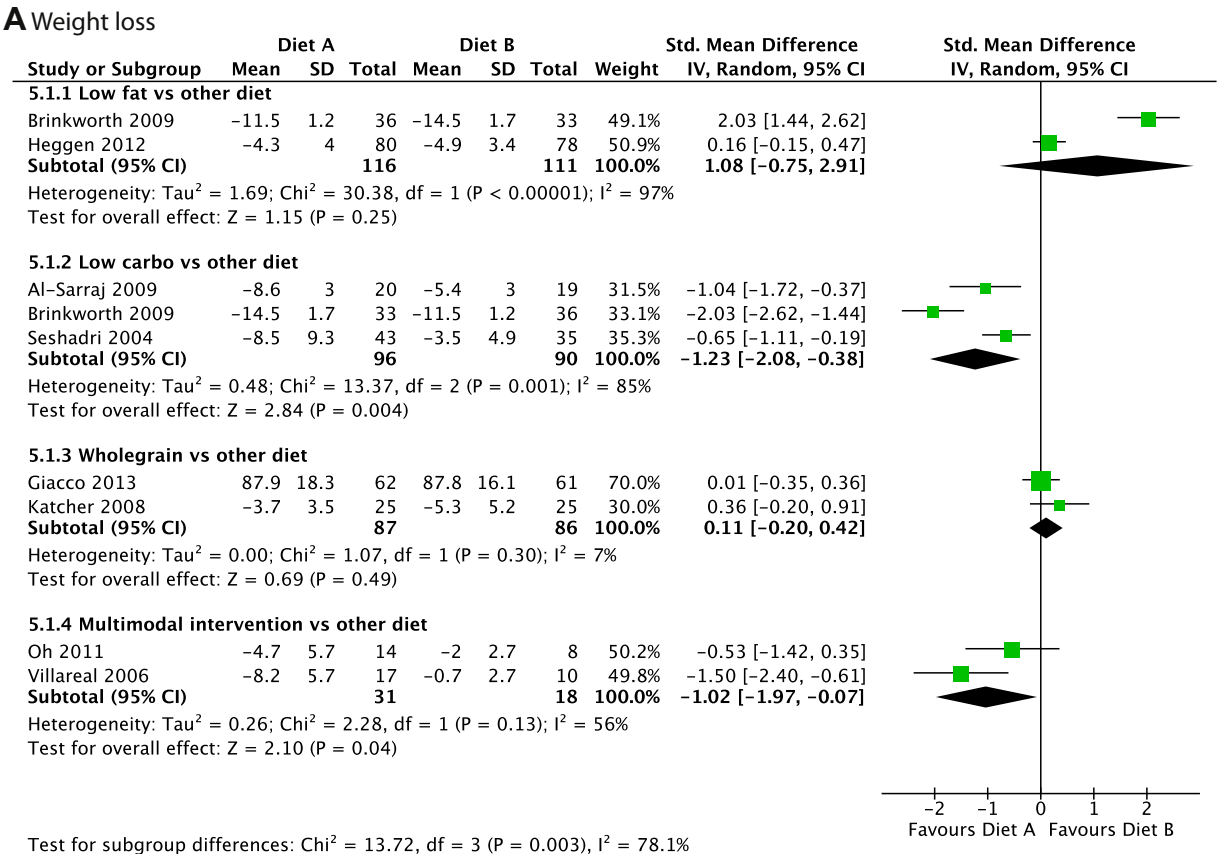

Fig. 5. Forest plots summarizing the effects of different dietary approaches on secondary outcome.

pattern was inversely associated with concentrations of CRP and IL-6 [66]. The Nurses' Health Studies (n = 35 340 and n = 89 311 in its two cycles [67]) identified a dietary pattern that was positively correlated with concentrations of IL-6, CRP, and others. The pattern represented a diet relatively high in sugar-sweetened soft drinks, refined grains, diet soft drinks,

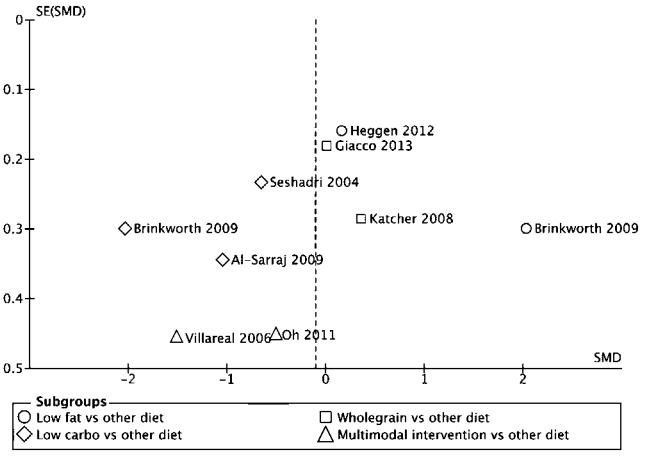

Fig. 6. Funnel plot for weight reduction.

and processed meat. We also found evidence that CRP and insulin are dependent on weight loss.

Some studies have reported that abdominal adiposity is associated with elevation of CRP levels and independent of body mass index (BMI), which is a measure of general adiposity. The proportion of people with elevated CRP was significantly higher in individuals with abdominal adiposity than in control subjects, although they had a similar BMI [68] because adipose tissue is a major source of proinflammatory cytokines such as IL-6 and TNF-α, and these two cytokines increase hepatic lipogenesis [69,70] and trigger a systemic acute-phase response [71].

Fruits and vegetables rich in polyphenols (e.g., flavonoids) have a beneficial effect, related to polyphenols' antioxidant capacity, on the human body and inflammation [72,73].

Applicability of evidence

The RCTs included people from the working population of North America, Europe, and Asia. The participants of the included RCTs seem to satisfactorily represent the population with high incidence of MetS. Patients were recruited from inpatient and outpatient health services from North America, Europe, and Asia. The sex ratio in the included RCTs was not always balanced.

Quality of evidence

In most of the included studies, risk of selection bias was low or unclear. Although blinding of participants or providers might not be possible in RCTs on dietary interventions, adequate blinding of outcome to assessors should be intended.

Only a third of the RCTs included in this meta-analysis did report adequate blinding of outcome assessment. Five studies had high risk for attrition bias because of high dropout rates. Therefore, it is known that studies with patients suffering from MetS have unusually high dropout rates.

Limitations

There are significant difficulties in a meta-analysis of such varied interventions. A major limitation is the limited number of studies included. Only a few studies could be included in our meta-analyses. The comparably high heterogeneity and the small number of studies per outcome make it difficult to generalize results. Only two RCTs directly compared whole versus refined grains. Both studies had contrary results. Therefore, further studies are needed.

The control diets were different in terms of the specific macronutrients composition. Also, the study participants sometimes had different baseline characteristics (e.g., components of MetS). This seems typical regarding the multiplex characteristics of MetS. Other than this heterogeneity, inflammatory markers have high intra- and interindividual biological variability, depending on circadian rhythm, hormonal status, comorbidities, medication, and even test assay.

Although all included studies were RCTs, most of them failed to report on allocation concealment and assessor blinding. Thus, all of these features introduced heterogeneity and confounding effects in the analysis. In general, the adherence to dietary recommendations is weak among people suffering from MetS (median dropout rate = 21.46%). Funnel plots were asymmetrical for weight loss, indicating risk of publication bias (see Fig. 4).

Implications for further research

Additional research should involve large trials that compare all of these diets in participants with similar characteristics for the same duration and the same control diet (e.g., conventional diet). In addition, further studies should aim to ensure an equal caloric intake. It would also be interesting to be able to distinguish between body weight loss–dependent and body weight loss–independent immunomodulatory effects of certain dietary approaches. Further investigations should also try to analyze several pro- and anti-inflammatory factors.

Implications for clinical practice

Individualized dietary patterns that are easy to implement in everyday life are major advantages of dietary approaches for immunomodulation in MetS. The best dietary pattern for patients with MetS would consist of whole grains, unsaturated fatty acids, and diet high in secondary phytochemicals in a low-carbohydrate fashion.

Conclusions

Dietary approaches have a positive effect on immune markers. This meta-analysis revealed that low-fat diets can reduce CRP, though this seems to be dependent on weight loss. However, low-carbohydrate diets had the effect of reducing weight and fasting insulin effectively. Although low-carbohydrate diets are convenient to achieve weight control, reducing saturated fatty acids and enriching immunoactive biosubstances (vitamins, flavonoids, and unsaturated fatty acids) seems to be the best strategy against MetS.

Acknowledgments

This review was supported by a grant from the Corona-Foundation, Germany. The funding source had no influence on the design or conduct of the review; the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript. The authors would like to express their appreciation to Dr. R. Stange, Berlin, Germany, for critically revising the manuscript. The authors declare that they have no competing interests.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.nut.2015.09.010.

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