REVIEW

Effects of a Paleolithic Diet on Cardiovascular Disease Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

There is some evidence supporting the beneficial effects of a Paleolithic Diet (PD) on cardiovascular disease risk factors. This diet advises consuming lean meat, fish, vegetables, fruits, and nuts and avoiding intake of grains, dairy products, processed foods, and added sugar and salt. This study was performed to assess the effects of a PD on cardiovascular disease risk factors including anthropometric indexes, lipid profile, blood pressure, and inflammatory markers using data from randomized controlled trials. A comprehensive search was performed in the PubMed, Scopus, ISI Web of Science, and Google Scholar databases up to August, 2018. A meta-analysis was performed using a random-effects model to estimate the pooled effect size. Meta-analysis of 8 eligible studies revealed that a PD significantly reduced body weight [weighted mean difference (WMD) = −2.17 kg; 95% CI: −3.48, −0.87 kg], waist circumference (WMD = −2.90 cm; 95% CI: −4.51, −1.28 cm), body mass index (in kg/m^2) (WMD = −1.15; 95% CI: −1.68, −0.62), body fat percentage (WMD = −1.38%; 95% CI: −2.08%, −0.67%), systolic (WMD = −4.24 mm Hg; 95% CI: −7.11, −1.38 mm Hg) and diastolic (WMD = −2.95 mm Hg; 95% CI: −4.72, −1.18 mm Hg) blood pressure, and circulating concentrations of total cholesterol (WMD = −0.22 mg/dL; 95% CI: −0.42, −0.03 mg/dL), TGs (WMD = −0.23 mg/dL; 95% CI: −0.46, −0.01 mg/dL), LDL cholesterol (WMD = −0.13 mg/dL; 95% CI: −0.25, −0.01 mg/dL), and C-reactive protein (CRP) (WMD = −0.41 mg/L; 95% CI: −0.81, −0.008 mg/L) and also significantly increased HDL cholesterol (WMD = 0.05 mg/dL; 95% CI: 0.005, 0.10 mg/dL). However, sensitivity analysis revealed that the overall effects of a PD on lipid profile, blood pressure, and circulating CRP concentrations were significantly influenced by removing some studies, hence the results must be interpreted with caution. Although the present meta-analysis revealed that a PD has favorable effects on cardiovascular disease risk factors, the evidence is not conclusive and more well-designed trials are still needed. *Adv Nutr* 2019;0:1–13.

Keywords: Paleolithic diet, Paleolithic nutrition, anthropometric indexes, lipid profile, blood pressure, C-reactive protein, meta-analysis

Introduction

Cardiovascular diseases (CVDs) are a main public health concern worldwide, being the leading cause of mortality, accounting for 30 percent of all global deaths (1). According to the last estimation of the WHO, 7.3 million and 6.2 million died annually because of coronary artery disease and stroke, respectively (2). The development of CVDs is associated with obesity, diabetes, smoking, lack of physical activity, and harmful alcohol intake (3, 4). Furthermore, hemodynamic (hypertension) and metabolic stressors (dyslipidemia and hyperglycemia) have been established as important CVD risk factors (3–5).

Long-standing findings on the relevance of diet for CVDs have shown that diet might highly contribute to the incidence of CVDs. Many such studies have mostly focused on nutrients, foods (6, 7), and food groups (8–10), whereas less emphasis has been devoted to dietary patterns. Epidemiological research has shown that assessment of dietary patterns instead of single foods or nutrients can provide a better understanding of how dietary factors mutually affect

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Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; GL, glycemic load; PD, Paleolithic diet; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; WMD, weighted mean difference.

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the risk of diseases such as all-cause or CVD mortality (11, 12). Several meta-analyses have revealed beneficial effects of some dietary patterns such as the Dietary Approach to Stop Hypertension (DASH), Mediterranean diet, and Healthy Eating Index (HEI) on CVD risk factors (13–17).

A Paleolithic diet (PD) is another dietary regimen based on foods commonly eaten during the Old Stone Age (18), which mostly suggests consuming lean meat, fish, eggs, fruits, vegetables, roots, and nuts but eliminating grains, dairy products, processed foods, and added sugar and salts (19). This dietary pattern contains lower sodium, whereas it has high contents of protein and some micronutrients such as vitamins C and E, carotenes, and fiber with lower caloric intake from carbohydrate and refined fat (20–22). Whereas the changes in the ancient genome over a long period from the Paleolithic era (2.6 million to 10,000 y ago) varied slightly, dietary patterns with the emergence of modern foods have faced significant changes (23).

Previous studies reported that CVDs are less prevalent among existing hunter-gatherer tribes around the world such as those in Papua New Guinea than among industrialized populations (24). These findings could be due to their conventional lifestyle and their especially healthy dietary pattern (that is, PD) (25), whereas the Western diet with its high content of saturated fat, salt, and processed foods has been implicated in chronic diseases like CVDs (26–28).

Also, previous studies reported positive effects of a PD on energy intake, body composition, insulin sensitivity, and cardiovascular disease risk markers (19, 25, 29). Despite several randomized controlled trials (RCTs) investigating a PD, there is considerable controversy regarding the clinical benefits of this dietary pattern. Although a positive effect of a PD on risk factors for metabolic syndrome has been reported (30), another study found no effect of a PD on anthropometric indexes after a 24-mo follow-up (31). These controversies also exist for other CVD risk factors like lipid profile and blood pressure (19, 25).

Findings of previous RCTs are inconsistent regarding the effects of a PD on cardiometabolic markers. Therefore, the aim of the present systematic review and meta-analysis of published RCTs was to assess the effect of this dietary pattern on CVD risk factors and to quantify its possible influences on lipid profile, blood pressure, anthropometric indexes, and inflammatory markers.

Materials and Methods

Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used as a guideline during all stages of the design, implementation, and reporting of the present systematic review and meta-analysis (32). Systematic computerized literature searches of PubMed (http://www.pubmed.com), ISI Web of Science (http://www.webofknowledge.com), Scopus (http://www.scopus.com), and Google Scholar (http://scholar.google.com) were performed up to August, 2018 without any restrictions. The combination of medical subject headings (MeSH) and non-MeSH keywords was selected as follows: ["Diet, Paleolithic" OR (Paleolithic AND diet*) OR (Paleo AND diet*) OR (Paleo AND nutrition*) OR (Paleolithic AND Nutrition) OR ("stone age" AND diet*) OR ("stone age" AND nutrition*) OR (caveman AND diet*) OR (caveman AND nutrition*) OR ("Hunter-Gatherer" AND diet*) OR ("Hunter-Gatherer" AND nutrition*) OR ("Paleolithic-type" AND diet*) OR ("Paleolithic-type" AND nutrition*)]. To find related studies, retrieved titles and abstracts were separately reviewed by 2 authors (HM and MM) and any disagreements were resolved by consultation with other investigators (AS-A, MH, and NR-J). Moreover, the references of included literature and related reviews were screened to determine more potentially relevant studies.

Eligibility criteria

Retrieved studies were included in our review if they met the following criteria: they *1*) were an original article with an RCT design; *2*) evaluated the effects of a PD on human beings; and *3*) assessed weight and body composition, circulating concentrations of blood lipids, blood pressure, and inflammatory markers as primary or secondary measures. Studies were excluded if they *1*) were conducted among children or adolescents aged younger than 18 y; *2*) reported duplicate data from other included studies; *3*) evaluated single diet components rather than a whole dietary pattern; or *4*) did not report the targeted outcomes.

Data extraction

Two independent researchers (HM and MM) summarized the following data which were double checked by other authors (AS-A and NR-J): first author's name, year of publication, country where the study was performed, study design, study period, participants' characteristics (number, age, sex, and health status), component of the dietary patterns consumed in the intervention and control groups, and the mean changes with corresponding SDs of measured outcomes in the intervention and control arms.

Quality assessment

Two reviewers (HM and MM) independently evaluated the methodological quality of the eligible studies via the Cochrane Collaboration's tool including 6 domains as follows: *1*) random sequence generation (selection bias); *2*) allocation concealment (selection bias); *3*) blinding of participants and personnel (performance bias); *4*) blinding of outcome assessment (detection bias); *5*) incomplete outcome data (attrition bias); and *6*) selective reporting (reporting bias). Blinding is not possible in dietary interventions, therefore the studies were judged regarding the other 5 items. Each domain was classified into 3 categories: low risk of bias, high risk of bias, and unclear risk of bias. According to the aforementioned domains, the overall quality of each individual study was considered as good (low risk for >2 items), fair (low risk for 2 items), or weak (low risk for <2 items) (33).

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Statistical analysis

To calculate the effect sizes for each outcome parameter, the mean changes and their SDs for the intervention and control groups or periods were extracted from each study and used to estimate the mean difference and its corresponding SE. A random-effects model was used to compute weighted mean differences (WMDs) with 95% CIs for conducting the meta-analysis (34). Between-study heterogeneity was tested by Cochran's Q test and quantified by the I-squared (I^2) statistic, where a significant Q test ($P < 0.05$) and a value for $I^2 > 75\%$ were considered to indicate considerable heterogeneity (35). Begg's rank correlation test and Egger's regression asymmetry test were performed for detecting potential publication bias as well as observing the symmetry of the funnel plots in which mean differences were plotted against their corresponding SEs (36, 37). Sensitivity analyses were also performed by removing each study one by one and recalculating the pooled estimates. All statistical analyses were conducted using STATA, version 11.2 (Stata Corp). Statistically significant values were defined as P values < 0.05.

Results

Study selection and characteristics

A total of 2979 studies were identified by the primary search of the electronic databases, and 1 additional study was found through the hand search of the citations of the included articles and related reviews. We selected 28 eligible studies which were full-text reviewed, and 20 of them were excluded for the following reasons: *1*) 7 studies reported no data on our target outcomes (38–44); *2*) 6 studies reported duplicated results which were published in another article (45–50); *3*) 5 studies had no control group (21, 29, 51–53); *4*) 1 study assessed the effect of a PD along with exercise (54); and *5*) 1 study assessed the acute effect of a PD intake (55). In total, 8 eligible studies were included in the present systematic review and meta-analysis (19, 25, 30, 31, 56–59). Details of the study selection process are shown in **Figure 1**.

The included studies were conducted in the Netherlands (30), United States (57, 59), Sweden (19, 25, 31, 58), and Australia (56). The publication date of articles ranged from 2007 to 2017. Seven trials were designed as parallel-group studies (25, 30, 31, 56–59) and 1 study used a crossover design (19), with the follow-up periods ranging from 2 wk to 2 y. In the studies of the present review, a PD as an intervention was compared with the usual diet of subjects (57) or other dietary patterns and guidelines such as the Nordic Nutrition Recommendations (31, 58), Australian Guide to Healthy Eating (56), dietary recommendations based on the guidelines of the American Diabetes Association (59), dietary recommendations based on the guidelines for a healthy diet of the Dutch Health Council (30), a diabetes diet designed in accordance with current diabetes dietary guidelines (19), and a Mediterranean-like diet (25).

A total of 266 subjects with mean age of 53 y were included in the analysis. The participants had different conditions of health status such as healthy subjects, postmenopausal women, patients with type 2 diabetes, multiple sclerosis, or ischemic heart disease, and subjects with characteristics of the metabolic syndrome. General characteristics of the selected trials are presented in **Table 1**.

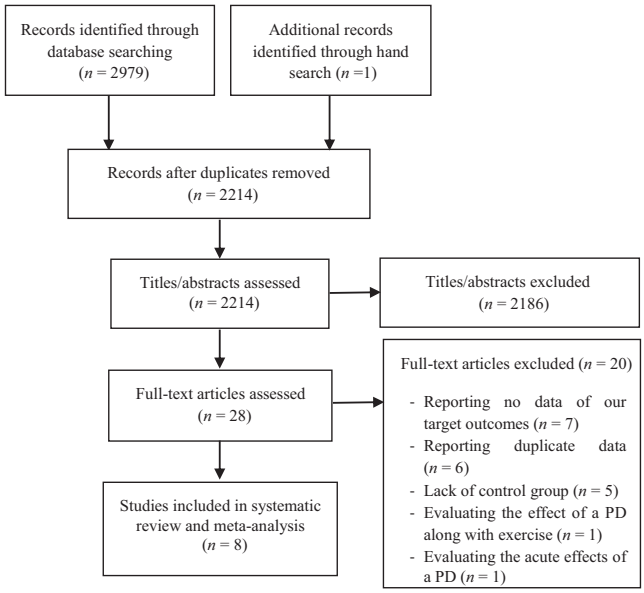

FIGURE 1 PRISMA flow diagram of the study selection process. PD, Paleolithic diet; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Risk of bias assessment.

Table 2 describes the risk of bias assessment based on different quality domains using the Cochrane Collaboration tool. After evaluating the quality of the 8 included studies, 7 of them were classified as of good quality (19, 25, 30, 31, 56–58). However, Masharani et al.'s study (59) was of fair quality and did not report their methods of allocation concealment and random sequence generation. Moreover, because blinding is impossible to perform for dietary intervention trials, the blinding of participants and investigators was not considered in all the studies.

Effects of a PD on weight, waist circumference, BMI, and body fat percentage.

Six trials assessed the effect of a PD on body weight measures (19, 25, 30, 31, 56, 59). The pooled effect size indicated a significant reduction in weight after a PD (WMD = −2.17 kg; 95% CI: −3.48, −0.87 kg, $P = 0.001$, **Figure 2**A). The between-study heterogeneity was significant (Cochran's $Q = 43.01$, $P < 0.001$, $I^2 = 88.4\%$); however, because of the limited number of studies, we could not perform subgroup analysis to find the potential sources of the observed heterogeneity.

Meta-analysis of 5 trials which reported the data on waist circumference (WC) (19, 25, 30, 31, 56) showed a significant effect of a PD on WC values (WMD = −2.90 cm; 95% CI: −4.51, −1.28 cm, $P < 0.001$, Figure 2B). There

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TABLE 1 Characteristics of included randomized controlled clinical trials in the systematic review[1]

Study (ref)	Country	Group: *n* and sex (F/M)	Mean age (y)	RCT design	Period (d)	Intervention diet	Control diet	Participants	Estimated effect sizes: WMD (95% CI)
Irish et al. (57)	United States	Intervention: 7 F/1 M Control: 8 F/1 M	Intervention: 35.4 Control: 37.1	Parallel	90	Modified Paleolithic diet	Usual diet	Relapsing-remitting multiple sclerosis	CRP (mg/L): −1.69 (−3.47, 0.09)
Genoni et al. (56)	Australia	Intervention: 22 F Control: 17 F	Intervention: 47 Control: 47	Parallel	28	Paleolithic diet: CHO: 27.8% Fat: 39.8% Pro: 26.8%	Australian Guide to Healthy Eating: CHO: 40.6% Fat: 32.6% Pro: 21.7%	Healthy women	Weight (kg): −1.99 (−2.94, −1.04) WC (cm): −1.90 (−3.09, −0.71) Body fat (%): −1.34 (−2.48, −0.20) SBP (mm Hg): −2.61 (−10.10, 4.88) DBP (mm Hg): −3.51 (−9.01, 1.99) CRP (mg/L): −0.57 (−1.62, 0.48) TC (mg/dL): −0.13 (−0.48, 0.22) TGs (mg/dL): −0.41 (−0.44, 0.16) HDL cholesterol (mg/dL): 0.04 (−0.06, 0.14) LDL cholesterol (mg/dL): −0.11 (−0.31, 0.09)
Masharani et al. (59)	United States	Intervention: 14 NR Control: 10 NR	Intervention: 58 Control: 56	Parallel	21	Paleolithic diet: CHO: 58.2% Fat: 27% Pro: 18.5%	American Diabetes Association recommendations: CHO: 54.4% Fat: 28.8% Pro: 20.3%	Patients with type 2 diabetes	Weight (kg): −0.30 (−1.38, 0.78) SBP (mm Hg): −2.00 (−12.08, 8.08) DBP (mm Hg): −1.00 (−8.27, 6.27) TC (mg/dL): −0.44 (−0.99, 0.11) TGs (mg/dL): −0.46 (−1.59, 0.67) HDL cholesterol (mg/dL): −0.05 (−0.21, 0.10) LDL cholesterol (mg/dL): −0.21 (−0.63, 0.21)
Stomby et al. (58)	Sweden	Intervention: 27 F Control: 22 F	NR	Parallel	720	Paleolithic diet: CHO: 30% Fat: 40% Pro: 30%	Nordic Nutrition Recommendations CHO: 55–60% Fat: 25–30% Pro: 15%	Overweight postmenopausal women	Body fat (%): −1.90 (−3.23, −0.57)
Mellberg et al. (31)	Sweden	Intervention: 34 F Control: 27 F	Intervention: 59.5 Control: 60.3	Parallel	720	Paleolithic diet: CHO: 30% Fat: 40% Pro: 30%	Nordic Nutrition Recommendations: CHO: 55–60% Fat: 25–30% Pro: 15%	Postmenopausal nonsmoking women with a BMI ≥27	Weight (kg): −4.90 (−5.96, −3.84) WC (cm): −5.30 (−7.03, −3.57) BMI: −0.80 (−1.55, −0.05) SBP (mm Hg): −3.70 (−9.57, 2.17) DBP (mm Hg): −1.60 (−5.16, 1.96) CRP (mg/L): −0.20 (−0.73, 0.33) TC (mg/dL): −0.28 (−0.66, 0.10) TGs (mg/dL): −0.26 (−0.45, −0.07) HDL cholesterol (mg/dL): −0.01 (−0.14, 0.12) LDL cholesterol (mg/dL): −0.14 (−0.43, 0.15)

(*Continued*)

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TABLE 1 (*Continued*)

Study (ref)	Country	Group: *n* and sex (F/M)	Mean age (y)	RCT design	Period (d)	Intervention diet	Control diet	Participants	Estimated effect sizes: WMD (95% CI)
Boers et al. (30)	Netherlands	Intervention: 13 F/5 M Control: 12 F/4 M	Intervention: 52 Control: 55.4	Parallel	14	Paleolithic diet: CHO: 32% Fat: 41% Pro: 24%	Healthy reference diet (based on the guidelines for a healthy diet of the Dutch Health Council): CHO: 50% Fat: 29% Pro: 17%	Subjects with characteristics of the metabolic syndrome	Weight (kg): −1.00 (−3.15, 1.15) WC (cm): −0.10 (−2.64, 2.44) BMI: −1.80 (−2.61, −0.99) SBP (mm Hg): −4.00 (−10.24, 2.24) DBP (mm Hg): −5.00 (−10.10, 0.10) CRP (mg/L): −0.50 (−1.95, 0.95) TC (mg/dL): −0.60 (−1.13, −0.07) TGs (mg/dL): −1.00 (−3.78, 1.78) HDL cholesterol (mg/dL): 0.20 (0.01, 0.39) LDL cholesterol (mg/dL):−0.30 (−0.76, 0.16)
Jonsson et al. (19)	Sweden	3 F/10 M	64	Crossover	90	Paleolithic diet: CHO: 32% Fat: 39% Pro: 24%	Diabetes diet designed in accordance with current diabetes dietary guidelines: CHO: 42% Fat: 34% Pro: 20%	Patients with type 2 diabetes	Weight (kg): −3.00 (−3.55, −2.45) WC (cm): −4.00 (−5.68, −2.32) BMI: −1.00 (−1.52, −0.48) SBP (mm Hg): −9.00 (−14.99, −3.01) DBP (mm Hg): −4.00 (−6.79, −1.21) CRP (mg/L): −0.60 (−1.67, 0.47) TC (mg/dL): −0.20 (−0.52, 0.12) TGs (mg/dL): −0.50 (−0.71, −0.29) HDL cholesterol (mg/dL): 0.08 (0.02, 0.14) LDL cholesterol (mg/dL): −0.10 (−0.33, 0.13)
Lindeberg et al. (25)	Sweden	Intervention: 14 M Control: 15 M	Intervention: 65 Control: 57	Parallel	84	Paleolithic diet: CHO: 40.2% Fat: 26.9% Pro: 27.9%	Mediterranean-like diet: CHO: 51.7% Fat: 24.7% Pro: 20.5%	Ischemic heart disease patients with WC >94 cm and increased blood glucose or known diabetes	Weight (kg): −1.20 (−3.29, 0.89) WC (cm): −2.70 (−4.86, −0.54) Body fat (%): −1.00 (−2.20, 0.20) SBP (mm Hg): 0.81 (−8.47, 10.09) DBP (mm Hg): 1.07 (−5.71, 7.85) TC (mg/dL): 0.39 (−0.27, 1.05) TGs (mg/dL): 0.28 (−0.19, 0.75) HDL cholesterol (mg/dL): 0.07 (−0.07, 0.21)

[1] BMI measured in kg/m^2. CHO, carbohydrate; CRP, C-reactive protein; DBP, diastolic blood pressure; F, female; M, male; NR, not reported; Pro, protein; ref, reference; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; WMD, weighted mean difference.

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TABLE 2 Risk of bias assessment for included randomized controlled clinical trials[1]

	Irish et al. (57)	Genoni et al. (56)	Masharani et al. (59)	Stomby et al. (58)	Mellberg et al. (31)	Boers et al. (30)	Jonsson et al. (19)	Lindeberg et al. (25)
Random sequence generation (selection bias)	+	+	?	+	+	+	+	+
Allocation concealment (selection bias)	?	?	?	?	?	?	?	?
Blinding of participants and personnel (performance bias)	−	−	−	−	−	−	−	−
Blinding of outcome assessment (detection bias)	−	−	−	?	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	?
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+
Score	3	3	2	3	4	4	4	3
Overall quality	Good	Good	Fair	Good	Good	Good	Good	Good

[1] +, positive assessment; −, negative assessment; ?, neutral assessment.

was significant heterogeneity between studies (Cochran's $Q = 16.47$, $P = 0.002$, $I^2 = 75.7\%$).

The effect of a PD on BMI measures was examined in 3 clinical trials (19, 30, 31). The results of meta-analysis showed that there was a significant effect of adherence to a PD on BMI reduction (WMD = −1.15 kg/m^2; 95% CI: −1.68, −0.62 kg/m^2, $P < 0.001$, Figure 2C). The between-study heterogeneity was nonsignificant (Cochran's $Q = 3.62$, $P = 0.163$, $I^2 = 44.8\%$).

The overall result of meta-analysis of 3 studies (25, 56, 58) evaluating the effect of adherence to a PD on body fat percentage showed a significant reduction (WMD = −1.38%; 95% CI: −2.08%, −0.67%, $P < 0.001$, Figure 2D), with no between-study heterogeneity (Cochran's $Q = 0.98$, $P = 0.614$, $I^2 = 0.0\%$).

Sensitivity analysis for all anthropometric parameters showed that the overall estimates were not influenced by elimination of any study. Moreover, no evidence of publication bias was found for weight ($P = 0.46$, Begg's test; $P = 0.34$, Egger's test), WC ($P = 0.80$, Begg's test; $P = 0.99$, Egger's test), BMI ($P = 1.00$, Begg's test; $P = 0.67$, Egger's test), and body fat percentage ($P = 1.00$, Begg's test; $P = 0.55$, Egger's test).

Effects of a PD on systolic blood pressure and diastolic blood pressure.

Six trials assessed the impact of a PD on blood pressure changes (19, 25, 30, 31, 56, 59). Adherence to a PD was found to significantly reduce both systolic blood pressure (SBP) (WMD = −4.24 mm Hg; 95% CI: −7.11, −1.38 mm Hg, $P = 0.004$, **Figure 3**A) and diastolic blood pressure (DBP) (WMD = −2.95 mm Hg; 95% CI: −4.72, −1.18 mm Hg, $P = 0.001$, Figure 3B), with no between-study heterogeneity (Cochran's $Q = 3.97$, $P = 0.554$, $I^2 = 0.0\%$ for SBP; Cochran's $Q = 3.38$, $P = 0.642$, $I^2 = 0.0\%$ for DBP).

Both of these effects of a PD were sensitive to the study by Jonsson et al. (19), yielding an effect size equivalent for SBP of WMD = −2.84 mm Hg (95% CI: −6.10, 0.42 mm Hg) and for DBP of WMD = −2.25 mm Hg (95% CI: −4.53, 0.03 mm Hg). There was no evidence of publication bias for SBP ($P = 0.26$, Begg's test; $P = 0.15$, Egger's test) or DBP ($P = 0.26$, Begg's test; $P = 0.34$, Egger's test).

Effects of a PD on circulating concentrations of total cholesterol, TGs, and HDL and LDL cholesterol.

The pooled effect size of 6 data sets (19, 25, 30, 31, 56, 59) represented a significant reducing effect of a PD on circulating concentrations of total cholesterol (TC) (WMD = −0.22 mg/dL; 95% CI: −0.42, −0.03 mg/dL, $P = 0.024$, **Figure 4**A), with no significant between-study heterogeneity (Cochran's $Q = 6.17$, $P = 0.290$, $I^2 = 19.0\%$).

The pooled mean difference of 6 data sets (19, 25, 30, 31, 56, 59) for the effects of a PD on circulating concentrations of TGs was −0.23 mg/dL (95% CI: −0.46, −0.01 mg/dL, $P = 0.037$, Figure 4B), with no significant between-study heterogeneity (Cochran's $Q = 10.74$, $P = 0.057$, $I^2 = 53.5\%$).

Six trials reported the effect of a PD on HDL cholesterol concentrations (19, 25, 30, 31, 56, 59). It was observed that adherence to a PD resulted in significantly increasing circulating concentrations of HDL cholesterol (WMD = 0.05 mg/dL; 95% CI: 0.005, 0.10, $P = 0.032$, Figure 4C), with no significant between-study heterogeneity (Cochran's $Q = 5.80$, $P = 0.326$, $I^2 = 13.8\%$).

The overall result of meta-analysis of 5 studies (19, 30, 31, 56, 59) evaluating the effect of adherence to a PD on circulating concentrations of LDL cholesterol showed that there was a significant reduction (WMD = −0.13 mg/dL; 95% CI: −0.25, −0.01 mg/dL, $P = 0.032$, Figure 4D). There was no significant heterogeneity between studies (Cochran's $Q = 0.76$, $P = 0.943$, $I^2 = 0.0\%$).

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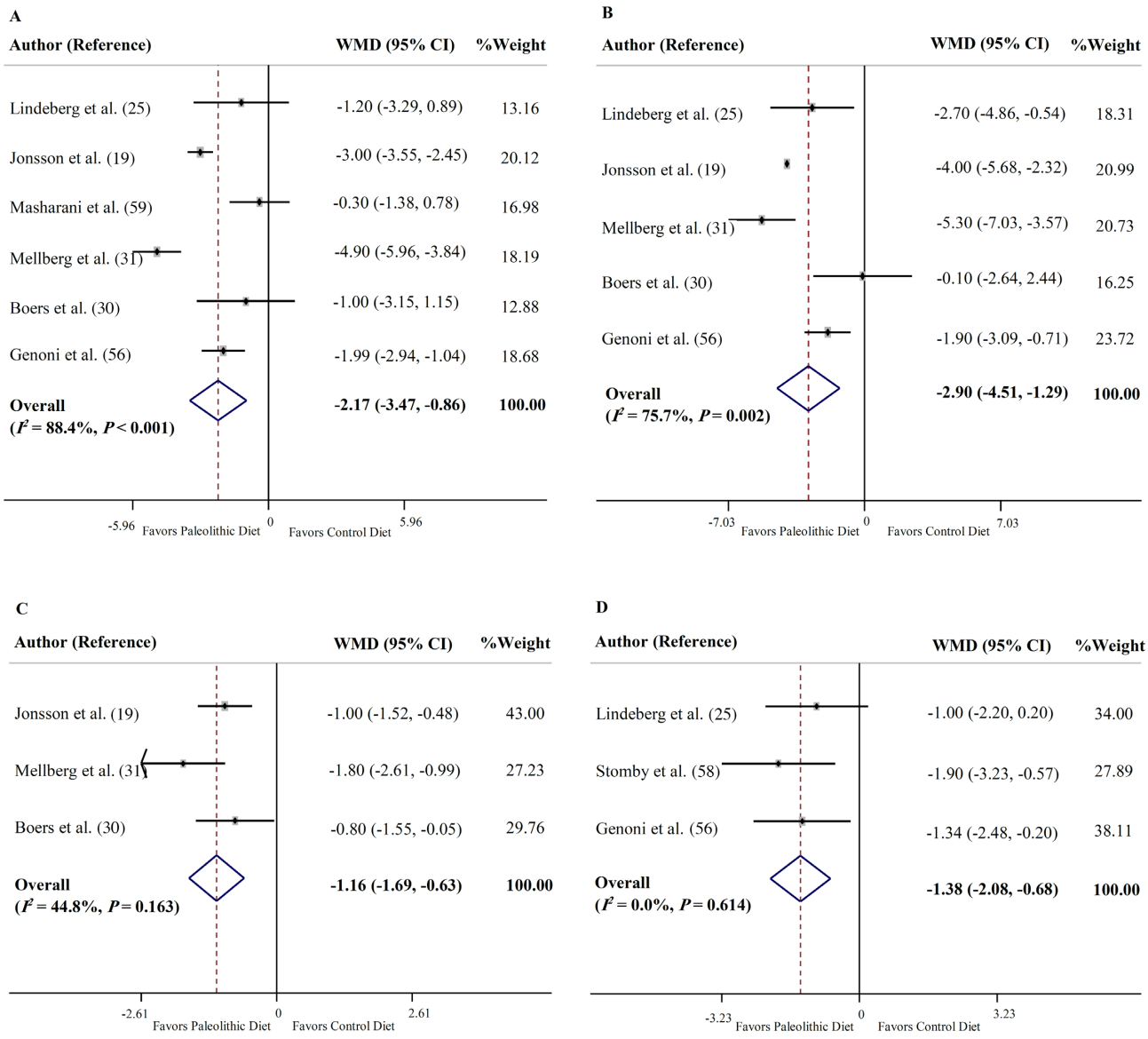

FIGURE 2 Forest plots of the effect of a Paleolithic diet on anthropometric indexes. (A) weight, (B) waist circumference, (C) BMI, (D) body fat. WMD, weighted mean difference.

The results of sensitivity analysis showed that removing the studies by Jonsson et al. (19) (P = 0.078), Mellberg et al. (31) (P = 0.092), Masharani et al. (59) (P = 0.075), and Boers et al. (30) (P = 0.053) changed the overall effect of a PD on circulating TC concentrations to a nonsignificant value. It was also observed that removal of any individual study, with the exception of that by Lindeberg et al. (25), altered the overall effect regarding circulating concentrations of TGs to a statistically nonsignificant result ($P \geq 0.053$). According to the sensitivity analysis for HDL cholesterol values, the overall effect of a PD was sensitive to the studies by Lindeberg et al. (25) (P = 0.106), Jonsson et al. (19) (P = 0.262), and Genoni et al. (56) (P = 0.096). Moreover, the sensitivity analysis indicated that except for Jonsson et al.'s study (19), exclusion of any study from the analysis changed the overall effect of a PD on circulating concentrations of LDL cholesterol to nonsignificant changes ($P \geq 0.053$).

No evidence of publication bias was found from studies evaluating the effect of a PD on the circulating concentrations of TC (P = 1.00, Begg's test; P = 0.93, Egger's test), TGs (P = 1.00, Begg's test; P = 0.70, Egger's test), and HDL cholesterol (P = 1.00, Begg's test; P = 0.75, Egger's test). Although Begg's test (P = 0.08) did not indicate significant publication bias for LDL cholesterol results, there was an evidence of publication bias based on Egger's test (P = 0.01). However, trim-and-fill analyses yielded results similar to the original which means it was unlikely that publication bias significantly affected results.

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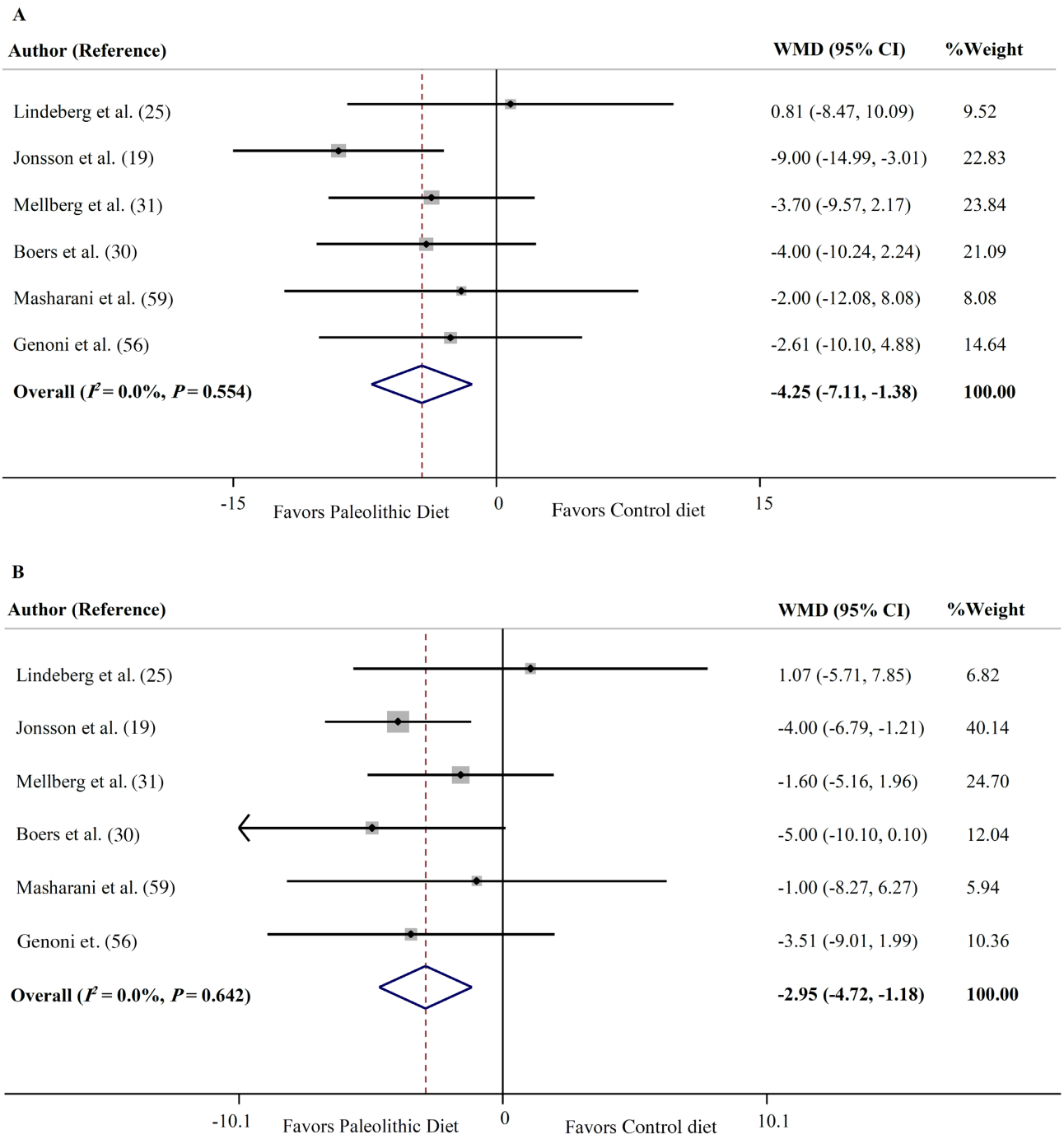

FIGURE 3 Forest plots of the effect of a Paleolithic diet on blood pressure. (A) systolic blood pressure, (B) diastolic blood pressure. WMD, weighted mean difference.

Effects of a PD on circulating C-reactive protein concentrations.

The quantitative analysis of C-reactive protein (CRP) values (5 trials) (19, 30, 31, 56, 57) indicated a significant effect of a PD in reduction of circulating CRP concentrations (WMD = −0.41 mg/L; 95% CI: −0.81, −0.008 mg/L, $P < 0.045$, **Figure 5**), with no between-study heterogeneity (Cochran's $Q = 2.81$, $P = 0.590$, $I^2 = 0.0\%$). The results of sensitivity analysis showed that except for Mellberg et al.'s study (31), exclusion of any study from the analysis changed the overall effect to a nonsignificant value ($P \geq 0.059$). Begg's test ($P = 0.22$) and Egger's test ($P = 0.05$) suggested no publication bias.

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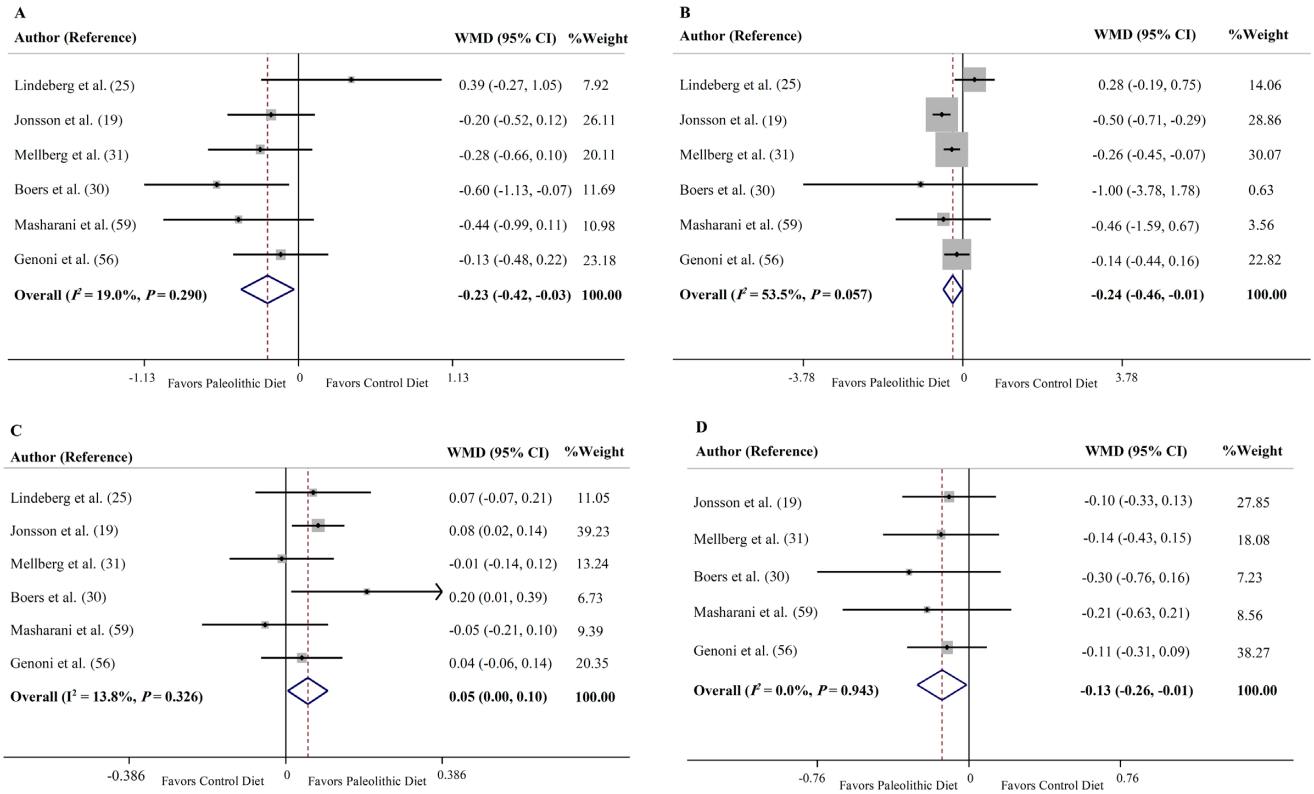

FIGURE 4 Forest plots of the effect of a Paleolithic diet on lipid profile. (A) total cholesterol, (B) TGs, (C) HDL cholesterol, (D) LDL cholesterol. WMD, weighted mean difference.

Discussion

To the best of our knowledge, the present systematic review and meta-analysis is the first such study covering the effects of adherence to a PD on cardiovascular disease risk factors. Our findings indicated that a PD could significantly decrease anthropometric indexes including weight, WC, BMI, and body fat percentage. The pooled analysis also showed that PD resulted in reduced circulating CRP concentrations, SBP, DBP, TC, LDL cholesterol, and TGs, and elevated circulating concentrations of HDL cholesterol. However, according to the sensitivity analysis, we found that the overall effect of a PD on lipid profile, blood pressure, and circulating CRP concentrations changed by removing some studies; thus, the effect of a PD in this field must be interpreted with caution.

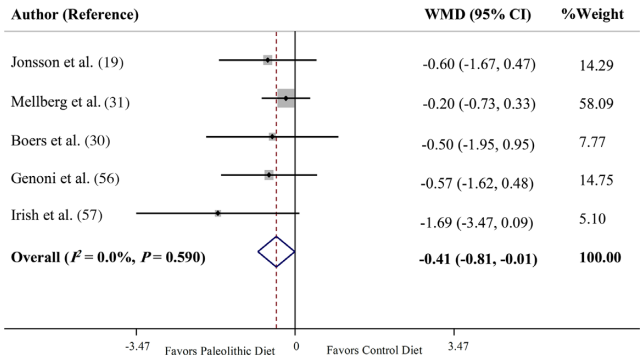

FIGURE 5 Forest plot of the effect of a Paleolithic diet on circulating C-reactive protein concentrations. WMD, weighted mean difference.

In the same vein, another meta-analysis of 4 RCTs suggested short-term improvements in metabolic syndrome components after consumption of a Paleolithic nutritional pattern; however, the beneficial changes of HDL cholesterol and fasting blood sugar values did not reach the significance level (60).

It has been observed that hunter-gatherers were generally lean and free from symptoms of chronic diseases such as CVDs owing to their diets (61, 62). In other words, their general health status got worse when their eating habits changed to an agricultural grain-based diet (62). Furthermore, after their transition to a Western diet, obesity, type 2 diabetes, atherosclerosis, and other CVDs became prevalent among them (63, 64). Considerable attempts were made to justify these findings and one of the suggested mechanisms was related to insulin sensitivity (65). Our ancestors consumed low-carbohydrate diets and their bodies became adapted to this condition. Moreover, the agricultural and industrial revolutions provided an oversupply of extra calories, especially from carbohydrates (66). Although evidence has shown that our gene-pool adapts to a novel nutritional environment (67),

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differences between populations as well as polymorphisms and gene variants may cause insulin resistance (60).

In addition, food-processing procedures often cause overconsumption of food additives such as salt, oils, and omega-6 fatty acids from vegetable oil, which have been described as risk factors for several chronic diseases (68–70). Furthermore, a diet rich in carbohydrate, fat, and processed foods can increase extracellular acidity, activate the zymogens, and trigger the inflammatory system (71). An acidic environment is favored by oxidative stress due to the abundance of reactive oxygen species, reactive nitrogen species, etc. Extracellular acidity also activates a wide range of enzymes involved in vesicular trafficking, autophagy, angiogenesis, proliferation, metastasis, apoptosis, etc. (72, 73).

There is little overlap between current foods and those of the Paleolithic era; our ancestors used almost no cereal grains, dairy products, oils, and processed foods. Although different PDs have been observed from the Paleolithic era and the proportions of total fat and carbohydrate varied mostly with latitude, all PDs were low in serum cholesterol–raising fat and also cereals, refined sugars, and dairy products. In essence, there is wide inconsistency in the way the modern PD is interpreted; however, this diet usually includes vegetables, fruits, nuts, roots, and meat and excludes foods such as dairy products, grains, sugar, processed oils, salt, alcohol, or coffee (74). Lindeberg et al. (25) found that a PD can improve glucose tolerance; however, this was independent of energy intake and macronutrient composition. In addition, Mellberg et al. (31) also reported that adherence to the prescribed protein intake was poor in the PD group in a 2-y RCT. Therefore, it can be mentioned that other components of a PD are of greater importance than macronutrient composition. It has been also suggested that avoidance of Western foods is more important than counting calories, or the fat, carbohydrate, or protein composition of a diet (25).

In this study, we showed that a PD can be an effective approach for weight management. It has been also reported that after administration of a PD, relative changes in the free leptin index correlated significantly with changes in WC (41), which was mainly due to the high intake of fiber as well as low intake of dairy products and refined sugars (41). Furthermore, it was proposed that a PD could raise secretion of incretin and anorectic gut hormones (glucagon-like peptide-1 and peptide YY) and they in turn improved feelings of satiety (56). The nature of this dietary pattern causes lower energy intake because the diet is satiating (75). In addition, the required energy density is lower in a PD owing to high amounts of fruits, vegetables, and protein intake (76). The water consumption in this diet is also thought to be satiating (77). We assume that alteration in the type of fiber consumed in a PD may have an important effect on the gut microbiome and this in turn can alter long-term health outcomes such as energy intake; however, this idea has not been investigated yet (78).

In addition, consumption of sugar in the Paleolithic era was considerably lower and the only natural sugars were fruits or honey. Owing to various confounding factors, evaluation of the effects of high refined-sugar intake is complicated in the long term. However, a study reported that consumption of high refined-sugar in the short term increased circulating concentrations of TGs and decreased circulating concentrations of HDL cholesterol (79). Moreover, the SFA contents of a PD are considerably lower than in the Western diet and this low intake of SFAs may partly explain our findings regarding the circulating concentrations of TC. The reduction of TG values can be due to greater loss of abdominal fat (80), lower glycemic load of the diet (81), and higher content of long-chain ω-3 fatty acids in a PD, whereas the higher dietary cholesterol content of a PD is negligible (82). Dietary SFAs are mainly found in meat, dairy products, and tropical oils; all of them are assumed to be associated with increased risk of CVDs.

Our analysis also showed a PD led to significant reduction in both SBP and DBP. Owing to high intake of fruit and vegetables, this dietary pattern is rich in potassium content (83) and therefore a PD can be effective in reducing blood pressure in hypertensive people (84).

In addition, the higher amount of phytochemicals in a PD was reported to decrease inflammation, which can describe our findings (85, 86). Indeed, it has been recommended to increase the daily consumption of fruits and vegetables as a primary preventive measure against CVDs because they can reduce circulating CRP concentrations (87).

The present meta-analysis has several limitations to be mentioned. One consideration to take into account with a PD is that it prohibits consumption of dairy products; so, it contains low calcium content that can cause reduction of bone density (88). Because the side effects of this dietary pattern were not assessed in the previous studies, recommendations for adherence to a PD with the aim of health promotion should be implemented with caution. Other limitations are that included studies were heterogeneous regarding intervention duration (from 2 wk to 2 y), the type of dietary patterns and guidelines which were recommended for subjects in the control groups (usual diet, Nordic Nutrition Recommendations, Mediterranean-like diet, etc.), and the health status of participants (healthy subjects, postmenopausal women, patients with type 2 diabetes, multiple sclerosis, ischemic heart disease, and metabolic syndrome), and doing subgroup analysis was not possible owing to the insufficient number of eligible studies. Moreover, no data were available on the genetic background of participants and possible polymorphisms, which may have a considerable effect on results. Another problem is the fact that the results were significantly influenced by the removal of several studies in our sensitivity analysis; so, the findings should be interpreted with caution.

Conclusion

Based on our analyses, a PD decreased the anthropometric indexes (weight, BMI, WC, and body fat percentage), blood pressure (SBP and DBP), lipid profile (LDL cholesterol, TGs, and TC; HDL cholesterol increased), and circulating CRP

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concentrations. However, we have insufficient evidence to make solid conclusions regarding the efficacy of a PD on improving CVD risk factors, mostly owing to a lack of qualified RCTs. Thus, putative long-term useful effects of different components of a PD on CVD risk factors need to be explored in additional well-designed large trials.

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The authors' contributions were as follows—MM and NR-J: conceived and designed the research; MM and HM: conducted the systematic research and study selection, and extracted the data; MM: analyzed the data; EG, HM, and NR-J: wrote the manuscript; MH, JM, and AS-A: reviewed or edited the manuscript; and all authors: read and approved the final manuscript.

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