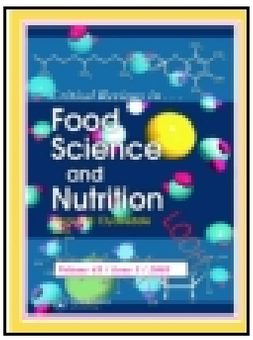

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REVIEW

The effect of paleolithic diet on glucose metabolism and lipid profile among patients with metabolic disorders: a systematic review and meta-analysis of randomized controlled trials

Mohammad Hassan Sohouli[a,b], Somaye Fatahi[c,a], Abolfazl Lari[b], Mojtaba Lotfi[d], Maryam Seifishahpar[e], Mihnea-Alexandru Găman[f], Seyedeh Tayebeh Rahideh[b], Saud K. AlBatati[g], Abdullah M. AlHossan[g], Sara A. Alkhalifa[g], Sara A. Alomar[g], and Ahmed Abu-Zaid[g,h]

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ABSTRACT

Objective: Several randomized clinical trials (RCTs) have investigated the effects of the Paleolithic diet (PD) in adult patients suffering from metabolic disorders. However, the results of these RCTs are conflicting. Therefore, we conducted a systematic review and meta-analysis to assess the effects of the PD in patients with metabolic disorders.

Methods: We searched the PubMed/Medline, Scopus, Cochrane Databases, Google Scholar, Web of Science, and Embase databases up to June, 2020. The data were pooled using a random-effects model. From the eligible publications, 10 articles were selected for inclusion in this systematic review and meta-analysis. The meta-analysis was performed using a random-effects model. The heterogeneity was determined using the I^2 statistics and the Cochrane Q test.

Results: The pooled results from the random-effects model showed a significant reduction of the homeostatic model assessment of insulin resistance (HOMA-IR) (weighted mean difference, WMD: −0.39, 95% CI: −0.70, −0.08), fasting insulin (WMD: −12.17 μU/mL, 95% CI: −24.26, −0.08), total cholesterol (WMD: −0.32 mmol/l, 95% CI: −0.49, −0.15), triglycerides (WMD: −0.29 mmol/L, 95% CI: −0.42, −0.16), low-density lipoprotein cholesterol (WMD: −0.35 mmol/L, 95% CI: −0.67, −0.03), blood pressure (BP)(WMD − 5.89 mmHg; 95% CI − 9.973 to − 1.86 for the systolic BP and WMD − 4.01 mmHg; 95% CI − 6.21 to − 1.80 for the diastolic BP values) and C-reactive protein (CRP) levels (WMD: −0.84, mg/L, 95% CI: −1.62, −0.06) in the PD group *versus* control group.

Conclusions: Our findings provide better insights into the effect of the PD on the modulation of the glucose and lipid metabolism factors in patients with metabolic disorders, providing comprehensive information for the development of future RCTs with a high quality design.

KEYWORDS
Meta-analysis; paleolithic diet; randomized controlled trials; systematic review; metabolic disorders

Introduction

The prevalence of the metabolic syndrome (MetS) and its related complications has increased at a worrying pace worldwide (Obeidat et al. 2015). The MetS is characterized by a group of related risk factors, namely abdominal obesity, high blood pressure (BP), hyperglycemia and dyslipidemia (Lusis, Attie, and Reue 2008). The MetS is associated with an increased risk of cardiovascular disease, type 2 diabetes mellitus (T2DM), cancer, neurodegenerative diseases, as well as other chronic diseases (Watanabe and Kotani 2020; Alberti et al. 2009). In addition to several genetic factors, environmental factors, e.g. physical activity and the composition of the diet, partake in the development of the MetS and its related risk factors (Xu et al. 2018; Galbete et al. 2013; Gorji et al. 2019). Thus, lifestyle changes and the adherence to a healthy diet play key roles in the prevention and treatment of MetS (Meng et al. 2020; Fatahi et al. 2018; Varkaneh Kord et al. 2020; Fatahi et al. 2020; Yamaoka and Tango 2012). Numerous studies have reported on the beneficial effects of certain nutrients or single foods in MetS patients, yet little attention has been paid to the dietary pattern of the subjects diagnosed with MetS (Williams et al. 2000; Tabrizi et al. 2020; Toro-Martín et al. 2017). However, recent papers have pointed out that dietary patterns are

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more reliable predictors of MetS and all-related causes of death *versus* individual nutrients or foods. Several meta-analyses have demonstrated the advantages of following a specific dietary pattern, e.g. the DASH approach, the Mediterranean Diet or the Nordic Diet in terms of improving glycemic and lipid indices in patients diagnosed with metabolic disorders (Bloomfield et al. 2016; Sayón-Orea et al. 2019; Ramezani-Jolfaie, Mohammadi, and Salehi-Abargouei 2019; Siervo et al. 2015).

A diet that has received appraisal from researchers and laymen alike is the Paleolithic diet (PD). The PD, Paleo diet or Stone Age diet, claims that eating like our prehistoric ancestors will make us leaner and less likely to develop diabetes, heart disease, cancer or other ailments (Österdahl et al. 2008; Manheimer et al. 2015). Several arguments in favor of the PD is that it is rich in proteins, fibers and antioxidants. In addition, subjects who follow the PD do not consume processed foods, sugars, refine grains, salt or vegetable oils (Cordain 2002; Österdahl et al. 2008). The PD could emerge as an interesting alternative since modern foods, such as the ones present in Western diets, have been linked with an increased risk of MetS, T2DM and obesity (Zhu et al. 2013; Kopp 2019; Li et al. 2017).

A couple of previously conducted trials have detected positive effects of the PD on biochemical parameters in patients with metabolic disorders. However, the results of several randomized controlled trials (RCTs) point out that there is great deal of controversy regarding the clinical benefits of the PD diet (Blomquist et al. 2018; Boers et al. 2014; Jönsson et al. 2009). Other papers did not report negative associations between the adherence to the PD and glucose and insulin levels (Jönsson et al. 2009; Lindeberg et al. 2007). Controversies also exist regarding the effects of the PD on other variables, e.g. the lipid profile and the blood pressure in patients with metabolic disorders (Mellberg et al. 2014; Blomquist et al. 2018).

Moreover, two meta-analyses have examined the effects of the PD on several biochemical parameters (Ghaedi et al. 2019; Manheimer et al. 2015), but due to the differences in findings, inclusion criteria, outcomes of interest, analyses and populations, the effects of the PD in metabolic disorders has yet to be established. Furthermore, in one of these meta-analyses (Manheimer et al. 2015), the search was limited to the year 2014 and the results of the RCTs published in recent years have not been included. Therefore, the aim of this systematic review and meta-analysis was to evaluate the effects of the PD on indices of the glucose metabolism and the lipid profile in patients with metabolic disorders.

Material and methods

Search strategy

This systematic review was executed in accordance with the criteria mentioned in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2015). The study protocol has been previously registered with the PROSPERO database (registration number: **CRD42019146180**). The study protocol was also granted ethical approval by the Regional Bioethics Committee of The Iran University of Medical Sciences (number **IR.IUMS.REC.1398.1203**).

The relevant articles were retrieved from five electronic databases: PubMed/Medline, Clarivate Analytics - Web of Science, Scopus, Cochrane and Google Scholar. The literature was systematically searched from inception until June 2020 using the specific MeSH and text keywords. **The specific search strategy is reported in the Supplementary Appendix Text.** The titles and the abstracts of the papers extracted from the relevant databases were separately reviewed by two researchers in order to identify related studies, and any differences were resolved in consultation with a third author. Moreover, we hand-searched the references of the identified articles to detect any potentially relevant manuscripts that might have not been tracked by our initial search.

Eligibility criteria

The studies that met the following criteria were selected for the full-text review: 1) RCTs evaluating the impact of the PD in patients with metabolic disorders; 2) studies recruiting adult subjects; 3) trials that reported sufficient data on the measured outcomes at baseline and at the end of study in each study group. The articles were excluded if they: 1) were observational studies; 2) lacked an appropriate control group; 3) were conducted in children, adolescents, pregnant or lactating women; 4) partially evaluated dietary components instead of a whole diet; 5) did not report sufficient data on the measured outcomes in both the intervention and the control group.

Data extraction

The eligible papers were independently reviewed by two investigators and the following data were extracted: the first author's name, the study location, the publication year, the RCT design (cross-over or parallel), the participants' characteristics (gender, age, type of metabolic disorder), the sample size (intervention and placebo groups), the duration of the intervention, the profile of the diet in each group and the mean SD of the measured outcomes in the study groups.

Quality assessment

The quality of the included RCTs was methodologically assessed in accordance with the Cochrane risk of bias criteria (Higgins 2011). Two authors subjectively rated each study as having a high, low, or unclear risk of bias based on the following items: allocation concealment; blinding of outcome assessment; blinding of participants and personnel; incomplete outcome data; random sequence generation; selective reporting; and other bias. Due to the impossibility of blinding in dietary interventions, the trials were judged based on the other items. After classifying each domain into 3 categories (low-risk of bias, high-risk of bias and unspecified risk of bias), the overall quality of each study was rated

as good (low-risk for >2 units), fair (low-risk for 2 cases) or poor (low-risk for <2 items). In addition, the NutriGrade (Grading of Recommendations Assessment, Development, and Evaluation) scoring system was used to evaluate the quality of the current study (Schwingshackl et al. 2016). The NutriGrade checklist is a valid 10-point scoring system that measures several factors that could influence the quality of the study. This scale includes 7 items *1*) risk of bias, study quality, and study limitations, *2*) precision, *3*) heterogeneity, *4*) directness, *5*) publication bias, *6*) funding bias, *7*) study design.

Statistical analysis

The data analysis was carried out using the STATA version 12.0 and RevMan V.5.3 software. When the data was expressed in studies in another format, standard calculations were used to obtain the means and SDs (Higgins 2011; Hozo, Djulbegovic, and Hozo 2005). For example, using the following formula, we extracted the SDs changes that have not been reported in the analyzed studies: SD changes = square root [(SD baseline 2 + SD final 2) - (2 × R × SD baseline × SD final)]. In addition, to calculate the SD using the standard error of the mean (SEM), the SEM was multiplied by the square root of the number of individuals in each group. The I-squared (I^2) statistics was used to investigate heterogeneity. If a I^2 >50% was reported or there was a discrepancy between the data of the trials, the source of the heterogeneity could be identified (Higgins et al. 2003). A predefined subgroup analysis was performed based on the duration of the adherence to the diet and the health status of the individuals to identify potential sources of heterogeneity. To evaluate the contribution of each study to the overall mean difference and the presence of publication bias, a sensitivity analysis and the Egger's test were used, respectively (Egger et al. 1997).

Results

Search results

In the initial systematic search, a total of 800 studies was identified. Following the elimination of duplicates, 486 articles remained. Based on the title and abstract screening, 462 irrelevant articles were excluded and 24 articles remained for the eligibility assessment. Finally, we included 10 RCTs in the meta-analysis and excluded 14 studies that did not meet our inclusion criteria. Figure 1 displays the literature search and selection process.

Study characteristics

The characteristics of the eligible RCTs are presented in Table 1. Seven RCTs were conducted in Sweden (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Stomby et al. 2015; Otten et al. 2016; Fontes-Villalba et al. 2016; Blomquist et al. 2018), two RCTs in the United States (Masharani et al. 2015; Pastore, Brooks, and Carbone 2015) and one RCT in The Netherlands (Boers et al. 2014). All the articles were published between 2007 and 2018. Seven studies used a parallel design (Lindeberg et al. 2007; Masharani et al. 2015; Boers et al. 2014; Mellberg et al. 2014; Stomby et al. 2015; Otten et al. 2016; Blomquist et al. 2018) and three studies used a cross-over design (Jönsson et al. 2009; Fontes-Villalba et al. 2016; Pastore, Brooks, and Carbone 2015). The follow-up of the intervention ranged from 2 (Boers et al. 2014) to 24 (Mellberg et al. 2014; Stomby et al. 2015; Otten et al. 2016; Blomquist et al. 2018) weeks. Three RCTs examined the effects of the PD in T2DM patients (Jönsson et al. 2009; Masharani et al. 2015; Fontes-Villalba et al. 2016), four in overweight/obese postmenopausal women (Mellberg et al. 2014; Stomby et al. 2015; Otten et al. 2016; Blomquist et al. 2018), one in patients with ischemic heart disease (Lindeberg et al. 2007), one in patients with MetS (Boers et al. 2014) and one in adult patients with hypercholesterolemia (Pastore, Brooks, and Carbone 2015). In our study, the primary outcomes were the measurement of several components of the glucose metabolism and of the lipid profile, namely the levels of fasting blood sugar (FBS), insulin, the homeostatic model assessment of insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). In addition, our secondary outcome included the systolic and diastolic blood pressure (SBP and DBP, respectively) and the C-reactive protein (CRP). The results of the quality assessment of the included papers is presented in Table 2. Moreover, the evaluation of the quality of the present meta-analysis based on the NutriGrade score system resulted in a score of 8.4 (very good quality).

Meta-analysis

The effect of PD on FBS, HbA1c, insulin and HOMA-IR

The quantitative meta-analysis of seven and six treatment arms displayed a significant decrease in insulin levels (WMD: −12.17 μU/mL, 95% CI: −24.26, −0.08, P = 0.04) and of the HOMA-IR (WMD: −0.39, 95% CI: −0.70, −0.08, P = 0.013) in the PD group *versus* controls. However, the pooled results did not show a significant effect of the PD on HbA1c (WMD: −0.07 mmol/L, 95% CI: −0.24, −0.11, P = 0.47) and FBS (WMD: −0.15, 95% CI: −0.55, −0.26, P = 0.48). No heterogeneity was detected in the trials for FBS (Cochran *Q* test, P = 0.39, I^2=0.0%) and HOMA-IR (Cochran *Q* test, *P* = 0.11, I^2=44.0%). However, a significant heterogeneity was observed between these RCTs for insulin (Cochran *Q* test, P = 0.024, I^2=58.8%) and HbA1c (Cochran *Q* test, *P* = 0.041, I^2=54.4%) (Figure 2). Subgroup analyses were performed to find the possible origin of the heterogeneity. The duration of the intervention (≤12 weeks or >12 weeks) and the baseline health status of the participants (the type of metabolic disorder) were considered as factors of heterogeneity on the overall effect size for insulin.

The subgroup analyses based on the duration of the intervention (≤12 weeks or >12 weeks) and on the type of

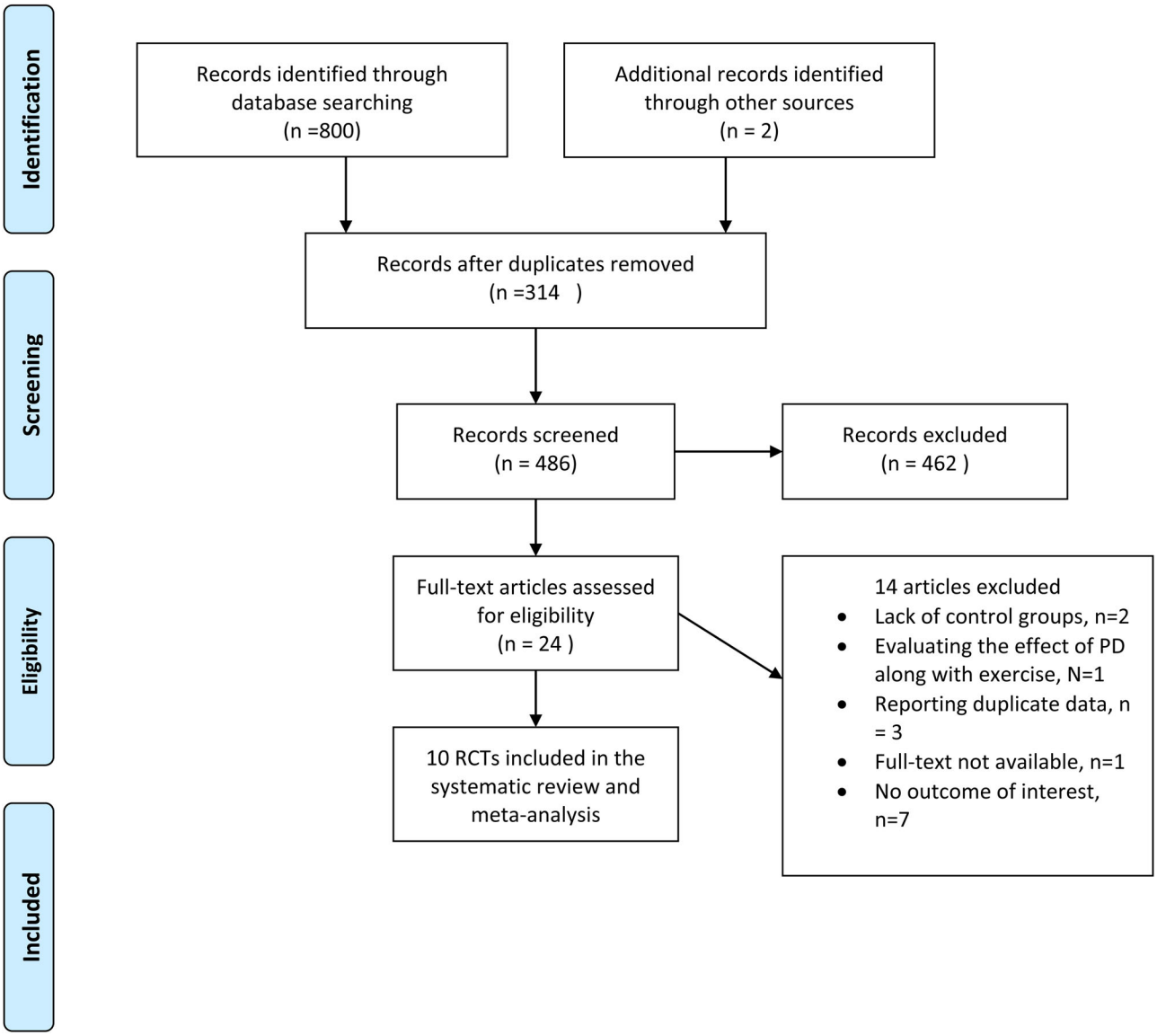

Figure 1. Flow chart of study selection process.

metabolic disorder revealed no beneficial effect of the PD on FBS. According to the results of the subgroup analyses, a greater reduction in insulin levels was detected in the RCTs examining T2DM patients (WMD: −41.00 μU/mL, 95% CI: −59.92, −22.08) and in the RCTs with a follow-up duration of ≤12 weeks (WMD: −23.28 μU/mL CI: −44.82, −1.73). Moreover, when the subjects were stratified according to their health status, a significant reduction in the HOMA-IR (WMD: −0.44, 95% CI: −0.83, −0.04) was seen in obese or overweight subjects. The subgroup analysis for HbA1c was not possible as there were not enough studies in each group (Supplementary Figures 1–3).

The effect of PD on the lipid profile

The pooled data from 8 RCTs showed a significant decrease of TC (WMD: −0.32 mmol/L, 95% CI: −0.49, −0.15, P < 0.001), TG (WMD: −0.29 mmol/L, 95% CI: −0.42, −0.16, P < 0.001) and LDL-C (WMD: −0.35 mmol/L, 95% CI: −0.67, −0.03, P = 0.032) in the PD group. However, PD did not exert a significant effect on HDL-C (WMD: 0.05 mmol/L, 95% CI: −0.06, 0.16, P = 0.34). No significant heterogeneity was observed between these trials for TC (Cochran *Q* test, $P = 0.87$, I^2=0.0%) or TG (Cochran *Q* test, $P = 0.14$, I^2=35.5%). However, a significant heterogeneity was observed between the analyzed studies for HDL-C (Cochran Q test, P = 0.001, I^2=72.2%) and LDL-C (Cochran Q test, P = 0.000, I^2=79.7%). The duration of the intervention and the type of patients enrolled in these RCTs were considered as factors of heterogeneity on the overall effect size (Figure 3).

The results of the subgroup analysis demonstrated that a greater reduction in TC, LDL-C and TG was detected in subjects diagnosed with obesity or overweight (WMD: −0.31 mmol/L, 95% CI: −0.49, −0.12 for TC; WMD: −0.20 mmol/L, 95% CI: −0.35, −0.04 for LDL-C; and WMD: −0.23 mmol/L, 95% CI: −0.33, −0.13 for TG) and when the duration of the intervention was >12 weeks (WMD: −0.32 mmol/L, 95% CI: −0.50, −0.13 for TC and WMD: −0.46 mmol/L, 95% CI: −0.90, −0.02 for LDL-C;

Table 1. The characteristics of the randomized controlled trials included in this study.

Study ID	Country	Study design	Participants	Sample size	Intervention diet	Control diet	Duration(day)	Outcomes
Lindeberg et al. 2007 **(23)**	**Sweden**	*Parallel*	*Ischemic heart disease patients*	*Intervention: 14* *Control: 15*	*Paleolithic diet:* *CHO: 40.2%* *Fat: 26.9%* *Pro: 27.9%*	*Mediterranean-like diet:* *CHO: 51.7%* *Fat: 24.7%* *Pro: 20.5%*	84	*HbA1c* *Fasting blood sugar* *Fasting insulin* *HOMA-IR*
Jönsson et al. 2009 **(22)**	**Sweden**	*Cross-over*	T2DM patients	*13*	*Paleolithic diet:* *CHO: 32%* *Fat: 39%* *Pro: 24%*	*Diabetes diet designed in accordance with the current diabetes dietary guidelines:* *CHO: 42%* *Fat: 34%* *Pro: 20%*	90	*Fasting blood sugar* *HbA1c* *Fasting insulin* *HOMA-IR* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure* *CRP*
Masharani et al. 2015 **(34)**	**United States**	*Parallel*	T2DM patients	*Intervention: 14* *Control: 10*	*Paleolithic diet:* *CHO: 58.2%* *Fat: 27%* *Pro: 18.5%*	*American Diabetes Association recommendations:* *CHO: 54.4%* *Fat: 28.8%* *Pro: 20.3%*	21	*Fasting blood sugar* *HbA1c* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure*
Boers et al. 2014 (**21**)	**Netherlands**	*Parallel*	Subjects with characteristics of the metabolic syndrome	*Intervention: 18* *Control: 16*	*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%*	14	*Fasting blood sugar* *Fasting insulin* *HOMA-IR* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure* *CRP*
Mellberg et al. 2014 (**24**)	**Sweden**	*Parallel*	Overweight/obese postmenopausal	*Intervention: 34*	*Paleolithic diet:*	*Nordic Nutrition*	720	*Fasting blood sugar*

(*continued*)

Table 1. Continued.

Study ID	Country	Study design	*Participants*	Sample size	Intervention diet	Control diet	*Duration(day)*	Outcomes
			women	*Control: 27*	*CHO: 30%* *Fat: 40%* *Pro: 30%*	*Recommendations:* *CHO: 55–60%* *Fat: 25–30%* *Pro: 15%*		*Fasting insulin* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure* *CRP*
Stomby et al. 2015 (**31**)	**Sweden**	*Parallel*	*Overweight/obese postmenopausal*	*Intervention: 27*	*Paleolithic diet:*	*Nordic Nutrition*	*720*	*Fasting blood sugar*
			women	*Control: 22*	*CHO: 30%* *Fat: 40%* *Pro: 30%*	*Recommendations* *CHO: 55–60%* *Fat: 25–30%* *Pro: 15%*		*Fasting insulin* *HOMA-IR* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure*
Otten et al. 2016 (**32**)	**Sweden**	*Parallel*	Overweight/obese postmenopausal	*Intervention: 25*	*Paleolithic diet:*	*Nordic Nutrition*	*720*	*Fasting blood sugar*
			women	*Control: 16*	*CHO: 30%* *Fat: 40%* *Pro: 30%*	*Recommendations* *CHO: 55–60%* *Fat: 25–30%* *Pro: 15%*		*Fasting insulin* *HOMA-IR* *Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol* *Systolic blood pressure* *Diastolic blood pressure*
Fontes-Villalba et al. 2016 (**33**)	**Sweden**	*Cross-over*	T2DM patients	*13*	*Paleolithic diet:* *N/A*	*Diabetes diet designed :* *N/A*	*84*	*Fasting insulin*
Blomquist et al. 2018 (**20**)	**Sweden**	*Parallel*	*Overweight/obese postmenopausal*	*Intervention: 33*	*Paleolithic diet:*	*Nordic Nutrition*	*720*	*HOMA-IR*
			women	*Control: 25*	*CHO: 30%* *Fat: 40%* *Pro: 30%*	*Recommendations* *CHO: 55%* *Fat: 30%* *Pro: 15%*		*Triglycerides* *HDL cholesterol* *LDL cholesterol* *Total cholesterol*
Moher et al. 2015 (35)	**United States**	*Cross-over*	*Adults with hypercholesterolemia*	*20*	*Paleolithic diet:*	*traditional heart-healthy diet*	*120*	*Triglycerides*
					CHO: 23% *Fat: 40%* *Pro: 37*	*CHO: 60%* *Fat: 23%* *Pro: 17%*		*HDL cholesterol* *LDL cholesterol* *Total cholesterol*

CHO, carbohydrate; CRP, C-reactive protein; DBP, diastolic blood pressure; NR, not reported; Pro, protein; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins. HOMA-IR, homeostatic model assessment of insulin resistance. T2DM, type 2 diabetes mellitus. HbA1c, glycated hemoglobin.

Table 2. Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool.

Study, Year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall assessment of risk of bias
Lindeberg et al. 2007 **(23)**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Low**	**Low**	**Unclear**
Jönsson et al. 2009 **(22)**	**Low**	**Unclear**	**Unclear**	**Low**	**Low**	**Low**	**Unclear**
Masharani et al. 2015 **(34)**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
Boers et al. 2014 **(21)**	**Low**	**Unclear**	**Unclear**	**Unclear**	**Low**	**Low**	**Unclear**
Mellberg et al. 2014 **(24)**	**Low**	**Unclear**	**Low**	**Low**	**Low**	**Unclear**	**Unclear**
Stomby et al. 2015 **(31)**	**Low**	**Low**	**Unclear**	**Low**	**Low**	**Low**	**Unclear**
Otten et al. 2016 **(32)**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Low**	**Low**	**Unclear**
Fontes-Villalba et al. 2016 **(33)**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
Blomquist et al. 2018 **(20)**	**Low**	**Low**	**Unclear**	**Low**	**Unclear**	**Low**	**Unclear**
Moher et al. 2015 (35)	**Low**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**

WMD: −0.27 mmol/L, 95% CI: −0.39, −0.15 for TG). However, the subgroup analyses revealed that PD had no effect on HDL-C based on the duration of the intervention or on the type of metabolic disorder (Supplementary Figures 4–7).

The effect of PD on SBP and DBP

The meta-analysis of 6 RCTs based on the random effects model evidenced a significant reduction in SBP (WMD − 5.89 mmHg; 95% CI − 9.973 to − 1.86, P = 0.004) and DBP (WMD − 4.01 mmHg; 95% CI − 6.21 to − 1.80, P < 0.001) in the PD group, with no significant heterogeneity among the studies (Cochran Q test, P = 0.848, I^2=0.0%) and (Cochran Q test, P = 0.91, I^2=0.0%), respectively (Figure 4).

Moreover, the stratification based on the type of patients and the duration of the intervention revealed a significant reduction in SBP and DBP patients diagnosed with obesity or overweight (WMD: −5.77 mmHg, 95% CI: −11.02, −0.52,for SBP; WMD: −4.30 mmHg, 95% CI: −6.90, −1.71, for DBP) and when the follow-up duration was of >12 weeks (WMD: −5.96 mmHg, 95% CI: −11.81, −0.10, for SBP; WMD: −3.61 mmHg, 95% CI: −6.69, −0.53, for DBP) (Supplementary Figures 8 and 9).

Effects of PD on CRP levels

The meta-analysis of 3 RCTs concluded that CRP levels decreased significantly in the PD group (WMD: −0.84, mg/L, 95% CI: −1.62, −0.06, P = 0.034), with a significant heterogeneity noted among the studies (I^2=73.4%, P = 0.023) (Figure 5). The subgroup analysis for CRP was not possible as there were not enough studies in each group.

Sensitivity analysis and publication bias

We assessed the effect of each individual study on the overall effect size using the leave-one-out method. The findings remained robust after the sequential elimination of the studies (Supplementary Figures 10–12). There was no evidence of publication bias in the visual inspection of the funnel plot. Moreover, the results of the Egger's regression test supported the absence of a significant publication bias for SBP (P = 0.18), DBP (P = 0.50), TC (P = 0.29), LDL-C (P = 0.81), HDL-C (P = 0.16), TG (P = 0.13), HbA1c (P = 0.23), FBS (P = 0.42), insulin (P = 0.14), HOMA-IR (P = 0.08) or CRP (P = 0.81) (Supplementary Figures 13–15).

Discussion

This meta-analysis showed that the PD had no significant effect on FBS, HbA1c or HDL-C, but improved insulin levels, HOMA-IR, BP, CRP and the components of the lipid profile based on the duration of the intervention and the health status in patients diagnosed with metabolic disorders.

Firstly, the data pooled from 7 (for the insulin levels) and 6 RCTs (for the HOMA-IR) detected a significant effect of the PD on insulin and HOMA-IR compared with the control diet, respectively. In addition, the results of the subgroup analysis showed that in the trials conducted in T2DM patients and with a follow-up period of ≤12 weeks, the reduction in insulin levels was more pronounced. Moreover, the PD further reduced the HOMA-IR in obese or overweight subjects. These results could indicate a greater effect of this diet in people with various degrees of insulin resistance, such as patients suffering from obesity or diabetes. However, our results contradict the findings of Manheimer et al. (Manheimer et al. 2015) and Jamba et al. (Jamka et al. 2020), possibly due to differences in the studied populations, the number of analyzed studies and the inclusion criteria employed. In other words, we tried to examine the effects of the PD in patients suffering from metabolic disorders, in contrast to other meta-analyses which have examined subjects with other conditions as well. Even though the PD did not result in a significant alteration of FBS as compared to the control diet, our findings regarding the effects of the PD on FBS and HbA1C are consistent with previous reports (Manheimer et al. 2015; Jamka et al. 2020). However, older evidence suggests that FBS improves with the adherence to a low-carbohydrate diet, especially in T2DM patients (Wang et al. 2018; Boden et al. 2005). Recently, the PD has been shown to reduce FBS in overweight and obese individuals who also associated T2DM. However, these papers did not detect a significant change in the subjects who followed the PD combined with physical exercise for three weeks *versus* the PD alone (Otten et al. 2016). The absence of a change in the glucose concentration and the more pronounced effect of the PD on insulin levels during the intervention which lasted ≤12 weeks may be related to the potentially harmful effects of the PD on the composition of the microbiota. Genoni et al. (Genoni et al. 2020) hypothesized that the long-term use of the PD may not be beneficial to the gut homeostasis because it leads to an imbalance of the intestinal microbiota *via* reducing the abundance of helpful gut

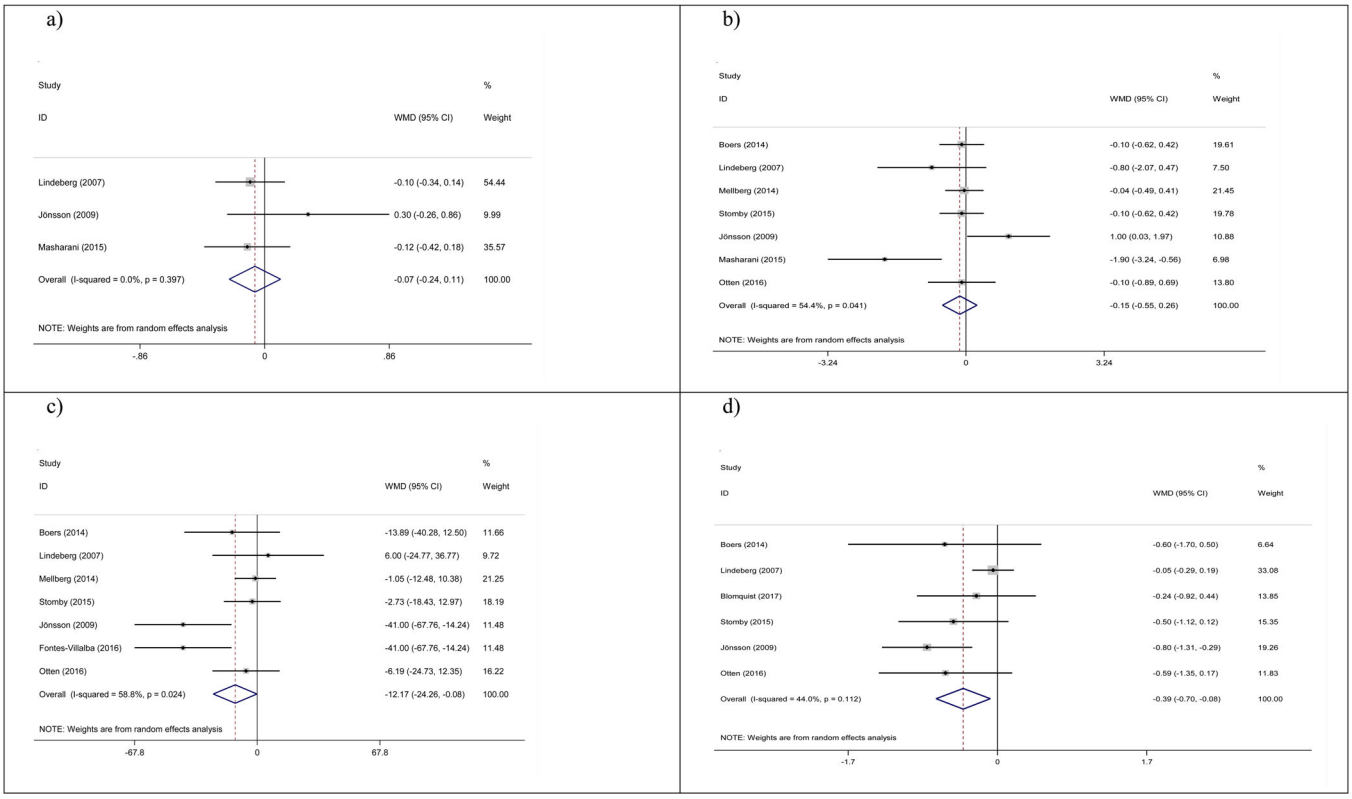

Figure 2. Forest plots from the meta-analysis of clinical trials investigating the effects Paleolithic diet on (a) HbA1c, (b) glucose, (c) insulin and d) HOMA-IR. WMD: weighted mean difference.

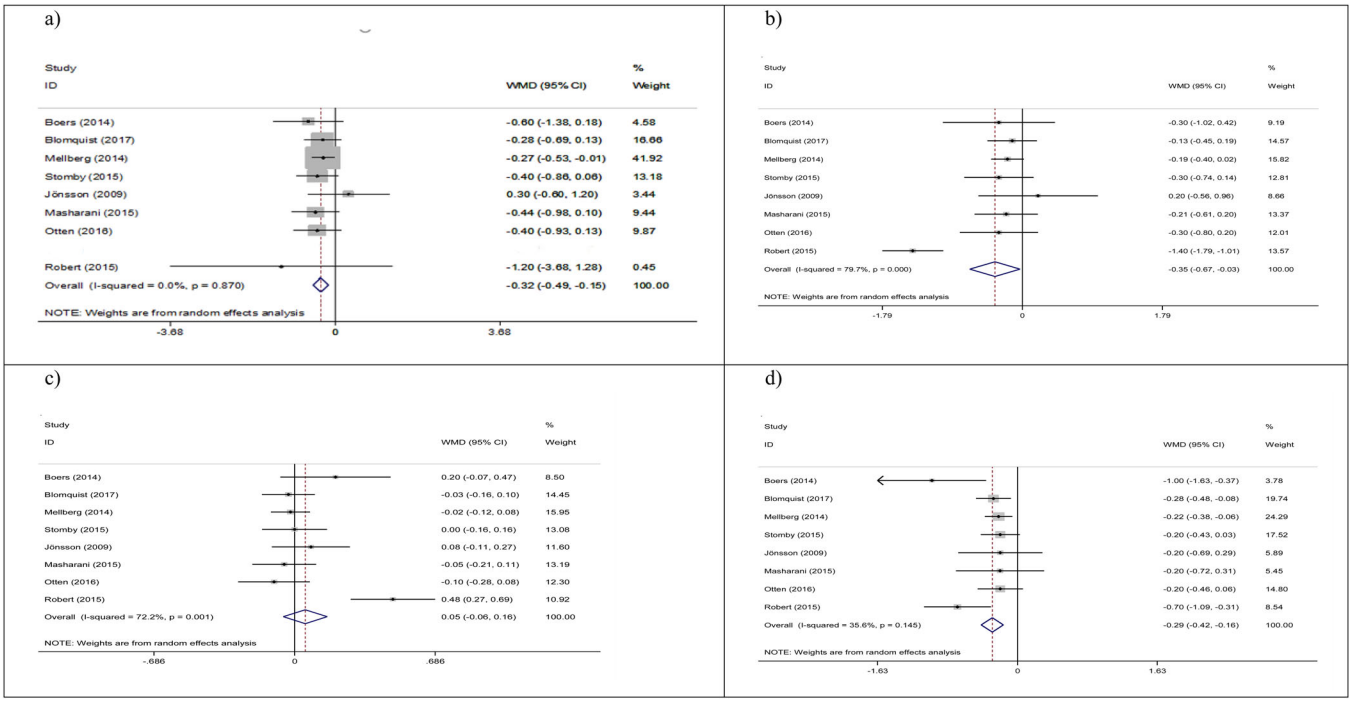

Figure 3. Forest plots from the meta-analysis of clinical trials investigating the effects Paleolithic diet on (a) cholesterol, (b) LDL, (c) HDL and d) TG. WMD: weighted mean difference.

bacteria and increasing the production of trimethylamine-N-oxide. Previous studies have detected an association between an imbalanced microbiota and an impaired glucose metabolism (Gérard and Vidal 2019).

The benefic impact of the PD on several components of the glucose metabolism might be related to the increased intake of fibers and dietary antioxidants, e.g. vitamins E and C, as well as to a reduced consumption of refined grains

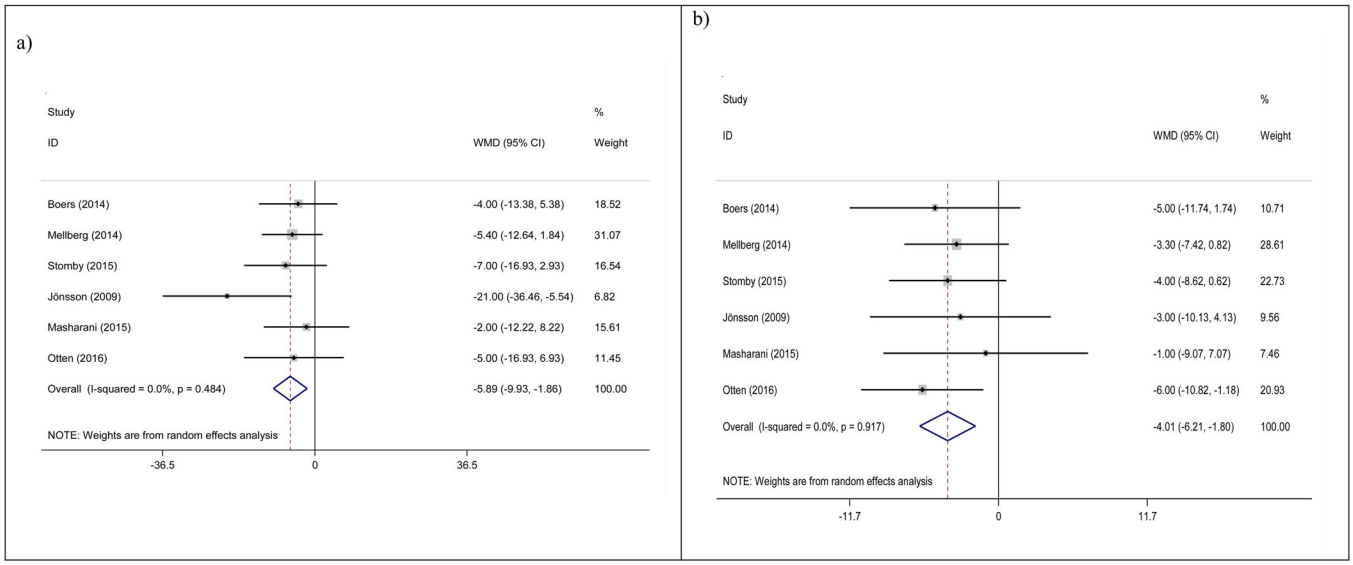

Figure 4. Forest plots from the meta-analysis of clinical trials investigating the effects Paleolithic diet on (a) SBP and (b) DBP. WMD: weighted mean difference.

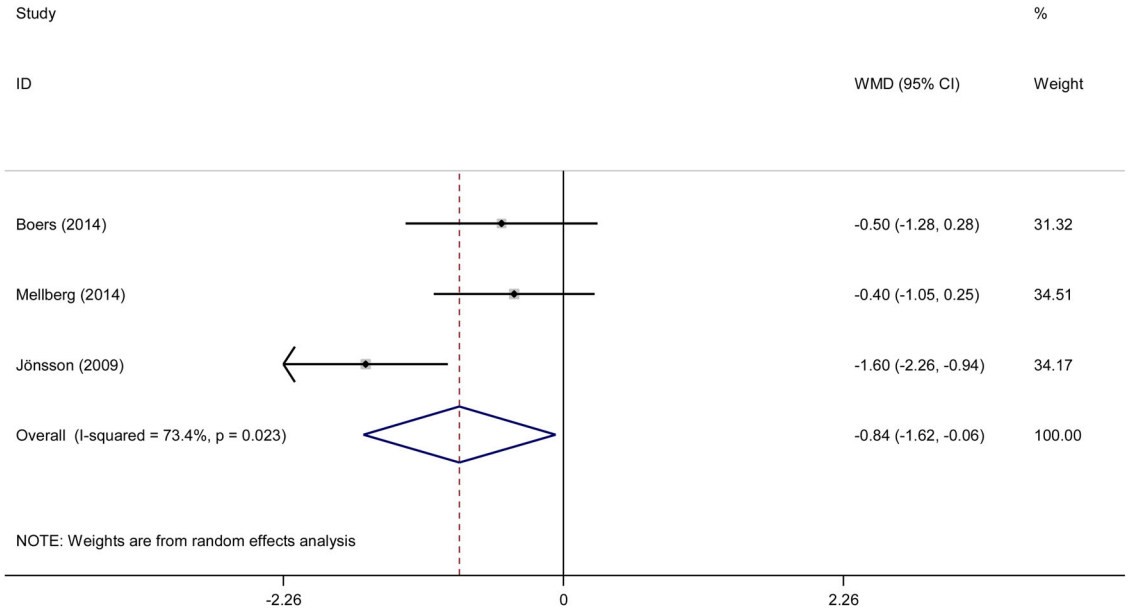

Figure 5. Forest plots from the meta-analysis of clinical trials investigating the effects Paleolithic diet on CRP. WMD: weighted mean difference.

and sugars in the PD *versus* other modern era diets (Cordain 2002; Jew, Abumweis, and Jones 2009). Moreover, data from clinical trials have reported that the PD improves insulin sensitivity by increasing adiponectin and leptin levels. Adiponectin levels seem to increase because the intake of fat affects the expression of the PPARγ (Jönsson et al. 2009; Masharani et al. 2015; Fontes-Villalba et al. 2016).

Secondly, data from 8 trials were pooled to evaluate the influence of the PD on the lipid profile. The PD reduced TC, TG and LDL-C, but failed to influence HDL-C. The subgroup analysis revealed a significant effect of the PD on TC, TG and LDL-C which was more noticeable when the duration of the intervention was of >12 weeks and in the subjects suffering from obesity or overweight. Contrastingly, the previously published meta-analyses (Ghaedi et al. 2019; Manheimer et al. 2015) detected a beneficial effect of the PD on HDL-C, but the influence of the PD on the other components of the lipid profile was consistent with our findings. In our study, the PD only increased HDL-C by about 0.05 mmol/L. The lack of significance reported in our study could be due to the differences in basal HDL-C levels, as well as to the number of analyzed studies which might have affected the data analysis.

One of the reasons behind the reduction in TC, TG and LDL-C could be related to an increase in the levels of lipoprotein enzymes which is associated with a decrease in the concentrations of lipids in the blood. Moreover, because the cellular levels of lipoprotein enzymes increase, there is a reduction of the expression of cell surface receptors and thus the synthesis of the aforementioned components of the lipid profile decreases (Masharani et al. 2015). Furthermore, epidemiological studies have reported that the PD is abundant in polyphenols, e.g. flavonoids, as well as lignin, which are known for their lipid-lowering properties (Pastore,

Brooks, and Carbone 2015; Lindeberg et al. 2007). In addition, subjects who follow the PD have a reduced intake of refined sugars as well as saturated fatty acids (SFA), and a consequent elevated intake of omega-3, mono unsaturated fatty acids (MUFA). The fatty acids contained in this diet are capable to reduce TG and TC levels (Howard and Wylie-Rosett 2002; Eaton and Eaton III 2000) as opposed to the components of Western diets.

Our findings also illustrate that the PD resulted in significant reductions in SBP and DBP. The effect of the PD on blood pressure was greater in obese or overweight individuals who were followed-up for more than 12 weeks. Thus, we may hypothesize that the PD improves the functioning of the endothelium and of the vasculature in obese or overweight subjects (Bhatta et al. 2017). The PD is rich in potassium and magnesium due to its high content in fruits and vegetables and has a poor sodium content since it limits the consumption of processed foods, explaining why the PD is effective in lowering blood pressure (Eaton and Eaton III 2000; Palmer and Clegg 2016). In addition, previous studies have reported that PD leads to weight loss and that the PD is rich in phytochemicals, explaining why the PD can lower blood pressure and inflammation levels (Eaton and Eaton III 2000; Hosseini et al. 2018; Obert et al. 2017). Our results also showed a significant decrease in CRP concentrations.

The current paper detailed the results of a systematic review and meta-analysis which evaluated the effects of the PD on the glucose metabolisms, the lipid profile and on other biochemical factors in patients with metabolic disorders. We analyzed the data derived from 10 RCTs with a total of 342 subjects suffering from metabolic ailments. Furthermore, we performed subgroup analyses to assess the effect of the PD on each of these factors. In addition, a low degree of heterogeneity and a low risk of publication bias was detected in our study. Moreover, we observed a stronger causal relationship due to the inclusion of studies with a RCT design. However, in most of the studies included in this meta-analysis, the influences of several confounding factors, e.g. the genetic background, the diet used by the control group, and the adherence to the diet among the participants could not be assessed. The small number of studies included in this meta-analysis could be another limitation of our paper.

Conclusion

According to our findings, the PD improved insulin levels and HDL-C, and reduced insulin resistance, blood pressure, TC, LDL-C, TG and CRP levels in patients with metabolic disorders. However, more studies with different designs and of a higher quality are needed to confirm the findings of our study.

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Authorship

Mh.S. and S.F. carried out the concept, design and drafting of this study. M.G. and A.L. searched databases, screened articles and extracted data. S.F. and H.O. performed the acquisition, analysis, and interpretation of data. Mh.S and M.G. critically revised the manuscript. All authors approved the final version of the manuscript.

Disclosure statement

None of the authors had any personal or financial conflicts of interest.

Consent for publication

All authors of this manuscript declared their consent for publication.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

DBP	diastolic blood pressure
CRP	C-reactive protein
ES	effect size
FBS	fasting blood sugar
HbA1c	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment of insulin resistance
LDL-C	low-density lipoprotein cholesterol
MetS	metabolic syndrome
PD	Paleolithic diet
SBP	systolic blood pressure
TC	total cholesterol
TG	triglycerides
T2DM	type 2 diabetes mellitus
RCT	randomized controlled trials
WC	waist circumference
WMD	weighted mean difference.

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Supplemental added to complete or make up a deficiency More (Definitions, Synonyms, Translation)