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INTERVENTION DESIGN PROPOSAL

Paleo Nutritional Intervention for Type 2 Diabetes Mellitus: A Systematic Reevaluation and Consensus Report; Definition and Macronutrient Proposal for Trials

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ABSTRACT

Background: Dietary interventions, including the Paleo diet (PD) play a crucial role in the treatment of patients with type 2 diabetes mellitus (T2DM). However, the clinical significance of them remains ambiguous due to limited conclusive studies.
Objective: We conducted a systematic review to reevaluate existing research on the PD in individuals with T2DM, specifically focusing on whether this diet demonstrates a discernible improvement in metabolic biomarkers, further aiming to assess variables of interest (clinical definition, macronutrient ranges, and glycemic index of a PD) across trials.
Methods: Online databases were searched for clinical trials and systematic reviews that included the PD as an intervention on patients with T2DM, from which 32 publications were selected. A random effects model was utilized to assess the difference in reported metabolic biomarkers from baseline to end-of-intervention time point. Variables of interest were analyzed across trials.
Results: Four articles met inclusion criteria. The overall effect for the PD intervention across pooled studies was only significant for DBP (P<.001). Significant heterogeneity was found among pooled studies for the PD (FBG [P=.03; I^2=67%], glucose AUC_{0-120} [P=.002; I^2=84%], SBP [P<.001; I^2=93%], TC [P=.007; I^2=80%], LDL [P<.001; I^2=99%], and TG [P=0.04; I^2=69%]) and the control diets (wt [P<.001; I^2=99%], wc [P<.001; I^2=99%], sodium:potassium ratio [P<.001; I^2 = 96%], and HDL [P<.001; I^2=87%]). A PD definition, macronutrient ranges, and glycemic index was proposed for conducting future trials.
Conclusion: The inconclusiveness of the PD for T2DM was due to a number of inconsistencies across trials and systematic reviews. As a result, we propose consistency of PD definition (archeological definition and no modern-day interpretations, assumptions, or allowances of excluded foods), standardized macronutrient percentages, disease diagnosis, trial time length, and equal training across groups for all future trials. A standard control diet, such as the ADA diet, should be used as a comparison. The reduction in DBP across pooled results suggests that the PD may have a beneficial impact on metabolic markers related to T2DM.

Introduction

Epidemiology

To gain a comprehensive perspective on the importance of readdressing the Paleo diet (PD) for type 2 diabetes mellitus (T2DM) patients, it is crucial to emphasize the compelling epidemiology surrounding this disease. Despite the well-established impact of dietary choices, the global prevalence and incidence of T2DM continues to rise. The Center for Disease Control and Prevention revealed in 2022 that 130 million adults (40%) of the US population currently live with either T2DM or prediabetes, with an additional 1.4 million new cases emerging in 2019.[1] Additionally, there is a disproportionate prevalence of T2DM among Native Americans, an indigenous population historically aligned with the principles associated with the PD lifestyle.[1,2] Over recent decades a noticeable shift has been observed regarding an increase in sedentary lifestyles within this population.[1,2] Based on these trends, it is imperative to explore the role of the PD in treating T2DM.

The Paleo Diet as Medical Nutrition Therapy

Over the years, the American Diabetes Association

(ADA) has played a vital role in offering dietary recommendations for the management of T2DM. According to Evert et al,[3] ADA recognizes the effectiveness of medical nutrition therapy (MNT) diets in improving both primary biomarkers, such as glycated hemoglobin A1c (HbA1c), and secondary indicators associated with the disease, including weight (wt), blood pressure (BP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). In the consensus report by Evert et al,[3] various stand-alone diets, such as the Mediterranean, vegetarian, vegan, DASH, low-fat, or low-carbohydrate diets, have demonstrated positive outcomes in managing T2DM. However, when examining the PD, the report demonstrated mixed findings.

The consensus report documents that the PD (characterized as meat, seafood, eggs, nuts, fruits, and vegetables) shares a combination of several dietary characteristics with the other diets.[3] These include an emphasis on increased consumption of non-starchy vegetables, fruits, and fiber, while reducing saturated fatty acids and starchy carbohydrates, in addition to also avoiding ultra-processed foods, including dairy, sugar, and alcohol (as seen in *Table 1* of the Evert et al[3] study). According to these findings, the components of the PD are well-aligned with the dietary constituents that have been associated with positive outcomes in reducing the risk of T2DM and improving associated biomarkers.[3–5] This raises concerns about the validity of the Evert et al[3] consensus report statements that indicate the PD is not effective for improving T2DM biomarkers.

Addressing Intervention Inconsistencies

The inconclusive results of the PD being ineffective for T2DM may be due to the fact that there are various inconsistencies across trials in assessment data, presented tabulated data, and trial intervention criteria.[6–14] Allowed dietary foods, assessed macronutrient ranges, trial timepoints, and adherence are essential variables to consider among trials.[6,9,10,12] As well, the number of treatment arms and ways of assessing the PD against controls remain as equally important.[7] Throughout systematic reviews, primary disease inclusion criteria and the number of studies included are also equally inconsistent.[8,11,14] Thus, these inconsistencies create challenges among literature reviewers making it difficult to trust the findings of the presented data. Thus, necessitating a reevaluation of all the available evidence. The re-examining of the evidence can assist in establishing a more structured MNT intervention approach for conducting future large-scale translational trials involving the PD, which in turn, could provide further insights about the diet and its role in clinical research.

Objective

Given the impact diet has on the management and prevention of T2DM combined with the limited studies to date utilizing the PD for T2DM, it is evident that there is a need to explore the effectiveness of a PD intervention for disease management. Therefore, the purpose of this study is to: 1) reevaluate existing research on the impact of PD in individuals with T2DM, specifically focusing on whether this diet improves T2DM primary and secondary biomarkers, and 2) provide a structured intervention approach for future large-scale translational trials.

Methods

Eligibility Criteria

For this review, only articles that met specific criteria were included. The eligible articles consisted of human clinical trials and systematic reviews, specifically assessing the impact of the PD on adults aged 18 years and older with T2DM. The review allowed for comparisons between the PD and other diets used as evidence-based nutritional approaches. Additionally, studies that included populations with comorbidities of cardiovascular conditions were considered, as long as T2DM or Metabolic Syndrome (MetS) was the primary diagnosis. This decision was due to T2DM subjects having increased risk of cardiovascular morbidity and mortality.[10] However, studies focusing on obesity were excluded, as this is a secondary diagnosis with glucose disorders. Studies that focused on diets other than the PD as the primary treatment arm, such as ketogenic, vegan, vegetarian, Mediterranean, DASH, ADA, low or high macronutrient, low-calorie, fasting, calorie-restriction, or any other diet were excluded. Studies with three treatment arms were excluded, as authors wanted a clear distinction of PD compared to other diets alone without any other variables. Literature review articles were also excluded from this review. Furthermore, studies involving healthy adult populations or combinations of herbal supplements were deemed ineligible.

Information Sources

To identify relevant articles, an extensive search strategy included sources that were available as full-text or open-access articles from following electronic databases: PubMed, BioMed Central, Google Scholar, EBSCO, Academy of Nutrition and Dietetics, and ResearchGate. The final results are charted in Table 1.

Search Strategy

The search for relevant studies was conducted by the authors (KD, JH, and MW) from September 1st, 2022 to June 13th, 2023. The search terms used combined MeSH terms, specifically "Paleo* AND diabetes," "Paleo* AND metabolic syndrome," "Paleo* AND T2DM," and "Paleo* AND Type 2 diabetes." The authors applied filters to include only human studies, articles written in English, and those published from the year 2000 onwards. It is important to note that setting a cutoff date for accessing research serves several purposes: 1) it ensures the currency of the information, as scientific knowledge is continually evolving; 2) it helps ensure the quality and validity of the included studies to maintain rigorous standards; and 3) it enables authors to focus on recent studies, facilitating efficient data collection.

Selection Process

The reviewers, JH and MW, independently screened a total of thirty-two publications. A subsequent search was completed during screening by KD to ensure all literature covering the associated topic was located. Each article underwent screening to determine its eligibility of inclusion based on its investigation of the impact of a PD on T2DM. Subsequently, the reviewers discussed the results and made necessary amendments to the screening outcomes for data extraction. The evaluation process involved assessing the titles, abstracts, and full texts of all publications. In

Table 1: Critical Appraisal of Studies Exploring the Paleo Diet and Glucose Disorders

Study ID	Methods	Comprehensive Search	Quality Appraisal	Exclude	Include In:		
					Software Analysis	Diet Analysis	Macronutrient Analysis
Andrikopoulos [23]	R	Y	N	Y	N	N	N
Bligh et al [32]	R	Y	N	Y	N	N	N
Boers et al [6]	RCSS	Y	Y	N	Y	Y	Y
Carter et al 17]	SR	Y	N	Y	N	N	N
de la O et al [33]	P	Y	N	Y	N	N	N
de Menezes et al [21]	RCT	Y	N	Y	N	N	N
Doepp [34]	R	Y	N	Y	N	N	N
Fontes-Villalba et al [25]	A- RCrT	Y	Y	Y	N	N	N
Frassetto et al [22]	RCrT	Y	Y	N	N	N	N
Gyorkos et al [	RCT	Y	Y	N	N	N	N
Jamka et al [8]	SR	Y	Y	N	N	N	N
Janssen [35]	R	Y	N	Y	N	N	N
Jönsson et al [9]	RCrT-P	Y	Y	N	Y	Y	Y
Jönsson et al [19]	CT	Y	Y	Y	N	N	N
Jönsson et al [26]	A- RCrT	Y	Y	Y	N	N	N
Kopp [36]	R	Y	N	Y	N	N	N
Lindberg et al [10]	RCT	Y	Y	N	Y	Y	Y
Manheimer et al [11]	SR	Y	Y	N	N	N	N
Markofski et al [24]	SAS	Y	Unclear	Y	N	N	N
Mårtensson et al [27]	A- RCT	Y	Y	Y	N	N	N
Masharani et al [12]	RCT	Y	Y	N	Y	Y	Y
Olivieri [37]	R	Y	N	Y	N	N	N
Otten et al [28]	A- RCT	Y	Y	N	N	N	N
Otten et al [29]	A- RCT	Y	Y	Y	N	N	N
Otten et al [13]	RCT	Y	Y	Y	N	N	N
Schwingshackl et al [20]	P	Y	N	Y	N	N	N
Shemirani et al [18]	RCT	Y	Unclear	Y	N	N	N
Sohouli et al [14]	SR	Y	Y	N	N	N	N
Stomby et al [31]	A- RCT	Y	Y	Y	N	N	N
Stomby et al [30]	A- RCT	Y	Y	Y	N	N	N
Tarantino et al [38]	R	Y	N	Y	N	N	N
Wendorf & Goldfine [2]	R	Y	N	Y	N	N	N

Acronyms: Y, yes; N, no; RCT, randomized controlled trial; CT, controlled trial; R, review; SR, systematic review; RCrT, randomized crossover trial; RCrT-P, randomized crossover pilot trial; RCSS, randomized controlled single-blinded, pilot study; P, proposal; A-RCT, analysis of a RCT or an exploratory findings study of a RCT; A-RCrT, analysis of a RCrT or an exploratory findings study of a RCrT; SAS, single arm study.

cases where the full text was not readily available, the authors of the respective articles were contacted to obtain the complete text for inclusion in the current review. Any disagreements regarding study selection and data extraction were resolved through consensus and constructive discussions.

Data Collection Process

The process of data-charting was developed collaboratively, involving discussions on the variables to be extracted. One reviewer, JH, independently charted and continuously updated the data through an iterative process of relevance. The data extraction by JH, MW, and PK, encompassed various aspects, including systematic review characteristics, trial characteristics, and risk of bias assessment. The authors synthesized data by further charting it through software analysis.

Data Items

We sought all results compatible with each outcome domain, including data from various time points (ranging from baseline, to weeks, to months) and analyses (human controlled trials and systematic reviews) to ensure a comprehensive evaluation. Outcomes included a change in primary biomarkers, such as fasting blood glucose (FBG), HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin (FI), and glucose area under the curve (AUC). Secondary biomarkers were also utilized for assessing metabolic outcomes including anthropometrics (wt, body mass index [BMI], waist circumference [wc], and fat percentage), cardiovascular biomarkers (BP [systolic (SBP) or diastolic (DBP)], and VO_2max), lipid biomarkers (total cholesterol [TC], LDL, HDL, and TG), and inflammatory biomarkers (C-reactive protein [CRP], tumor necrosis factor-alpha [TNFα], and interleukin-6 [IL-6]). Authors collected various characteristics directly from the included studies, aiming to clarify unaddressed information in the selected articles. Specific variables of interest were previous systematic review characteristics, including the number of studies used in each review and the included primary morbidities. Furthermore, the variables in individual studies are described here as: timepoints, definition of the PD due to the variation of the allowed foods in PD protocols, distribution of macronutrients between clinical trials, and glycemic index of the PD.

Study Risk of Bias Assessment

To ensure rigorous analysis, we utilized the Checklist for Randomized Controlled Trials (RCTs) for use in critically appraising the current systematic review.[15,16] This comprehensive appraisal process evaluates the judgment and effectiveness of studies, enabling authors to determine their applicability in practice.[15,16] The included studies were categorized based on predefined inclusion and exclusion criteria, with two reviewers (KD and JH) independently assessing the risk of bias. Bias was further assessed a second time by PK.

Effect Measures

To examine RCTs for the meta-analysis, the reviewers used Cochrane RevMan software. For examining biomarker continuous outcomes, inverse variance statistical methods, mean difference effects measure, and random effects analysis mode were utilized to calculate change from baseline to end-of-intervention in both the intervention and control groups. Mean differences were calculated for FBG and BP, to compare the average difference in blood plasma levels between the PD group and the control group. Standard mean calculations were used for examining macronutrient ranges. All statistics and P values were reported and formatted using AMA guidelines.

Synthesis Methods

Data tabulation included the creation of tables, figures, forest plots, and other graphical representations to present data effectively. A random effect model was chosen due to the anticipated heterogeneity among studies. No subgroup analyses were conducted, as there was not enough consistent data to explore these areas. Sensitivity analysis was performed by excluding studies with a high risk of bias to assess the validity and reliability of the synthesized results.

Certainty Assessment

Out of the thirty-two studies reviewed, 56% met the criteria and were rated as 'Yes' for quality appraisal, indicating a higher level of certainty of effectiveness of the studies. These studies fit initial inclusion criteria, had robust designs, adequate sample sizes, and low risk of bias, suggesting a higher confidence in their findings. However, a nearly equal proportion of studies (44%) were rated as ‘No’ or 'Unclear' for some criteria, indicating exclusion, limited information, or insufficient reporting in those areas. These 44% of studies were initially excluded from the analyses and their exclusion did not impact the overall certainty of evidence for the assessed outcomes. See Table 1.

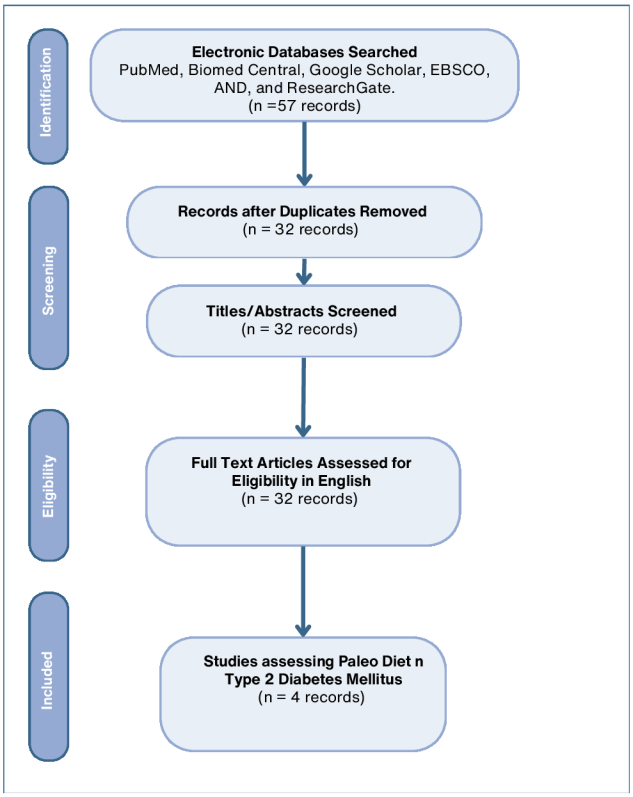
Results

Study Selection

The initial search identified thirty-two studies based on titles and abstract assessment using the search criteria outlined. Twenty-eight studies were excluded after a thorough evaluation because they did not meet the inclusion criteria (Figure 1). Four were excluded

because one was a systematic review evaluating the Mediterranean diet and not the PD,[17] one was an ongoing protocol that included hepatic comorbidities with T2DM,[18] one was an exploratory study expanding on the 2007 Lindberg et al study,[19] and one was a protocol proposal.[20] Two were trials whose outcomes measured basic anthropometrics or net acid excretion and not T2DM primary, cardiovascular, or lipid serum markers;[21,22] two were trials assessing healthy adult populations;[23,24] two were exploratory findings expanding on the 2009 Jönsson et al study;[25,26] and two studies were examining the PD with exercise against a control group.[7,13] Additionally, three articles were found to be systematic reviews with meta-analysis; however although the outcomes included the impact of a PD on T2DM primary and secondary biomarkers, there were inconsistencies between morbidity and number of studies, making it difficult to analyze through Cochrane software.[8,11,14] Furthermore, five were exploratory RCTs further evaluating PD and

Figure 1. Flow Chart



the PD with exercise on additional tertiary biomarkers of the 2017 Otten et al study.[27,31] Lastly, eight were literature reviews either sharing opinion on the topic, diet was not aligned with historical PD principles, or the article was written prior to the year 2,000.[2,32–38] See Figure 1.

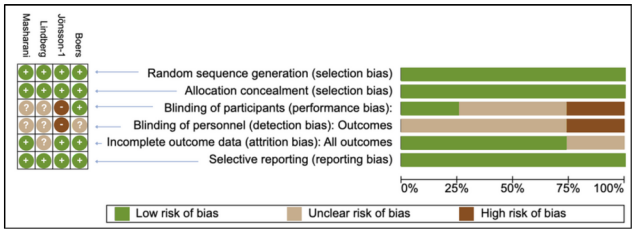
Study Characteristics

In total, four RCTs articles were kept and included in the random effects model software analysis. However, to gain a more comprehensive understanding of the inclusivity of the PD on metabolic outcomes of T2DM between the systematic reviews,[8,11,14] the authors of this study needed to look deeper into why there were inconsistencies in the number of studies and included morbidities across these particular studies. Therefore, the systematic reviews were re-included into the review for rudimentary analysis since they met original inclusion criteria. This comprehensive analysis would also aim to provide insights for included morbidities and number of studies, while adding more insight into the reasons for variations in individual studies.

Results of Risk of Bias in Studies

In the current systematic review of studies examining the relationship between the PD and T2DM, the authors (KD and JH) conducted a thorough assessment of the risk of bias for each included study (Figure 2). This assessment was similar to previous systematic review assessments. Therefore, authors chose to have a third researcher (PK) further assess bias. The overall risk was found to be low as illustrated in Figure 2. Even though there was a low risk of bias, this does not imply that the designs of the studies were similar, as indicated by the high heterogeneity.

Figure 2. Bias Assessment



Changes in Diabetes Biomarkers Following the Paleo Diet

Individual Systematic Reviews

The systematic reviews yielded different conclusions for the PD on T2DM biomarkers. Jamka et al[8] included 5 studies (Table 2). When comparing pre- and post-intervention, the authors observed statistically significant reductions in means between the experimental (E) and control (C) groups using fixed effects model and statistically significant differences for FBG (mean 6.8 mmol/l to 5.1 mmol/l, mean *diff*: 0.899, SE 0.39, *P*=.021) in one individual study.[8] The study demonstrated several markers appearing to favor the PD for individual studies on forest plot analysis. However, pooled studies did not reach significance.[8]

Jamka et al[8] concluded the PD diet does not exhibit superiority compared to other healthy diets in improving metabolic markers within this particular population. Nonetheless, the control diet did not supersede the PD either, suggesting that the PD could yield favorable results in forthcoming trials designed more effectively.

Alternatively, the study by Sohouli et al[14] included ten studies examining the PD and determined differing results (Table 2). The inclusion of criteria for the Sohouli et al[14] study encompassed primary morbidities distinct from T2DM or MetS with glucose disorders as secondary conditions, such as obesity and hypercholesterolemia. [14]The meta-analysis revealed a significant decrease in the FI levels and HOMA-IR (WMD: -12.17 IU/mL, 95% CI -24.26 to -0.08, *P*=.04 and WMD: -0.39, 95% CI -0.70 to -0.08, *P*=.013), whereas no significant effects were found for HbA1c and FBG.[14] It should be noted that while the CI for the reduction in FI levels (-24.26 to -0.08 IU/mL) encompasses a wide range, the observed decrease still aligns with favorable outcomes in managing insulin resistance and related metabolic disorder.[14] The analysis revealed a noteworthy heterogeneity among the PD studies that measured FI and HbA1c biomarkers (I^2=58.8%, *P*=.024 and I^2=54.4%, *P*=.041).[14] During subgroup analysis, greater reduction in FI was observed in T2DM subjects, WMD: 41.00 IU/mL, 95% CI (59.92-22.08).[14] Also, RCTs with a 12-week follow-up period exhibited a notable reduction in FI, WMD: -23.28 IU/mL, CI (-44.82 to -1.73).[14] Furthermore, overweight or obese subjects with metabolic conditions demonstrated a significant decrease in HOMA-IR, WMD: -0.44, 95% CI (-0.83 to -0.04).[14]

Table 2. Systematic Review Characteristics

Study	n=599	Studies Included in their Review	Included Morbidities	B	FO	UO
Jamka et al [8]	98	Boers et al.[6] Fontes-Villalba et al.[25] Jönsson et al., 2009 Lindberg et al.[10] Masharani et al., 2015	MetS T2DM T2DM T2DM & IHD T2DM	Primary		FBG HbA1c HOMA-IR FI Glucose AUC_{0-120} Insulin AUC_{0-120}
Manheimer et al [11]	159	Boers et al.[6] Jönsson et al.[9] Lindberg et al.[10] Melberg et al., 2014	MetS T2DM T2DM & IHD Obesity	Primary Secondary	Waist circ. SBP DBP TG	FBG HDL
Sohouli et al [14]	342	Boers et al.[6] Blomquist et al., 2018 Fontes-Villalba et al.[25] Jönsson et al.[9] Lindberg et al.[10] Masharani et al.[12] Melberg et al., 2014 Moher et al., 2015 Otten et al., 2016 Stomby et al., 2015	MetS Obesity T2DM T2DM T2DM & IHD T2DM Obesity Hypercholesterolemia Obesity Obesity	Primary Secondary	HOMA-IR FI CRP SBP DBP TC LDL TG	FBG HbA1c HDL

Acronyms: B, biomarker; FO, favorable outcomes; UO, unfavorable outcomes; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; IHD, ischemic heart disease; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A; HOMA-IR homeostatic model assessment of insulin resistance measurement; FI, fasting insulin; CRP, c-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride.

However, insufficient data precluded subgroup analysis for HbA1c levels.[14] It was further reported that significant decreases were observed in secondary biomarkers including TC, TG, LDL, SBP, DBP, and CRP (WMD: 0.32 mmol/L, 95% CI 0.49-0.15, *P*<.001; WMD: 0.29 mmol/L, 95% CI 0.42-0.16, *P*<.001; WMD: 0.35 mmol/L, 95% CI 0.67-0.03, *P*=.032; WMD: 5.89 mmHg; 95% CI 9.973-1.86, *P*=.004; WMD 4.01 mmHg; 95% CI 6.21-1.80, *P*<.001; and WMD: 0.84 mg/L, 95% CI 1.62-0.06, *P*=.034). Nonetheless, significant heterogeneity was observed between the studies that assessed HDL and LDL (*P*=.001, I^2=72.2% and I^2=79.7%, *P*<.001) suggesting Manheimer et al[11] reviewed 4 studies (Table 2), and saw greater pooled improvements in wc (*P*=.05) and TG (*P*=.03). Pooled improvements for overall Z effect size were also observed in both SBP and DBP (*P*=.05) in the PD, while a significant trend in TG was observed for heterogeneity (I^2=85.6%) among studies.[11] Additionally, FBG and HDL levels were found to be favorable, yet, non-significant.[11]

Individual Trials

Across four studies, the implementation of the PD diet has been documented to improve primary outcomes.[6,9,10,12] Boers et al[6] study examined the effects of PD on MetS and showed significant improvements of FBG (PD: mean 0.4 mmol/l, SD 0.5, *P*=.01 vs ID: mean -0.3 mmol/l, SD 0.4, *P*<.001), FI (PD: mean -2.7 mU/l, SD 5.0, *P*=.03 vs ID: mean -1.4 mU/l, SD 3.2, *P*=.14), and HOMA-IR (PD: mean -0.9, SD 1.5, *P*=.03 vs ID: mean 0.5, SD 0.9, *P*=.06) in the PD group when analyzing paired differences. A significant reduction in secondary biomarkers, including TC (-0.52 mmol/l, *P*=.037; PD: mean -07 mmol/l, SD 0.7, *P*<.001 vs ID: mean -0.4 mmol/l, SD 0.5, *P*=.02), SBP (-9.1 mmHg, *P*=.015; PD: mean -8.5 mmHg, SD 12.0, *P*=.01 vs ID: mean -4.2 mmHg, SD 5.6, *P*=.02), DBP (-5.2 mmHg, *P*=.038; PD: mean -8.0 mmHg, SD 8.3, *P*<.001 vs ID: mean -3.5 mmHg, SD 5.6, *P*=.03), and TG (-0.89 mmol/l, *P*=.001; PD: mean -0.9 mmol/l, SD 1.1, *P*<.001 vs ID: mean 0.1 mmol/l, SD 0.4, *P*=.63) was also observed.[6] An increase in HDL levels (0.15 mmol/l; *P*=.013) was observed in the PD group when compared to the control group, and significant improvements were shown in TG/HDL ratio for glucose tolerance and TC/HDL ratio for lipid screening (PD: mean -0.8, SD 1.2,

P=.01 vs ID: mean 0.2, SD 0.3, *P*=.08 and PD: mean -0.5, SD 0.7, *P*=.01 vs ID: mean 0.9, SD 1.3, *P*=.03).[6] Additionally, there was a non-significant decrease in LDL in the PD group.[6] A post-hoc test analyzing paired differences revealed a significant difference (PD: mean -0.3 mmol/l, SD 0.5, *P*=.02 vs ID: mean -0.2 mmol/l, SD 0.5, *P*=.18).[6] Both groups saw improvements in wc and wt, however, there was an average of 1.32 kg greater weight loss in individuals eating a PD.[6] Inflammatory markers were not significant during paired group analyses.[6] In summary, the number of MetS characteristics in the PD group had a greater decrease (-1.07 characteristics; *P*=.01) than the control group.[6] See Table 3.

During an analysis of differences between diet groups, Jönsson et al[9] stated the changes in FBG were non-significant (diff -0.5mmol/l, *P*=.08). There was a substantial decrease in HbA1c by at least -0.4% (*P*=.01) units showing significant risk reduction for cardiovascular disease (diff -0.4% Mono-S, *P*=.02),[9] a more specific indication in diagnosing T2DM. They additionally revealed a significant difference in HDL (*diff* 0.08 mmol/l, *P*=.03), TG (*diff* -0.4 mmol, *P*=.003), DBP (*diff* -4 mmHg, *P*=.03), wt (*diff* -3 kg, *P*=.01), BMI (*diff* -1 kg/m2, *P*=.04), and wc (*diff* -4 cm, *P*=.02) when comparing the difference between diets.[9] Although significant, it should be noted that BMI and wc differences were small. During within-group analyses, lower mean values were observed in the PD group, compared to the control group, revealing a significant risk reduction for cardiovascular disease for the following biomarkers: HbA1c (PD: mean 5.5%, SD 0.7, *P*<.001 vs DD: mean 5.9%, SD 0.9, *P*=.001), TG (PD: mean 1.0 mmol/l, SD 0.5, *P*=.003 vs DD: mean 1.5 mmol/l, SD 0.7, *P*=.70), SBP (PD: mean 140 mmHg, SD 12, *P*=.048 vs DD: mean 149 mmHg, SD 22, *P*=.70), wt (PD: mean 81 kg, SD 13, *P*=.005 vs DD: mean 84 kg, SD 15, *P*=.052), BMI (PD: mean 28 kg/m2, SD 5, *P*=.01 vs DD: mean 29 kg/m2, SD 6, *P*=.03), wc (PD: mean 94 cm, SD 9, *P*=.01 vs DD: mean 98 cm, SD 11, *P*=.02), and FBG (PD: mean 7.0 mmol/l, SD 1.4, *P*=.01 vs DD: mean 7.5 mmol/l, SD 1.4 *P*=.20).[9] Biomarkers, such as HOMA2-IR (PD: mean 1.4, SD 0.6, *P*=.01 vs DD: mean 1.4, SD 0.4, *P*=.052), HOMA2 %S (PD: mean 89%S, SD 45, *P*=.02 vs DD: mean 79%S, SD 23, *P*=.04), and FI (PD: mean 69 pmol/l, SD 30 *P*=.02 vs DD: mean 67 pmol/l, SD 20, *P*=.06) also resulted in lower P values indicating their significance of disease risk compared to the control group.[9] However, HOMA2-IR between diet group comparisons equated to zero with no significant difference (*d*=0, *P*=0.9),[9] suggesting that PD may not reduce the risk for increased HOMA-IR. Lastly, TC reduced equally (PD: -1.3 mmol/l, 5.1 to 5.9, mean 4.3 mmol/l, SD 1.2 *P*<.001 vs DD: -1.3 mmol, 5.5 to 6.4, mean 4.5 mmol/l, SD 1.2 *P*=.001) and CRP did not reach significance between or within group analyses.[9] See Table 3.

During within-group analyses, the Lindberg et al[10] study found significant improvements in FBG (PD: -1.7 mmol/l, mean 6.8 mmol/l, SD 1.3 to mean 5.1 mmol/l, SD 1.0, *P*<.003 vs MD: -0.9 mmol/l, mean 7.1 mmol/l, SD 1.8 to mean 6.2 mmol/l, SD 1.4 *P*<.07), FI (PD: -16 pmol/l, mean 102 pmol/l, SD 36 to mean 86 pmol/l, SD 36, *P*<.047 vs MD: -22 pmol/l, mean 123 pmol/l, SD 68 to mean 101 pmol/l, SD 53, *P*<.15), HOMA-IR (PD: −0.24, mean 0.62, SD 0.38 to mean 0.39, SD 0.36, *P*<.01 vs MD: −0.19 mean 0.75, SD 0.53 to mean 0.55, SD 0.46, *P*<.03), wt (PD: -5.0 kg, mean 91.7 kg, SD 11.2 to mean 86.7 kg, SD 11.3, *P*<.001, vs MD: -3.8 kg, mean 96.1 kg, SD 2.4 to mean 92.2 kg, SD 12.9, *P*<.001), and wc (PD: -5.6 cm, mean 105.8 cm, SD 7.6 to mean 100.2 cm, SD 7.7, *P*<.001 vs MD: -2.9 cm, mean 106.6 cm, SD 8.0 to mean 103.6 cm, SD 8.6, *P*<.004) within the PD group when compared to baseline.[10] They also observed substantial reductions in fat mass (PD: -3.9 kg, mean 28.7 kg, SD 5.4 to mean 24.9 kg, SD 4.5, *P*<.007 vs MD: -2.3 kg, mean 33.0 kg, SD 8.6 to mean 30.8 kg, SD 8.7, *P*<.001).[10] It should be noted that changes in both groups were significant for HOMA-IR, wt, wc, and fat mass. While comparing differences between groups, there was a significant difference in FBG at the 12-week timepoint (PD: mean 5.1 mmol/l, SD 1.0 vs MD: mean 6.2 mmol/l , SD 1.4, *P*<.02).[10] See Table 3.

Interestingly, Masharani et al[12] found that individuals who were most insulin resistant and followed the PD, had the most improvement in HOMA-IR, which was not seen in the control group (PD: *r* =0.40, *P*=.02 vs AD: *r* =0.39, *P*=.3). Although both groups had significant improvements in HbA1c (*P*=.04) compared to baseline, the PD group had a slightly higher percentage of improvement versus the control group (PD: 0.3%, mean -0.3%, SD 0.49 vs AD: 0.2%, mean -0.18%, SD 0.24).[12] In addition to HbA1c, the PD group saw greater improvements in FBG and HOMA-IR primary biomarkers than the control group when compared to baseline (PD: mean -1.3mmol/l, SD 1.4, *P*=.008 vs AD: mean 0.6 mmol/l, SD 1.8, *P*=.4, and PD: mean 1.3, SD 2.6, *P*=.09 vs AD: mean 1.0, SD 1.9, *P*=.10), respectively,[12] but both groups saw improvements. Additionally, secondary biomarkers revealed significantly decreased levels of TC (PD: mean -26 mg/dl, SD 27, *P*=.003 to AD: mean -9 mg/dl, SD 25, *P*=.20), LDL (PD: mean -15 mg/dl, SD 22, *P*=.02 to AD: mean -7 mg/dl, SD 1 7, *P*=.20), and wt (PD: mean -2.4

Table 3. Trial Characteristics

Study ID	S	A	M	F	Primary Dx	Length	Comparison	Evaluation of Study Results
PD vs Diet								
Boers et al [6]	34	53.5	9	25	MetS	2 wks	DHC- Isoenergetic	Significant improvements in FBG, HOMA-IR in paired differences. Significant reduction in secondary bi markers TC, SBP, DBP, and TG. Increase in HDL, TG/HDL ratio for both glucose tolerance and lipid screening. Non-significant decrease in LDL. Significant improvement in paired differences in post hoc test. Both groups saw improvements in waist circumference, wt, but PD was greater. Inflammatory markers were not different. MetS characteristics decreased more in the PD group.
Jönsson et al [9]	13	64	10	3	T2DM	12 wks	EASD	Significant improvements in FBG, FI, HOMA-IR, wt, and waist circumference. Non-significant reductions in fat mass. Changes in both groups were significant for HOMA-IR, wt, waist circumference, and fat mass. Significant improvements in FBG between groups.
Lindberg et al [10]	29	Any	29	0	T2DM & IHD	12 wks	Med-like Diet	Non-significant improvements in FBG and HbA1c. Significant difference in HDL, DBP, wt, BMI, and waist circumference. Lower mean values in the PD group, indicating significant risk reduction for CVD for HbA1c, TG, SBP, BMI, waist circumference, and FBG. FI, HOMA2-IR, and HOMA2-IR% had lower p values, indicating significance in disease risk. HOMA2-IR was non-significant in group comparisons and may point to not having disease risk reduction for HOMA-IR. TC reduced equally between groups and CRP did not reach significance.
Masharani et al [12]	24	58	14		T2DM	2 wks	ADA Diet	People most insulin resistant had the best improvements in HOMA-IR. Both groups saw significant improvements in HbA1c, but PD had a slightly higher %. The PD group saw greater improvements in FBG and HOMA-IR, but both groups saw improvements. Significant decreases in TC, LDL, wt, and significant improvements in HDL.

Acronyms: S, sample size or number of participants; A, age; F, female; M, male; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; IHD, ischemic heart disease; DHC, Dutch Health Council Isoenergetic Healthy Diet; EASD, european association for the study of diabetes; ADA, American Diabetes Association; Med-like, Mediterranean-like; PD, paleo diet; FBG, fasting blood glucose; FI, fasting insulin; HbA1c, glycated hemoglobin A; HOMA-IR, homeostatic model assessment of insulin resistance measurement; %, percentage; wt, body weight; BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure;TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, c-reactive protein.

kg, SD 0.7, *P*<.001 to AD: mean -2.1 kg, SD 1.9, *P*=.004), and significantly improved levels of HDL (PD: mean -8 mg/dl, SD 7, *P*=.001 to AD: mean -6 mg/dl, SD 8, *P*=.03) within the PD group when compared to baseline.[12] See Table 3.

Results of Synthesis

Software Analysis of Trial Outcome Measures

To assess biomarker changes, the authors calculated the difference between the mean baseline values and the mean values at the end of the intervention. However, calculating these changes presented some challenges. Data collection methods varied among the trials, with some trials featuring multiple timepoints, while others had just one. Additionally, metric unit conversions were necessary across studies. The authors further observed minor inconsistencies between tables 3 and 5 in the Boers et al[6] study, adding to the complexity of the calculations required for software input.

The evaluation of individual studies demonstrated favorable outcomes for the PD in FBG and HbA1c in one study,[12] glucose AUC_{0-120} in one study[10] SBP, DBP, and LDL in one study,[9] and TG in one study.[6] However, the control group saw favorable outcomes in CRP and TC,[9] sodium:potassium,[12] and HDL.[6] Waist circumference was favorable for the PD group in one study[10] and in the control group in one study.[9] Pooled studies only saw favorable outcomes for DBP (*P*<.001). See Supplementary file.

Paleo Diet Characteristics

There is a common misconception regarding the dietary components of the PD. This may add to confusion when prescribing this intervention and designating allowed or restricted foods. Our objective concerning PD characteristics was two-fold: firstly, to comprehensively define the PD by examining the range of allowed foods across original PD trials included in our analysis (non-secondary exploratory PD, T2DM trials), and secondly, to review recent evidence supporting this definition. This meticulous approach is crucial in addressing potential heterogeneity and improper diet prescriptions that may lead to inconclusive or mixed results. To achieve this, authors

Table 4. Paleo Diet Shared Dietary Characteristics

Diet Type	Non-Starchy Vegetables and Fruits	Fiber	Reduced SFA	Reduced Starchy Carbohydrates	Reduced Processed Foods	Meat
USDA-DGA	√		√		√	√
Mediterranean	√				√	√
Vegetarian/Vegan	√				√	
Low-fat	√		√			√
Very low-fat	√	√	√			√
Low-carbohydrate	√			√	√	√
Very low-carbohydrate	√			√	√	√
DASH Diet	√		√		√	√

Acronym: USDA, United States Department of Agriculture; DGA, Dietary Guidelines for Americans; DASH, Dietary approaches to Stop Hypertension.Note: Reduced processed foods is defined as limited amounts of or the full elimination of processed foods allowed in the diet, including but not limited to dairy, added sugar, salt, and alcohol, either independently or in combination. Data reference conversion from Evert et al. (2019) consensus report.

initially listed the shared dietary characteristics of the PD from the Evert et al[3] study and then separately assessed individual trial characteristics based on included studies in this systematic review (Table 4 and Table 5).

Assessment of Trial Macronutrient Ranges
Authors additionally measured the mean of macronutrients across included trials. Carbohydrate and fat ratios reported for PD endpoints varied substantially, whereas protein ratios reported were relatively similar.[6,9,10,12]

Glycemic Index, AUC, and Urinary Biomarkers
Glycemic load (GL) and index (GI) reported for Jönsson et al[9] (GL = PD: mean 63 g, SD 23 vs D: mean 111 g, SD 41, *P*<.001 and GI = PD: mean 50, SD 5 vs D: mean 55, SD 6; *P*=.01) and Lindberg et al[10] (GL = PD: mean 65, SD 30 vs MD: mean 122, SD 28, *P*<.001) are relatively lower in the PD groups. AUC, an index of glucose excursion after glucose loading and utilized for calculating glycemic index, is important when discussing GL and GI, as it touches on gastrointestinal absorption of carbohydrates. Compared to control diets, Boers et al[6] (PD: mean -18 mmol/l, SD 170 x min vs ISO: mean 9 mmol/l, SD 98 x min) and Lindberg et al[10] (PD: mean -90 mmol/l, SD 143 x min vs MD: mean -80 mmol/l, SD 168 x min) saw a higher decrease of glucose AUC_{0-120} in the PD group.[6,10] However, during forest plot analysis, authors found no significance for pooled studies and only one study demonstrated statistical significance.[10] Glucose AUC_{0-120} also was documented at - 20%, *P*<.001 post-6 weeks and -8% after 12 weeks.[10] The results of this study lend credence to the PD intervention, as a significant decrease (26%, *P*<.001) over the full 12-week period was observed only in the PD group for glucose AUC_{0-120}[10]

Reporting Biases
In our comprehensive assessment of the studies included in this review, we identified little risk of bias. Notably, we found a low risk of bias in certain domains, specifically selection bias, reporting bias, and attrition bias primarily due to the transparent and well-documented procedures for participant selection, data reporting, and the minimal loss of participants during the study duration. However, the blinding of personnel, which we assessed as unclear risk, aligned with a broader issue commonly faced in dietary research. Blinding is often particularly challenging in dietary intervention studies due to the very nature of dietary interventions involving substantial changes in participants' eating habits and dietary research often

Table 5. Analysis of Paleo Diet Trial Characteristics

Author	M	N	F	V	E	S	RV	H	L	P	G	O	A	C	VP	SP	K+	FI	LC	R	D
Boers et al [6]	√	√	√	√	√	√	√	-	x	-	x	x	√	-	-	-	-	√	-	-	x
Jönsson et al [9]	√	√	√	√	√	√	-	-	√	√	√	√	√	-	-	√	-	√	-	√	√
Lindberg et al [10]	√	√	√	√	√	√	√	-	√	√	√	√	√	-	-	√	-	√	-	√	√
Masharani et al [12]	√	√	√	√	√	√	-	√	x	x	x	√	-	-	-	√	x	-	-	-	x

Acronyms: M, meat; N, nuts or seeds, F, fruit; V, non-starchy vegetables; E, eggs; S, seafood; RV, root vegetables; H, honey; L, legumes or beans; P, potatoes; G, grains; O, hydrogenated oils or refined oils; A, alcohol; C, coffee; VP, vinegar products; SP, sauce products, K+, increase potassium; FI, fiber; LC, low carb; R, allows for excluded foods with restrictions on foods; D, dairy.

Legend:
☐ = PD characteristic of current day trends,
☐ = PD characteristics of reported evidence of true indigenous eating trends in addition to current day trends,
☐ = PD exclusions,
√ = included in diet,
x = excluded in diet,
- = no data

Table 6. Assessment of Trial Macronutrient Ranges

Author	CHO (%)	Fiber (g)	PRO (%)	FAT (%)	SFA (%)	Mono (%)	Poly (%)
Boers et al [6]	32	34	24	41	10	-	-
Jönsson et al [9]	32	21	24	39	19	30	14
Lindberg et al [10]	40.2	21.4	27.9	26.9	7.7	10.7	5.8
Masharani et al [12]	58.2	-	18.5	27.0	3.6	14.8	6.3
Mean	**40.6**	**25.4**	**23.6**	**33.5**	**10.1**	**18.5**	**8.7**

Acronyms: CHO, carbohydrate; PRO, protein; FAT, fat; SFA, saturated fatty acids; Mono, monounsaturated fatty acids; Poly, polyunsaturated fatty acids.

Legend:
☐ = macronutrients,
☐ = fiber content of carbohydrate intake,
☐ = fatty acid content of fat intake,
- = no data

relies on subjective outcome measures (self-reported dietary intake or behavioral changes).

Certainty of Evidence

We assess certainty for the outcomes analyzed using Cochrane software and considered various criteria, including study design, risk of bias, and consistency to provide an overall evaluation of the quality and reliability of the evidence. The studies included RCTs, which are considered a robust study design. Nonetheless, while the general bias assessment according to JBI tools found certain domains to have low risk, upon closer examination, assessment bias was identified, which pointed to conflicting variables and findings.

Discussion

Key Findings of Published Interventions

When reporting the results of individual studies, significant improvements for T2DM primary and secondary biomarkers were demonstrated across trials for the PD groups (Table 3).[6,9,10,12] However, in many instances control groups also had significant findings (Table 3).[6,9,10,12] The findings in this current review were the same in the consensus by Evert et al,[3] the Jamka et al[8] review, as well as this study's analysis (Supplementary file). In addition, throughout this evaluation, inconsistent variables were found across studies (varying time points, inconsistent number of studies and included morbidities in systematic reviews, variation of the allowed foods in PD protocols, and distribution of macronutrients between clinical trials). These inconsistencies along with a limited number of included studies and the existing data, makes it difficult to determine whether the PD can mitigate risk, alleviate symptoms, or resolve disease in T2DM. Thus, the disorganized unstructured approach in methodologies and design across the studies reviewed continues to produce unreliable results. Henceforth, the development of comprehensive intervention guidelines is imperative for future trials to ensure more reliable data.

Proposed Intervention Design

Limiting Heterogeneity to Enhance Precision of Future Trials

Heterogeneity was observed across all included studies: 1) The variation in the number of studies included,[8,11,14] 2) the inclusion of secondary morbidities,[14] and 3) inconsistency of reported biomarkers in individual studies.[6,9,10,12] In the current study, three of the four analyzed studies assess a majority of primary and secondary outcome measures.[6,9,10,12] However certain biomarkers (Fat %, BMI, M, TNF-α, IL-6, and VO_2max) were not uniformly studied across trials. For the remaining clinical indicators, this review found a significant heterogeneity for the PD between studies that assessed: FBG (P=.03; I^2=67%) and glucose $_{0-120}$ (P=.002; I^2=84%), SBP (P<.001; I^2=93%), TC (P=.007; I^2=80%), LDL (P<.001; I^2=99%), and TG (P=.04; I^2=69%) (Supplementary File). However, this review found a significant heterogeneity for the control diet between studies that assessed: wt (P<.001; I^2=99%), wc (P<.001; I^2=99%), sodium:potassium ratio (P<.001; I^2=96%), and HDL (P<.001; I^2=87%), as indicated by a high risk heterogeneity percentages (Supplementary File). The high heterogeneity in the studies makes it challenging to trust the findings. Therefore, standardizing protocols and procedures for future trials can reduce variability of outcomes.

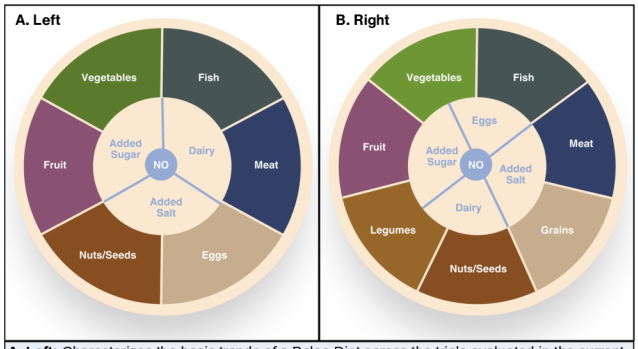
Defining the Paleo Diet for the Intervention

It was determined during the analysis of diet characteristics that the studies in this review prescribed a basic PD trend of lean meat, fish and seafood, fruit, non-starchy vegetables, nuts, and eggs, with an exclusion of dairy products, salt, and sugar. See Figure 3. However, it can be determined from reviewing the PD interventions it appears that these trials follow a modern definition authored by Dr. Cordain in his 2007 book “The Paleo Diet: Lose Weight and Get Healthy by Eating the Food You Were Designed to Eat,” which advises in Chapter 2 “The Ground Rules for the Paleo Diet” not to consume: 1) legumes, 2) starch from grains, and 3) starch from tubers.[39,40] Paleolithic nutrition, however, was peer-reviewed and published by Dr. Boyd Eaton prior to this publication in a 1985 article that clearly addressed the consumption of the aforementioned foods was normal in this population.[41] The article addresses 50-80% of plant food consumption, and that wild sources contain less starch and calories than domesticated sources.[41] While Dr. Cordain's 2007 book offers valuable insights into the Paleo diet, its suitability for clinical trials may be limited due to the evolving nature of scientific knowledge. Similar can be stated about the early works of Dr. Eaton. Incorporating current archaeological evidence[42] ensures that dietary interventions are based on the most up-to-date and comprehensive understanding of our ancestors' dietary habits.

Subsequently, this review conducted research on the historical definition of the PD, adhering to archeological peer-reviewed evidence and rigorous scientific standards. This approach ensured incorporation of up-to-date and high-quality information, contributing to both a precise definition and data validity. Notably, many studies have tried to define the PD and there have been various interpretations.[33] However, as seen

with de la O et al,[33] many are unsuitable research attempts to blend current-day eating trends to food habits during this era. After doing extensive investigations of the plant foods eaten during the Paleolithic era, comprehensive studies revealed that Neanderthals consumed non-starchy vegetables (leaves, above ground vegetables, herbs, bulbs, fennel), starchy vegetables (roots, tubers), grains, legumes, fruits (palm fruits and berries) plant fats (tree nuts, seeds, olives) and a variety of other plant life (mushrooms, grasses, moss, and tree shrubs, tree bark, aquatic plants, and flowers.[42–44] In addition to these plant foods, it is well-known that lean meats, birds, and marine animals were also consumed.[42–44] This supports Dr. Eaton's previous works. Moreover, after analyzing the basics of the PD through these archeological peer-reviewed sources,[42–44] we determined that plants take up at least 70% of the PD (Figure 3), further supporting Dr Eaton's data. This includes plant fats (nuts, seeds, olives, and coconuts).

Figure 3. Paleo Diet Characteristics Across Trials



A. Left: Characterizes the basic trends of a Paleo Diet across the trials evaluated in the current study. Adopted from Cordain, L. (2002). The Paleo Diet. NJ: John Wiley & Sons, Inc. Pages: 20, 23-24. Retrieved October 16th, 2023.

B. Right: Characterizes the Paleo Diet based on archaeological and ethnographic data. Adopted from Shipley GP, Kindscher K. Evidence for the Paleoethnobotany of the Neanderthal: A Review of the Literature. Scientifica (Cairo).

Legend:
The center of the diagram"blue dividing lines" emphasizes food not included in the diet, as indicated by light blue colored markings.

The outer rim "beige dividing lines" emphasizes foods included in the diet, as indicated by the tan colored markings.

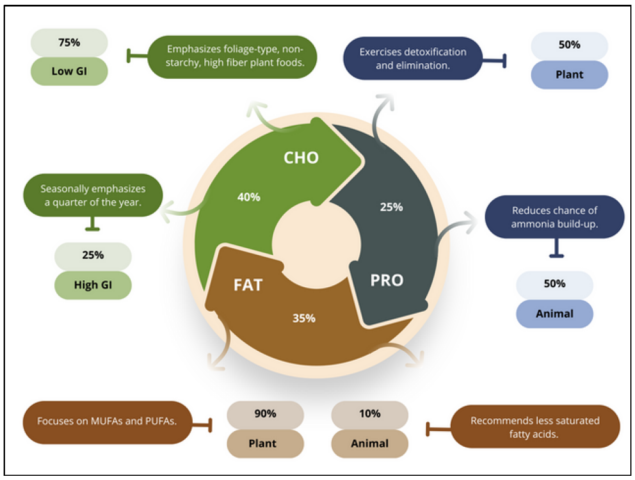
However, this review is not centered on examining food components as its primary objective, and therefore these results should be taken with caution.

It was further documented that legumes may have been significantly consumed, since Neanderthals were found to have cooked meals.[42] Nuts, seeds, fruits, and grains were reported to have been foraged and eaten seasonally when these plants yielded produce,[42] concluding although they did eat starchy plant varieties, they ate very limited amounts only when the non-domesticated environment permitted their growth. Thus, based on the evidence from these findings, the definition of a PD should be described as "*consuming lean meats, birds, marine animals, and animal marrow; all organic vegetables (including roots and tubers), tree shrubs and bark, fruit, nuts and seeds, grains, legumes, grasses, flowers, aquatic plants, mushrooms, and moss; while excluding ultra-processed and domesticated foods, including added sugar, added salt, dairy, and eggs.*"[42–44] As previously mentioned, this review's focus was not centered on defining a PD, rather establishing a basis for future trials.

Paleo Diet Macronutrient Cycle for the Intervention

Mean ratios across trials were 40.6% for carbohydrates, 33.5% for fat, and 25.4% for protein. This is consistent with reviews evaluating current-day indigenous tribes, as Kuipers et al[45] studied African indigenous tribes and found mean macronutrient percentages to be an average of 39-40% carbohydrate and 28% protein intake.[45] Studies also determined individuals consuming a PD with reduced carbohydrates felt more satiated per calorie while consuming a reduced energy intake.[10;45] From these findings, it is proposed that trials introduce a structured ratio for macronutrients for studying the PD on T2DM, with 40% CHO, 35% FAT, and 25% PRO with less than 10% of fat coming from animal sources.[9;10;27;42;45]

Figure 4: Paleo Macronutrient Ranges Across Trials- The Macronutrient Cycle



Glycemic Indices for the Intervention

In the articles screened, it was documented that the PD had relatively lower glycemic indices, thereby improving glycemic dysfunction.[9;12;14] Glycemic control is determined by HbA1c and glucose, as well, insulin levels are further decided by the amount of

carbohydrate in the diet or rate of carbohydrate absorption.[25,46] Simple carbohydrate, ultra-processed, and high-glycemic foods in standard diets increase absorption rate, surging circulation with increased blood glucose levels. This causes pancreatic beta cell hypersecretion and can lead to cell damage. Complex carbohydrate, fibrous, low-glycemic plant foods have a decreased absorption rate.[46] This allows pancreatic beta cells to produce adequate insulin in response. It was proposed that a PD has a low-glycemic index of 50,[9] which could explain the relative balancing of blood glucose and improvements in diabetes indices in the current analyzed studies. Since the PD limits foods with higher GI, such as specific grains, fruits, nuts, and seeds,[42] and eliminates domesticated and ultra-processed foods,[42–44] this could be the reason behind improved glycemic control. Considering this evidence, the current intervention proposes to use a PD glycemic handout in future trials that list foods that maintain a daily GI of ≤ 50-55, and would further suggest incorporating the following table into medical literature for referencing glycemic indexes associated with the PD, by the current study definition. See Table 7.

Intervention Basics

Trial Length. The mean trial length was 7 weeks. However, it is suggested to conduct dietary interventions for a minimum of 12 weeks to see its true effect on changes in blood parameters and tolerability. Time points should include blood work on 30 days, 60 days, and 90 days.

Target Sample. A starting sample of at least twenty-five (n=25) adults was the mean of included trials. Two of the studies performed power calculations,[9,10] whereas the third and fourth studies used data from previous studies.[6,12] To ensure the data was consistent, the authors decided to perform an additional power calculation utilizing a sample calculator from ClinCalc. Given that the study proposal intervention includes two independent study groups with continuous means, we used a 90% power at a significance level of 5% for type-I error. Using power of 90% in lieu of 80% increases the confidence of the findings, type-II error, precision, and replicability. Based on the only study that utilized FI as the basis for their change in primary outcomes,[12] we used a SD of 15%. We estimated an enrollment ratio of 1, and a minimum decrease of 15% in the experimental group. This provided us with a suggested starting sample of thirty-six (n=36). While 80% power suggested a starting sample of twenty-eight (n=28). With an even gender distribution, this should be an appropriate starting point. Authors determined measuring glucose AUC_{0-120} may make client's lab visit seem difficult, therefore, opted out of measuring this biomarker for ease of lab testing

Table 7: Paleo Diet Glycemic Index- Culinary Profile

Food	Glycemic Index					Culinary Profile	
	≤ 40 GI	40-50 GI	50-55 GI	55-60	≥ 60 GI	Seasonal	Descriptive Foods
Lean Meat	0 GI					No	Grass-fed, free range caged-free, and hormone-free
Seafood	0 GI					No	
Fruits raw	Blackberries, blueberries, cherries, grapefruits, guava, lemon, lime, oranges, pears, plum, prunes, soursop	Apple, apricot, banana, durian, grapes, kiwi, mango, nectarine, papaya, strawberry, watermelon, avocado,	Dates, fig, pomegranate, lychee	Cantaloupe, cherimoya, jackfruit, peach, pineapples	Persimmon, pomelo	Yes	Organic, non-GMO, colorful, and ripe
Vegetables	Carrots, cauliflower, lettuce, broccoli, cabbage, radicchio, sprouts, swiss chard, endive, cilantro, parsley, mustard greens, collard greens, jicama, onions, scallions, leeks, peppers, tomato, spinach, eggplant, ginger, winter squash, summer squash, green beans, cucumber, brussels, okra, nopales, zucchini	Wasabi root	Corn, parsnips, yam, green peas	Beet root, pumpkin gourd, sweet potato, rosehip, rutabaga, potato, arrowroot, star anise, red potato, cassava root		No	Organic, non-GMO, colorful, and ripe
Nuts	Cashews, peanuts, pistachio, pecan		Chestnut	Coconut		Yes	Organic and non-GMO
Seeds	Pumpkin seeds, sesame seeds	Lotus	Quinoa			Yes	Organic and non-GMO
Mushrooms	Button, cremini, portobello, shiitake, oyster, porcini, morel, enoki, chanterelle, maitake, hedgehog, chicken of the woods, black trumpet, wood blewit, shimeji, reishi, lions mane, matsutake, and giant puffball					No	Organic and non-GMO
Tree Bark		Cinnamon, birch, slippery elm, white willow				No	Organic and non-GMO
Legumes	Lima beans, chickpeas, black beans, butter beans, kidney beans, soy beans, pigeon pea, chocolate bean, vanilla bean, adzuki bean, lentil, navy bean, pinto beans	Black eyed peas, mung beans		Broad beans, fava beans, asparagus bean		No	Organic, non-GMO, and colorful
Grains	Barely, rye	Bulgur, white rice, wheat	Basmati rice, brown rice, buckwheat	Couscous, wild rice, teff, spelt, amaranth, triticale, millet		Yes	Organic and non-GMO
Eggs	0 GI					No	Free range and caged-free
Honey				Honey			100% organic

All indices referenced in text.Adopted from: Mazmanyan, V. (2022). Glycemic index chart: Complete (600+) list from all sources. Food Struct. Available from https://foodstruct.com/glycemic-index-chart

Table 8: Proposed Interventions

Experimental Group Paleo Diet			
Length	**Time Points**	**Structured Paleo Diet Definition**	**Macronutrient Ranges**
12 week	• 30 days • 60 days • 90 days	Consuming lean meats, seafood, all vegetables, tree bark, legumes, mushrooms, and moss, and seasonally consuming nuts, seeds, fruits and grains in minimal amounts	CHO 40%, FAT 35%, PRO 25%
Eliminates domesticated foods: ultra processed foods, dairy, and alcohol			
Standard Diabetes Diet			
Length	**Time Points**	**Structured ADA Diet Definition**	**Macronutrient Ranges**
12 week	• 30 days • 60 days • 90 days	Choose carbohydrates that come from vegetables, whole grains, fruits, beans (legumes), and dairy products. Avoid carbohydrates that contain excess added fats, sugar, or sodium. Choose "good" fats over "bad" ones. Avoid unhealthy saturated fats (red meat and other animal proteins, butter, lard) and trans fats (hydrogenated fat found in snack foods, fried foods, commercially baked goods). Choose protein sources that are low in saturated fat. Bake, broil, steam, or grill instead of frying. If frying, use healthy oils like olive or canola oil. Try to eat fatty fish. Limit intake of sugar-sweetened beverages. Limited sodium to 2,300 mg/day or less.	The ADA no longer recommends specific amounts for carbohydrate, fat, or protein intake. We recommend an equal distribution of CHO 40%, FAT 35%, PRO 25% to reduce variability of outcomes
Allows domesticated foods: ultra processed foods, dairy, and limited amounts of alcohol			

Acronyms and Abbreviations: CHO, carbohydrates; FAT, fat; PRO, protein.

procedures.

Biomarker Measurements. All time point check-ins should be accompanied by consistent monthly fasting blood draws and urinary analyses for all of the following markers: FBG, HbA1c, HOMA-IR, FI, CRP, TC, LDL, HDL, TG, sodium:potassium, and net acid excretion, whereas anthropometrics (FAT%, wt, wc, and BMI) are measured with calipers, scale, and measuring tape. These should be consistent across trials.

We chose the ADA diet because it is the standard of care for those with T2DM. We recommend that a well-structured intervention, irrespective of adherence to specific macronutrient ranges, should align with the suggested ranges due to lifestyle compliance and adherence to the intervention's structured definition of the PD. This is supported by the observation that most foods on the GI chart fall under the 50-55 GI level. We hypothesize a significant change in biomarkers, favoring the PD.

Implications in Diet Research

There are several implications to acknowledge in this review. First, although the sample sizes were established by using power calculations, the number of study participants in the trials were fairly small.[6,9,10,12] To address this limitation researchers can increase sample sizes based on 90% power calculations in replicated studies to enhance reliability of findings. One systematic review included additional studies with distinct morbidities from T2DM.[14] Confounding factors, such as having various stages of metabolic disease (MetS,[6] T2DM and IHD,[10] and T2DM[9,12]), having varying time points at the end-of-interventions (2 weeks[6,12] and 12 weeks[9,10]), or allowing medications[9,12], also impact outcomes, potentially obscuring the diets effects and generating higher heterogeneity across pooled trials. In addition, one could say that in Jonsson et al[9] the GL was significantly less in the PD group than the DD, thus explaining why wc was significantly reduced in the PD group. Likewise, in the Lindberg et al[10] study, the control group was told that a MD was healthy, whereas the PD group had training. These differences could bias the results. To solve this, future studies should ensure that both groups receive equal levels of education and training on GI or GL of the foods to isolate the effects of the diets themselves. We further noticed adverse effects and compliance issues in the PD group of Jonsson et al,[9] as well as meal catering in Boers et al[6]. These factors further complicate findings. Furthermore, the dietary guidelines and restrictions for the PD were not the same across all trials.[6,9,10,12]

None of the studies assessed in this systematic review adhered to a historically defined PD intervention,[6,9,10,12] and in most cases included foods that would normally be absent during the Paleolithic era were permitted, specifically hydrogenated oils[9,10,12] and alcohol[6,9,10]. It was found that the studies reported the intake of these foods during the PD protocol[9,10,12], pointing to compliance issues. It is common knowledge that the inclusion of alcohol, saturated fatty acids, and trans-fats have adverse effects on health, particularly increasing risk of heart disease and insulin resistance. Nevertheless, these studies still managed to find both significant and non-significant findings leading to large and small improvements in metabolic biomarkers.[6,9,10,12] Therefore, having a firm definition for future trials should not only improve reliability of results, but we hypothesize reported results will be clinically favorable for the PD. Similarly, set macronutrient ranges reduce variability of outcomes, while glycemic index handout will present a larger picture into what foods are included in this lifestyle. Most importantly, not all the clinical trials were compared against the same control diet, which makes an important point to consider when extrapolating the

data.

Conclusion

The authors of this study originally decided to perform this review under the assumption that the PD was not given the proper credit in a recent consensus report. After a comprehensive analysis of the evidence, it was found that the consensus report was valid. However, findings also revealed the inconclusiveness of the PD for T2DM was due to a number of inconsistencies across trials and systematic reviews. As a result, researchers propose consistency of PD definition (archeological definition and no modern-day interpretations, assumptions, or allowances of excluded foods), standardized macronutrient percentages, disease diagnosis (only T2DM), trial time length (12 weeks to evaluate true effects), and equal training across groups for all future trials. A proposal for PD macronutrient ranges and definition has been reported in this study, and subsequent publications to review these components for future trials is warranted. By utilizing these variables in consistency throughout trials, research could authenticate conclusive results establishing PD eating patterns as an acceptable diet to be added to the Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes, 2024 guidelines.

No significant effects on T2DM were found for control diets (AD, ID, DD, and MD) across trials, likely due to variability. A consistent control diet, such as the ADA diet, which is the standard of care for T2DM, should be used as a comparison to the PD. The reduction in diastolic blood pressure across pooled results suggest that the PD may have a beneficial impact on metabolic markers related to T2DM. However, due to variability in PD intervention definition and macronutrient ranges, along with several other inconsistencies, the effect of the PD on T2DM remains inconclusive. New trials utilizing a consistent, reliable archaeological-based historical definition, standardized macronutrient ranges, disease diagnosis, trial time length, and equal training across groups should be conducted to establish conclusivity of its effects on primary end-points.

Protocol and Registration

This systematic review was drafted and reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Checklist (PRISMA, 2022). Studies are assessed based on the updated checklists from Joanna Briggs Institute (JBI, 2017). All studies were charted in tables and are listed. A final protocol has been registered at OSF.

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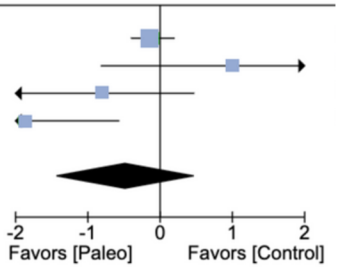
Supplementary File. Software Analysis of Trial Outcome Measures

Fasting Blood Glucose (mmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-0.4	0.5	18	-0.3	0.4	16	38.3%	-0.10 [-0.40 , 0.20]
Jönsson-1	-0.1	1.5	7	-1.1	1.8	6	16.2%	1.00 [-0.82 , 2.82]
Lindberg	-1.7	1.7	14	-0.9	1.8	15	23.2%	-0.80 [-2.07 , 0.47]
Masharani	-1.3	1.4	14	0.6	1.8	10	22.3%	-1.90 [-3.24 , -0.56]
Total (95% CI)			**53**			**47**	**100.0%**	**-0.49 [-1.44 , 0.46]**

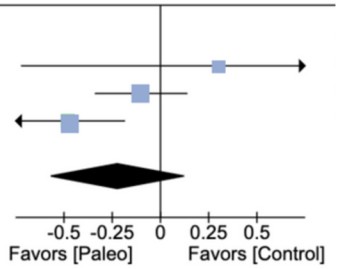
Heterogeneity: Tau² = 0.59; Chi² = 9.17, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



HbA1c (%)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	0	0	0	0	0	0		Not estimable
Jönsson-1	-0.7	0.7	7	-1	1.1	6	9.6%	0.30 [-0.72 , 1.32]
Lindberg	-0.13	0.26	14	-0.03	0.39	15	47.8%	-0.10 [-0.34 , 0.14]
Masharani	-0.3	0.49	14	0.18	0.24	10	42.6%	-0.48 [-0.78 , -0.18]
Total (95% CI)			**35**			**31**	**100.0%**	**-0.22 [-0.57 , 0.12]**

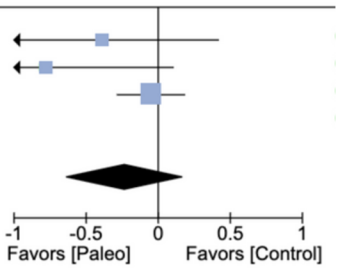
Heterogeneity: Tau² = 0.05; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



HOMA-IR

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-0.9	1.5	18	-0.5	0.9	16	18.7%	-0.40 [-1.22 , 0.42]
Jönsson-1	-1	1.1	7	-0.2	0.5	6	16.0%	-0.80 [-1.71 , 0.11]
Lindberg	-0.24	0.29	14	-0.19	0.36	15	65.3%	-0.05 [-0.29 , 0.19]
Masharani	0	0	0	0	0	0		Not estimable
Total (95% CI)			**39**			**37**	**100.0%**	**-0.24 [-0.64 , 0.17]**

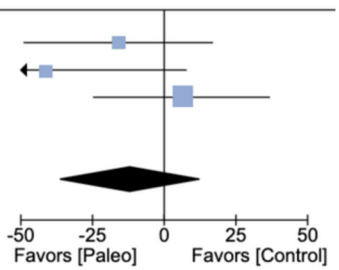
Heterogeneity: Tau² = 0.05; Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



Fasting Insulin (pmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-32	59	18	-16	38	16	37.8%	-16.00 [-49.01 , 17.01]
Jönsson-1	-49	61	7	-8	23	6	20.7%	-41.00 [-89.79 , 7.79]
Lindberg	-16	27	14	-22	54	15	41.6%	6.00 [-24.77 , 36.77]
Masharani	0	0	0	0	0	0		Not estimable
Total (95% CI)			**39**			**37**	**100.0%**	**-12.03 [-36.33 , 12.27]**

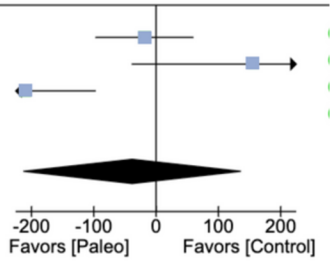
Heterogeneity: Tau² = 123.36; Chi² = 2.71, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



AUC Glucose 0-120

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-18	170	18	0.6	9	14	37.9%	-18.60 [-97.28 , 60.08]
Jönsson-1	-100	87	7	-256	230	6	27.1%	156.00 [-38.99 , 350.99]
Lindberg	-290	143	14	-80	168	15	35.0%	-210.00 [-323.31 , -96.69]
Masharani	0	0	0	0	0	0		Not estimable
Total (95% CI)			**39**			**35**	**100.0%**	**-38.22 [-212.45 , 136.00]**

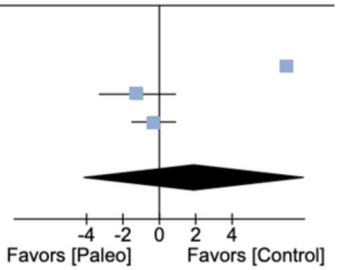
Heterogeneity: Tau² = 19240.67; Chi² = 12.50, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Weight (kg)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	0	0	0	0	0	0		Not estimable
Jönsson-1	-1	0.1	7	-8	0.1	6	33.9%	7.00 [6.89 , 7.11]
Lindberg	-5	3.3	14	-3.8	2.4	15	32.6%	-1.20 [-3.31 , 0.91]
Masharani	-2.4	0.7	18	-2.1	1.9	10	33.5%	-0.30 [-1.52 , 0.92]
Total (95% CI)			**39**			**31**	**100.0%**	**1.88 [-4.16 , 7.93]**

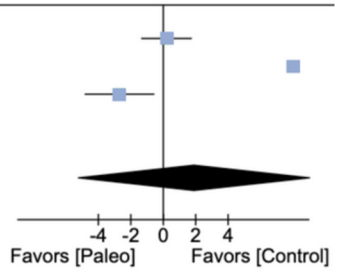
Heterogeneity: Tau² = 28.04; Chi² = 193.09, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Waist (cm)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-3.1	2	18	-3.3	2.4	14	33.3%	0.20 [-1.36 , 1.76]
Jönsson-1	-3	0.1	7	-11	0.1	6	33.8%	8.00 [7.89 , 8.11]
Lindberg	-5.6	2.8	14	-2.9	3.1	15	32.8%	-2.70 [-4.85 , -0.55]
Masharani	0	0	0	0	0	0		Not estimable
Total (95% CI)			**39**			**35**	**100.0%**	**1.89 [-5.25 , 9.03]**

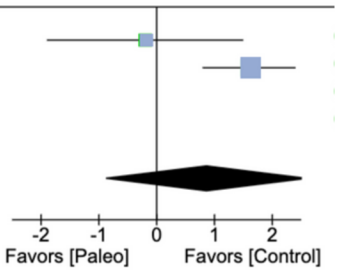
Heterogeneity: Tau² = 39.21; Chi² = 189.99, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



C-Reactive Protein (mg/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	0.2	2.8	18	0.4	2.1	14	41.0%	-0.20 [-1.90 , 1.50]
Jönsson-1	0.9	0.1	7	-0.7	1	6	59.0%	1.60 [0.80 , 2.40]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	0	0	0	0	0	0		Not estimable
Total (95% CI)			**25**			**20**	**100.0%**	**0.86 [-0.87 , 2.60]**

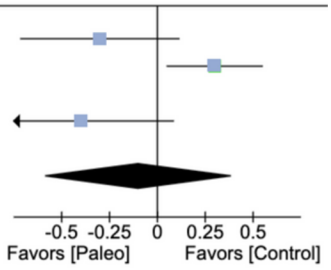
Heterogeneity: Tau² = 1.16; Chi² = 3.53, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Total Cholesterol (mmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-0.7	0.7	18	-0.4	0.5	14	32.3%	-0.30 [-0.72 , 0.12]
Jönsson-1	0.1	0.1	7	-0.2	0.3	6	38.1%	0.30 [0.05 , 0.55]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-0.6	0.6	14	-0.2	0.6	10	29.7%	-0.40 [-0.89 , 0.09]
Total (95% CI)			**39**			**30**	**100.0%**	**-0.10 [-0.59 , 0.38]**

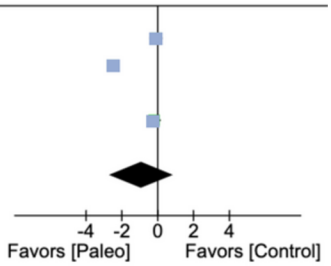
Heterogeneity: Tau² = 0.14; Chi² = 9.80, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



LDL (mmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-0.3	0.5	18	-0.2	0.5	14	33.3%	-0.10 [-0.45 , 0.25]
Jönsson-1	-2.7	0.1	7	-0.2	0.3	6	33.5%	-2.50 [-2.75 , -2.25]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-0.3	0.5	14	-0.1	0.4	10	33.2%	-0.20 [-0.56 , 0.16]
Total (95% CI)			**39**			**30**	**100.0%**	**-0.94 [-2.62 , 0.75]**

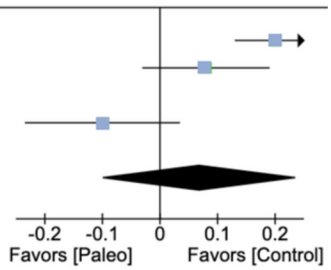
Heterogeneity: Tau² = 2.19; Chi² = 168.69, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



HDL (mmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	0	0.1	18	-0.2	0.1	14	36.1%	0.20 [0.13 , 0.27]
Jönsson-1	0.06	0.05	7	-0.02	0.13	6	33.0%	0.08 [-0.03 , 0.19]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-0.2	0.1	14	-0.1	0.2	10	30.9%	-0.10 [-0.23 , 0.03]
Total (95% CI)			**39**			**30**	**100.0%**	**0.07 [-0.10 , 0.23]**

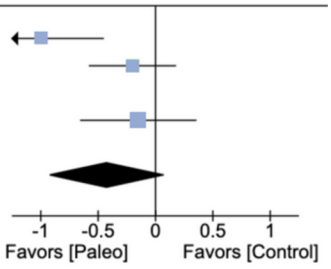
Heterogeneity: Tau² = 0.02; Chi² = 15.80, df = 2 (P = 0.0004); I² = 87%
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable



Triglycerides (mmol/l)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-0.9	1.1	18	0.1	0.4	14	30.3%	-1.00 [-1.55 , -0.45]
Jönsson-1	-0.4	0.5	7	-0.2	0.1	6	37.6%	-0.20 [-0.58 , 0.18]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-0.2	0.5	14	-0.05	0.7	10	32.1%	-0.15 [-0.66 , 0.36]
Total (95% CI)			**39**			**30**	**100.0%**	**-0.43 [-0.92 , 0.07]**

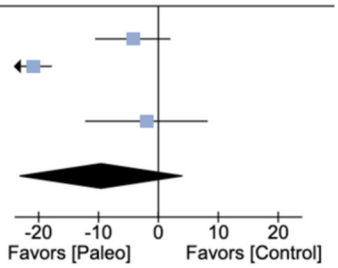
Heterogeneity: Tau² = 0.13; Chi² = 6.54, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



Systolic Blood Pressure (mmHg)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-8.5	12	18	-4.2	5.6	14	33.9%	-4.30 [-10.57 , 1.97]
Jönsson-1	-16	0.1	7	5	4	6	35.8%	-21.00 [-24.20 , -17.80]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-4	12	14	-2	13	10	30.3%	-2.00 [-12.22 , 8.22]
Total (95% CI)			**39**			**30**	**100.0%**	**-9.59 [-23.17 , 4.00]**

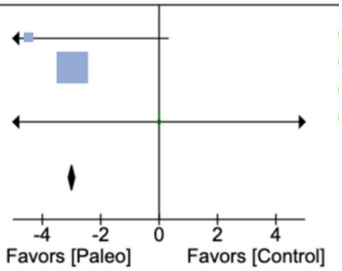
Heterogeneity: Tau² = 131.39; Chi² = 29.86, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



Diastolic Blood Pressure (mmHg)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-8	8.3	18	-3.5	5.6	14	0.1%	-4.50 [-9.33 , 0.33]
Jönsson-1	-4	0.1	7	-1	0.1	6	99.9%	-3.00 [-3.11 , -2.89]
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	-1	6	14	-1	7	10	0.0%	0.00 [-5.36 , 5.36]
Total (95% CI)			**39**			**30**	**100.0%**	**-3.00 [-3.11 , -2.89]**

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 53.94 (P < 0.00001)
Test for subgroup differences: Not applicable



Sodium:Potassium (mmol/mol)

Study or Subgroup	Paleo Diet Mean	SD	Total	Control Diet Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Boers	-1.11	0.97	18	-0.57	0.82	14	49.4%	-0.54 [-1.16 , 0.08]
Jönsson-1	0	0	0	0	0	0		Not estimable
Lindberg	0	0	0	0	0	0		Not estimable
Masharani	2	0.8	14	0.6	0.3	10	50.6%	1.40 [0.94 , 1.86]
Total (95% CI)			**32**			**24**	**100.0%**	**0.44 [-1.46 , 2.34]**

Heterogeneity: Tau² = 1.80; Chi² = 24.28, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable