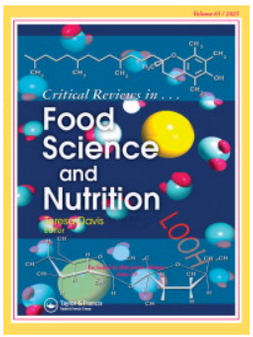

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The Paleolithic diet and chronic disease risk: a GRADE-assessed systematic review and dose-response meta-analysis of prospective cohort studies and randomized controlled trials

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REVIEW ARTICLE

The Paleolithic diet and chronic disease risk: a GRADE-assessed systematic review and dose-response meta-analysis of prospective cohort studies and randomized controlled trials

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ABSTRACT

This systematic review and meta-analysis evaluate the effects of the Paleolithic diet on cardiometabolic parameters and chronic disease outcomes by combining evidence from interventional and observational studies. We analyzed 19 randomized controlled trials (RCTs) and 12 prospective cohort studies identified through systematic searches. Both random-effects and fixed-effects meta-analyses, along with dose-response evaluations, were conducted for cohort studies. A fixed-effects model was applied when fewer than five comparisons were available to ensure model stability with limited data. Meta-analysis of RCTs demonstrated significant improvements in cardiometabolic markers including, fasting insulin [Weighted Mean Differences (WMD −1.01 [−1.45, −0.57], $p<0.001$], total cholesterol (WMD −0.15, [−0.24, −0.07], $p<0.001$), low-density lipoprotein cholesterol (WMD −0.24, [−0.40, −0.08], $p=0.003$), triglycerides (WMD −0.16, [−0.24, −0.08], $p<0.001$), body weight (WMD −1.74, [−2.57, −0.91], $p<0.001$), body mass index (WMD −1.12, [−1.42, −0.82], $p<0.001$), and diastolic blood pressure (WMD −3.28, [−4.55, −2.01], $p<0.001$). Cohort studies revealed 10% lower all-cause mortality risk (RR: 0.90, 95% CI: 0.87–0.94, $p<0.001$), 10% reduced cancer mortality (RR: 0.90, 95% CI: 0.85–0.97, $p=0.004$), and 16% lower coronary heart disease incidence (RR: 0.84, 95% CI: 0.70–1.00, $p=0.05$) among high adherers. The Paleolithic diet may provide significant benefits for cardiometabolic health and potentially lower the risk of chronic disease.

KEYWORDS

Cardiovascular diseases; Diabetes mellitus; Dietary patterns; Obesity; Paleolithic

Introduction

Non-communicable diseases, including heart disease, diabetes, and cancers, are a significant and enduring strain on health systems worldwide, accounting for 71% of all deaths globally (World Health Organization 2022). A primary driver of this burden is poor diet, which, according to the Global Burden of Disease study, contributed to approximately eight million deaths and 188 million disability-adjusted life years in 2019 alone (World Health Organization 2022). Various factors, including genetics and modifiable behaviors such as smoking, excessive alcohol use, physical inactivity, and an unhealthy diet, are associated with the development of chronic diseases (World Health Organization 2022).

A nutrient-focused approach that examines individual nutrients and specific food groups overlooks the complex synergistic/antagonistic relationships between nutrients, phytochemicals, and antinutrients in whole foods. Conversely, dietary pattern analysis provides a holistic evaluation of diet by assessing food quality, quantity, and frequency, thereby naturally incorporating nutrient interactions, dietary component correlations, and food matrix effects. This makes dietary pattern analysis both more biologically valid for assessing overall dietary impacts and more applicable to actual eating habits (Tapsell et al. 2016). Among the various dietary patterns, the Paleolithic diet has gained prominence in current nutrition trends as an approach that mimics the eating patterns of Paleolithic-era hominins (modern humans' bipedal ancestors) from 2.6 million to 10,000 years ago, a pre-agricultural period starkly different from modern societies. As hunter-gatherers, these hominins developed diets that varied geographically and climatically, necessitating constant migration in search of food. Despite these variations, their shared nutritional patterns offer key insights into how the discordance between ancestral and modern Western diets may underlie chronic disease development (Cordain et al. 2005). Paleolithic diets varied significantly in macronutrient balance and animal-to-plant food ratios. Still, they universally excluded foods absent in pre-agricultural times, including dairy, refined salt, alcohol, free sugars, cereals, and processed foods (Whalen et al. 2017). These consistent exclusions differentiate ancestral diets from modern eating

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patterns and may help explain current nutritional mismatches (Cordain et al. 2002).

The growing popularity of the Paleolithic diet has prompted rigorous scientific investigation, including studies examining its efficacy in managing chronic and metabolic disorders. Current evidence remains inconclusive, with studies reporting divergent outcomes: some demonstrate beneficial effects on diabetes risk reduction, metabolic syndrome, cardiovascular health, and cancer prevention (Kowalski and Bujko 2012; Manheimer et al. 2015; Pastore et al. 2015), while others report either neutral outcomes (Osterdahl et al. 2008) or potential adverse effects (Smith et al. 2014). This inconsistency underscores the need for additional high-quality research to establish definitive clinical guidelines.

While previous reviews have often focused on one study type, a comprehensive understanding requires synthesizing both experimental and long-term observational evidence. Randomized controlled trials (RCTs) provide the most substantial evidence for the efficacy of the diet in improving biomarkers under controlled conditions. In contrast, prospective cohort studies reveal their association with clinical endpoints, such as disease incidence and mortality, in populations over time. To address this, we conducted a systematic review with a dose-response meta-analysis of both RCTs and prospective cohort studies, incorporating the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. The primary objective of this study is to provide a dual-perspective synthesis to determine the efficacy of the Paleolithic diet for improving cardiometabolic risk factors based on RCTs, and to assess the association between adherence to a Paleolithic dietary pattern and the risk of chronic disease incidence and mortality based on prospective cohort studies.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Table 1) (Page et al. 2020) and was prospectively registered in the PROSPERO database (CRD420251082486). The conduct of the meta-analysis was informed by the methodological standards outlined by Cochrane.

Search strategy

We conducted a systematic literature search in the Web of Science, PubMed, and Scopus databases for relevant records published from the inception of these databases until June 26, 2025. Our strategy employed a combination of Medical Subject Headings and free-text terms (see Supplemental Table 2 for the complete list of search terms). No language restrictions were imposed. We also performed manual reference list searches of all included articles to identify any further eligible records and ensure a thorough search.

Eligibility and study selection

All identified articles were systematically evaluated using the PICO framework, as recommended by Cochrane. Studies were considered eligible if they met the following criteria: (a) they were randomized controlled trials (RCTs) or prospective observational studies; (b) participants were general adult populations (aged 18 or older); (c) the primary focus was adherence to the Paleolithic diet; (d) metabolic outcomes were assessed in RCTs, while cohort studies examined all-cause or cause-specific mortality and the incidence of non-communicable diseases; and (e) quantitative results were provided, including mean differences with standard deviation (SD) or standard error (SE) of the mean, or effect estimates (such as odds ratios [ORs], hazard ratios [HRs], or risk ratios [RRs]) along with 95% confidence intervals (CIs) across different Paleolithic Diet Score categories (Supplemental Tables 3 and 4).

Data extraction

Two independent investigators, FB and MB, extracted the data from the selected studies and collected the following information: the first author's name, year of publication, study name (for cohort studies), country, mean age or age range (in years), follow-up period, total sample size, study arms (for RCTs), number of cases (in cohort studies), intervention and comparator details (for RCTs), dietary assessment method, and reported effect estimates with 95% CIs for mortality or chronic disease incidence across Paleolithic diet adherence categories (in cohort studies). For RCTs, MDs, SDs, or SEs were extracted from the most fully adjusted models, which included the covariates included in the multivariable analyses. Conflicts in data extraction were settled through discussion between the reviewers, with unresolved issues being arbitrated by a senior researcher (SJ).

Quality assessment methodology

Two independent reviewers (FB and MB) conducted all quality assessments. Disagreements were resolved through discussion or, if needed, by arbitration from a senior reviewer (SJ). To assess the quality of RCTs, we employed the Cochrane Risk of Bias Tool 2.0, evaluating five domains: randomization methodology, protocol adherence, data completeness, outcome measurement, and reporting transparency. Each domain received a rating of "low risk," "some concerns," or "high risk" (Higgins et al. 2011). The methodological quality of the prospective cohort studies was appraised using the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al. 2016). The ROBINS-I tool evaluates seven bias domains, including confounding, participant selection, and outcome measurement, to categorize overall risk. Studies were rated as low (low risk in all domains), moderate (low to moderate risk in all domains), or high (serious risk in any domain).

Statistical analysis

We employed DerSimonian and Laird random-effects models for data synthesis (Tufanaru et al. 2015). When fewer than five comparisons were available, we applied fixed-effects models. This approach is standard in meta-analysis to prevent unreliable variance estimates and overfitting that can occur with random-effects models when the number of studies is limited (Tufanaru et al. 2015). Relative risk (RR) estimates were calculated by comparing natural log-transformed RRs and their SEs between extreme diet score categories using the most adjusted models. Hazard ratios were treated as equivalent to RRs, consistent with prior methodology (Zhang and Kai 1998). Weighted mean differences (WMD) were pooled as the summary effect measure for continuous outcomes from RCTs, as all studies for a given outcome reported results in consistent and convertible units (Lin et al. 2025). For crossover trials, we conducted paired analyses using a correlation coefficient of 0.5 (Elbourne et al. 2002). Sex-stratified results were analyzed as independent studies. Heterogeneity was evaluated using Cochran's Q test and I^2 statistics, with an I^2 value greater than 50% indicating substantial heterogeneity (Chen and Peace 2021). To investigate the sources of heterogeneity and assess the robustness of the results, we conducted both subgroup and sensitivity analyses. Subgroup analyses were restricted to cases with 10 or more available comparisons. Among RCTs, we stratified studies by intervention duration (<24 vs. ≥24 weeks). For analyses with ≥10 comparisons, publication bias was assessed through: (1) funnel plot visualization, (2) formal statistical tests (Begg's and Egger's) (Freeman and Sutton 2020), and (3) Duval and Tweedie's trim-and-fill method to adjust for asymmetry (Duval and Tweedie 2000). Sensitivity analyses involved iterative exclusion of individual studies to evaluate their impact on pooled estimates (Mathur and VanderWeele 2020).

We conducted dose-response meta-analyses to assess the relationship between each 1-point increment in adherence to the Paleolithic diet score within cohort studies. Our analytical approach incorporated several modeling strategies: (1) restricted cubic spline models with three and four knots, (2) linear models, and (3) quadratic models. Model selection was guided by the Akaike Information Criterion, where lower values indicated better model fit (Schwarz 1978). We assessed non-linearity using Wald tests (Orsini et al. 2012) and implemented one-stage dose-response meta-analyses with restricted maximum likelihood estimation (Crippa et al. 2019). When necessary, we recalibrated effect sizes by resetting the lowest exposure category as the reference (Hamling et al. 2008). All statistical analyses were executed in Stata 14 (StataCorp), with significance thresholds established at $p < 0.05$.

GRADE assessment

We assessed evidence certainty using the GRADE approach for RCTs as high-certainty evidence (Guyatt et al. 2008). Using the revised GRADE framework, we evaluated the reliability of each finding for prospective cohort studies. A key change is that observational studies are now initially considered to have high certainty. However, because they are not randomized, they are automatically downgraded by two levels, resulting in a "low" certainty rating. This initial rating was then modified using the ROBINS-I tool to assess biases and consider other factors, such as imprecision or a large effect size. A high or moderate grade signifies strong confidence in the result, while low or very low grades indicate limited or weak confidence (Schünemann et al. 2019). These ratings were then adjusted based on five potential downgrading factors: (1) methodological limitations (high risk of bias), (2) inconsistent results ($I^2 > 50\%$ with $p < 0.0.5$ for heterogeneity), (3) indirect applicability, (4) imprecise effect estimates (95% CIs crossing minimally important difference), or (5) suspected publication bias. Conversely, we considered upgrading evidence quality when observing: (1) significant dose-response gradients, (2) substantial effect magnitudes, or (3) residual confounding that would likely weaken observed associations (Schünemann et al. 2019).

Results

Literature research

As shown in Supplemental Figure 1, our search strategy yielded 1,593 studies from systematic database searches and manual searches. Following the removal of duplicates and screening of titles and abstracts, we excluded 1,562 studies. The remaining 31 articles underwent a full-text review, which included 19 RCTs and 12 prospective cohort studies.

The 19 included RCTs (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Fontes-Villalba et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Otten et al. 2019; Jospe et al. 2020; Sampaio et al. 2020; Franklin et al. 2022; Shemirani et al. 2022; Pieta et al. 2023; Zdzieblik et al. 2024) examined the impact of the Paleolithic diet score on metabolic and cardiovascular markers, such as fasting blood glucose (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Genoni et al. 2016; Otten et al. 2016, 2019; Shemirani et al. 2022; Pieta et al. 2023), insulin (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Genoni et al. 2016; Otten et al. 2016, 2019; Shemirani et al. 2022; Pieta et al. 2023), homeostasis model assessment-estimated insulin resistance (HOMA-IR) (Lindeberg et al. 2007; Jönsson et al. 2009; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Shemirani et al. 2022), hemoglobin A1c (HbA1c) (Lindeberg et al. 2007; Masharani et al. 2015; Jospe et al. 2020), total cholesterol (Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Jospe et al. 2020; Shemirani et al. 2022), low-density lipoprotein (LDL) cholesterol (Jönsson et al. 2009;

Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Jospe et al. 2020; Shemirani et al. 2022), high-density lipoprotein (HDL) cholesterol (Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Jospe et al. 2020; Shemirani et al. 2022), triglycerides (Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Jospe et al. 2020; Shemirani et al. 2022; Pieta et al. 2023), body weight (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Fontes-Villalba et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Otten et al. 2019; Jospe et al. 2020; Sampaio et al. 2020; Franklin et al. 2022; Shemirani et al. 2022; Pieta et al. 2023; Zdzieblik et al. 2024), body mass index (BMI) (Jönsson et al. 2009; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Otten et al. 2016; Blomquist et al. 2018; Otten et al. 2019; Sampaio et al. 2020; Pieta et al. 2023; Zdzieblik et al. 2024), waist circumference (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Stomby et al. 2015; Genoni et al. 2016; Otten et al. 2016; Jospe et al. 2020; Sampaio et al. 2020; Shemirani et al. 2022), C-reactive protein (Jönsson et al. 2009; Blomquist et al. 2017; Jospe et al. 2020), systolic (Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2018; Jospe et al. 2020; Zdzieblik et al. 2024), and diastolic (Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2018; Jospe et al. 2020; Zdzieblik et al. 2024) blood pressure.

A total of 12 prospective cohort studies examined the relationship between adherence to the Paleolithic diet score and various health outcomes, including mortality from all causes (Whalen et al. 2017; Cheng et al. 2018a; Bonaccio et al. 2021; Rydhög et al. 2024), cardiovascular disease (Whalen et al. 2017; Cheng et al. 2018a; Bonaccio et al. 2021; Rydhög et al. 2024), cancer (Whalen et al. 2017; Cheng et al. 2018a; Bonaccio et al. 2021; Rydhög et al. 2024) and other causes (Whalen et al. 2017; Bonaccio et al. 2021; Rydhög et al. 2024), along with the incidence of type 2 diabetes (Hirahatake et al. 2019a; Shah et al. 2021; Rydhög et al. 2024), cardiovascular disease (Hirahatake et al. 2019b; de la O et al. 2022), coronary heart disease (Hirahatake et al. 2019b; Shah et al. 2021; Rydhög et al. 2024), stroke (Hirahatake et al. 2019b; Rydhög et al. 2024), and cancer (Haridass et al. 2018; Cheng et al. 2018b; Shah et al. 2023; Xiao et al. 2023).

Characteristics of randomized controlled trials

Table 1 presents the baseline demographic and clinical characteristics of participants in the included randomized controlled trials. All included trials utilized a parallel design, except for two crossover studies (Jönsson et al. 2009; Fontes-Villalba et al. 2016). Among the included RCTs, study sites were distributed internationally, with one trial each conducted in Germany (Zdzieblik et al. 2024), Poland (Pieta et al. 2023), Iran (Shemirani et al. 2022), New Zealand (Jospe et al. 2020), Brazil (Sampaio et al. 2020), Denmark (Otten et al. 2019), Australia (Genoni et al. 2016), the United States (Masharani et al. 2015), Spain (Fontes-Villalba et al. 2016), and 10 studies in Sweden (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Franklin et al. 2022). Intervention periods ranged from 4 to 96 weeks across studies. The studies enrolled participants ranging from 13 to 179 in both the intervention and control arms. The included studies primarily investigated specific population subgroups, including athletes (Pieta et al. 2023; Zdzieblik et al. 2024), individuals with metabolic syndrome (Shemirani et al. 2022), and various cohorts with weight-related conditions: women with overweight (Franklin et al. 2022), general participants with overweight or obesity (Jospe et al. 2020; Sampaio et al. 2020), and postmenopausal women with overweight/obesity (Jönsson et al. 2009; Mellberg et al. 2014; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Fontes-Villalba et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Otten et al. 2019). Additional populations studied included healthy women (Genoni et al. 2016), patients with type 2 diabetes mellitus (Jönsson et al. 2009; Masharani et al. 2015; Fontes-Villalba et al. 2016), and those with ischemic heart disease (Lindeberg et al. 2007). The studies implemented diverse Paleolithic dietary interventions, including a standard Paleolithic diet [17 trials (Lindeberg et al. 2007; Jönsson et al. 2009; Mellberg et al. 2014; Masharani et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Fontes-Villalba et al. 2016; Genoni et al. 2016; Otten et al. 2016; Blomquist et al. 2017, 2018; Otten et al. 2019; Jospe et al. 2020; Sampaio et al. 2020; Franklin et al. 2022; Pieta et al. 2023; Zdzieblik et al. 2024)]; a Paleolithic-based low-carbohydrate diet incorporating calorie-counting or portion-control methods [one trial (Shemirani et al. 2022)]; and modified Paleolithic diet approaches [one trial (Boraxbekk et al. 2015)]. Control conditions exhibited similar variability, including a mixed diet [1 trial (Zdzieblik et al. 2024)]; rational diet [1 trial (Pieta et al. 2023)]; moderate-carbohydrate diet with calorie-counting or portion-control method [1 trial (Shemirani et al. 2022)]; low-fat diet [2 trials (Otten et al. 2016; Franklin et al. 2022)]; Mediterranean diets [2 trials (Lindeberg et al. 2007; Jospe et al. 2020)]; intermittent fasting [1 trial (Jospe et al. 2020)]; Guidelines Substantiated Diet [1 trial (Sampaio et al. 2020)]; Nordic Nutrition Recommendations [5 trials (Mellberg et al. 2014; Boraxbekk et al. 2015; Stomby et al. 2015; Andersson et al. 2016; Otten et al. 2019)]; prudent diet [2 trials (Blomquist et al. 2017, 2018)]; Australian Guide to Healthy Eating [1 trial (Genoni et al. 2016)]; American Diabetes Association [1 trial (Masharani et al. 2015)]; Diabetes diet [2 trials (Jönsson et al. 2009; Fontes-Villalba et al. 2016)].

Table 1. Properties of randomized controlled trials evaluating the effects of Paleolithic diet scoring on cardiometabolic risk factors.

Study, year	Country	Study design	Follow-up duration	Participants	Group study	Mean age	Intervention or comparator	Outcome
Zdzieblik et al. 2024	Germany	Parallel	6 weeks	Athletes 14 M	Intervention *n* = 5	21 ± 1	Paleolithic diet	Weight BMI
					Control *n* = 9	26 ± 5	Mixed diet	SBP DBP
Pieta et al. 2023	Poland	Parallel	8 weeks	Athletes 25 M	Intervention *n* = 5	21 ± 2.2	Paleolithic diet	Weight BMI
					Control *n* = 9	23 ± 2.2	Rational diet	FBS Insulin TG
Shemirani et al. 2022	Iran	Parallel	10 weeks	Metabolic syndrome 69: 48 F, 21 M	Intervention *n* = 17	42.8 ± 9.6	Paleolithic-based low-carbohydrate diet with calorie-counting method	Weight FBS Insulin
					Control *n* = 18	43.6 ± 9.9	Moderate-carbohydrate diet with calorie-counting method	HOMA-IR TC
					Intervention *n* = 17	44.3 ± 9.1	Paleolithic-based low-carbohydrate diet with portion-control method	TG HDL-c
					Control *n* = 17	40.8 ± 8	Moderate-carbohydrate diet with portion-control method	
Franklin et al. 2022	Sweden	Parallel	24 weeks	Women with overweight 62 F	Intervention *n* = 32	60 ± 2.2	Paleolithic diet	Weight
					Control *n* = 30	60 ± 2.9	Low-fat diet	
Jospe et al. 2020	New Zealand	Parallel	48 weeks	Participants with overweight 179: 109 F, 70 M	Intervention *n* = 46	42.6 ± 9.6	Paleolithic diet	Weight WC
					Control *n* = 68	44.2 ± 11.7	Mediterranean diets	HbA1c TC
					Intervention *n* = 46	42.6 ± 9.6	Paleolithic diet	TG LDL-c
					Control *n* = 133	75 ± 55.2	Intermittent fasting	HDL-c SBP DBP CRP
Sampaio et al. 2020	Brazil	Parallel	8 weeks	Participants with obesity 155: 126 F, 29 M	Intervention *n* = 82	39.6 ± 11	Paleolithic diet	Weight BMI
					Control *n* = 73	40.3 ± 12.1	Guidelines Substantiated Diet	
Otten et al. 2019	Denmark	Parallel	96 weeks	Postmenopausal women with obesity 70 F	Intervention *n* = 26	61 ± 1	Paleolithic diet	Weight BMI
					Control *n* = 23		Nordic Nutrition Recommendations	FBS Insulin
Blomquist et al. 2018	Sweden	Parallel	96 weeks	Postmenopausal women with overweight 58 F	Intervention *n* = 33	60 ± 5.5	Paleolithic diet	Weight BMI
					Control *n* = 25	62 ± 5.7	Prudent diet	HOMA-IR TC TG LDL-c HDL-c SBP DBP
Blomquist et al. 2017	Sweden	Parallel	96 weeks	Postmenopausal women 70 F	Intervention *n* = 35	60.0 ± 5.6	Paleolithic diet	Weight HOMA-IR
					Control *n* = 35	61 ± 7	Prudent diet	TC TG LDL-c HDL-c CRP
Otten et al. 2016	Sweden	Parallel	96 weeks	Postmenopausal women with obesity 41 F	Intervention *n* = 25	61 ± 6	Paleolithic diet	Weight BMI
					Control *n* = 16	62 ± 6	Low-fat diet	FBS Insulin HOMA-IR TC TG LDL-c HDL-c SBP DBP

(*Continued*)

Table 1. Continued.

Study, year	Country	Study design	Follow-up duration	Participants	Group study	Mean age	Intervention or comparator	Outcome
Genoni et al. 2016	Australia	Parallel	4 weeks	Healthy women 39 F	Intervention *n* = 22 Control *n* = 17	47 ± 13	Paleolithic diet Australian Guide to Healthy Eating	Weight WC FBS Insulin TC TG LDL-c HDL-c SBP DBP
Andersson et al. 2016	Sweden	Parallel	96 weeks	Postmenopausal women 49 F	Intervention *n* = 27 Control *n* = 22	NR	Paleolithic diet Nordic Nutrition Recommendations	Weight BMI FBS HOMA-IR TC TG SBP
Masharani et al. 2015	USA	Parallel	5 weeks	Type 2 diabetes mellituse	Intervention *n* = 14 Control *n* = 10	58 ± 8 56 ± 13	Paleolithic diet American Diabetes Association	Weight FBS Insulin HbA1c TC TG LDL-c HDL-c SBP DBP
Stomby et al. 2015	Sweden	Parallel	96 weeks	Postmenopausal women with overweight and obesity 49 F	Intervention *n* = 27 Control *n* = 22	NR	Paleolithic diet Nordic Nutrition Recommendations	Weight BMI WC FBS Insulin HOMA-IR TC TG LDL-c HDL-c SBP DBP
Boraxbekk et al. 2015	Sweden	Parallel	23 weeks	Postmenopausal women with overweight 20 F	Intervention *n* = 9 Control *n* = 11	61.1 ± 1.6 61.6 ± 1.7	Modified Paleolithic diet Nordic Nutrition Recommendations	Weight BMI WC FBS Insulin HOMA-IR
Fontes-Villalba et al. 2016	Spain	Cross-over	12 weeks	Type 2 diabetes mellitus 13: 3 F, 10 M	Intervention *n* = 13 Control *n* = 13	64 ± 6	Paleolithic diet Diabetes diet	Weight
Mellberg et al. 2014	Sweden	Parallel	96 weeks	Postmenopausal women with obesity 49 F	Intervention *n* = 27 Control *n* = 22	59.5 ± 5.5 60.3 ± 5.9	Paleolithic diet Nordic Nutrition Recommendations	Weight WC FBS Insulin TC TG LDL-c HDL-c SBP DBP
Jönsson et al. 2009	Sweden	Cross-over	12 weeks	Type 2 diabetes mellitus 13: 3 F, 10 M	Intervention *n* = 7 Control *n* = 6	64 ± 6 64 ± 6	Paleolithic diet Diabetes diet	Weight BMI WC FBS Insulin HOMA-IR TC TG LDL-c HDL-c SBP DBP CRP

(*Continued*)

Table 1. Continued.

Study, year	Country	Study design	Follow-up duration	Participants	Group study	Mean age	Intervention or comparator	Outcome
Lindeberg et al. 2007	Sweden	Parallel	12 weeks	Ischemic heart disease 29 M	Intervention $n=14$ Control n = 15	65 ± 10 57 ± 7	Paleolithic diet Mediterranean diet	Weight WC FBS Insulin HbA1c HOMA-IR

BMI: Body mass index; CRP: C-reactive protein; F: Female; FBS: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; LDL-C: Low-density lipoprotein cholesterol; M: Male; NR: Not reported; TC: Total cholesterol; TG: Triglyceride; WC: Waist circumference.

Table 2. The impact of a Paleolithic diet score on cardiovascular disease risk in randomized controlled trials.

				Pooled estimates*	Heterogeneity	GRADE● Downgrade	
Outcome	No. trials	No. intervention	No. control	Weighted mean differences ([95%CI], p)	I^2, p	Risk of bias Inconsistency Indirectness Imprecision Publication bias	Certainty of evidence
Glycemic status							
Fasting blood glucose, mmol/L	13	252	217	−0.04, [−0.14, 0.04], $p=0.31$	51.9%, $p=0.01$	□ ■ □ ■ □	⊕⊕◯◯ LOW
Fasting blood insulin, pmol/L	12	238	207	−1.01 [−1.45, −0.57], $p<0.001$	67.5%, $p<0.001$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
HOMA-IR	10	209	181	−0.25 [−0.63, 0.11], $p=0.17$	96.8%, $p<0.001$	□ ■ □ ■ □	⊕⊕◯◯ LOW
HbA1c, mmol/L	4	120	226	0.09 [−0.03, 0.22], $p=0.13$	85.2%, $p<0.001$	□ ■ □ ■ □	⊕⊕◯◯ LOW
Lipid profiles							
Total cholesterol, mmol/L	13	341	405	−0.15, [−0.24, −0.07], $p<0.001$	82.8%, $p<0.001$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
LDL cholesterol, mmol/L	12	314	383	−0.24, [−0.40, −0.08], $p=0.003$	80.7%, $p<0.001$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
HDL cholesterol, mmol/L	12	314	383	−0.007, [−0.02, 0.01], $p=0.54$	3.5%, $p=0.41$	□ □ □ ■ □	⊕⊕⊕◯ MODERATE
Triglycerides, mmol/L	14	355	416	−0.16, [−0.24, −0.08], $p<0.001$	86.9%, $p<0.001$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
Anthropometric variables							
Body weight, kg	21	524	576	−1.74, [−2.57, −0.91], $p<0.001$	67.7%, $p<0.001$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
Waist circumference, cm	12	182	284	−0.77, [−2.26, 0.71], $p=0.31$	70.9%, $p<0.001$	□ ■ □ ■ □	⊕⊕◯◯ LOW
Body mass index, kg/m^2	10	255	222	−1.12, [−1.42, −0.82], $p<0.001$	49.3%, $p=0.03$	□ ■ □ □ □	⊕⊕⊕◯ MODERATE
Inflammatory marker							
C-reactive protein, nmol/L	4	126	229	0.32, [−0.22, 0.29], $p=0.81$	34.3%, $p=0.21$	□ ■ □ □ □	⊕⊕◯◯ LOW
Blood pressure							
Systolic blood pressure, mmHg	11	279	354	−3.15, [−6.72, 0.42], $p=0.08$	89.9%, $p<0.001$	□ ■ □ ■ □	⊕⊕◯◯ LOW
Diastolic blood pressure, mmHg	9	246	325	−3.28, [−4.55, −2.01], $p<0.001$	32.0%, $p=0.16$	□ □ □ □ □	⊕⊕⊕◯ MODERATE

*The data are presented as weighted mean differences (WMDs) with 95% confidence intervals (CIs), calculated using the generic inverse variance method under either random-effects or fixed-effects models. The corresponding pseudo 95% CIs for these WMDs were directly derived from the original MDs and their 95% CIs. Between-study heterogeneity was evaluated using the Cochran Q test and measured using the I^2 statistic, with an I^2 value of 50% or greater indicating substantial heterogeneity.

●Following the GRADE framework, evidence from randomized controlled trials is initially classified as high certainty but may be downgraded based on five key domains. Outcomes that were downgraded are marked with filled black squares.

Findings from a meta-analysis of randomized controlled trials

As indicated in Table 2, following a Paleolithic diet was linked to significantly lower levels of fasting insulin (WMD −1.01 pmol/L, [−1.45, −0.57], $p<0.001$; heterogeneity: $I^2=67.5\%$, $p<0.001$)], total cholesterol (WMD −0.15 mmol/L, [−0.24, −0.07], $p<0.001$; heterogeneity: $I^2=82.8\%$, $p<0.001$), LDL cholesterol (WMD −0.24 mmol/L, [−0.40, −0.08], $p=0.003$; heterogeneity: $I^2=80.7\%$, $p<0.001$), triglycerides (WMD −0.16 mmol/L, [−0.24, −0.08], $p<0.001$; heterogeneity: $I^2=86.9\%$, $p<0.001$), body weight (WMD −1.74 kg, [−2.57, −0.91], $p<0.001$; heterogeneity: $I^2=67.7\%$, $p<0.001$), BMI (WMD −1.12 kg/m^2, [−1.42, −0.82], $p<0.001$; heterogeneity: $I^2=49.3\%$, $p=0.03$), and diastolic blood pressure (WMD −3.28 mmHg, [−4.55, −2.01], $p<0.001$; heterogeneity: $I^2=32.0\%$, $p=0.16$). However, no significant association was observed between the Paleolithic diet score and fasting blood

glucose (WMD −0.04 mmol/L, [−0.14, 0.04], $p = 0.31$; heterogeneity: 51.9%, $p = 0.01$), HbA1c (WMD 0.09 mmol/L, [−0.03, 0.22], $p = 0.13$; heterogeneity: $I^2 = 85.2\%$, $p < 0.001$), HOMA-IR (WMD −0.25 [−0.63, 0.11], $p = 0.17$; heterogeneity: $I^2 = 96.8\%$, $p < 0.001$), HDL cholesterol (WMD −0.007 mmol/L, [−0.02, 0.01], $p = 0.54$; heterogeneity: $I^2 = 3.5\%$, $p = 0.41$), waist circumference (WMD −0.77 cm, [−2.26, 0.71], $p = 0.31$; heterogeneity: 70.9%, $p < 0.001$), C-reactive protein (WMD 0.32 nmol/L, [−0.22, 0.29], $p = 0.81$; heterogeneity: $I^2 = 34.3\%$, $p = 0.21$), and systolic blood pressure (WMD −3.15 mmHg, [−6.72, 0.42], $p = 0.08$; heterogeneity: $I^2 = 89.9\%$, $p < 0.001$). The corresponding forest plots for these outcomes are provided in Supplemental Figures 2–15.

Subgroup analyses based on intervention duration revealed that the significant associations between the Paleolithic diet and several health outcomes were dependent on the study duration. Specifically, in interventions lasting less than 24 weeks, the beneficial relationships between the Paleolithic diet and improvements in fasting insulin, total cholesterol, LDL cholesterol, body weight, and BMI were no longer statistically significant. Conversely, for the outcomes of fasting blood glucose and HOMA-IR, a significant association with the diet was explicitly demonstrated in studies where the intervention period exceeded 12 weeks (Supplemental Figure 16–27).

The Cochrane risk of bias evaluation for the included RCTs is presented in Supplemental Figure 28, showing both summary and individual trial assessments. Most studies were rated as having a low or unclear risk of bias across all domains. Despite two trials showing high risk in specific domains, the collective evaluation suggested negligible overall risk of bias in the analysis.

Characteristics of prospective cohort studies

Table 3 outlines the key features of the included prospective cohort studies. The included studies were carried out in Sweden (Rydhög et al. 2024), the United States (Whalen et al. 2017; Haridass et al. 2018; Cheng et al. 2018a, 2018b; Hirahatake et al. 2019a; 2019b; Xiao et al. 2023), France (Shah et al. 2021, 2023), Spain (de la O et al. 2022), and Italy (Bonaccio et al. 2021). The study participants' ages ranged from 22 to 104 years. Most of the cohort studies assessed mixed-sex populations, except for five that specifically studied females (Haridass et al. 2018; Cheng et al. 2018a, 2018b; Shah et al. 2021, 2023). Follow-up durations varied across studies, spanning 6.25 to 30 years. All studies used food frequency questionnaires (FFQs) to assess Paleolithic diet scores, with 1 study additionally employing food record questionnaires (Rydhög et al. 2024). The methodological quality of the 12 prospective cohort studies examining the relationship between adherence to a Paleolithic diet and chronic disease or mortality risk was evaluated using the ROBINS-I tool. The results are summarized in Supplemental Table 5. The overall quality of the evidence was moderate. The majority of studies (9 out of 12, 75%) were judged to have a moderate risk of bias. The remaining three studies (25%) were assessed as having a low risk of bias. No studies were deemed to have a serious or critical risk of bias.

Findings from a meta-analysis of prospective cohort studies

Table 4 demonstrate a significant inverse association between adherence to Paleolithic dietary patterns and risk of all-cause mortality (RR 0.90 [0.87, 0.94], $p < 0.001$; heterogeneity: $I^2 = 76.6\%$, $p = 0.005$), cancer mortality (RR 0.90 [0.85, 0.97], $p = 0.004$; heterogeneity: $I^2 = 1.7\%$, $p = 0.38$), other-cause mortality (RR 0.84 [0.74, 0.95], $p = 0.004$; heterogeneity: $I^2 = 20.5\%$, $p = 0.28$), type 2 diabetes mellitus incidence (RR 0.91 [0.85, 0.98], $p = 0.01$; heterogeneity: $I^2 = 0.5\%$, $p = 0.36$), cardiovascular disease incidence (RR 0.84 [0.70, 1.0], $p = 0.05$; heterogeneity: $I^2 = 84.1\%$, $p = 0.01$), coronary heart disease incidence (RR 0.90 [0.86, 0.95], $p < 0.001$; heterogeneity: $I^2 = 8.3\%$, $p = 0.33$), and cancer incidence (RR 0.90 [0.83, 0.97], $p = 0.004$; heterogeneity: $I^2 = 73.7\%$, $p = 0.01$). However, our analysis revealed no statistically significant associations between Paleolithic diet scores and mortality from cardiovascular disease (RR 0.94 [0.88, 1.0], $p = 0.05$; heterogeneity: $I^2 = 56.2\%$, $p = 0.07$), incidence of cardiovascular disease (RR 0.84 [0.70, 1.0], $p = 0.05$; heterogeneity: $I^2 = 84.1\%$, $p = 0.01$), or incidence of stroke (RR 0.89 [0.78, 1.02], $p = 0.09$; heterogeneity: $I^2 = 0.0\%$, $p = 0.73$). The corresponding forest plots are available in Supplemental Figures 29–37.

No subgroup analyses were possible due to the limited number of comparable cohorts ($n < 10$) available for assessment.

Dose-response assessment criteria were met by all included cohort studies (Figures 1 and 2). Tests for non-linearity were non-significant (Pnon-linear > 0.05 for all outcomes), justifying the use of linear models. Significant inverse dose-response relationships were observed for all-cause mortality ($p = 0.004$), cancer mortality ($p = 0.004$), other-cause mortality ($p = 0.01$), and coronary heart disease incidence ($p < 0.001$). Linear dose-response analysis revealed no significant inverse associations for cardiovascular disease mortality ($p = 0.05$), cardiovascular disease incidence ($p = 0.13$), stroke incidence ($p = 0.27$), cancer incidence ($p = 0.21$), or type 2 diabetes incidence ($p = 0.06$).

Sensitivity analysis

In RCTs, sensitivity analyses (Supplemental Figures 38–49) demonstrated robust overall effect estimates, with no significant changes observed upon sequential exclusion of individual studies, except for fasting blood glucose, HOMA-IR, and systolic blood pressure. The exclusion of particular studies significantly influenced effect estimates for specific outcomes; specifically, Jönsson et al.'s removal affected fasting blood sugar (Jönsson et al. 2009), Shemirani et al.'s (2022) exclusion impacted HOMA-IR, and Andersson et al.'s (2016) omission altered systolic blood pressure results. Sensitivity analyses were not conducted in the cohort studies due to insufficient data, with fewer than 10 cohort comparisons available for each outcome measure.

Table 3. Features of prospective cohort studies investigating the link between Paleolithic diet adherence and the risk of chronic diseases or mortality.

Author, year	Study name (country)	Age	Gender	Cases/total sample size	Follow-up time	Paleo diet index (scoring categories)	Method of measurement of exposure	Outcome	Adjustment for confounders
Rydhög et al. 2024	Malmö Diet and Cancer Study (Sweden)	44–74	Both	10,092/24,104 3,606/24,104 3,108/24,104 1,824/24,104 2,988/24,104 2,259/24,104 3,995/24,104	18 years	Paleolithic Diet Fraction (0–90)	7-day food record and 168-item FFQ	All-cause mortality Cancer mortality Cardiovascular disease mortality Other causes of mortality Coronary disease incidence Ischemic stroke incidence Type 2 diabetes incidence	Age, body mass index, total energy intake, leisure time physical activity, smoking, alcohol intake, education, living alone at baseline, sex, and being born in Sweden
Xiao et al. 2023	Prostate, Lung, Colorectal, and Ovarian (USA)	55–74	Both	694/74,721	9.2 years	Plant-based Paleolithic diet (14–70)	137-item FFQ	Colorectal cancer incidence	Age, sex, race, education levels, family history of colorectal cancer, history of colon comorbidity, and history of diverticulitis or diverticulosis, history of colorectal polyp, history of diabetes, history of aspirin use, total energy intake, body mass index at baseline, smoking status, and physical activity level
Shah et al. 2023	Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (French)	40–65	Female	3,968/65,574	20 years	Paleolithic diet (14–70)	FFQ	Breast cancer incidence	Age, educational level, physical activity, smoking status, family history of breast cancer, breastfeeding, age at menarche, age at first full-term birth, history of benign breast disease, ever use of contraceptive pill, ever use of menopausal hormone therapy, mammography in the last follow-up cycle, body mass index, and energy intake
de la O et al. 2022	Seguimiento Universidad de Navarra (Spain)	38 ± 12	Both	165/18,210	12.2 years	Paleolithic diet (11–55)	136-item FFQ	Cardiovascular disease incidence	Sex, age, and total energy intake, alcohol intake, smoking status, body mass index, physical activity, prevalent hypertension, hypertriglyceridemia, hypercholesterolemia, diabetes, cancer, depression, family history of cardiovascular disease, education level, smoking-pack-years, napping, watching television, sitting time, snacking between meals, and following special diets
Shah et al. 2021	Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (French)	40–65	Female	3,292/70,991 12,504/70,991	20 years	Paleolithic diet (14–70)	FFQ	Type 2 diabetes incidence Coronary disease incidence	Age, family history of diabetes or hypertension, educational level, hypercholesterolemia, hypertension, and energy intake, smoking status, physical activity and body mass index
Bonaccio et al. 2021	Moli-sani Study (Italy)	≥35	Both	1,237/24,325 444/24,325 483/24,325 310/24,325	8.2 years	Paleolithic diet (14–70)	FFQ	All-cause mortality Cardiovascular disease mortality Cancer mortality Other causes of mortality	Age, sex, energy intake, education, household income, leisure-time physical activity, smoking status, body mass index, diabetes, hypertension, hyperlipidemia, history of cardiovascular disease, history of cancer at baseline
Hirahatake et al. 2019a	Women's Health Initiative (USA)	50–79	Both	306/5809 127/5809 79/5809	12.4 years	Paleolithic diet (13–65)	FFQ	Cardiovascular disease incidence Coronary disease incidence Ischemic stroke incidence	Age, race, education, income, marital status, physical activity, smoking, body mass index, WHI study arm, geographical region, smoking × time, systolic blood pressure × time, diastolic blood pressure × time, age at type 2 diabetes mellitus diagnosis, energy intake, insulin use, blood pressure, and history of high cholesterol
Hirahatake et al. 2019b	The Coronary Artery Risk Development in Young Adults (USA)	18–30	Both	680/4,719	30 years	Paleolithic diet (0–90)	FFQ	Type 2 diabetes incidence	Age, race, sex, CARDIA study center, education, smoking status, physical activity, total energy intake, body mass index, average fruit, vegetable, whole grain, red meat, fish, and dairy intake

(*Continued*)

Table 3. Continued.

Author, year	Study name (country)	Age	Gender	Cases/total sample size	Follow-up time	Paleo diet index (scoring categories)	Method of measurement of exposure	Outcome	Adjustment for confounders
Haridass et al. 2018	California Teachers Study cohort (USA)	22–104	Female	346/133,479	16 years	Paleolithic diet (13–65)	103-item FFQ	Breast cancer incidence	Age, race, breast cancer family history, age at menarche, oral contraceptive use, parity status, smoking status, socioeconomic status, physical activity, total energy intake, total alcohol intake, and body mass index
Cheng et al. 2018a	Iowa Women's Health Study (USA)	55–69	Female	18,687/35,221 7,064/35,221 4,665/35,221	26 years	evolutionary-concordance (14–70)	127-item FFQ	All-cause mortality Cardiovascular disease mortality Cancer mortality	Age, smoking status, education, body mass index, physical activity, total energy intake, hormone replacement therapy use, marital status, and chronic disease
Cheng et al. 2018b	Iowa Women's Health Study (USA)	55–69	Female	1,731/35,221	26 years	evolutionary-concordance (14–70)	127-item FFQ	Colorectal cancer incidence	Age, smoking status, education, body mass index, physical activity, total energy intake, hormone replacement therapy use, marital status, and chronic disease
Whalen et al. 2017	REasons for Geographic and Racial Differences in Stroke (USA)	≥45	Both	All-cause mortality Cardiovascular disease mortality Cancer mortality Other causes of mortality	6.25 years	Paleolithic diet (14–70)	98-item FFQ	2,513/21,423 863/21,423 728/21,423 822/21,423	Sex, race, total energy intake, body mass index, physical activity, smoking, annual income, and hormone replacement therapy use at baseline in an age group

BMI: body mass index; FFQ: food frequency questionnaire.

Publication bias

The analysis found no significant evidence of publication bias for any of the health variables examined. This conclusion was supported by the results of both Begg's and Egger's statistical tests, which consistently returned non-significant *p*-values across all outcomes, including fasting blood glucose, fasting insulin, HOMA-IR, all cholesterol subtypes (total, LDL, and HDL), triglycerides, body weight, BMI, waist circumference, and both systolic and diastolic blood pressure (Supplemental Figures 50–61 and Supplemental Table 6). Publication bias for cohort study outcomes could not be adequately assessed because of insufficient data (fewer than 10 cohort comparisons per outcome).

GRADE assessments

As indicated in Table 2 and Supplemental Table 7, the GRADE framework was employed to evaluate the impact of Paleolithic diets on cardiometabolic risk factors in RCTs. The evidence certainty was rated very low for HbA1c and low for fasting blood sugar, HOMA-IR, waist circumference, C-reactive protein, and systolic blood pressure, primarily due to concerns over inconsistency and imprecision. For the remaining outcomes, the evidence was classified as moderate, with downgrades applied only for inconsistency.

The GRADE assessments of the association between Paleolithic dietary patterns and mortality/chronic disease outcomes in prospective cohort studies (presented in Table 4 and Supplemental Table 8) demonstrated very low certainty of evidence for cardiovascular disease incidence, low certainty for stroke incidence and cancer incidence, moderate certainty for all-cause mortality, cardiovascular disease mortality, type 2 diabetes mellitus, and high certainty for cancer mortality, other-cause mortality, coronary heart diseaseincidence.

Discussion

This study presents a novel, dual-perspective synthesis of the Paleolithic diet, integrating evidence from experimental trials and observational data. Our findings indicate that the Paleolithic diet is efficacious for improving a cluster of key cardiometabolic risk factors, as demonstrated by RCTs. Furthermore, observational data suggest that a dietary pattern aligned with Paleolithic principles is associated with a lower risk of mortality and incidence of major chronic diseases. Our meta-analysis of RCTs demonstrates that the Paleolithic diet effectively reduces fasting insulin, total cholesterol, LDL cholesterol, triglycerides, body weight, BMI, and diastolic blood pressure. However, no significant effects were observed for fasting glucose, HOMA-IR, HbA1c, HDL cholesterol, waist circumference, C-reactive protein, or systolic blood pressure. Notably, the Paleolithic diet exhibited robust inverse associations with all-cause mortality, cancer mortality, other-cause mortality, type 2 diabetes mellitus incidence, coronary heart disease incidence, and cancer incidence. In contrast, the Paleolithic diet did not significantly reduce cardiovascular mortality and stroke risk, highlighting

Table 4. The association between the Paleolithic diet score and the risk of chronic disease and mortality in prospective cohort studies.

		Pooled estimates*			Heterogeneity	Dose-response meta-analysis (per 1 point of score)	GRADE●
Outcome	No. cohort comparisons	No. cases	No. participants	Risk ratio ([95%CI], *p*)	I^2, *p*	Risk ratio ([95%CI], *p*)	Certainty of evidence
All-cause mortality	4	86,163	105,073	0.90 ([0.87, 0.94], $p<0.001$)	76.6%, $p=0.005$	0.99 ([0.991, 0.998], Plinear = 0.004)	⊕⊕⊕◯ MODERATE
Cardiovascular disease mortality	4	11,479	105,073	0.94 ([0.88, 1.0], $p=0.05$)	56.2%, $p=0.07$	0.99 ([0.992, 1.00], Plinear = 0.05)	⊕⊕⊕◯ MODERATE
Cancer mortality	4	9,482	105,073	0.90 ([0.85, 0.97], $p=0.004$)	1.7%, $p=0.38$	0.99 ([0.991, 0.998], Plinear = 0.004)	⊕⊕⊕⊕ HIGH
Other-cause mortality	3	2,956	69,852	0.84 ([0.74, 0.95], $p=0.004$)	20.5%, $p=0.28$	0.99 ([0.986, 0.998], Plinear = 0.01)	⊕⊕⊕⊕ HIGH
Type 2 diabetes mellitus	3	7,967	99,814	0.91 ([0.85, 0.98], $p=0.01$)	0.5%, $p=0.36$	0.99 ([0.994, 1.00], Plinear = 0.06)	⊕⊕⊕◯ MODERATE
Cardiovascular disease	2	471	24,019	0.84 ([0.70, 1.0], $p=0.05$)	84.1%, $p=0.01$	0.97 ([0.953, 1.00], Plinear = 0.13)	⊕⊕◯◯ VERY LOW
Coronary heart disease	3	15,619	100,904	0.90 ([0.86, 0.95], $p<0.001$)	8.3%, $p=0.33$	0.99 ([0.991, 0.996], Plinear < 0.001)	⊕⊕⊕⊕ HIGH
Stroke	2	2,338	29,913	0.89 ([0.78, 1.02], $p=0.09$)	0.0%, $p=0.73$	0.99 ([0.978, 1.00], Plinear = 0.27)	⊕⊕◯◯ LOW
Cancer	4	6,739	308,995	0.90 ([0.83, 0.97], $p=0.004$)	73.7%, $p=0.01$	0.99 ([0.982, 1.00], Plinear = 0.21)	⊕⊕◯◯ LOW

*p-values were calculated using generic inverse variance fixed-effects models. To evaluate between-study heterogeneity, the Cochran Q statistic and the I^2 statistic (where values ≥50% indicate substantial heterogeneity) were applied.

●For evidence quality assessment, we applied the GRADE framework, which classifies prospective cohort studies as high-certainty evidence by default. This initial rating was then modified through the evaluation of five potential downgrading domains (using the ROBINS-I tool for risk of bias) and three potential upgrading domains. In our visual representation, filled black squares mark specific outcomes where either downgrading or upgrading adjustments were applied based on these criteria.

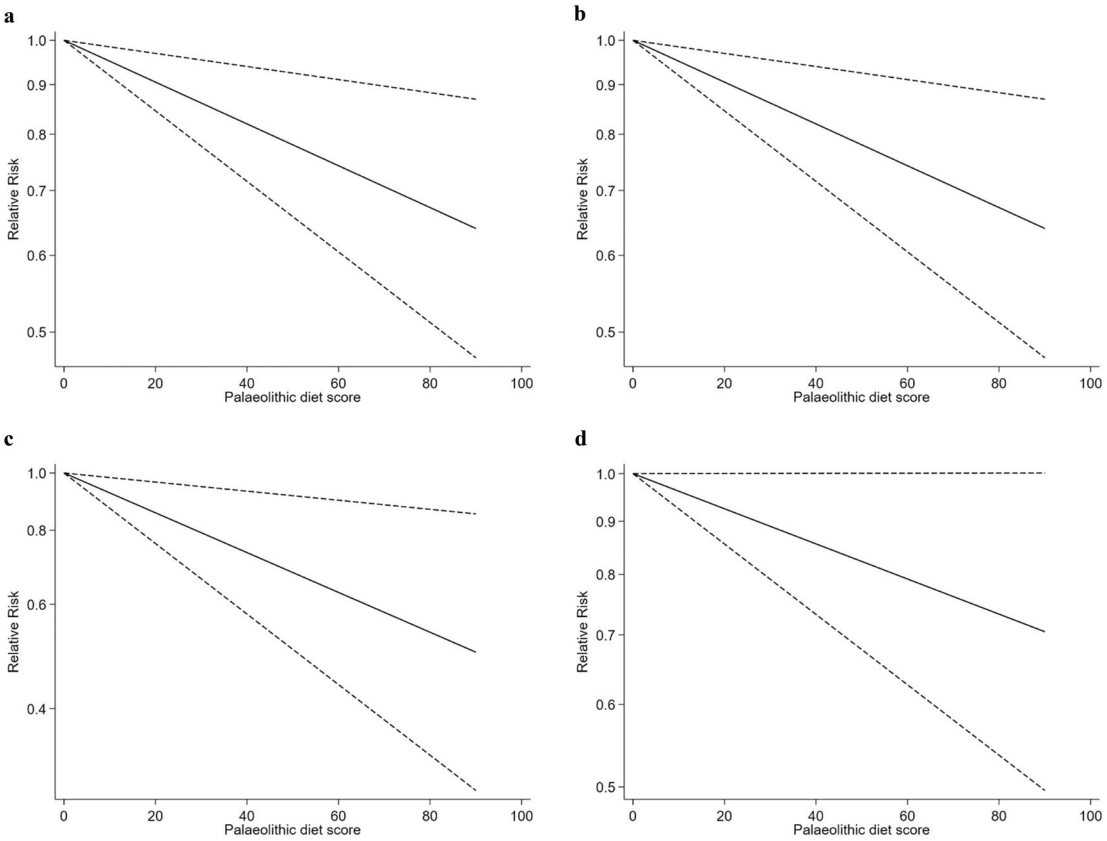

Figure 1. (a) all-cause mortality (RR per diet score = 0.99, 95% CI: 0.991–0.998; *P*-linear = 0.004, *P*-non-linear = 0.83); (b) cardiovascular disease mortality (RR = 0.99, 95% CI: 0.992–1.00; *P*-linear = 0.05, *P*-non-linear = 0.62); (c) Cancer mortality (RR = 0.99, 95% CI: 0.991–0.998; *P*-linear = 0.004, *P*-non-linear = 0.83); (d) Other-cause mortality (RR = 0.99, 95% CI: 0.986–0.998; *P*-linear = 0.01, *P*-non-linear = 0.08). Solid lines represent relative risks (RR), and dotted lines indicate 95% confidence intervals.

potential divergences in long-term health impacts between these dietary patterns. The high heterogeneity (I^2 > 75% for most Paleolithic diet outcomes) indicates the need for cautious interpretation and further investigation into moderating factors such as diet composition, adherence levels, and baseline population characteristics.

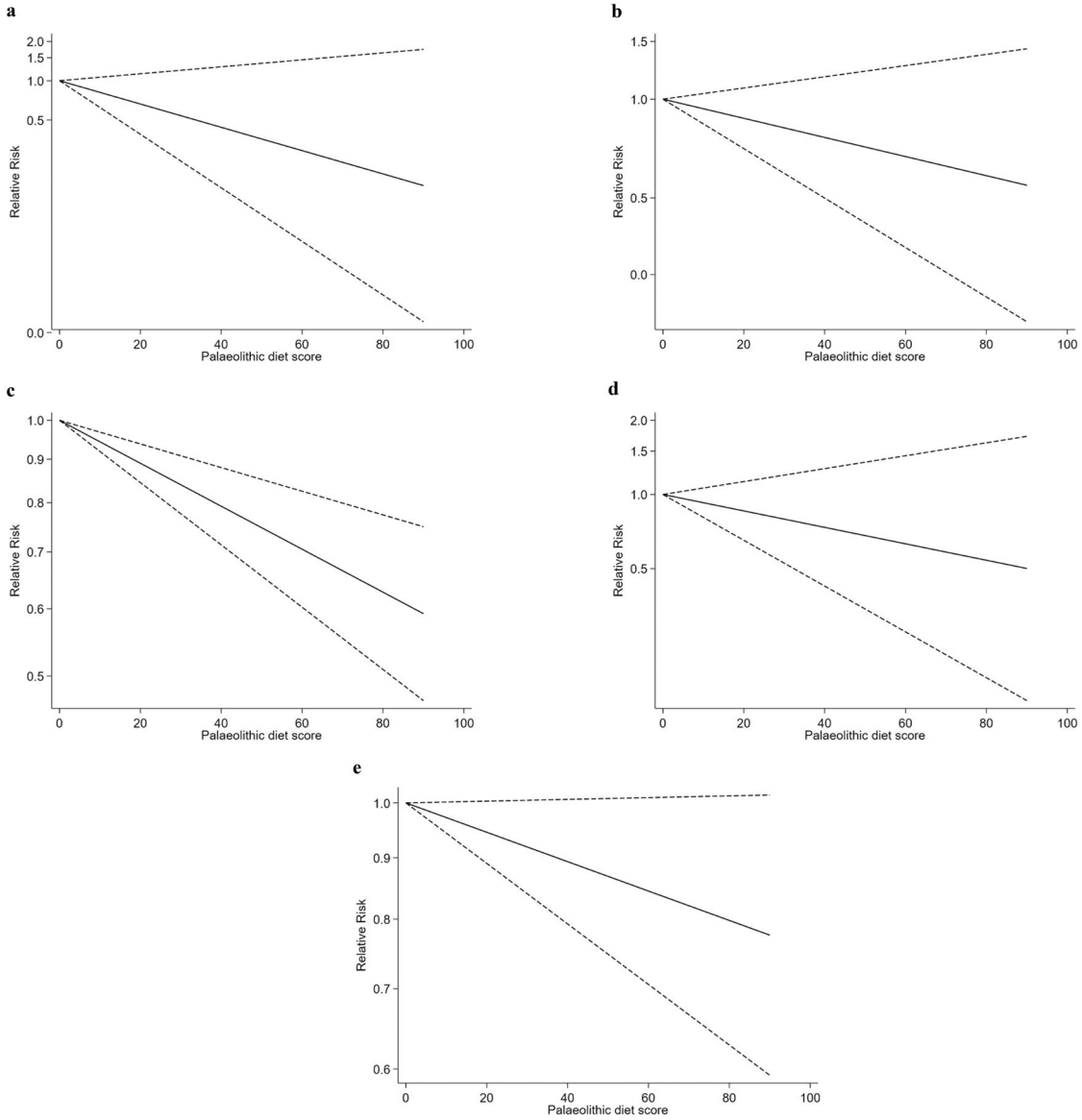

Figure 2. (a) cardiovascular incidence (RR per diet score = 0.97, 95% CI: 0.953–1.00, *P*-linear = 0.13, *P*-non-linear = 0.58); (b) coronary heart disease (RR per diet score = 0.99, 95% CI: 0.991–0.996, *P*-linear < 0.001, *P*-non-linear = 0.39); (c) cancer incidence (RR per diet score = 0.99, 95% CI: 0.982–1.00, *P*-linear = 0.21, *P*-non-linear = 0.13); (d) stroke incidence (RR per diet score = 0.99, 95% CI: 0.978–1.00, *P*-linear = 0.27, *P*-non-linear = 0.54); (e) type 2 diabetes mellites (RR per diet score = 0.99, 95% CI: 0.994–1.00, *P*-linear = 0.06, *P*-non-linear = 0.54). Solid lines represent relative risks (RR), and dotted lines indicate 95% confidence intervals.

A principal contribution of this review lies in its capacity to integrate evidence of short-term efficacy with data on long-term associations. These significant reductions in all-cause and cancer mortality, as well as in type 2 diabetes and coronary heart disease incidence observed in cohort studies, can be plausibly explained by the consistent improvements in core cardiometabolic risk factors demonstrated in our RCT analysis. The Paleolithic diet's fundamental exclusion of ultra-processed foods, refined sugars, grains, and dairy, coupled with its emphasis on whole foods like lean meats, fish, fruits, vegetables, and nuts, engages multiple synergistic biological pathways.

The Paleolithic diet is inherently low in refined carbohydrates and high-glycemic-index foods, which minimizes postprandial glucose spikes and reduces the demand for insulin secretion. By eliminating grains and added sugars, the diet lowers the intake of rapidly digestible carbohydrates, thereby improving insulin sensitivity. Studies suggest that the diet's high fiber content, derived from fruits and vegetables, further moderates glucose absorption, while its emphasis on lean proteins and healthy fats enhances cellular insulin signaling pathways, such as increased adiponectin levels, which promote glucose uptake in muscles and adipose tissue (Masharani et al. 2015; Fontes-Villalba et al. 2016). Additionally, the diet's high protein and healthy fat content promote satiety and reduce de novo lipogenesis, leading to lower triglyceride and LDL cholesterol levels. By avoiding trans fats and refined carbohydrates, the Paleolithic diet reduces hepatic very low-density lipoprotein production and enhances lipid clearance. Additionally, the diet's emphasis on whole foods increases intake of phytosterols and polyphenols, which further improve lipid profiles by inhibiting

cholesterol absorption and oxidation (Liu et al. 2023). Furthermore, the Paleolithic diet is naturally high in potassium and magnesium due to its emphasis on fruits and vegetables, and is inherently low in sodium, as it excludes processed foods. This nutrient profile contributes to the diet's efficacy in reducing blood pressure (Palmer and Clegg 2016). The exclusion of processed foods, industrial seed oils, and dairy reduces the intake of pro-inflammatory compounds, such as advanced glycation end-products and excessive omega-6 fatty acids. Instead, the Paleolithic diet's abundance of antioxidants (from berries, leafy greens, and nuts) and omega-3s (from wild-caught fish and grass-fed meat) modulates inflammatory cytokines and lowers C-reactive protein levels. This anti-inflammatory environment mitigates chronic low-grade inflammation, a key driver of metabolic syndrome and insulin resistance (Hart et al. 2021). In addition, nutrient-dense foods in the Paleolithic diet (e.g., organ meats, nuts, and seeds) provide cofactors (e.g., CoQ10, magnesium) that enhance mitochondrial efficiency and reduce oxidative stress, improving energy metabolism and reducing lipid peroxidation (Jiang et al. 2021). In total, the Paleolithic diet's multifaceted approach, targeting insulin sensitivity, inflammation, lipid metabolism, gut health, and oxidative stress, aligns with ancestral dietary patterns, offering a therapeutic strategy for cardiometabolic disorders. However, variations in individual responses, potential nutrient gaps (e.g., calcium), and the reduced bioavailability of certain beneficial compounds from minimally processed plant foods (e.g., lycopene, beta-carotene) warrant careful monitoring and personalization. Furthermore, the potential for higher intake of antinutrients (e.g., oxalates and enzyme inhibitors) requires investigation. Further research is needed to optimize its long-term efficacy, safety, and nutritional adequacy from this perspective.

The findings of the current study align with and expand upon the results of prior research investigating the effects of the Paleolithic diet on cardiometabolic risk factors. For instance, Manheimer et al. (2015) conducted a systematic review and meta-analysis focusing on metabolic syndrome, reporting significant improvements in fasting blood sugar and blood pressure among individuals adhering to the Paleolithic diet, which is consistent with our observations of reduced blood pressure and improved insulin resistance. Similarly, de Menezes et al. (2019) reported that the Paleolithic diet reduces body weight, BMI, and waist circumference, corroborating our results on the anthropometric benefits. Their meta-analysis, however, primarily focused on short-term interventions (≤12 weeks). In contrast, our inclusion of longer-duration studies (up to 24 weeks) revealed sustained improvements in metabolic markers, particularly in overweight/obese individuals. Contrastingly, Sohouli et al. (2022) reported mixed outcomes for glucose metabolism, noting significant reductions in fasting insulin and HOMA-IR, but no significant changes in HbA1c or fasting blood glucose. These discrepancies may stem from differences in study populations; our analysis included a more heterogeneous group with varying baseline metabolic conditions and intervention designs. For example, Sohouli et al. (2022) emphasized the lipid-lowering effects of the Paleolithic diet, which our study confirmed, particularly for triglycerides and LDL cholesterol. Still, we also identified subgroup-specific benefits, such as greater total cholesterol reduction in longer interventions (greater than 12 weeks). Overall, while previous meta-analyses have demonstrated the potential of the Paleolithic diet to improve specific metabolic parameters, our study provides a more comprehensive synthesis by incorporating diverse populations, longer follow-ups, and additional outcomes, such as C-reactive protein and blood pressure. This reinforces the Paleolithic diet's role as a viable dietary strategy for managing metabolic disorders; however, further high-quality, long-term RCTs are warranted to address remaining inconsistencies and optimize dietary guidelines.

Our systematic review and meta-analysis significantly advances the current evidence base on Paleolithic diets by addressing critical methodological limitations observed in prior studies. A key distinction lies in our comprehensive inclusion of novel prospective cohort studies ($n = 12$) examining mortality and disease incidence. This broader cohort data provides essential insights into long-term health outcomes beyond the shorter-term metabolic markers typically captured in RCTs. Furthermore, we rigorously applied the GRADE methodology to explicitly evaluate and transparently report the certainty of evidence for all outcomes, both from RCTs and cohort studies, a level of methodological rigor and standardization often lacking in earlier syntheses. Crucially, we conducted dose-response meta-analyses across the cohort studies to quantify the relationship between incremental increases in Paleolithic diet adherence and health outcomes, thereby moving beyond simple comparisons of high versus low adherence to model the shape of these associations. Our analytical approach was also strengthened by employing analysis to account for expected heterogeneity and conducting extensive subgroup and sensitivity analyses to explore sources of variation and robustness of the results.

Our dose-response meta-analysis of cohort studies revealed significant linear inverse relationships between incremental adherence to the Paleolithic diet and significantly reduced risks of all-cause mortality, cancer mortality, other-cause mortality, and coronary heart disease incidence. These results suggest a graded, quantitative association: for each unit increase in Paleolithic diet, there was a proportional decrease in disease risk, supporting the hypothesis that even moderate improvements in dietary alignment with Paleolithic principles may yield measurable health benefits. Notably, the absence of non-linearity ($P_{non\text{-}linear} > 0.05$ for all outcomes) implies that the benefits do not plateau abruptly within the observed adherence range, reinforcing the potential value of progressive dietary modifications. However, the lack of significant dose-response associations for cardiovascular mortality, stroke incidence, and type 2 diabetes incidence may reflect either true biological thresholds or limitations in the scoring systems' ability to capture critical dietary components that differentially influence these outcomes.

This research has multiple strengths, including its use of a systematic review and meta-analysis of both RCTs and

prospective cohort studies, which allows for a meticulous and comprehensive assessment of the Paleolithic diet's effect on cardiometabolic health. The research demonstrates methodological strength through the application of GRADE frameworks for quality assessment, ensuring transparency and reliability in its conclusions. A key advancement is the inclusion of dose-response meta-analyses, which reveal linear relationships between increasing adherence to a Paleolithic diet and reduced risks of all-cause mortality, cancer mortality, and coronary heart disease incidence. This provides nuanced insights beyond simple high-versus-low adherence comparisons. The analysis benefits from examining diverse populations across multiple countries and assessing a wide range of outcomes from metabolic markers to long-term disease endpoints.

However, the study faces limitations, including substantial heterogeneity ($I^2 > 75\%$) in many outcomes, likely due to variations in diet composition and adherence levels across studies. Relatively short intervention durations constrain the evidence in most RCTs (≤24 weeks) and the inherent limitations of observational data in cohort studies. Additional challenges include inconsistent definitions of the Paleolithic diet across studies, potential publication bias in some outcomes, and moderate evidence certainty (GRADE ratings of very low to moderate) for several endpoints. While the findings contribute significantly to understanding the potential benefits of this dietary pattern, these limitations highlight the need for further high-quality, long-term studies with standardized dietary protocols to strengthen clinical recommendations.

Conclusion

This systematic review and meta-analysis demonstrate that the Paleolithic diet has a dual-faceted potential. In the RCTs, it is an efficacious intervention for improving crucial cardiometabolic risk factors, including insulin resistance, dyslipidemia, and elevated blood pressure. In the long term, adherence to this dietary pattern is associated with a lower risk of all-cause and cancer mortality, as well as incidence of type 2 diabetes and coronary heart disease. While the diet aligns with principles of whole-foods-based nutrition, its long-term sustainability and nutritional adequacy should be considered. The findings support the utility of the Paleolithic diet as both a therapeutic dietary strategy for managing cardiometabolic risk and a preventive dietary pattern for public health. Future long-term, pragmatic RCTs are needed to confirm the causal role of this diet in chronic disease prevention.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committees of Ahvaz Jundishapur University of Medical Sciences (approval number: IR.AJUMS.REC.1404.312).

Authors contributions

F.B. and M.B.: systematic search; F.B. and M.B.: study selection; F.B. and M.B.: data extraction; F.B.: contributed to the conception, design of the work, analysis, and interpretation of the data; F.B.: drafting the manuscript; S.J. and A.A.: critical editing of the manuscript. All authors approved the final version for submission.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

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