EFFECTS OF POPULAR DIETS ON ANTHROPOMETRIC AND CARDIOMETABOLIC PARAMETERS: AN UMBRELLA REVIEW OF META-ANALYSES OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

The prevalence of overweight, obesity, and their related complications is increasing worldwide. Purpose of this umbrella review was to summarise and critically evaluate the effects of different diets on anthropometric parameters and cardiometabolic risk factors.

Medline, Embase, Scopus, Cochrane Database of Systematic Reviews and Web of Science, from inception to April 2019, were used as data source to select meta-analyses of RCTs that examined the effects of different diets on anthropometric parameters and cardiometabolic risk factors. Strength and validity of the evidence was assessed through a set of predefined criteria. Eighty articles reporting 495 unique meta-analyses were examined, covering a wide range of popular diets: low-carbohydrate (n=21 articles), high-protein (n=8), low-fat (n=9), palaeolithic (n=2), low glycaemic index/load (n=12), intermittent energy restriction (n=6), Mediterranean (n=11), Nordic (n=2), vegetarian (n=9), Dietary Approaches to Stop Hypertension or DASH (n=6), and portfolio dietary pattern (n=1). The methodological quality of most articles (n=65; 81%), evaluated using the AMSTAR-2 questionnaire, was low or critically low. The strength of evidence was generally weak. The most consistent evidence was reported for Mediterranean diet, with suggestive evidence of an improvement in weight, BMI, total cholesterol, glucose and blood pressure. Suggestive evidence of an improvement in weight and blood pressure was also reported for DASH diet. Low-carbohydrate, high-protein, low-fat and low-glycaemic index/load diets showed suggestive and/or weak evidence of a reduction in weight and BMI, but contrasting evidence for lipid, glycaemic and blood pressure parameters, suggesting potential risks of unfavourable effects. Evidence for palaeolithic, intermittent energy restriction, Nordic, vegetarian and portfolio dietary patterns was graded as weak.

Among all the diets evaluated, Mediterranean diet had the strongest and most consistent evidence of a positive effect on both anthropometric parameters and cardiometabolic risk factors.

The review protocol has been registered on PROSPERO (ID: CRD42019126103).

Keywords: Diet; Review; Meta-analysis; Weight; Risk factors

INTRODUCTION

With the increasing number of overweight and obese people worldwide (1), there is a growing public health concern on body size and dietary habits. Current data show that about 42% of adults has tried to lose weight at some point in life (2). In response to the ubiquity of weight-loss efforts, diets that promise rapid and easy weight loss by limiting certain foods or macronutrients are constantly emerging, attracting public attention and generating considerable debate. The effectiveness of a diet, however, is measured not only by its ability to induce weight loss in a short time. Several other factors such as their overall nutritional quality and the long-term effects on cardiometabolic risk factors should be carefully considered (3).

Numerous clinical trials have evaluated the impact of dietary interventions on weight and biomarkers related to metabolic disorders so far (4,5), and many meta-analyses have been published (6-8). Meta-analyses are powerful tools that can overcome difficulties in performing large-scale randomized controlled trials, but include the possible bias related to variation in quality and empirical validation. It has been recently reported that over half of the meta-analyses published are flawed and unnecessary (9), and that the production of poor-quality and redundant meta-analyses can contribute to the spread of misleading dietary concepts (10,11).

The assessment of the quality and credibility of existing evidence may have implications for both clinical practice and public health. Umbrella reviews are overviews of systematic

reviews and meta-analyses that provide a comprehensive and systematic evaluation of the scientific literature available for a specific research topic and offer the possibility to understand the strength of evidence and extent of potential biases (12). To the best of our knowledge, no previous umbrella reviews have assessed the strength and validity of the evidence available on dietary approaches to the treatment of obesity and overweight. Our aim, therefore, was to describe and critically evaluate the impact of different diets and/or dietary patterns on human health, by considering their effects on anthropometric parameters and cardiometabolic risk factors.

METHODS

An umbrella review of meta-analyses of randomized controlled trials was conducted according to the Joanna Briggs Institute Umbrella Review Methodology (13). The review protocol has been registered on PROSPERO (ID: CRD42019126103).

Search Strategy

The systematic literature search was independently conducted by 2 authors (DM and AD). Any discrepancy was resolved through consultation with a third independent reviewer (LL). The systematic computerized literature search was performed in Medline, Embase, Scopus, Cochrane Database of Systematic Reviews and Web of Science databases, from inception to April 2019. Additional studies were searched by checking references of the identified articles, and by consulting experts in the field. The following search terms were used in combination as MeSH terms and text words: "diet*" and its variants, with the words "weight", "body mass index", "BMI", "plasma lipids", "cholesterol", "LDL-cholesterol", "HDL-cholesterol", "triglycerides", "glycated hemoglobin", "insulin", "blood pressure" and their variants, and the words "meta-analysis", "systematic reviews" and their variants. A more exhaustive search strategy list, for each database, is provided in **Supplementary Table 1**. The most updated or

complete publication was used when more than one article was present for a meta-analysis. If an article presented meta-analyses for more than a health outcome, each of these was included separately. Missing data or additional information were requested from the corresponding authors of the articles.

Data Selection

Eligibility criteria are summarized in **Supplementary Table 2**, by following the PICOS (Population, Intervention, Comparison, Outcome, Study) design format. Inclusion criteria were the following: i) Population: adults (≥18 years); ii) Intervention: all diets or dietary patterns; iii) Comparison: any other dietary intervention; iv) Outcome: weight, body mass index (BMI), total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, insulin, glycated haemoglobin, systolic blood pressure, diastolic blood pressure; v) Study design: meta-analyses of randomized controlled trials.

Exclusion criteria were the following: i) Population: non adults (< 18 years), pregnancy and post-partum; ii) Intervention: not specific diet or dietary pattern; iii) Outcome: any other outcome out of the inclusion criteria; iv) Study design: systematic reviews of randomized controlled trials without quantitative analysis, meta-analyses not reporting comprehensive data (e.g. effect size and 95% confidence intervals (CI)), meta-analyses of observational studies. The decision to include studies was based on the title, abstract, and full-text screening.

Data extraction and Quality assessment

Three independent researchers (AR, MDA, and LB) achieved consensus on which data to extract from each eligible meta-analysis, using a standard form. The following data were extracted: first author and year of publication, number of included studies, intervention diet, control diet, number of subjects assigned to the intervention group, number of subjects assigned to the control group, duration of the intervention, study population, outcome(s) of

interest, effect size measurements, and quality of the studies included in each meta-analysis. Data were grouped according to the type of dietary intervention. Within each diet outcomes were categorised as following: body weight (kg), BMI (kg/m^2), total cholesterol (mmol/L), low density lipoprotein (LDL) cholesterol (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L), triglycerides (mmol/L), glucose (mmol/L), insulin (μU/mL), glycated haemoglobin (%), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). When data were provided in mg/dL or pmol/L, they were transformed into mmol/L or μIU/mL for consistency of results.

Three authors (CDB, DN and EM) independently evaluated the methodological quality of the included meta-analyses. Disagreements were resolved by discussion with a fourth investigator (MD). The Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) questionnaire was used to identify the high-quality meta-analyses (14). This instrument has 16 items in total, with an overall rating based on weaknesses in critical domains. Critical domains were as following: adequacy of the literature search, risk of bias from individual studies included in the review, appropriateness of meta-analytical methods, consideration of risk of bias when interpreting the results of the review, and assessment of presence of publication bias.

Data Analysis

For each unique meta-analysis, we estimated the summary effect and 95% confidence intervals (CIs) using both fixed-effect and random-effect models (DerSimonian Laird method). Heterogeneity among studies was evaluated using the I^2 statistic (15). Where I^2 exceeded 50% or 75%, the heterogeneity was considered substantial or considerable, respectively. The 95% prediction interval (PI) was calculated to predict the range of effect size that would be expected in a new original study, after accounting for both the uncertainty of the summary effect estimated in the random-effect model and the heterogeneity among individual studies (16). The possible presence of small-study effects was estimated by using the Egger's regression

asymmetry test (17). We investigated if small studies tended to give larger estimates of effect size than large studies by calculating the standard error (SE) of the effect size (under random-effect model) for the largest study of each meta-analysis. The largest study was defined on the basis of the smallest SE. If the p-value for Egger's test was <0.10 and the largest study had smaller effect size compared to the summary effect size, both criteria for existence of small-study effects were fulfilled (18). All statistical analyses were conducted using Review Manager (RevMan, version 5.3 for Macintosh; The Cochrane Collaboration, Copenhagen, Denmark) and the statistical package PASW 20.0 for Macintosh (SPSS Inc., Chicago, IL).

As previously proposed (19,20), observed associations were categorized as convincing or not, by using the following criteria: significance at $p \leq 0.05$ and $p \leq 0.001$; inclusion of ≥2,500 or ≥5,000 total participants; absence of considerable heterogeneity ($I^2 < 50\%$); 95% PI excluding the null value, and absence of small-study effects. Convincing evidence was assigned to associations with a significance of $p \leq 0.001$ for both random- and fixed-effect models, ≥5,000 total participants, not large heterogeneity between studies ($I^2 < 50\%$), 95% PI excluding the null value, and no evidence of small-study effects (if it could be tested). Highly suggestive evidence was assigned to associations with a significance of $p \leq 0.001$ for both random- and fixed-effect models, ≥5,000 total participants, and not considerable heterogeneity between studies ($I^2 = 50\text{-}75\%$). Suggestive evidence was assigned to associations with a significance of $p \leq 0.001$ for the random-effect model and 2,500-5,000 total participants. Weak evidence was assigned to associations with a significance of $p \leq 0.05$ for the random-effect model. No-evidence was assigned to associations where significance threshold was not reached ($p > 0.05$).

RESULTS

Search results

The selection process is shown in **Figure 1**, in accordance with the Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Initial database and other searches

yielded 27,627 articles. After eliminating duplicates, 12,469 articles were excluded on the basis of title and abstract, and 105 on the basis of full text assessment. A total of 80 articles (6-8,21-97) met the inclusion criteria and were included in the analysis, covering a wide range of diets: low-carbohydrate (n=21 articles), high-protein (n=8), low-fat (n=9), palaeolithic (n=2), low glycaemic index/load (n=12), intermittent energy restriction (n=6), Mediterranean (n=11), Nordic (n=2), vegetarian (n=9), Dietary Approaches to Stop Hypertension or DASH (n=6), and portfolio dietary pattern (n=1).

Study characteristics and quality

Characteristics and methodological quality of the meta-analyses included are reported in **Table 1**. There was a great variability in terms of definition of the intervention diets: as regards low-carbohydrate diets, for example, some studies have defined "low-carbohydrate" the diets containing ≤45% of total energy from carbohydrates (23,28,34,36,38), others the diets that include carbohydrates for ≤26% (33) or even less (≤10%) (26) of the total energy. Similarly, for high-protein diets, in some meta-analyses the high-protein content was defined as >20% of total energy (42), while in others >25% (43) or between 25 and 35% (41,45). A high variability was also observed among vegetarian diets, where some meta-analyses included lacto-ovo-vegetarian and vegan diets altogether (85,86,89-91), while others considered lacto-ovo-vegetarian (84,87,88) or vegan (87,88,92) diets specifically. A consistent heterogeneity was also present for control diets. In fact, most meta-analyses had as "control" any other dietary intervention, without specific indication. The methodological quality of the included meta-analyses, determined by the AMSTAR-2 questionnaire (for additional information see **Supplementary Table 3**), was moderate-to-high only in six meta-analyses on low-carbohydrate diets (6,26,27,36,37,39), in two meta-analyses on low glycaemic index/load (58,64) and vegetarian diets (91,92), and in one meta-analysis on low-fat diet (52), intermittent energy restriction (71), Mediterranean diet (8), Nordic diet (83), and portfolio dietary pattern (97),

respectively. There were no meta-analyses with moderate or high methodological quality for high-protein, palaeolithic and DASH diets. Although most meta-analyses (n=73; 91%) performed a quality/risk of bias assessment using validated tools or criteria set by the authors, only 27 (34%) accounted for risk of bias in individual studies when interpreting/discussing the results of the meta-analysis (for additional information see **Supplementary Table 4**).

Anthropometric parameters

Figure 2 summarizes the characteristics and the strength of evidence of the meta-analyses of randomized controlled trials that evaluated the effects of diets on anthropometric parameters. With regard to body weight, suggestive evidence was observed for low-carbohydrate (23,24,28), low-fat (52), Mediterranean (74,76) and DASH (96) diets. Weak or no evidence was reported for high-protein, palaeolithic, low glycaemic index/load and vegetarian diets, as well as for intermittent energy restriction and portfolio dietary pattern. When the outcome BMI was analysed, suggestive evidence was observed only for low-fat (52) and Mediterranean (74,76) diets.

Lipid profile

Figure 3 summarizes the characteristics and the strength of evidence of the meta-analyses of randomized controlled trials that evaluated the effects of diets on lipid profile. With regard to total cholesterol, suggestive evidence was reported for low-fat (52), low glycaemic index/load (67) and Mediterranean (76) diets. Meta-analyses evaluating LDL cholesterol reported suggestive evidence for low-fat (49) and low glycaemic index/load (67) diets, while meta-analyses evaluating HDL cholesterol reported suggestive evidence for low-carbohydrate (23,24,38), low-fat (49) and Mediterranean (75) diets. Finally, suggestive evidence for triglycerides was reported in three meta-analyses comparing low-carbohydrate to other dietary interventions (24,38) and low-fat diets (23), in one meta-analysis comparing high-

protein to low-calorie diets (44), and in one meta-analysis comparing low-fat to other dietary interventions (49).

Glycaemic profile

Figure 4 summarizes the characteristics and the strength of evidence of the meta-analyses of randomized controlled trials that evaluated the effects of diets on glycaemic profile. With regard to glucose, suggestive evidence was reported only for Mediterranean diet (79). On the other hand, one meta-analysis (24) comparing low-carbohydrate diets (as defined by the investigators of each trial) to other dietary interventions reported suggestive evidence for insulin. Weak or no evidence was reported by all the meta-analyses evaluating glycated haemoglobin.

Blood pressure

Figure 5 summarizes the characteristics and the strength of evidence of the meta-analyses of randomized controlled trials that evaluated the effects of diets on systolic and diastolic blood pressure. Suggestive evidence was reported for low-carbohydrate, Mediterranean and DASH diets. In particular, evidence from 1 meta-analysis (24) comparing low-carbohydrate diets (as defined by the investigators of each trial) to other dietary interventions, four meta-analyses (75,76,79,80) on Mediterranean diet and two meta-analyses (81,94) on DASH diet were graded as suggestive.

Evaluation of bias, heterogeneity, and strength of evidence

The effects of the diets studied on body weight and cardiometabolic risk factors are reported in **Supplementary Table 5**. By applying our evidence classification criteria, based on the evaluation of the level of significance for both random- and fixed-effect calculations, the sample size, the heterogeneity, the 95% PI, and the presence of small study effects, only a

limited number of meta-analyses provided suggestive evidence, and no meta-analyses provided highly suggestive or convincing evidence. Detailed information on the assessment of the strength of evidence is reported in **Supplementary Tables 6-7**.

A summary of the results reported in the meta-analyses of randomized controlled trials included is reported in **Figure 6**. Among all the diets evaluated, only Mediterranean diet showed significant positive effects for all the parameters analysed, without evidence of negative effects.

DISCUSSION

The present is the first umbrella review providing a comprehensive overview and a critical evaluation of the effects of different popular diets on body weight and cardiometabolic risk factors. The overall analysis comprised 80 different meta-analyses of randomized controlled trials that evaluated low-carbohydrate, high-protein, low-fat, palaeolithic, low glycaemic index/load, intermittent energy restriction, Mediterranean, Nordic, vegetarian, DASH, and portfolio dietary patterns. Over 80% of the meta-analyses included showed low methodological quality and the strength of evidence, assessed using evidence classification criteria, was generally weak. Notably, Mediterranean diet was the only diet that demonstrated significant and positive effects for all the parameters analysed, without evidence of potential adverse effects.

Over the past few decades, a wide range of dietary strategies have been promoted to reduce body weight. Some of these diets have been characterised by the modulation of macronutrients (e.g., low-carbohydrate, high-protein, and low-fat diets), while others focused on dietary patterns as a whole (e.g., Mediterranean, Nordic, vegetarian, DASH, and portfolio dietary models). To date, several meta-analyses including dietary intervention trials have been published, but to the best of our knowledge no umbrella reviews evaluating the strength of evidence for such meta-analyses have been yet performed.

In the present umbrella review, the largest number of meta-analyses was found for low-carbohydrate diets. Their definition varied greatly, and cut-off ranged from 50 to 130 g/day, or 26% to 45% energy from carbohydrates. Four meta-analyses (33,34,36,39), conducted on participants with type 2 diabetes, compared low-carbohydrate with high-carbohydrate diets, reporting no significant effects on weight. The other meta-analyses compared low-carbohydrate with low-fat diets (6,21-23,28,29,37) or other dietary interventions (24,27,30,31,32,35,40), reporting contrasting results. Evidence of a significant reduction in body weight was observed especially in the short term (6 months), and in studies with more extreme carbohydrate restriction. When the follow-up period or the amount of carbohydrates increased, the effect was attenuated. As to the other parameters, we observed weak or suggestive evidence of an improvement in glycaemic profile and blood pressure, and conflicting results for lipid profile, with an increase in total and LDL cholesterol reported in 12 meta-analyses. The negative effects of low-carbohydrate diets on lipid parameters may be related to the fact that people on low-carbohydrate diets tend to eat less vegetables and fruits rich in micronutrients and fibre, and more animal-derived foods (98).

As to high-protein diets, they are one of the most popular weight loss-strategy. Several mechanisms have been proposed to explain their supposed superiority over conventional weight-loss diets, including a higher level of satiety and an increase in energy expenditure (99) . Our analysis showed that the quality of published meta-analyses on high-protein diets is critically low, and the number of participants is relatively small. Weak or no evidence of a reduction in anthropometric parameters and blood pressure was reported, while data on lipid and glycaemic profiles were discordant. Increased saturated fat and lower fibre intake can potentially contribute to the observed increase in LDL cholesterol, glucose and HbA1c, questioning the safety of high-protein diets in the long term.

With regard to low-fat diets, the proportion of fat in the present umbrella review was ≤30% of energy intake, according to the Dietary Guidelines recommendation on fat intake.

Suggestive evidence of weight and BMI reduction was reported in the meta-analysis by Hooper et al. (52), which includes the Women's Health Initiative Dietary Modification Trial and compared low-fat to high fat diets. The other meta-analyses comparing low-fat to high-fat (53), low-carbohydrate (51,53) and other dietary interventions (32,47,48,53) reported weak or no evidence. As to the lipid profile, low-fat diets resulted in a greater reduction in total and LDL cholesterol compared with high-fat diets or other dietary interventions, but also in a significant worsening of HDL cholesterol and triglycerides. This negative effect is probably determined by the type of fat and the quality of carbohydrates consumed (100).

The most consistent findings were observed in studies that included dietary patterns such as Mediterranean and DASH diets. Both dietary patterns are high in fruits, vegetables, fish and nuts, and indices measuring adherence to these diets have been associated with lower risk of cardiovascular events, diabetes and cancer. In the present analysis, Mediterranean diet showed suggestive evidence of a reduction in weight, BMI, total cholesterol, glucose and blood pressure, and weak evidence of an improvement in LDL and HDL cholesterol, triglycerides, insulin and glycated haemoglobin. No meta-analyses reported detrimental effects. DASH diet, on the other hand, reported suggestive evidence of a positive effect on weight and blood pressure, and weak evidence for BMI and total cholesterol. With regard to the other dietary patterns, the evidence was less consistent, since most studies had a limited sample size, and many meta-analyses were of low methodological quality. We found weak evidence of an improvement in total, LDL cholesterol, and blood pressure with Nordic diet, weak evidence of an improvement in anthropometric parameters, total and LDL cholesterol, glucose, glycated haemoglobin and blood pressure with vegetarian diets, and weak evidence of an improvement in total and LDL cholesterol, triglycerides and blood pressure with portfolio dietary pattern. Altogether, these results corroborate observational findings indicating that dietary patterns that emphasise vegetables, fruits, whole grains, and plant-based protein, and limit sugar,

sodium, and red and processed meat, are consistently associated with decreased risk of cardiovascular and metabolic diseases (20,101).

As to the other popular diets studied, the present umbrella review showed many criticisms. For palaeolithic diet, a weight loss plan based upon the premise of consuming only foods available during the Stone Age (102), the number of participants was very small and the follow-up was short. In addition, extensive publication bias, selective outcome reporting, and potential conflict of interests were detected. With regard to intermittent energy restriction, a dietary approach that has gained greater popularity as a way for losing weight alternative to the conventional weight-loss diets, our systematic literature search led to the identification of 6 meta-analyses of randomized controlled trials published in the last 3 years. Intermittent energy restriction includes diverse interventions such as alternate day fasting, the 5:2 diet, and longer cyclic periods of restricting energy intake or fasting, interchanged by periods of ad libitum energy intake. The number of clinical trials and participants, however, was very small, most studies were performed by the same authors, and the follow-up was generally short. With the exception of a meta-analysis that reported weak evidence of a greater reduction in insulin (70), all the other meta-analyses evaluating weight, lipid profile, glucose metabolism and blood pressure reported no evidence of a superiority of intermittent energy restriction over continuous energy restriction.

The present umbrella review has several limitations that should be considered. First of all, the included meta-analyses showed relevant differences in terms of populations, methods, duration of interventions, study quality, and definition of intervention and control diets. Second, despite the relatively high number of meta-analyses published, a limited number of clinical trials were available for many diets evaluated. Third, when multiple meta-analyses of randomised controlled trials existed for an outcome, often the results were not concordant in direction of effect and/or statistical significance. Such a difference in the final results could be

explained mainly by the framing of the question and differences in inclusion criteria, comparisons, populations and statistical methods used.

In conclusion, through a systematic and comprehensive search we were able to include a vast number of meta-analyses that assessed the effects of different popular diets on weight and cardiometabolic risk factors. Among all the diets and dietary patterns evaluated, Mediterranean diet had the strongest and most consistent evidence, with no meta-analyses reporting detrimental effects. Suggestive evidence of an improvement in body weight and blood pressure was also reported for DASH diet. Low-carbohydrate, high-protein, low-fat and low-glycaemic index/load diets, on the other hand, showed positive effects on weight loss, but also potential risks of unfavourable lipid, glycaemic or blood pressure parameters. The strength of evidence for the other diets evaluated was weak or not statistically significant. Overall, these findings highlight the strengths and limitations of most popular diets, confirming that the best results, in terms of weight and cardiometabolic risk amelioration, are obtained with balanced dietary patterns such as Mediterranean diet.

Contributors:

MD and FS designed the study protocol. DM, AD and LL conducted the systematic literature search. CDB, DN and EM performed the quality assessment. AR, MDA and LB performed data extraction. MD and GP performed the statistical analysis. MD, GP, CF, MG and JG wrote the first draft of the manuscript. FS critically reviewed the manuscript and contributed to important intellectual content. All authors contributed to writing and reviewing the manuscript. MD is the guarantor of the paper.

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Table 1. Characteristics of meta-analyses of randomized controlled trials included in the umbrella review according to dietary interventions

Meta-analyses	Intervention diet	Control diet	Study population	Duration	Quality/risk of bias assessment	Outcomes	Quality of meta-analyses (AMSTAR-2)
Low-carbohydrate diets							
Nordmann, 2006 [21]	Low-carb (≤60g CHO)	Low-fat (≤30% of TE)	Overweight/obese	>6m, >12m	Criteria set by authors	Weight, TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	Critically low
Hession, 2009 [22]	Low-carb /High-protein[1]	Higher-carb/Low-fat[2]	Overweight/obese	>6m, >12m	Criteria set by authors	Weight, TC, LDL-c, HDL-c, TG, glucose, systolic BP, diastolic BP	Critically low
Hu, 2012 [23]	Low-carb (≤45% of TE)	Low-fat (≤30% of TE)	Overweight/obese	6-24m	No	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, systolic BP, diastolic BP	Critically low
Santos, 2012 [24]	Low-carb*	Other diets	Obese	3-24m	Criteria set by authors	Weight, BMI, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Ajala, 2013 [25]	Low-carb*	Other diets	T2DM	6-12m	The Cochrane Collaboration's tool	HbA1c	Critically low
Bueno, 2013 [26]	VLCKD (≤50g CHO or ≤10% of TE)	Low-fat (≤30% of TE)	Overweight/obese	12-24m	The Cochrane Collaboration's tool	Weight, LDL-c, HDL-c, TG, systolic BP, diastolic BP	High
Naude, 2014 [27]	Low-carb*	Balanced energy restricted diets	Overweight/obese, T2DM	3-6m, 12-24m	The Cochrane Collaboration's tool	Weight	Moderate
Alexandraki, 2015 [28]	Low-carb (≤45% of TE)	Low-fat (≤30% of TE)	Overweight/obese	6m, 12m	The Cochrane Collaboration's tool	Weight	Critically low
Sackner-Bernstein, 2015 [29]	Low-carb (≤120g CHO)	Low-fat (≤30% of TE)	Overweight/obese	2-24m	No	Weight	Critically low
Fan, 2016 [30]	Low-carb (≤130g CHO)	Other diets	T2DM	3-48m	Jadad scale	Weight, HbA1c	Critically low
Hashimoto, 2016 [31]	Low-carb*	Other diets	Overweight/obese	2-24m	AMSTAR	Weight	Critically low
Mansoor, 2016 [6]	Low-carb (≤20% of TE)	Low-fat (≤30% of TE)	Overweight/obese	6-24m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, systolic BP, diastolic BP	High
Steckhan, 2016 [32]	Low-carb*	Other diets	Metabolic syndrome	1-24m	The Cochrane Collaboration's tool	Weight, insulin	Low
Meng, 2017 [33]	Low-carb (≤26% of TE) or ≤130g/d of CHO	Higher-carb (45-60% of TE)	T2DM	3-24m	Jadad scale	Weight, TC, LDL-c, HDL-c, TG, glucose, HbA1c	Critically low
Snorgaard, 2017 [34]	Low-carb (≤45% of TE)	Higher-carb (45-60% of TE)	T2DM	<12m, ≥12m	The Cochrane Collaboration's tool	Weight, BMI, LDL-c, HbA1c	Critically low
Huntriss, 2018 [35]	Low-carb*	Other diets	T2DM	12m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, HbA1c, systolic BP, diastolic BP	Critically low

Sainsbury, 2018 [36]	Low-carb (≤45% of TE)	Higher-carb (>45% of TE)	T2DM	6m, 12m	The Cochrane Collaboration's tool	Weight, HbA1c	Moderate
van Zuuren, 2018 [37]	Low-carb (≤40% of TE)	Low-fat (≤30% of TE)	T2DM	<2m, 2-4m, 4-6m, >6m, 24m	The Cochrane Collaboration's tool /ROBINS-I tool	Weight, BMI, LDL-c, HDL-c, TG, glucose, HbA1c, systolic BP, diastolic BP	Moderate
Gjuladin-Hellon, 2019 [38]	Low-carb (≤45% of TE)	Low-fat (≤35% of TE)	Overweight/obese	6-24m	The Cochrane Collaboration's tool	TC, LDL-c, HDL-c, TG	Critically low
Korsmo-Haugen, 2019 [39]	Low-carb (≤40% of TE)	Higher-carb (>40% of TE)	T2DM	3-24m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, HbA1c, systolic BP, diastolic BP	High
McArdle, 2019 [40]	Low-carb*	Other diets	T2DM	3-52m	The Cochrane Collaboration's tool	Weight, HbA1c	Critically low
High-protein diets							
Santesso, 2012 [7]	High-protein*	Lower protein	Different health status	>1m	No	Weight, BMI, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Wycherley, 2012 [41]	High-protein (25-35% of TE)	Lower protein (12-18% of TE)	Different health status	1-13m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, systolic BP, diastolic BP	Critically low
Ajala, 2013 [25]	High-protein*	Other diets	T2DM	6-12m	The Cochrane Collaboration's tool	HbA1c	Critically low
Dong, 2013 [42]	High-protein (>20% of TE)	Lower protein (15-20% of TE)	T2DM	1-6m	Criteria set by authors	Weight, TC, LDL-c, HDL-c, TG, glucose, HbA1c, systolic BP, diastolic BP	Critically low
Schwingshackl, 2013 [43]	High-protein (≥25% of TE)	Lower protein (≤20% of TE)	Different health status	12-24m	The Cochrane Collaboration's tool /Jadad scale	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Clifton, 2014 [44]	High-protein*	Low calorie diets	Different health status	13-52m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Johansson, 2014 [45]	High-protein (25-30% of TE)	Other diets	Different health status	0.8-2m	Criteria set by authors	Weight	Critically low
Zhao, 2018 [46]	High-protein*	Lower protein	T2DM	1-24m	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Low-fat diets							
Astrup, 2000 [47]	Reduced fat*	Other diets	Non-diabetic	2-12m	No	Weight	Critically low
Avenell, 2004 [48]	Low-fat*	Other diets	Overweight/Obese	12m	Criteria set by authors	Weight	Critically low

Schwingshackl, 2013 [49]	Low-fat (≤30% of TE)	Other diets, Higher-fat (>30% of TE), Low-carb (<50g CHO), LGI/LGL, MUFA	Overweight/Obese	>3m	The Cochrane Collaboration's tool /Jadad scale	TC, LDL-c, HDL-c, TG,	Critically low
Wu, 2014 [50]	Low-fat (≤30% of TE)	Usual diet	Women	1-12m	Jadad scale	TC, LDL-c, HDL-c, TG	Critically low
Boaz, 2015 [51]	Low-fat (≤30% of TE)	Low-carb (≤45% of TE)	Overweight/Obese	1-8.7y	No	Weight	Critically low
Hooper, 2015 [52]	Low-fat (≤30% of TE)	Higher-fat (>30% of TE)	Different health status	0.5-8y	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	High
Tobias, 2015 [53]	Low-fat*	Other diets, Higher-fat, Low-carb, usual diet	Different health status	1-10y	The Cochrane Collaboration's tool	Weight	Low
Steckhan, 2016 [32]	Low-fat*	Other diets	Metabolic syndrome	1-24m	The Cochrane Collaboration's tool	Weight	Low
Lu, 2018 [54]	Low-fat (≤30% of TE)	Higher-fat (>30% of TE)	Overweight/Obese	2-24m	The Cochrane Collaboration's tool /Jadad scale	TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	Low
Paleolithic diet							
Manheimer, 2015 [55]	Paleolithic	Other diets	Metabolic syndrome	0.5-6m	The Cochrane Collaboration's tool	HDL-c, TG, glucose, systolic BP, diastolic BP	Low
Ghaedi, 2019 [56]	Paleolithic	Other diets	Different health status	0.5-24m	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	Low
Low glycaemic index/load diets							
Opperman, 2004 [57]	Low glycaemic index*	Higher glycaemic index	Different health status, T2DM	<6m	Criteria adapted from the Cochrane EPOC Group	TC, LDL-c, HDL-c, TG, HbA1c	Critically low
Thomas, 2007 [58]	Low glycaemic index/load*	Higher glycaemic index/load	Overweight/Obese	1.3-6m	Criteria set by authors	Weight, BMI, TC, HDL-c, TG, glucose, insulin	High
Thomas, 2010 [59]	Low glycaemic index*	Higher glycaemic index	T2DM	1-6m	Criteria set by authors	HbA1c	Critically low
Ajala, 2013 [25]	Low glycaemic index/load*	Other diets	T2DM	6-12m	The Cochrane Collaboration's tool	HbA1c	Critically low
Fleming, 2013 [60]	Low glycaemic index*	Higher glycaemic index	Overweight/Obese	<3m	U.S. Preventive Services Task Force Quality Rating Criteria	TC, LDL-c, HDL-c, TG	Critically low
Goff, 2013 [61]	Low glycaemic index*	Higher glycaemic index	Different health status, T2DM	>1m	Jadad scale	TC, LDL-c, HDL-c, TG	Low
Schwingshackl, 2013 [62]	Low glycaemic index/load*	Higher glycaemic index/load	Different health status	6-17m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Wang, 2015 [63]	Low glycaemic index*	Higher glycaemic index	T2DM	<36m	Jadad scale	HbA1c	Critically low
Clar, 2017 [64]	Low glycaemic index*	Higher glycaemic index	Participants with CVD	>3m	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	High
Evans, 2017 [65]	Low glycaemic index/load*	Higher glycaemic index/load	Healthy adults	<18m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Low
Ojo, 2018 [66]	Low glycaemic index*	Higher glycaemic index	T2DM	<22m	The Cochrane Collaboration's tool /CASP RCT Checklist	Glucose, HbA1c	Critically low

Zafar, 2019 [67]	Low glycaemic index*	Other diets	Overweight/Obese	<26m	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, glucose	Low
Intermittent energy restriction							
Alhamdan, 2016 [68]	ADF	VLCD	Overweight/obese	2-3m	Downs and Black checklist	Weight	Critically low
Headland, 2016 [69]	IER	CER	Different health status	>12m	The Cochrane Collaboration's tool	Weight	Critically low
Cioffi, 2018 [70]	IER§	CER	Different health status	2-6m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Harris, 2018 [71]	IER°	Ad libitum/CER^	Overweight/obese	3-12m	The Cochrane Collaboration's tool	Weight	Moderate
Harris, 2018 [72]	IER°	Ad libitum/CER^	Overweight/obese	3m	JBI SUMARI critical appraisal tool	Weight, TC, LDL-c, HDL-c, TG, glucose, insulin	Critically low
Roman, 2018 [73]	IER	CER	Overweight/obese	3-13m	The Cochrane Collaboration's tool	Weight	Critically low
Mediterranean diet							
Esposito, 2011 [74]	Mediterranean	Other diets	Different health status	1-60m	Jadad scale	Weight, BMI	Critically low
Kastorini, 2011 [75]	Mediterranean	Other diets	Overweight/obese	1-48m	Criteria set by authors	HDL-c, TG, glucose, systolic BP, diastolic BP	Critically low
Nordmann, 2011 [76]	Mediterranean	Low-fat (≤30% of TE)	Overweight/obese	24m	Criteria set by authors	Weight, BMI, TC, LDL-c, HDL-c, glucose, insulin, systolic BP, diastolic BP	Critically low
Ajala, 2013 [25]	Mediterranean	Other diets	T2DM	6-12m	The Cochrane Collaboration's tool	HbA1c	Critically low
Huo, 2015 [77]	Mediterranean	Other diets	T2DM	1-48m	The Cochrane Collaboration's tool	Weight, BMI, TC, LDL-c, HDL-c, TG, glucose, insulin, HbA1c, systolic BP, diastolic BP	Critically low
Esposito, 2015 [78]	Mediterranean	Other diets	Different health status	1-60m	The Cochrane Collaboration's tool	HbA1c	Low
Garcia, 2016 [79]	Mediterranean	Other diets	Different health status	1-52m	The Cochrane Collaboration's tool	HDL-c, TG, glucose, systolic BP, diastolic BP	Low
Gay, 2016 [80]	Mediterranean	Other diets	Different health status	6-48m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low
Ndanuko, 2016 [81]	Mediterranean	Other diets	Different health status	2-24m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low
Nissensohn, 2016 [82]	Mediterranean	Other diets	Overweight/obese	24m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low
Rees, 2019 [8]	Mediterranean	Other diets	Primary and secondary prevention	≥3m	The Cochrane Collaboration's tool	TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	High
Nordic diet							
Ndanuko, 2016 [81]	Nordic	Other diets	Different health status	2-24m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low

Ramezani-Jolfaie, 2018 [83]	Nordic	Typical or Danish diets	Different health status	0.5-6m	The Cochrane Collaboration's tool	TC, LDL-c, HDL-c, TG, Systolic BP, diastolic BP	High
Vegetarian diets							
Yokoyama, 2014 [84]	Vegetarian, LOV	Non-vegetarian diets	Different health status	1.5-13m	No	Systolic BP, diastolic BP	Critically low
Yokoyama, 2014 [85]	Vegetarian	Non-vegetarian diets	T2DM	1-18.5m	The Cochrane Collaboration's tool	Glucose, HbA1c	Critically low
Barnard, 2015 [86]	Vegetarian	Non-vegetarian diets	Different health status	3-26m	The Cochrane Collaboration's tool	Weight	Low
Huang, 2015 [87]	Vegetarian, LOV, vegan	Non-vegetarian diets	Different health status	2.3-24m	Jadad scale	Weight	Critically low
Wang, 2015 [88]	Vegetarian, LOV, vegan	Non-vegetarian diets	Different health status	2.3-24m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG	Critically low
Yokoyama, 2017 [89]	Vegetarian	Non-vegetarian diets	Different health status	>1.5m	Jadad scale	TC, LDL-c, HDL-c, TG	Critically low
Picasso, 2018 [90]	Vegetarian	Non-vegetarian diets	Different health status	1.5-18.5m	The Cochrane Collaboration's tool	HDL-c, TG, glucose, systolic BP, diastolic BP	Low
Viguiliouk, 2018 [91]	Vegetarian	Non-vegetarian diets	T2DM	1-18.5m	The Cochrane Collaboration's tool	Weight, BMI, LDL-c, HDL-c, TG, glucose, HbA1c, systolic BP, diastolic BP	Moderate
Lopez, 2019 [92]	Vegan	Non-vegan diets	Different health status	0.8-18.5m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	High
DASH diet							
Shirani, 2013 [93]	DASH	Other diets	Different health status	0.8-6m	No	Glucose, insulin	Critically low
Saneei, 2014 [94]	DASH	Other diets	Different health status	0.5-6.5m	Criteria set by authors	Systolic BP, diastolic BP	Critically low
Siervo, 2015 [95]	DASH	Other diets	Different health status	0.5-6m	Jadad scale	TC, LDL-c, HDL-c, TG, glucose, systolic BP, diastolic BP	Critically low
Gay, 2016 [80]	DASH	Other diets	Different health status	6-48m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low
Ndanuko, 2016 [81]	DASH	Other diets	Different health status	2-24m	The Cochrane Collaboration's tool	Systolic BP, diastolic BP	Critically low
Soltani, 2016 [96]	DASH	Low-calorie diets	Different health status	2-13m	The Cochrane Collaboration's tool	Weight, BMI	Low
Portfolio dietary pattern#							
Chiavaroli, 2018 [97]	Portfolio	Energy matched diets	Dyslipidemia	1-6m	The Cochrane Collaboration's tool	Weight, TC, LDL-c, HDL-c, TG, systolic BP, diastolic BP	High

ADF = alternate day fasting; AMSTAR = Assessment of multiple systematic reviews; BMI = body mass index; BP = blood pressure; CER = continuous energy restriction; CHO = carbohydrates; DASH = dietary approaches to stop hypertension; EPOC = Effective Practice and Organisation of Care; HbA1c = glycated haemoglobin; HDL-C = high density lipoprotein cholesterol; IER = intermittent energy restriction; JBI SUMARI = Joanna Briggs Institute's System for the Unified Management, Assessment and Review of Information; LDL-C = low density lipoprotein cholesterol; LGI/LGL = low glycaemic index/low glycaemic load diets (total fat >30% of daily energy consumption, CHO <50% of daily energy consumption, and LGI foods); LOV = lacto-ovo-vegetarian diet; MUFA = high monounsaturated fatty acid diet (total fat >30% of daily energy consumption and MUFA >12% of daily energy consumption); ROBINS-I = Risk of Bias In Non-randomised Studies of Interventions; T2DM = type 2 diabetes mellitus; TC = total cholesterol; TE = total energy; TG = triglycerides; VLCD = very low calorie dieting (<800 kcal/d); VLCKD = very-low-carbohydrate ketogenic diets (≤50 g/d of CHO or ≤10% of daily energy from CHO); [1] = low carbohydrate (≤60 g/d of CHO)/ketogenic diets (<40 g/d of CHO); [2] = low fat (≤30% of daily energy from fat)/high carbohydrate conventional diets, energy restricted; * = as defined by the investigators of each trial; [§] = IER defined as 75% of energy restriction on "fast" days, with a maximum cut-off of 500/660 kcal/day for females/males, respectively; ° = IER defined as consumption of ≤800 kcal on at least one day, but no more than six days in a week; ^ = control defined as "ad libitum" diet (no intervention) or advice to continuously follow a reduced calorie diet of approximately 25% of

estimated daily energy requirements; # = The Portfolio dietary pattern was defined as including the following components: 1–3 g/day plant sterols, 15–25 g/day viscous fibres (from oats, barley, psyllium, legumes, eggplants, okra), 35–50 g/day plant protein and 25–50 g/day nuts

Legend to figures

Figure 1. Flow diagram of the study selection process

Figure 2. Summary and strength of evidence of meta-analyses of randomized controlled trials evaluating anthropometric parameters

green = suggestive evidence; orange = weak evidence; grey = no evidence
AMSTAR = a measurement tool to assess systematic reviews; BMI = body mass index; DASH = dietary approaches to stop hypertension; GI = glycaemic index; GL = glycaemic load; IER = intermittent energy restriction; NA = not available; * number of total participants

Figure 3. Summary and strength of evidence of meta-analyses of randomized controlled trials evaluating lipid profile
green = suggestive evidence; orange = weak evidence; grey = no evidence

AMSTAR = a measurement tool to assess systematic reviews; DASH = dietary approaches to stop hypertension; GI = glycaemic index; GL = glycaemic load; HDL-c = high density lipoprotein cholesterol; IER = intermittent energy restriction; LDL-c = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; NA = not available; * number of total participants

Figure 4. Summary and strength of evidence of meta-analyses of randomized controlled trials evaluating glycaemic profile

green = suggestive evidence; orange = weak evidence; grey = no evidence
AMSTAR = a measurement tool to assess systematic reviews; HbA1c = glycated haemoglobin; DASH = dietary approaches to stop hypertension; GI = glycaemic index; GL = glycaemic load; IER = intermittent energy restriction

Figure 5. Summary and strength of evidence of meta-analyses of randomized controlled trials evaluating blood pressure

green = suggestive evidence; orange = weak evidence; grey = no evidence
AMSTAR = a measurement tool to assess systematic reviews; BP = blood pressure; DASH = dietary approaches to stop hypertension; GI = glycaemic index; GL = glycaemic load; IER = intermittent energy restriction; NA = not available; * number of total participants

Figure 6. Summary of the results reported in meta-analyses of randomized controlled trials included in the umbrella review according to dietary interventions

green = evidence of a positive effect; grey = evidence of no effect; red = evidence of a negative effect
The size of the circles reflects the number of unique meta-analyses available
BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension; HDL-C = high density lipoprotein cholesterol; ER = Energy Restriction; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides