TITLE

Effects of a Mediterranean diet on blood pressure: A systematic review and meta-analysis of randomised controlled trials and observational studies

SHORT TITLE

Mediterranean diet and blood pressure

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis investigating effects of MedDiet on blood pressure in randomised controlled trials (RCTs) and associations of MedDiet with risk of hypertension in observational studies.

Methods: PubMed, The Cochrane Library and EBSCOhost were searched from inception until January 2020 for studies that met the following criteria: 1) participants aged ≥18 years, 2) RCTs investigating effects of a MedDiet versus control on BP, 3) Observational studies exploring associations between MedDiet adherence and risk of hypertension. Random-effects meta-analyses were conducted. Meta-regression and subgroup analyses were performed for RCTs to identify potential effect moderators.

Results: Nineteen RCTs reporting data on 4137 participants and 16 observational studies reporting data on 59,001 participants were included in the meta-analysis. MedDiet interventions reduced systolic and diastolic BP by a mean -1.4 mmHg (95% CI: -2.40 to -0.39 mmHg, p=0.007, I^2=53.5%, Q=44.7, τ^2=1.65, df=19) and -1.5 mmHg (95% CI: -2.74 to -0.32 mmHg, p=0.013, I^2=71.5%, Q=51.6, τ^2=4.72, df=19) versus control, respectively. Meta-regression revealed that longer study duration and higher baseline systolic BP was associated with a greater decrease in BP, in response to a MedDiet ($p<0.05$). In observational studies, odds of developing hypertension were 13% lower with higher versus lower MedDiet adherence (95% CI: 0.78 to 0.98, p=0.017, I^2=69.6%, Q=41.1, τ^2=0.03, df=17).

Conclusions: Data suggest that MedDiet is an effective dietary strategy to aid BP control, which may contribute towards the lower risk of CVD reported with this dietary pattern. This study was registered with PROSPERO: CRD42019125073.

KEY WORDS: Mediterranean diet, blood pressure, hypertension, cardiovascular disease

INTRODUCTION

Hypertension is associated with increased risk of ischemic heart disease, stroke, chronic kidney disease, and neurodegenerative diseases and is a significant tractable cause of worldwide morbidity and mortality [1–3]. Despite substantial advances in the pharmacotherapy of hypertension, the global burden of this condition continues to increase. Indeed, by 2025 it is estimated that there will be over 1.6 billion hypertensive individuals worldwide [4]. Identifying effective strategies to help control blood pressure (BP) and prevent or treat hypertension, either alone or alongside pharmacotherapy, is therefore of paramount importance.

Diet is an effective modulator of BP [5,6] and, given the likely cumulative and synergistic effect of individual foods and dietary compounds [7], dietary patterns including the Mediterranean diet (MedDiet) may be particularly effective in aiding BP control. The MedDiet emphasises high consumption of fruits and vegetables, legumes, tree nuts, whole grains, fish and olive oil. Fish, poultry and red wine are consumed in moderate amounts, whilst red and processed meat consumption is relatively low [8,9]. Numerous observational studies have reported reduced risk of hypertension with higher MedDiet adherence [10–13], whilst several randomised controlled trials (RCTs) have demonstrated BP lowering effects of MedDiet interventions [14–16]. Nevertheless, the reported effects of a MedDiet on BP are inconsistent, with several studies reporting minimal or no effect of this dietary pattern [17–20], which could be related to differences in study design (e.g. observational studies vs. RCTs, study duration, paired vs. independent groups, type of control group) or participant characteristics (e.g. age, health status, baseline BP).

Meta-analysis of existing studies could help resolve the ambiguity around the effects of a MedDiet on BP, and identify factors that could account for the varying results reported in the

literature. Such knowledge could be used to optimise and target future MedDiet interventions for BP reduction. To this end, we conducted a systematic review and meta-analysis of RCTs investigating the effects of MedDiet interventions on BP, and examined factors that could account for the divergent effects reported in the literature. In addition, we also explored associations between MedDiet adherence and risk of hypertension in observational studies. Meta-analysis of RCTs allowed us to assess the effects of the MedDiet on BP in controlled experimental settings, where studies include a standardised, well-defined intervention with strict study inclusion/ exclusion criteria and allow direct cause-effect relationships to be established [21,22]. Meanwhile, meta-analysis of observational studies allowed us to explore effectiveness of a MedDiet in real-world circumstances where the composition of the diet and characteristics of participants may be more variable, yet with larger sample sizes and longer follow up than is feasible in most intervention studies [21,22]. Consequently, the inclusion of both RCTs and observational studies in this review is complementary [21,22], with each study design providing an important piece of information about the potential role of a MedDiet in BP control.

METHODS

The current systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [23], and was registered with the PROSPERO database (CRD42019125073).

Literature search

PubMed, The Cochrane Library, and EBSCOhost (including MEDLINE, SPORTDiscus, PsycINFO, and CINAHL) were searched from inception through to 21st January 2020 for relevant articles. Search terms related to the MedDiet and BP, with MeSH terms utilised where

appropriate (details of the specific search strategy for each database can be found in Supplemental Digital Contents 1). Reference lists of eligible studies and review articles were also searched for potentially relevant articles. No publication date or language restrictions were applied. To minimise potential publication bias, grey literature was included in search results.

Study selection

The following criteria were applied to identify articles for inclusion in this systematic review and meta-analysis:

General criteria

1) Both RCTs and observational studies were included.
2) Only studies with adult participants (aged ≥18 years) were included. Participant were not excluded based on health status or smoking history.

RCTs

1) No exclusion criteria were made based around the design of the RCT (i.e., cross-over or parallel design, intervention duration, blinding, or type of control group)
2) RCTs which tested the effect of a MedDiet (defined as such by the authors of each study) alone or in combination with other lifestyle, clinical or pharmacological interventions were included providing the study included a comparable and valid control group. For example, if the MedDiet was combined with exercise, the control group must also undergo the same exercise intervention.

Observational studies

1) No exclusion criteria were made based around the design of observational studies (i.e., cross-sectional, case-control, or prospective studies).
2) Studies reporting associations between MedDiet adherence and odds of hypertension were included, providing the MedDiet was compared against a reference or control group. We did not include studies exploring linear associations between MedDiet adherence and blood pressure because beta values may not be comparable between studies.
3) No exclusion criteria were applied based on the method used to define MedDiet adherence.

Two researchers (OC and NM) independently screened the titles and abstracts of retrieved articles to evaluate their eligibility for inclusion in the review and later compared notes to reach a consensus. Disagreements about the eligibility of potential studies were resolved by a third reviewer (MS). Potential studies that could not be excluded based on assessment of title and abstract were moved to the full-text stage of the review for further evaluation. Full-texts of the selected articles were appraised critically against the study inclusion/ exclusion criteria by two researchers (OC and NM), and a third researcher (MS) helped resolve any disputes.

Data extraction

Data were extracted by one investigator (AG) and checked for accuracy by a second investigator (OMS). The following information was extracted from the eligible articles: author, year of publication, study design, study duration, sample size, details of the intervention (control and MedDiet), age, sex, ethnicity, BMI, baseline and post-intervention measurements of systolic and diastolic BP (RCTs), risk of hypertension (observational studies).

Assessment of study quality

Risk of bias of the included studies was evaluated by one investigator (AG) and checked for accuracy by a second investigator (OMS). The Cochrane risk of bias tool [24] was used to evaluate RCTs. Studies were classified as high risk, low risk or, when insufficient detail were reported, unknown risk of bias. The Newcastle-Ottowa tool was used to evaluate risk of bias in observational studies. Studies were classified as high quality (≥7 stars), medium quality (4-6 stars) or low quality (0-3 stars) [25]. An adapted version of this tool was used for evaluating cross-sectional studies [26]. A third reviewer (MS) resolved any disputes.

Statistical analysis

Statistical analyses were conducted by KD. A random effects meta-analysis was conducted using the *metafor* package [27] in R version 3.6.3 [28]. For analysis of the effects of MedDiet on BP in RCTs, sample size, mean and standard deviation (SD) of BP measurements for MedDiet and control groups were extracted and used in the analyses. Standard error of the mean (SEM) and confidence intervals (CI) were back-calculated to SD, as required, using standard methods [24]. In circumstances in which baseline measurements were not reported, the sample size, means and SD of the difference were used. Alternatively, the sample size, mean difference and the p value of the difference were used if SD of the difference was not available. For observational studies reporting associations between MedDiet adherence and risk of hypertension, odds ratios were extracted, alongside information on 95% CI and sample size of the population. Where odds ratios were not provided but studies met the review inclusion criteria, odds ratios were calculated using raw counts for the number of participants with hypertension. Additional data were requested from authors where necessary.

Correlations for paired data were determined using standard methods of back-calculation from studies where mean, SD, and SD of the difference or exact p-values were presented [18,19,29]. The mean of these values was used in the calculation of relevant effect sizes, with sensitivity analysis performed using the highest and lowest correlation calculated from these studies. The correlations for systolic BP were as follows: r=0.39 [29], r=0.61[19], and r=0.71 [18]. The correlations for diastolic BP were as follows: r=0.51 [29], r=0.55 [19], and r=0.55 [18].

For the PREDIMED trial, to avoid duplication of single participants within the meta-analysis, data from Casas et al. [16] were used for the main analysis because this has the longest duration follow-up of the identified studies. To identify whether the use of alternative PREDIMED datasets would have influenced our results, we conducted sensitivity analyses where data were substituted in turn for other PREDIMED sub-studies [30,31]. Where studies included measurements at multiple time-points, the final study end-point was used for analysis to enable the effects of the entire study duration to be considered.

Subgroup analyses were undertaken to investigate the influence of participant characteristics (healthy participants vs. high CVD risk participants), study design (paired participants vs. independent groups) and control diet (low fat vs. habitual vs. other) for RCTs. Random effects meta-regression was performed to investigate the relationship between changes in BP in response to MedDiet interventions and baseline BP, age, BMI, and intervention duration.

Heterogeneity between trials was estimated using restricted maximum likelihood and assessed using the I-squared statistic, Tau-squared statistic and the Chi-squared statistic. Case-deletion diagnostics were performed to investigate influential studies within each analysis. This included determination of externally studentized residuals, DFFITS values, Cook's distances,

covariance ratios, estimates of τ^2 and estimates of the Q-statistic when each study is removed in turn. Sensitivity analyses were performed by repeating the analysis of main effects with influential studies removed, to determine whether these studies markedly affected the overall conclusions [27]. Small study effects were explored with funnel plots and by quantifying Egger's linear regression intercept. A large and statistically significant Egger's statistic indicates the presence of small study effects.

RESULTS

Overview

A total of 2025 articles were identified through database screening and other sources, after removal of duplicates. After screening the titles and abstracts, 388 full texts were retrieved for further evaluation. A total of 35 studies were identified as suitable for inclusion in the quantitative synthesis, of which 19 were RCTs and 16 were observational studies (Figure 1).

Participant demographics and study characteristics

RCTs

The total number of participants across the 19 RCTs was 4137 (Table 1). The median number of participants per study was 144 (range: 12 – 1128), the median participant age was 53.0 (range: 25.0 – 70.9) years, and the median study duration was 26 (range: 1.4 – 260) weeks. Of the 19 RCTs, 16 were parallel and 3 were crossover study designs. The majority of studies investigated effects of the MedDiet in participants defined as possessing high CVD risk (n=11). Studies were also conducted in healthy individuals (n=5), participants with obesity and the metabolic syndrome (n=1), liver disease (n=1), and obesity, type II diabetes or coronary heart disease (n=1). Various forms of MedDiet were provided across studies including a MedDiet (n = 14), a MedDiet supplemented with olive oil (n = 2), a MedDiet supplemented with nuts (n

= 1), a MedDiet supplemented with olive oil and nuts (n = 1), a low GI MedDiet (n=1), and a MedDiet with energy restriction (n = 1). In addition, a range of different control treatments were employed including a low fat diet (n = 8) [16–18,20,32–35], participants habitual diet (n=5) [14,15,36–38], a prudent diet (n=1) [39], a Palaeolithic diet (n=1) [40], a Central European diet (n=1) [41], a vegan diet (n=1) [19], a low GI diet (n=1), and an energy-restricted low fat diet (n=1) [42].

Observational studies

The total number of participants from the 16 observational studies was 59,001 (Table 2), and the median number of participants per study was 2781 (range: 433 – 14,057). There were 14 cross-sectional and 2 prospective studies included in the analysis. Diet was assessed via food frequency questionnaires in 14 studies and 24-hour dietary recalls in two studies, one of which also involved food weighing. A range of scores were used to define MedDiet adherence, including: the 55-point Panagiotakos MedDietScore (n= 4) [43], 14-point MEDAS score (n=3) [44], an adapted 8-point Trichopoulou score (excluding olive oil; n=1) [45], the Modified 9-point Trichopoulou Score (n=1) [46], a custom 30-point MedDiet score (n=1) [10], a 52-point Lebanese MedDiet score (n=1) [47], a 60-point MedTypeDietScore (n=1) [48], a modified 17-point MedDiet score (n=1) [49], an 11-point Pyramid MedDiet score (n=1) [50], and the MED-LITE score (n=1) [12]. In addition, one study derived a MedDiet adherence score *a posteriori* via principal component analysis [51].

Effects of MedDiet interventions on systolic BP

MedDiet intervention reduced systolic BP by mean -1.4 mmHg compared with control (95% CI: -2.4 to -0.4 mmHg, p = 0.007, Figure 2). The degree of heterogeneity between studies was moderate (I^2 = 53.5%, Q = 44.7, τ^2 = 1.65, df = 19). Sensitivity analyses revealed that the

effects of MedDiet interventions on systolic BP remained similar throughout the range of correlation coefficients identified for paired comparisons (r=0.39: -1.4 mmHg, 95% CI: -2.5 to -0.4 mmHg, p = 0.007; r = 0.71: -1.4 mmHg, 95% CI: -2.5 to -0.4 mmHg, p = 0.008). The substitution of datasets from the PREDIMED cohort had a mixed effect on the findings (Domenech et al. [31]: -1.6 mmHg decrease, 95% CI: -2.7 to -0.5 mmHg, p = 0.004; Toledo et al. [30]: -0.6 mmHg decrease, 95% CI: -1.2 to 0.0 mmHg, p = 0.059). Case-deletion diagnostics revealed one influential study for the effect of MedDiet interventions on systolic BP [36] (Supplemental Digital Content 2). The influential effect of Itsiopoulos et al. [36] was due primarily to the large study weighting of 16.0% combined with a large DFFITS value. Between-study heterogeneity reduced substantially when this study was excluded from the model. However, the removal of this influential study did not alter the overall estimate of effect size (-1.6 mmHg, 95% CI: -2.7 to -0.6 mmHg, p = 0.002).

Meta-regression analysis revealed that longer study duration was associated with greater decrease in systolic BP (slope: -0.017 [CI: -0.028 to -0.006] mmHg for each 1 day increase in study duration; p = 0.003; Supplemental Digital Content 3). Additionally, higher baseline systolic BP was associated with significantly greater reduction in response to MedDiet intervention (slope: -0.091 [CI: -0.161 to -0.021] mmHg for each 1 mmHg higher systolic BP at baseline; p = 0.011; Supplemental Digital Content 4; n=19). The effect of MedDiet interventions on systolic BP was not significantly associated with participant age (p = 0.205; n=19) or baseline BMI (p = 0.536; n=18). Subgroup analysis revealed no influence of participant health status (healthy vs. high CVD risk; p=0.336), study design (parallel vs. crossover; p=0.764) or control diet (low fat vs. habitual vs. other; p=0.801) on the effect of the MedDiet interventions on systolic BP. Inspection of the funnel plot and Egger's regression

intercept for systolic BP revealed evidence of small study effects (p = 0.007; Supplemental Digital Content 5).

Effects of MedDiet interventions on diastolic BP

MedDiet intervention reduced diastolic BP by mean -1.5 mmHg compared with control (95% CI: -2.7 to -0.3 mmHg, p = 0.013, Figure 3). The degree of heterogeneity between studies was moderate (I^2 = 71.5%, Q = 51.6, τ^2 = 4.72, df = 19). Sensitivity analyses revealed that the effects of MedDiet intervention on diastolic BP remained similar throughout the range of correlation coefficients identified for paired comparisons (r=0.51: -1.5 mmHg , 95% CI: -2.7 to -0.3 mmHg, p = 0.013; r=0.55: -1.5 mmHg decrease, 95% CI: -2.7 to -0.3mmHg, p = 0.013). The substitution of datasets from the PREDIMED cohort did not alter the findings (Domenech et al. [31]: -1.1 mmHg, 95% CI: -1.8 to -0.5mmHg, p < 0.001; Toledo et al. [30]: -0.9 mmHg, 95% CI: -1.4 to -0.5 mmHg, p < 0.001).

Case-deletion diagnostics revealed one influential study for the effect of MedDiet intervention on diastolic BP (Casas et al. [16] B; Supplemental Digital Content 6). The influential effect of Casas et al. [16] is due to this study being an outlier within the analysis, as demonstrated by large changes in model fit with case-deletion, despite average study weighting. However, the removal of this influential study did not alter the overall estimate of effect size (-1.2 mmHg decrease, 95% CI: -2.1 to -0.2 mmHg, p = 0.019).

Meta-regression analysis revealed that longer study duration was associated with greater decrease in diastolic BP (slope: -0.020 [CI: -0.032 to -0.008] mmHg for each 1 day increase in study duration; p=0.003; Supplemental Digital Content 7). The effect of MedDiet intervention on diastolic BP was not affected by the age (p = 0.260, n=19), BMI (p = 0.453, n=18), baseline

diastolic BP (p = 0.106, n=19) or health status of participants (healthy vs. high CVD risk; p = 0.265), nor by the study design (parallel vs. crossover; p = 0.194) or control diet (low fat vs. habitual vs. other; p=0.694). Inspection of the funnel plot and Egger's regression intercept for diastolic BP revealed little evidence of small study effects for diastolic BP (p = 0.523; Supplemental Digital Content 8).

Associations between MedDiet adherence and risk of hypertension

Meta-analysis of the observational studies demonstrated that higher versus lower MedDiet adherence was associated with a mean decrease of 13% in the odds of developing hypertension (OR: 0.87 [95% CI: 0.78 to 0.98], p = 0.017, Figure 4). The degree of heterogeneity between studies was moderate (I^2 = 69.6%, Q = 41.1, $\tau 2$ = 0.03, df = 17). Case-deletion diagnostics revealed one influential study for the effect of MedDiet adherence on hypertension prevalence [52]. The study by Vicinanza et al. [52] was a substantial outlier, as identified by large changes in all model fit parameters after removal of this study, and moderate study weighting (Supplemental Digital Content 9). However, the removal of this influential study did not alter the overall estimate of the OR (OR: 0.94 [95% CI: 0.89 to 0.99], p = 0.035). Subgroup analysis demonstrated that the relationship between Mediterranean diet adherence and hypertension prevalence did not differ between longitudinal and cross-sectional studies (p = 0.865). Inspection of the funnel plot and Egger's regression intercept for hypertension prevalence revealed evidence of small study effects (p = 0.003; Supplemental Digital Content 10).

Study quality and risk of bias

Overall, the quality of RCTs included in this meta-analysis was mixed (Supplemental Digital Content 11 and 12). There was a low risk of attrition bias in all included studies but over 25% of RCTs showed high risk of selection bias, performance bias and detection bias. Likewise, in

over 25% of RCTs, insufficient information was provided to assess the risk of selection bias, performance bias and reporting bias. Of the two prospective studies included in this review, one had a moderate quality score of 6 [11] and one had a high quality score of 7 [53] (Supplemental Digital Content 13). Twelve of the cross-sectional studies had moderate quality scores of 4-6 [10,12,13,47,48,50,51,54–57] whilst two cross-sectional studies had low quality scores of 2 [52,58] (Supplemental Digital Content 14).

DISCUSSION

The results of this systematic review and meta-analysis demonstrate that intervention with a MedDiet reduces systolic and diastolic BP by mean -1.4 mmHg and -1.5 mmHg, respectively. Meta-regression analysis revealed that longer study duration was associated with greater decreases in both systolic and diastolic BP. Furthermore, higher baseline BP was associated with significantly greater reductions in systolic, but not in diastolic, BP in response to a MedDiet. Further supporting evidence for a beneficial role of the MedDiet for BP control under real world conditions was provided by analysing data from observation studies, which showed an overall 13 % reduction in the risk of hypertension with higher versus lower adherence to the MedDiet.

The results of this study are broadly consistent with the findings of three meta-analyses published in 2016, which reported overall reduction in systolic BP of -1.1 to -3 mmHg and diastolic BP of -0.7 to -2 mmHg following MedDiet intervention [59–61]. However, crucially, our findings are based on the analysis of 19 RCTs compared with only 3-6 studies in these earlier reviews, which adds confidence to our results. The effects of MedDiet interventions on BP were also explored in a more recent network meta-analysis by Schwingshackl and colleagues [62], who contrasted the BP lowering effects of different dietary patterns,

administered for 12 or more weeks, to individuals with elevated BP. Compared with a low-fat diet, the MedDiet reduced systolic and diastolic BP by mean -1.7 and -1.5 mmHg, respectively – findings similar to those of the current study. Interestingly, Schwingshackl and colleagues identified the MedDiet as the 3rd most effective dietary pattern for reducing diastolic BP after the Dietary Approach to Stop Hypertension (DASH) and the Palaeolithic diet – both of which, like the MedDiet, are rich in plant-based foods [62]. Since these findings were based on indirect comparisons of the efficacy of these dietary patterns, which weakens the conclusions to be drawn compared with the synthesis of direct evidence [63], future RCTs that compare the efficacy, and also the acceptability, of these dietary patterns for BP reduction would be valuable in informing future public health guidelines and interventions. Finally, effects of the MedDiet on BP were evaluated as part of a recent Cochrane Review exploring the effectiveness of a MedDiet in primary and secondary prevention of CVD [64]. In that study, MedDiet interventions significantly reduced systolic (-2.9 mmHg) and diastolic (-2.0 mmHg) BP in primary prevention settings when compared against minimal to no intervention. Conversely, effects in other settings were not significantly different to control [64]. This study did not explore overall effects of a MedDiet on BP, instead focusing on small sub-group analyses including 1-4 studies where participants were split by CVD status (primary or secondary prevention) and type of control group (minimal vs alternative dietary intervention), which limits the statistical power to detect an effect. Moreover, as that study only included interventions with minimum 3 months duration, the effects of shorter MedDiet interventions could not be determined [64]. Therefore, overall, our study provides new information on the potential role of a MedDiet for BP control and builds upon the findings of previous research.

Although the BP lowering effects of a MedDiet observed here are quantitatively small, on a population level, such small reductions in BP are likely to be important. Indeed, a -2 mmHg

reduction in systolic BP has been estimated to decrease the risk of death from stroke by 10 % and from ischemic heart disease by 7 % [65]. The MedDiet may also reduce CVD risk via multiple other mechanisms [66–69], such that the overall cardioprotective benefits of this dietary pattern are likely to be much greater. Therefore, a MedDiet could be recommended as part of public health guidelines to reduce population risk of hypertension and CVD. To this end, meta-regression analysis revealed two novel findings which may be useful in the design of future intervention studies or public health guidelines for BP reduction. Firstly, we found a positive association between study duration and the magnitude of reduction in both systolic and diastolic BP following a MedDiet, suggesting that longer term consumption of this dietary pattern may maximise BP lowering effects. These findings echo those from our recent meta-analysis in which we observed a similar positive association between the duration of MedDiet intervention and effects on measures of endothelial function such as flow mediated dilation [66]. Secondly, we observed greater reductions in systolic BP in individuals with higher baseline systolic BP values, indicating that these individuals are an important population target for future MedDiet interventions for BP reduction.

Strengths and limitations

The current study has several strengths. Firstly, we undertook a number of sensitivity analyses which demonstrated the robustness of our findings. These included exploring whether substitution of other PREDIMED datasets would influence the results of our analyses, thus overcoming the potential consequences of arbitrary decisions made in selecting the 'best' dataset for inclusion from this large-scale RCT. In addition, by undertaking sub-group and meta-regression analyses, we have provided novel information on factors that moderate the BP-lowering effects of the MedDiet, including intervention duration and baseline BP. Interestingly, recent data from the NuAge trial suggests that the BP lowering effects of a

MedDiet are also moderated by medication status [15]. Specifically, individuals taking anti-hypertensive medication experienced a less pronounced reduction in BP with consumption of a MedDiet compared with individuals not taking anti-hypertensives, which could be due to overlapping mechanisms of action or a reduced capacity to further lower BP with diet when accounting for the effects of the medication. Given the nature of our analysis, it was not possible to explore the modulating impact of anti-hypertensive medication use on BP lowering effects of the MedDiet, which is acknowledged as a limitation of this analysis and warrants further research. In a similar manner, we were unable to identify whether weight loss contributed towards the BP lowering effects of a MedDiet in this analysis given insufficient data available on change in BMI/ body weight in published studies. Nevertheless, a MedDiet without weight change has been shown to elicit BP lowering effects, suggesting that weight loss is not essential to reduce BP with consumption of this dietary pattern [16]. A further limitation of this meta-analysis is the quality of included studies, which was mixed. Most of the observational studies included in this review were cross-sectional, for which there is a greater risk of reverse causality compared with prospective studies. Nevertheless, we found no difference in the results between cross-sectional and prospective trials, suggesting that our findings were not influenced by this factor.

Conclusions and future directions

The results from this meta-analysis suggest that the MedDiet is an effective dietary strategy to reduce BP and to decrease risk of hypertension, which may contribute towards the lower CVD risk reported with this dietary pattern. Our findings that the MedDiet is increasingly effective when consumed over a prolonged period and when administered to individuals with elevated baseline BP may help inform public health guidelines and the design of future RCTs.

A number of questions regarding effects of the MedDiet on BP remain unanswered, and could be explored in future research. Firstly, further studies are needed to established whether particular MedDiet components may be driving the BP lowering effects of this dietary pattern. It has been suggested that the low sodium content of the MedDiet may play a key role in its BP lowering effects [12]. However, it is also possible that the high content of nitrate-rich vegetables [67] – which have been shown to lower BP by up to 10 mmHg in several RCTs [70–72] - fish [73], or other foods or bioactives, could be key. Better understanding of the 'active' components of this diet could be valuable for further refining dietary recommendations for BP reduction. Additional research to identify groups of individuals who may be particularly receptive to the BP lowering effects of a MedDiet is also warranted to help develop targeted nutritional interventions [74]. Most studies to date have evaluated BP in a clinical setting, and additional research exploring effects of the MedDiet on 24 hour ambulatory BP is warranted, which is superior to clinic BP in predicting cardiovascular outcomes [75]. Furthermore, additional prospective cohort studies are warranted to explore longitudinal associations between MedDiet adherence and risk of hypertension, given most observational studies to date are cross-sectional. Such studies should include large sample sizes with diverse participant characteristics to identify potential effect moderators to further inform the design and conduct of RCTs.

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The systematic review was conceived by MS and OMS. The study was planned and designed by OC, NM, KD, JM, AG, AM, JCM, OMS and MS. JM performed the searches. OC and NM screened the titles, abstracts, and full texts of retrieved papers, with guidance from MS. AG extracted data and assessed risk of bias. OMS checked the accuracy of extracted data and verified risk of bias. KD performed the statistical analysis. OMS and KD interpreted the data and drafted the manuscript. OC, NM, JM, AG, AM, JCM and MS further contributed towards the writing and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Figure legends

Figure 1. Flow diagram of the selection process of studies included in this meta-analysis

Figure 2. Forest plot of the effects of a MedDiet on systolic BP in RCTs

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List of Supplemental Digital Content

Supplemental Digital Content 1-14. Microsoft Word Document.

Table 1. Summary of baseline data reported in randomised controlled trials investigating effects of the Mediterranean diet on blood pressure

Author	Study design	Health status	Sample size	Male (n)	Age (y)	BMI (kg/m^2)	Duration (wks)	Type of intervention	Type of control
Assaf-Balut et al. (2019)	Parallel	High CVD risk	697	0	MedDiet: 33.0 Control: 32.5	MedDiet: 23.2 Control: 23.7	24-26	MedDiet + EVOO + nuts	Low fat diet
Bajerska et al. (2018)	Parallel	Obesity + MS	144	0	-	-	16	MedDiet	Central European diet
Casas et al. (2016)	Parallel	High CVD risk	160	74	MedDiet + EVOO: 66.7 MedDiet + nuts: 65.8 Control: 66.3	MedDiet + EVOO: 29.4 MedDiet + nuts: 28.7 Control: 29.1	260	MedDiet + EVOO MedDiet + nuts	Low fat diet
Ceriello et al. (2014)	Parallel	High CVD risk	24	17	-	MedDiet: 29.8 Control: 29.2	13	MedDiet + EVOO	Low fat diet
Davis et al. (2017)	Parallel	Healthy	149	84	MedDiet: 71.0 Control: 70.9	MedDiet: 26.7 Control: 27.1	26	MedDiet	Habitual diet
de Lorgeril et al. (1994)	Parallel	High CVD risk	605	550	MedDiet: 53.5 Control: 53.5	MedDiet: 25.8 Control: 25.8	104	MedDiet	Habitual diet
Esposito et al. (2004)	Parallel	High CVD risk	180	99	MedDiet: 44.3 Control: 43.5	MedDiet: 27.9 Control: 28.1	104	MedDiet	Prudent diet
Itsiopoulos et al. (2011)	Crossover	High CVD risk	27	16	59	30.7	13	MedDiet	Habitual diet
Jennings et al. (2019)	Parallel	Healthy	1128	503	MedDiet: 70.7 Control: 71.0	MedDiet: 26.7 Control: 26.6	52	MedDiet	Habitual diet
Jospe et al. (2020)*	Parallel	Healthy	114	34	MedDiet: 44.2 Control: 42.6	MedDiet: 32.5 Control: 34.1	52	MedDiet	Paleo diet
Lee et al. (2015)	Crossover	Healthy	24	0	25.6	23.0	1.4	MedDiet	Habitual diet

Maiorino et al. (2017)	Parallel	High CVD risk	215	106	MedDiet: 52.4 Control: 51.9	MedDiet: 29.7 Control: 29.5	208	MedDiet	Low fat diet
Osella et al. (2018)*	Parallel	High CVD risk	100	57	MedDiet: 58.4 Control: 57.5	-	26	Low GI MedDiet	Low GI diet
Properzi et al. (2018)	Parallel	Liver disease	51	26	MedDiet: 51.0 Control: 53.0	MedDiet: 31.5 Control: 30.2	12	MedDiet	Low fat diet
Rogerson et al. (2018)	Parallel	Healthy	24	6	MedDiet: 25.0 Control: 26.0	MedDiet: 23.1 Control: 25.1	4	MedDiet	Vegan diet
Ryan et al. (2013)	Crossover	High CVD risk	12	6	55.0	32.0	6	MedDiet	Low fat
Shai et al. (2008)*	Parallel	Obese/ T2DM/ /CHD	213	178	MedDiet: 53.0 Control: 51.0	MedDiet: 31.2 Control: 30.6	104	MedDiet (restricted calories)	Low fat diet (restricted calories)
Tuttle et al. (2008)	Parallel	High CVD risk	101	75	MedDiet: 58.0 Control: 58.0	MedDiet: 30.0 Control: 31.0	104	MedDiet	Low fat diet
Vincent-Baudry et al. (2005)	Parallel	High CVD risk	169	69	MedDiet: 50.8 Control: 51.6	MedDiet: 28.7 Control: 28.7	12	MedDiet	Low fat diet

MedDiet = Mediterranean diet; EVOO = Extra Virgin Olive Oil; CVD = Cardiovascular Disease; MS = Metabolic Syndrome; T2DM = Type II Diabetes. *Values presented for groups used in the statistical analysis only.

Table 2. Summary of observational studies investigating associations between Mediterranean diet adherence and risk of hypertension

Author	Study design (follow up duration)	Sample size	Male (n)	Age (y)	BMI (kg/m^2)	Dietary assessment method	MedDiet score
Alvarez et al. (2006)	Cross-sectional	578	249	≥18	-	FFQ	Custom 30-point MedDiet score
Alvarez-Alvarez et al. (2019)	Cross sectional	6620	3427	64.8	32.3	FFQ	14-point MEDAS Score
Cherfan et al. (2018)	Cross-sectional	2014	976	41.3	26.9	FFQ	52-point Lebanese MedDiet Score
Diaz-Gutierrez et al. (2019)	Prospective (10.2 years)	14057	4637	35.2	23.1	FFQ	8-point Trichopoulou Score (excluding alcohol)
Foscolou et al. (2016)	Cross-sectional	724	315	74.0	29.0	FFQ	55-point MedDietScore
Georgousopoulou et al. (2017)	Cross-sectional	2749	1369	74.5	28.4	FFQ	55-point MedDietScore
Grosso et al. (2014)	Cross-sectional	3090	1295	51.7	25.4	FFQ	55-point MedDietScore
Grosso et al. (2015)	Cross-sectional	8821	4291	-	28.1	FFQ	60-point MedTypeDietScore
Heindel et al. (2019)	Cross-sectional	2813	1651	60.1	28.8	FFQ	Modified 9-point Trichopoulou Score
Jackson et al. (2019)	Prospective (15 years)	5324	0	52.4	24.9	FFQ	Modified 17-point MedDiet score (minus olive oil)
Kanauchi et al. (2015)	Cross-sectional	433	433	45.3	24.8	FFQ	11-point Pyramid Score

Karageorgou et al. (2019)	Cross-sectional	3552	1463	43.7	25.5	24 hour dietary recall	Principal component analysis
La Verde et al. (2017)	Cross-sectional	1814	813	≥18	-	FFQ	MED-LITE score
Sánchez-Taínta et al. (2008)	Cross-sectional	3204	1380	67.2	29.9	FFQ	14-point MEDAS
Tyrovolas et al. (2014)	Cross-sectional	2732	1352	73.9	28.4	FFQ	55-point MedDietScore
Vicinanza et al. (2017)	Cross-sectional	476	202	70.4	26.7	FFQ	14-point MEDAS

MedDiet = Mediterranean diet; FFQ = Food Frequency Questionnaire.

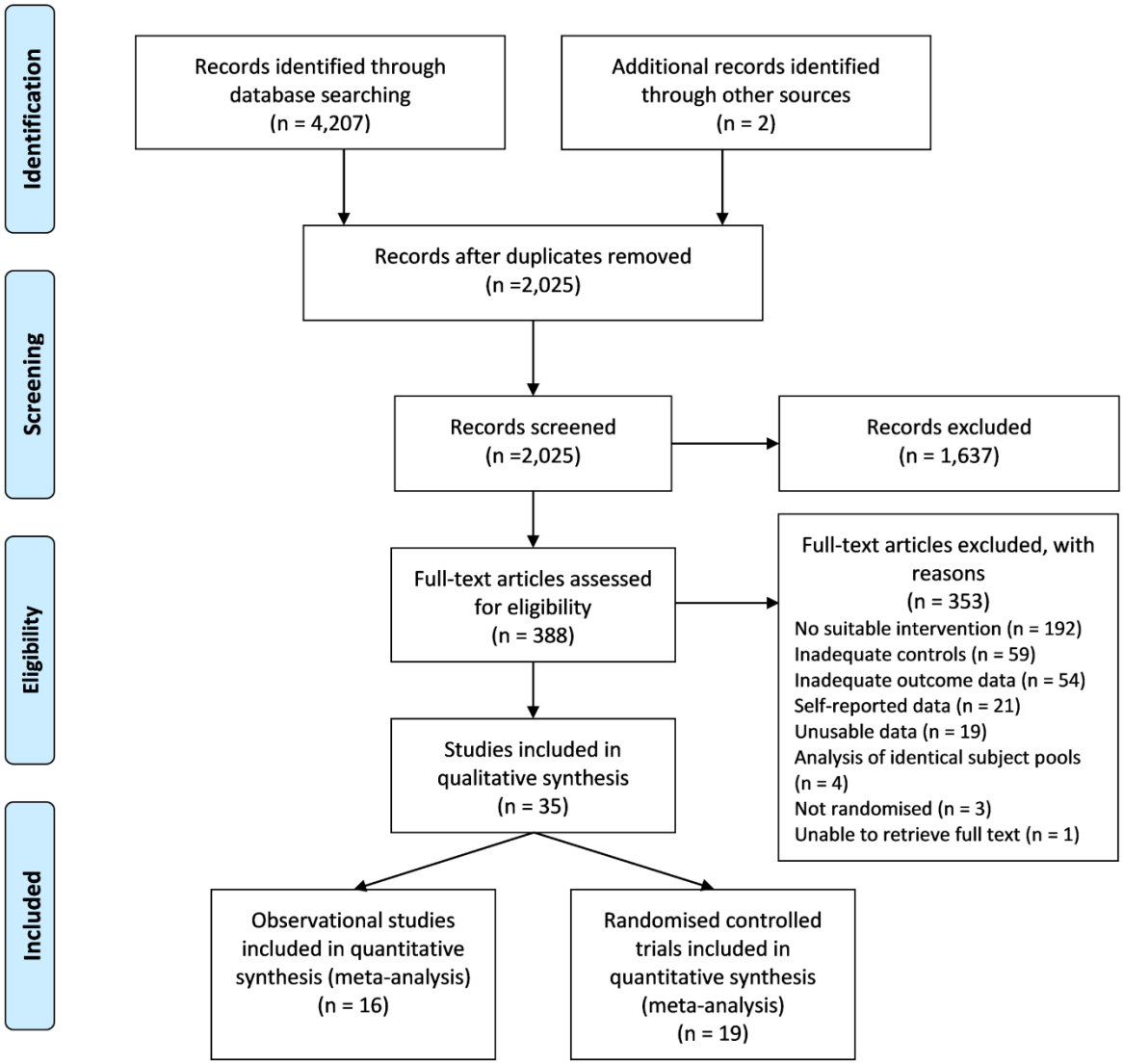

Figure 1. Flow diagram of the selection process of studies included in this meta-analysis

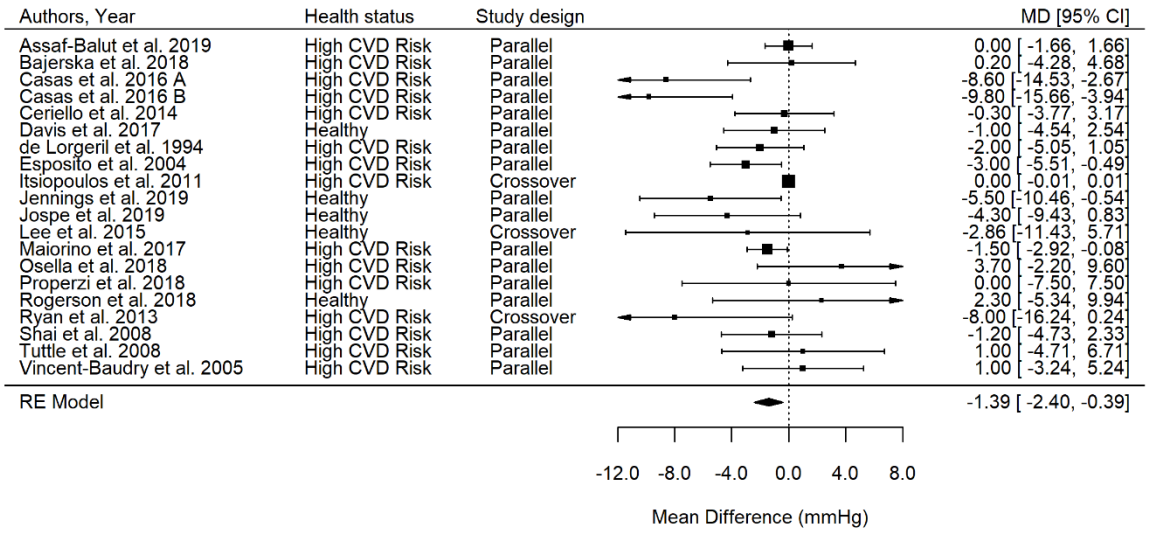

Figure 2. Forest plot of the effects of a MedDiet on systolic BP in RCTs

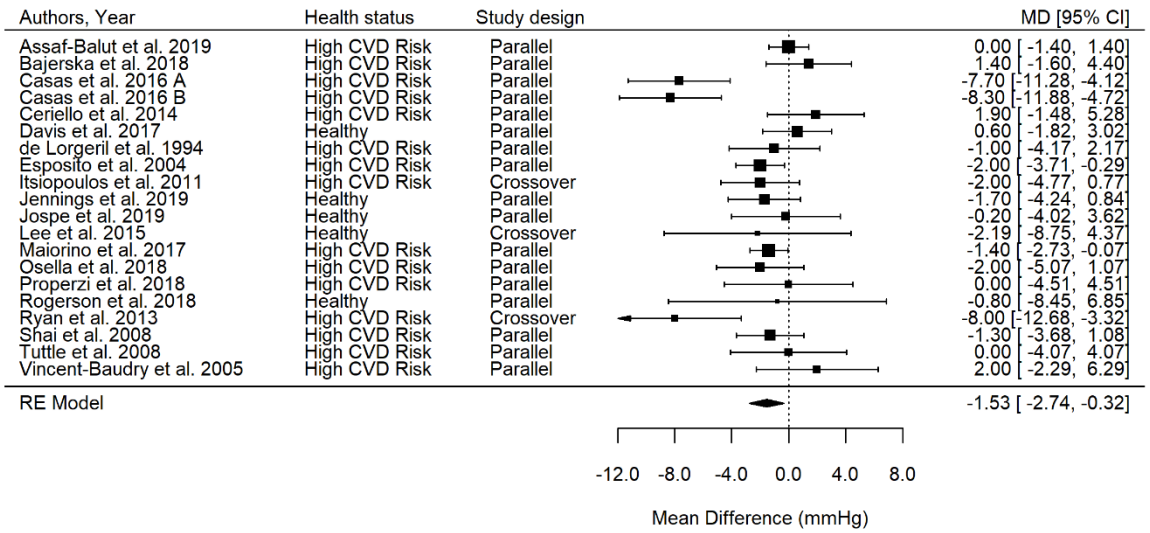

Figure 3. Forest plot of the effects of a MedDiet on diastolic BP in RCTs

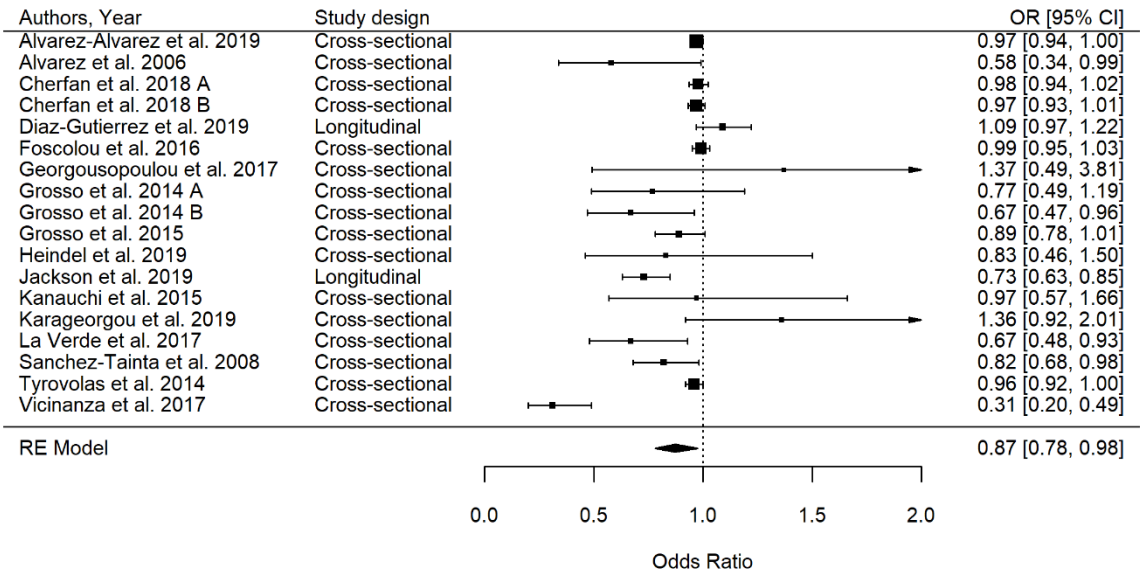

Figure 4. Forest plot of the associations between MedDiet adherence and risk of hypertension in observational studies