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Systematic Review of the Mediterranean Diet for Long-Term Weight Loss

Running Head: Mediterranean Diet for Weight Loss

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STRUCTURED ABSTRACT

Background: Although the long-term health benefits of the Mediterranean diet are well-established, its efficacy for weight loss at ≥ 12 months in overweight or obese individuals is unclear. We therefore conducted a systematic review of randomized controlled trials (RCTs) to determine the effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels after ≥ 12 months.

Methods: We systematically searched MEDLINE, EMBASE, and the Cochrane Library of Clinical Trials for RCTs published in English or French and with follow-up ≥ 12 months that examined the effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels in overweight or obese individuals trying to lose weight.

Results: Five RCTs (n=998) met our inclusion criteria. Trials compared the Mediterranean diet to a low-fat diet (4 treatment arms), a low-carbohydrate diet (2 treatment arms), and the American Diabetes Association diet (1 treatment arm). The Mediterranean diet resulted in greater weight loss than the low-fat diet at ≥ 12 months (range of mean values: -4.1 to -10.1 kg vs. 2.9 to -5.0 kg), but produced similar weight loss as other comparator diets (range of mean values: -4.1 to -10.1 kg vs. -4.7 to -7.7 kg). Moreover, the Mediterranean diet was generally similar to comparator diets at improving other cardiovascular risk factor levels, including blood pressure and lipid levels.

Conclusion: Our findings suggest that the Mediterranean diet results in similar weight loss and cardiovascular risk factor level reduction as comparator diets in overweight or obese individuals trying to lose weight.

INTRODUCTION

In the 1950s, the landmark Seven Countries Study identified a population in the Mediterranean region that enjoyed reduced rates of cardiovascular disease and cardiovascular mortality.[1] These individuals adhered to a regional diet that consisted of a high consumption of fruits and vegetables, monounsaturated fats (primarily from olive oil), and cereals; a moderate consumption of poultry, fish, and dairy products; and little to no consumption of red meat.[2, 3] Observational studies have associated this Mediterranean diet with good overall health.[3] Although the long-term health benefits of following the Mediterranean diet are well-established, its efficacy for weight loss at ≥12 months in overweight or obese individuals is unclear. We therefore conducted a systematic review of randomized controlled trials (RCTs) to examine the long-term effects of the Mediterranean diet on weight loss and cardiovascular risk factor levels among overweight and obese individuals trying to lose weight.

METHODS

Our systematic review was conducted according to a pre-specified protocol and is described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[4]

Search Strategy

We systematically searched MEDLINE (via Ovid), EMBASE (via Ovid), and the Cochrane Library of Clinical Trials from inception to January 2015 to identify RCTs that examined the effect of the Mediterranean diet on ≥12-month weight loss and cardiovascular risk reduction in overweight or obese individuals aged ≥18 years who were trying to lose weight. Our search terms consisted of medical subject headings, EMTREE terms, and keywords for the Mediterranean diet (Appendices 1-3). The search was restricted to RCTs published in English or in French. Moreover, we limited our MEDLINE and EMBASE searches to RCTs using a modified version of the McMaster RCT hedge[5] . We hand-searched the references of relevant RCTs, reviews, and meta-analyses retrieved by our database searches to identify additional RCTs.

Study Selection

We included RCTs that examined the efficacy of the Mediterranean diet for weight loss and cardiovascular risk factor level reduction with follow-up ≥12 months. Inclusion was restricted to RCTs comparing a diet that was explicitly described as “Mediterranean,” “Mediterranean-Style,” or “Mediterranean-inspired” to any active comparator diet, including but not limited to low-fat diets, low-carbohydrate diets, calorie-restricted diets, and diets that are part of the usual care for certain medical conditions. Trials with an exercise prescription and/or nutritional counseling in intervention or comparator arms were eligible for inclusion provided that ≥2 arms of the trial received the same exercise prescription and/or nutritional counseling. This was done to isolate the effect of the Mediterranean diet.

We excluded trials conducted in participants with malignancies or post-transplantation, as well as weight maintenance trials. We also excluded trials with a crossover design, unless the initial phase of the trial preceding the cross-over was randomized, controlled, and lasted ≥12 months; the initial phase of such trials was included. Finally, non-randomized trials, uncontrolled trials, and those that did not provide counseling or exercise interventions equally to ≥2 arms of the trial were designated as having an inappropriate control group and were thus excluded.

Data Extraction and Synthesis

Data were extracted by 2 independent reviewers, with disagreements resolved by consensus. Extracted data included data on study characteristics, study population, demographic and clinical characteristics, intervention characteristics, and use of any co-interventions such as exercise or counseling. All outcome data were extracted at 12 months, as well as at 6 months and in 6-month increments beyond 12 months, if available, until maximum follow-up.

Our primary endpoint was sustained weight loss, reported as mean weight change in kilograms or as a mean percentage change, at ≥12 months or longest follow-up. Secondary endpoints included mean change in body mass index (BMI), body fat, waist circumference, waist-hip ratio, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting insulin, homeostatic model assessment, and glycated hemoglobin (HbA1c) levels.

The quality of included trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[6] Quality assessment was conducted by 2 independent reviewers, with disagreements resolved by consensus. Given the amount of heterogeneity that was present in the designs, populations, and comparators among the included RCTs, we were unable to statistically pool data across trials.

RESULTS

Search Results

Our search yielded 2,432 potentially relevant publications (Appendix 4). Following the removal of duplicates, 1,069 publications underwent title and abstract screening. Of these, 78 were retrieved for full-text screening, and 5 were included in the systematic review.

Study Characteristics

The 5 included RCTs (n=998) randomized participants to a Mediterranean diet (6 treatment arms; n=492) or a low-fat diet (4 treatment arms; n=312), a low-carbohydrate diet (1 treatment arm; n=109), or the American Diabetes Association (ADA) diet (1 treatment arm; n=85) (Table 1). Follow-up ranged from 12 to 48 months, with 2 studies also reporting 6-month outcomes[7, 8].

The 5 RCTs possessed varying degrees of bias according to the Cochrane Collaboration's risk of bias assessment tool for RCTs. Most trials had a low or unclear risk of bias for sequence generation (5 trials), allocation concealment (4 trials), and blinding (4 trials). However, 1 RCT[7] was deemed to have a high risk of selective outcome reporting. Moreover, 2 RCTs[9, 10] were found to be high risk in 3 and 4 domains, respectively. In particular, these RCTs were at high risk of bias for incomplete outcome data and selective outcome reporting due to a high rate of loss to follow-up and incomplete outcome reporting, respectively (Appendix 5).

Participant Characteristics

The average age of participants ranged from 44 to 67 years (Table 1). On average, participants were borderline obese or obese, with mean BMIs ranging from 29.7 to 33.5 kg/m^2 and mean body weights ranging from 85.9 to 91.4 kg. Moreover, only 1 RCT assessed the effects of the Mediterranean diet in overweight but otherwise healthy individuals, of whom 90.1% were women.[10] The remaining 4 RCTs included participants with elevated cardiovascular disease risk, including participants with type 2 diabetes (3 trials), coronary heart disease (1 trial), or a recent myocardial infarction (1 trial). The 2 RCTs conducted in patients with cardiovascular disease consisted mainly of male participants (74-86%).[7, 8] The distribution of male and female participants was balanced in 2 RCTs[9, 11].

Weight Loss and Change in Other Anthropometric Measures

In general, the Mediterranean diet was modestly efficacious at reducing body weight (range of mean changes: -3.8 to -10.1 kg) at ≥12 months (Table 2). In 3 RCTs, the Mediterranean diet was significantly more efficacious for weight loss than a low-fat diet at ≥12 months.[8, 10, 11] However, the Mediterranean diet produced similar weight loss as other comparator diets at ≥12 months (range of mean changes: -4.7 to -7.7 kg).[8, 9]

The effect of the Mediterranean diet on BMI was similar to that for weight reduction (Table 2). At ≥12 months, the Mediterranean diet was more efficacious than a low-fat diet at reducing BMI (range of mean changes: -1.0 to -3.3 kg/m^2 vs. 1.4 to -1.8 kg/m^2), but similar to all other comparator diets (range of mean changes: -1.5 to -2.8 kg/m^2). Similar trends were observed when examining waist circumference (Table 2).

Other Cardiovascular Risk Factor Levels

The Mediterranean diet produced similar effects on measures of glycemic control as other diets but resulted in greater improvements in patients with type 2 diabetes (Table 3 and Appendix 6). In particular, participants with type 2 diabetes demonstrated significant improvement from baseline in levels of fasting glucose, serum insulin, and the homeostatic model assessment with the Mediterranean diet.[7-9, 11] The Mediterranean diet resulted in greater reductions in fasting glucose levels in patients with type 2 diabetes than comparator diets at ≥12 months (range of mean changes: -0.89 to -4.30 mmol/L vs. 0.67 to -3.10 mmol/L) and greater improvements in HbA1c levels.

Changes in lipid levels were generally similar with the Mediterranean diet as with comparator diets (Table 4). More specifically, the Mediterranean diet was similar to other diets with respect to changes in LDL-C and HDL-C levels. However, the Mediterranean diet resulted in greater reductions in triglyceride levels than comparator diets at ≥12 months (range of mean changes: -0.25 to -1.50 mmol/L vs. -0.03 to -0.70 mmol/L).

Only 3 RCTs reported changes in blood pressure, with available data suggesting that the

Mediterranean diet has similar effects on systolic and diastolic blood pressure levels as comparator diets (Table 5).[7, 8, 11] Only 1 trial demonstrated a significantly greater reduction in systolic and diastolic blood pressure at 12 months with the Mediterranean diet compared to a low-fat diet.[11] In the second trial[7], which consisted of participants with normal blood pressure at baseline, no difference between the Mediterranean diet and a low-fat diet was detected, with blood pressure increasing modestly in both groups during follow-up. In the third trial[8], no difference was observed between groups, though blood pressure decreased slightly in the 3 groups during follow-up.

DISCUSSION

Our systematic review was designed to examine the long-term (≥12 months) effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels among overweight and obese individuals trying to lose weight. We found that the Mediterranean diet is more efficacious for ≥12-month weight loss compared to low-fat diets, but not compared to other comparator diets. The Mediterranean diet also resulted in greater improvements in triglyceride levels but produced similar changes in other lipid levels and blood pressure. Furthermore, we found that it improved measures of glycemic control among patients with type 2 diabetes but not in normoglycemic individuals. Taken together, our findings suggest that the Mediterranean diet is efficacious for weight loss and cardiovascular risk level reduction in overweight or obese individuals, but not more so than other diets.

The findings from this systematic review add to the literature suggesting that there is no ideal diet for achieving sustained weight loss in overweight or obese individuals. This is consistent with the findings of our previous systematic review[12] of popular commercial diets, in which we found that Atkins, Weight Watchers, and Zone all produced similar weight loss at ≥12 months. Importantly, the weight loss at ≥12 months with the Mediterranean diet in the present systematic review is consistent with that observed with these commercial diets in the previous one. The similar weight loss achieved with these diets reduces the concern raised by the creators of some of these commercial diets[13-15] regarding the elevated consumption of carbohydrates associated with the Mediterranean diet[2]. The similar weight loss achieved across diets suggests that there is no optimal macronutrient composition for achieving sustained weight loss.

Rather, it has been suggested that a “3-stepped intensification of care approach” is more likely to yield clinically significant weight loss.[16] The first step is evidence-based lifestyle modification through diet, behavioural therapy, and physical activity.[16] Combining diet with physical activity has been found to increase weight loss compared to each of these interventions used alone[17-19], with physical activity unlikely to yield clinically significant weight loss unless it comprises a high level of aerobic exercise or is used in conjunction with a calorie-restricted diet.[17] The second step is the concurrent use of weight loss pharmacotherapies.[16] The third step is bariatric surgery for individuals for who interventions from the prior steps have failed and who suffer from severe obesity or moderate obesity with comorbidities.[16]

The Mediterranean diet has been the focus of many epidemiological studies, but the diet itself originated inauspiciously during the early- to mid-20th century. The dietary pattern consisting of the elevated consumption of fruits and vegetables, legumes, cereals, and olive oil was mostly followed in poor, rural regions of the Mediterranean.[3] Individuals in these communities enjoyed numerous health benefits, including reduced rates of cardiovascular disease, which were first described by the Seven Countries Study.[20] More recently, cohort studies have underscored the Mediterranean diet’s impact on overall health, suggesting that adherence to the Mediterranean diet is associated with up to 50% reduced risk of developing the metabolic syndrome[21], an increase in levels of biomarkers associated with healthy aging[22], and a reduced risk of mortality over 20 years[23].

The Prevencíon con Dieta Mediterránea (PREDIMED) RCT further highlighted the potential of the Mediterranean diet as an intervention for the primary prevention of cardiovascular disease. A total of 7,447 individuals at high risk of developing cardiovascular disease were randomized to the Mediterranean diet supplemented with olive oil, the Mediterranean diet supplemented with nuts, or a low-fat diet and followed for a median of 4.8 years. Compared with the low-fat diet, the Mediterranean diet was associated with an approximate 30% reduction in the primary, composite endpoint of myocardial infarction, stroke or cardiovascular death, with similar benefits observed in both Mediterranean diet arms.[24, 25] Other cardiovascular health benefits observed with the Mediterranean diet included: decreases in incident type 2 diabetes, peripheral artery disease, and atrial fibrillation rates; metabolic syndrome reversion; decreases in blood pressure, hypertension risk, and carotid atherosclerosis.[25] Many interactions were observed between Mediterranean diet and genetic determinants of intermediate and cardiovascular disease phenotypes. Often, the extent of these cardiovascular health benefits was correlated with the extent of adherence.[25]

There are several possible explanations for the differences in results between the aforementioned studies and our systematic review. In order to obtain the most rigorous form of evidence possible, we restricted inclusion to RCTs that compared the Mediterranean diet to active comparator diets. Much of the evidence for the Mediterranean diet's health benefits comes from observational studies,[21, 26] which often lack an appropriate comparator, and without the benefits of randomization, are prone to confounding and selection biases. In addition, several of these epidemiologic studies[23, 26, 27] focused on the overall health benefits of the Mediterranean diet without focusing on its use among overweight and obese individuals trying to lose weight. Finally, we excluded short-term trials, which are more likely to show a favourable benefit with the Mediterranean diet, focusing on RCTs with longer term follow-up data, as long-term weight loss represents a more important predictor of cardiovascular disease events[28].

Although previous knowledge syntheses have examined the Mediterranean diet for weight loss, many had several important methodological limitations. These include recent meta-analyses[29, 30] which pooled data across trials despite the presence of important heterogeneity in study design, durations of follow-up, and comparators. Moreover, previous reviews and meta-analyses[29-32] included RCTs that involved preferential nutritional counseling in Mediterranean diet treatment arms, which has been previously shown to increase 12-month weight loss[33]. The inclusion of such trials may partially explain the positive findings of these previous reviews and meta-analyses[29-32]. With inclusion restricted to trials with appropriate comparators and synthesis focused on the qualitative assessment of the available data in light of the substantial heterogeneity of included trials, the present systematic review has thus overcome the limitations of many previous studies in this area.

Limitations

Our systematic review has several potential limitations. First, our systematic review was designed to focus on high quality evidence from long-term RCTs. Consequently, only 5 RCTs were included, and these trials included a total of <1,000 patients. With heterogeneity in design, population, and comparator, we were unable to statistically pool data across trials. However, this finding highlights the dearth of rigorous trials in this area. Second, with 89.9% of included participants having established cardiovascular disease or type 2 diabetes, the generalizability of our results to the general population of overweight or obese individuals trying to lose weight is unclear. Nonetheless, the high proportion of such individuals allowed for the assessment of the Mediterranean diet in individuals with obesity-associated co-morbidities. Finally, our review was restricted to RCTs that explicitly mentioned the Mediterranean diet as a dietary intervention. This may have resulted in the exclusion of some RCTs that investigated diets with the alimentary and macronutrient composition of the Mediterranean diet without describing the intervention as such. However, this ensured that included RCTs studied the diet of interest.

CONCLUSION

Our systematic review was designed to investigate the effect of the Mediterranean diet on weight loss and cardiovascular risk factor levels among overweight or obese individuals trying to lose weight. Our results suggest that the Mediterranean diet results in greater weight loss than a low-fat diet, but similar weight loss as other comparator diets. The Mediterranean diet may also improve triglyceride levels as well as produce similar changes in blood pressure and other lipids as comparator diets. Although following the Mediterranean diet may result in some weight loss, and it likely has other health benefits, it does not appear to be superior to other diets when followed by overweight or obese individuals trying to lose weight.

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Table 1. Baseline Characteristics of Participants for Included Trials*

Study	Participants: Randomized	Participants: Analyzed†	Follow-Up (Months)	Population	Arms			Nutritional Counseling	Exercise Prescription	Age (y)	Female (%)	Weight (kg)	BMI (kg/m^2)
Shai 2008[8]	322	322‡	24	Bmi ≥ 27, Type 2 Diabetes Mellitus or Coronary Heart Disease	Mediterranean Diet (Calorie-restricted)	Low-Fat Diet (Calorie-restricted)	Low-Carbohydrate Diet	Yes	No	52	14	91.4	30.9
Esposito 2009[11]	215	215§	48	Overweight, Newly Diagnosed Type 2 Diabetes Mellitus#	Mediterranean Diet	Low-Fat Diet	–	Yes	Yes	52	50.7	85.9	29.7
Elhayany 2010[9]	259	179‖	12	Aged 30-65 y, Type 2 Diabetes Mellitus, BMI 27-34	Traditional Mediterranean Diet	Low-Carbohydrate Mediterranean Diet	American Diabetes Association Diet	Yes	Yes	55	48	86.7	31.4
Tuttle 2008[7]	101	77‖	24	<6 Weeks After First Myocardial Infarction	Mediterranean-Style Diet	Low-Fat Diet	–	Yes	No	58	26	NR	30
McManus 2001[10]	101	61‖	18	Overweight, Non-Smoking	Mediterranean-Style Moderate Fat Diet	Low-Fat Diet	–	Yes	No	44	90.1	91	33.5

Abbreviations: BMI=Body Mass Index; NR=Not Reported.
* Studies are listed in descending order of number of participants included in analyses of each trial.
† This represents the number of participants included in the analysis of outcomes at maximum follow-up.
‡ All 322 participants were included in the primary analyses, and the most recent values for weight and blood pressure were used.
§ Risk factors and nutrient intake was compared by using a test based on the values at the end of follow-up and a *t*-test based on differences from baseline. Due to a low rate of loss to follow-up, a complete case analysis was used for secondary outcomes.
‖ Only participants who attended follow-up were analyzed.
\# The timeframe by which a diagnosis of type 2 diabetes mellitus was considered “new” was not specified.

Table 2. Change in Body Weight and Other Anthropometric Measures at 12 Months and Maximum Follow-up*

Study†	Follow-Up (Months)	Weight		Body Mass Index		Waist Circumference	
		Baseline (kg)	Mean Change (kg)	Baseline (kg/m^2)	Mean Change (kg/m^2)	Baseline (cm)	Mean Change (cm)
Shai 2008[8]							
Mediterranean Diet (n=109)	12	91.1 ± 13.6	-4.7‡‖	31.2 ± 4.1	NR	106.2 ± 9.1	NR
Low-Fat Diet (n=104)		91.3 ± 12.3	-3.6‡‖	30.6 ± 3.2		105.3 ± 9.2	
Low-Carbohydrate Diet (n=109)		91.8 ± 14.3	-5.3‡‖	30.8 ± 3.5		106.3 ± 9.1	
Mediterranean Diet (n=109)	24	91.1 ± 13.6	-4.4 ± 6.0§	31.2 ± 4.1	-1.5 ± 2.2	106.2 ± 9.1	-3.5 ± 5.1
Low-Fat Diet (n=104)		91.3 ± 12.3	-2.9 ± 4.2	30.6 ± 3.2	-1.0 ± 1.4	105.3 ± 9.2	-2.8 ± 4.3
Low-Carbohydrate Diet (n=109)		91.8 ± 14.3	-4.7 ± 6.5§	30.8 ± 3.5	-1.5 ± 2.1	106.3 ± 9.1	-3.8 ± 5.2
Esposito 2009[11]							
Mediterranean Diet (n=108)	12	86.0 ± 10.4	-6.2 ± 3.2§	29.7 ± 3.4	-2.4 ± 1.6§	98 ± 10.1	-4.8 ± 3.0§
Low-Fat Diet (n=107)		85.7 ± 9.9	-4.2 ± 3.5	29.5 ± 3.6	-1.4 ± 0.9	98 ± 10	-3.5 ± 2.8
Mediterranean Diet (n=108)	24	86.0 ± 10.4	-4.9 ± 2.5§	29.7 ± 3.4	-1.9 ± 0.9§	98 ± 10.1	-4.4 ± 2.8§
Low-Fat Diet (n=107)		85.7 ± 9.9	-3.7 ± 2.1	29.5 ± 3.6	-1.1 ± 0.6	98 ± 10	-3.3 ± 2.5
Elhayany 2010[9]							
Mediterranean Diet (n=63)	12	85.5 ± 10.6	-7.4‖	31.1 ± 2.8	-2.6 ± 4.0‡	111.1 ± 9.1	-9.3 ± 12.0‡
Low-Carbohydrate Mediterranean Diet (n=61)		86.7 ± 14.3	-10.1‖	31.4 ± 2.8	-3.3 ± 4.0‡	112.7 ± 9.6	-10.4 ± 14.1‡
ADA Diet (n=55)		87.9 ± 13.7	-7.7‖	31.8 ± 3.3	-2.8 ± 4.6‡	113.4 ± 10	-9.1 ± 14.1‡
Tuttle 2008[7]							
Mediterranean-Style Diet (n=47)	12	NR	NR	30 ± 5	-2.0‡‖	NR	NR
Low-Fat Diet (n=46)				31 ± 6	-1.0‡‖		
Mediterranean-Style Diet (n=37)	24	NR	NR	30 ± 5	-1.0‡‖	NR	NR
Low-Fat Diet (n=34)				31 ± 6	0.0‡‖		
McManus 2001[10]							
Mediterranean-Style Moderate Fat Diet (n=27)	12	93 ± 32	-4.8 ± 5.2	34 ± 5	-2.0 ± 2.1	104 ± 12	-7.3 ± 6.3
Low-Fat Diet (n=13)		89 ± 30	-5.0 ± 7.3	33 ± 3	-1.8 ± 2.9	101 ± 11	-1.6 ± 9.2
Mediterranean-Style Moderate Fat Diet (n=31)	18	93 ± 32	-4.1 ± 6.5§	34 ± 5	-1.6 ± 2.5§	104 ± 12	-6.9 ± 9.1§
Low-Fat Diet (n=30)		89 ± 30	2.9 ± 7.7	33 ± 3	1.4 ± 3.3	101 ± 11	2.6 ± 10.5

Abbreviations: ADA=American Diabetes Association; NR=Not Reported.
Values are reported as: mean ± standard deviation, unless otherwise specified.
* Studies are listed in descending order of number of participants included in the analyses of each trial.
† N is the number of participants analyzed for each arm of the trial at a specific point of follow-up (shown in Table 1).
‡ Mean change was calculated as difference of means from baseline to follow-up from data of the publication.
§ $p<0.05$ vs. low-fat diet.
|| Reported in the publication without discernable standard deviation.

Table 3. Glycemic Control Measures of Participants at 12 months and Maximum Follow-Up*

Study†‡	Follow-Up (Months)	Fasting glucose Baseline (mmol/L)	Fasting glucose Mean Change (mmol/L)	Fasting insulin Baseline (μU/mL)	Fasting insulin Mean Change (μU/mL)	HOMA Baseline	HOMA Mean Change	HbA1c Baseline (%)	HbA1c Mean Change (%)
Esposito 2009[11]									
Mediterranean Diet (n=108)	12	9.0 ± 1.9	-2.3 ± 1.9§	15.6 ± 6.2	-2.0 ± 2.0	5.2 ± 1.7	-1.9 ± 0.5§	7.8 ± 0.9	-1.2 ± 1.0§
Low-Fat Diet (n=107)		8.8 ± 1.8	-1.1 ± 1.1	16.6 ± 7.2	-1.9 ± 1.9	5.3 ± 1.8	-1.5 ± 1.0	7.7 ± 0.9	-0.6 ± 0.6
Mediterranean Diet (n=108)	48	9.0 ± 1.9	-1.7 ± 1.1§	15.6 ± 6.2	-1.41 ± 1.28	5.2 ± 1.7	-1.5 ± 1.0§	7.8 ± 0.9	-0.9 ± 0.6§
Low-Fat Diet (n=107)		8.8 ± 1.8	-0.8 ± 0.8	16.6 ± 7.2	-0.8 ± 0.62	5.3 ± 1.8	-0.9 ± 0.6	7.7 ± 0.9	-0.5 ± 0.4
Elhayany 2010[9]									
Mediterranean Diet (n=63)	12	10.1 ± 1.8	-3.5 ± 2.2‖	12.1 ± 6.5	1.2 ± 9.1‖	5.0 ± 2.9	-1.3 ± 3.5‖	8.3 ± 1.0	-1.8 ± 1.3‖#
Low-Carbohydrate Mediterranean Diet (n=61)		10.5 ± 2.0	-4.3 ± 2.2‖	13.5 ± 5.7	2.3 ± 10.2‖	5.9 ± 4.0	-1.7 ± 4.4‖	8.3 ± 1.0	-2.0 ± 1.7#
ADA Diet (n=55)		10.3 ± 1.7	-3.1 ± 2.5‖	12.7 ± 6.2	0.9 ± 8.5‖	5.8 ± 3.3	-1.5 ± 3.9‖	8.3 ± 0.8	-1.6 ± 1.2‖

Abbreviations: ADA=American Diabetes Association; HOMA= Homeostatic Model Assessment; HbA1c=glycated hemoglobin.
Values are reported as: mean ± standard deviation, unless otherwise specified.
* Studies are listed in descending order of number of participants included in the analyses of each trial. The randomized controlled trial by McManus et al.[10] did not report glycemic control measures and was therefore not included in this table.
† N is the number of participants analyzed for each arm of the trial at a specific point of follow-up (shown in Table 1).
‡ Randomized controlled trials by Shai et al.[8] and Tuttle et al[7] reported glycemic control measures among diabetic and non-diabetic participants. Please see Appendix 6.
§ $p<0.05$ for difference between groups.
‖ Mean change was calculated as difference of means from baseline to follow-up from data of the publication.
# $p<0.05$ vs. ADA diet.

Table 4. Lipid Profiles of Participants at 12 months and Maximum Follow-Up*

Study†	Follow-Up (Month)	Total Cholesterol		Low-Density Lipoprotein Cholesterol		High-Density Lipoprotein Cholesterol		Triglycerides	
		Baseline (mmol/L)	Mean change (mmol/L)	Baseline (mmol/L)	Mean Change (mmol/L)	Baseline (mmol/L)	Mean Change (mmol/L)	Baseline (mmol/L)	Mean Change (mmol/L)
Shai 2008[8]**									
Mediterranean Diet (n=109)	24	NR	NR	3.18 ± 0.89	-0.14‡	1.02 ± 0.24	0.16‡	1.96 ± 0.76	-0.25‡
Low-Fat Diet (n=104)				3.03 ± 0.92	-0.001‡	1.00 ± 0.25	0.17‡	1.77 ± 0.70	-0.03‡
Low-Carbohydrate Diet (n=109)				3.03 ± 0.89	-0.08‡	0.97 ± 0.22	0.22‡§	2.05 ± 1.32	-0.27‡§
Esposito 2009[11]									
Mediterranean Diet (n=108)	12	5.7 ± 0.9	-0.39 ± 0.38§	NR	NR	1.1 ± 0.2	0.1 ± 0.12§	1.9 ± 0.8	-0.44 ± 0.57§
Low-Fat Diet (n=107)		5.6 ± 0.9	-0.25 ± 0.20			1.1 ± 0.2	0.025 ± 0.02	1.9 ± 0.8	-0.22 ± 0.45
Mediterranean Diet (n=108)	24	5.7 ± 0.9	-0.46 ± 0.32§	NR	NR	1.1 ± 0.2	0.12 ± 0.12§	1.9 ± 0.8	-0.47 ± 0.57§
Low-Fat Diet (n=107)		5.6 ± 0.9	-0.20 ± 0.20			1.1 ± 0.2	0.00 ± 0.02	1.9 ± 0.8	-0.28 ± 0.42
Elhayany 2010[9]									
Mediterranean Diet (n=63)	12	5.5 ± 0.8	-1.00 ± 1.09‡	3.2 ± 0.8	-0.57 ± 1.01‡	1.1 ± 0.2	0.00 ± 0.27‡	3.0 ± 0.7	-1.50 ± 0.76‡‖
Low-Carbohydrate Mediterranean Diet (n=61)		5.4 ± 0.9	-0.90 ± 1.29‡	3.1 ± 0.8	-0.64 ± 1.08‡‖	1.1 ± 0.2	0.11 ± 0.02‖#	3.2 ± 0.8	-1.30 ± 0.86‡‖
ADA Diet (n=55)		5.4 ± 0.9	-0.90 ± 1.14‡	3.0 ± 0.9	-0.32 ± 1.20‡	1.1 ± 0.2	-0.1 ± 0.29‡	3.1 ± 0.8	-0.70 ± 1.38‡
Tuttle 2008[7]**									
Mediterranean-Style Diet (n=47)	12	NR	NR	3.08 ± 0.96	-0.54 ‡	0.96 ± 0.26	0.15‡	1.90 ± 1.29	-0.53‡
Low-Fat Diet (n=46)				3.10 ± 1.11	-0.31‡	0.93 ± 0.28	0.13‡	1.55 ± 1.03	-0.02‡
Mediterranean-Style Diet (n=37)	24	NR	NR	3.08 ± 0.96	-0.47‡	0.96 ± 0.26	0.07‡	1.90 ± 1.29	-0.45‡
Low-Fat Diet (n=34)				3.10 ± 1.11	-0.57‡	0.93 ± 0.28	0.10‡	1.55 ± 1.03	-0.26‡

Abbreviations: ADA=American Diabetes Association; NR=Not reported.
Values are reported as: mean ± standard deviation, unless otherwise specified.
* Studies are listed in descending order of number of participants included in the analyses of each trial. The randomized controlled trial by McManus et al.[10] did not report changes in lipid profiles throughout follow-up and was therefore not included in this table.
† N is the number of participants analyzed for each arm of the trial at a specific point of follow-up (shown in Table 1).
‡ Mean change was calculated as difference of means from baseline to follow-up from data of the publication.
§ $p<0.05$ vs. low-fat diet.

|| $p<0.05$ vs. ADA diet.
# $p<0.05$ vs. Mediterranean diet.
** Reported with no discernable standard deviation.

Table 5. Blood Pressure of Participants at 12 months and Maximum Follow-Up*

Study	Follow-Up (Month)	Systolic Blood Pressure		Diastolic Blood Pressure	
		Baseline (mm Hg)	Mean Change (mm Hg)	Baseline (mm Hg)	Mean Change (mm Hg)
Shai 2008[8]					
Mediterranean Diet (n=109)	24	133.1 ± 14.1	-5.5 ± 14.3	80.6 ± 9.2	-2.2 ± 9.5
Low-Fat Diet (n=104)		129.6 ± 13.2	-4.3 ± 11.8	79.1 ± 9.1	-0.9 ± 8.1
Low-Carbohydrate Diet (n=109)		130.8 ± 15.1	-3.9 ± 12.8	79.4 ± 9.1	-0.8 ± 8.7
Esposito 2009[11]					
Mediterranean Diet (n=108)	12	139.0 ± 12.0	-5.1 ± 4.2‡	87.0 ± 8.0	-4.0 ± 3.0‡
Low-Fat Diet (n=107)		140.0 ± 12.0	-2.0 ± 1.9	86.0 ± 8.0	-3.0 ± 4.0
Mediterranean Diet (n=108)	24	139.0 ± 12.0	-4.5 ± 3.7	87.0 ± 8.0	-3.2 ± 2.8
Low-Fat Diet (n=107)		140.0 ± 12.0	-1.4 ± 1.7	86.0 ± 8.0	-2.5 ± 2.3
Tuttle 2008[7]					
Mediterranean-Style Diet (n=47)	12	118.0 ± 12.0	2.0 ± 20.8	71.0 ± 9.0	2.0 ± 12.7
Low-Fat Diet (n=46)		119.0 ± 12.0	5.0 ± 20.0	71.0 ± 8.0	2.0 ± 12.0
Mediterranean-Style Diet (n=37)	24	118.0 ± 12.0	5.0 ± 20.0	71.0 ± 9.0	3.0 ± 12.7
Low-Fat Diet (n=34)		119.0 ± 12.0	4.0 ± 17.0	71.0 ± 8.0	1.0 ± 11.3

Values are reported as: mean ± standard deviation, unless otherwise specified.
* Studies are listed in descending order of number of participants included in the analyses of each trial. Studies that did not report blood pressure changes throughout follow-up were not included in this table.
† N is the number of participants analyzed for each arm of the trial at a specific point of follow-up (shown in Table 1).
‡ $p<0.05$ vs. low-fat diet.

Research Highlights

- The long-term efficacy of the Mediterranean diet for weight loss in overweight or obese individuals was previously unclear.
- The Mediterranean diet is superior to low-fat diets for long-term weight loss.
- Given the popularity of the Mediterranean diet and the importance of weight management in light of the current obesity epidemic, this review provides essential information for public health improvement.

Appendix 1. Description of Literature Search on MEDLINE† (Through Ovid) for Trials Comparing the Mediterranean Diet to Control Diets.

Number	Search Term(s)	Results
1	exp Diet, Mediterranean/	1,722
2	mediterranean*.ti,ab,mp.	27,942
3	exp diet/ or diet*.ab,ti,mp.	592,889
4	2 AND 3	3,876
5	1 OR 4	3,876
6	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)	3,081,632
7	5 AND 6	1,035
8	Limit 7 to English or French	987

†Database contains references from 1946 – January 7, 2015

Appendix 2. Description of Literature Search on EMBASE + EMBASE Classic† (Through Ovid) for Trials Comparing the Mediterranean Diet to Control Diets.

Number	Search Term(s)	Results
1	exp Mediterranean diet/	3,388
2	mediterranean*.ti,ab,mp.	33,408
3	exp diet/ or diet*.ab,ti,mp.	762,245
4	2 and 3	5,674
5	1 or 4	5,674
6	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.	1,519,774
7	5 and 6	1,046
8	limit 7 to (english or french)	998

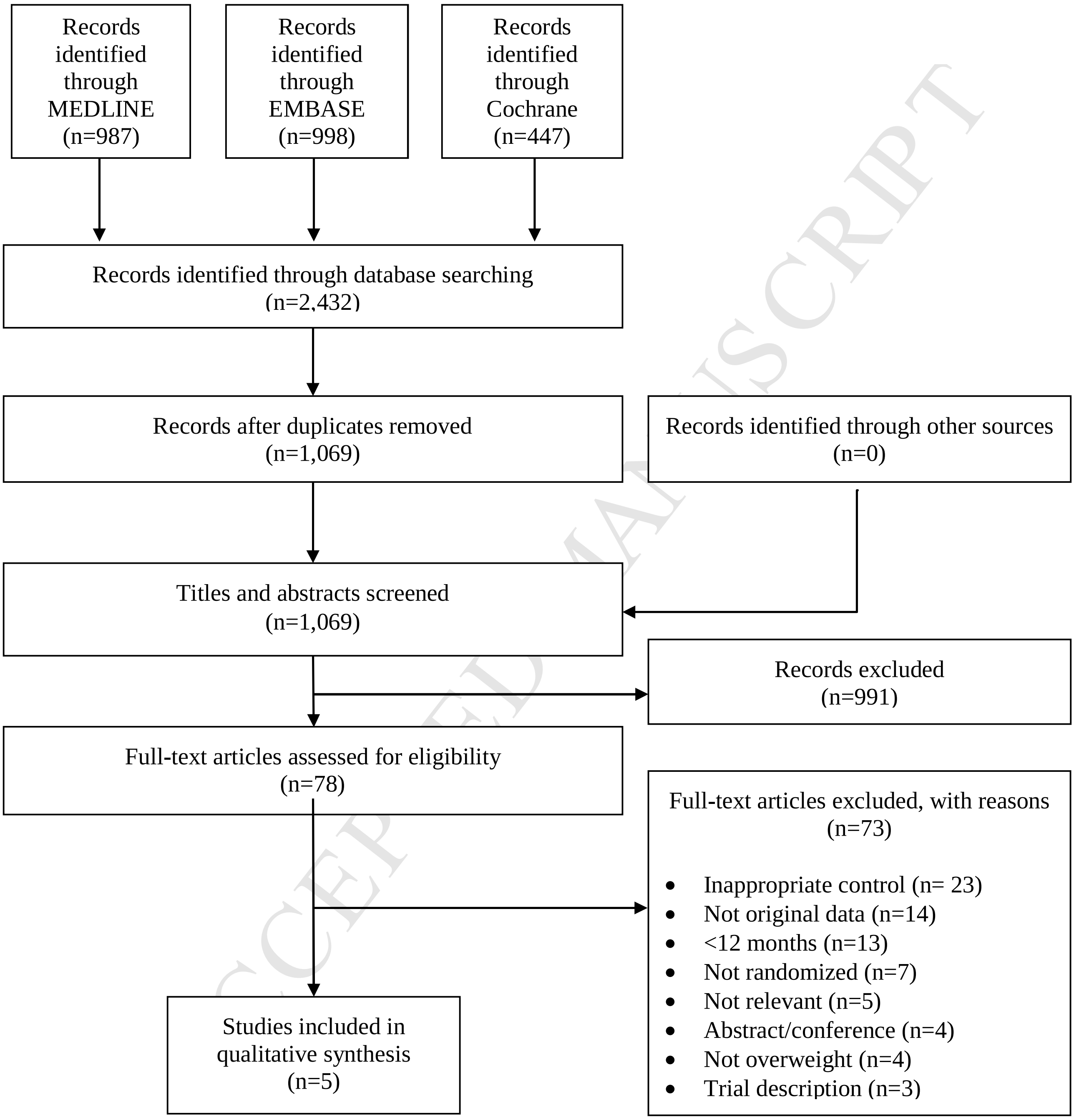
†Database contains references from 1947 to 2015 January 05.

Appendix 3. Description of Literature Search of The Cochrane Central Register of Controlled Trials† for Trials Comparing the Mediterranean Diet to Control Diets.

Number	Search Term(s)	Results
1	MeSH descriptor: [Diet, Mediterranean] explode all trees	196
2	mediterranean*	871
3	MeSH descriptor: [Diet] explode all trees	12,312
4	diet*	45,108
5	#3 or #4	47,319
6	#2 and #5	523
7	#1 or #6	523
8	#1 or #6 in Trials	447

†Database contains references from 1898 to December 2014.

Appendix 4. Flow Diagram Describing Systematic Literature Search for Randomized Controlled Trials Examining the Mediterranean Diet.



Appendix 5. Risk of Bias of Trials Comparing the Mediterranean Diet to an Active Comparator Diet*

Study†	Sequence Generation	Allocation Concealment	Blinding of participants, personnel, and outcome assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other sources of bias
Shai 2008[1]	Low	Unclear	Low	Low	Low	Low
Esposito 2009[2]	Low	Low	Low	Low	Low	Low
Elhayany 2010[3]	Unclear	Unclear	Unclear	High	High	High
Tuttle 2008[4]	Unclear	Low	Unclear	Low	High	Low
McManus 2001[5]	Low	High	High	High	High	Low

* Each criterion has been evaluated as being "High", "Low", or "Unclear" regarding the risk of bias following the guidelines of the Cochrane Collaboration's tool for assessing risk of bias.
† Studies are listed in descending order of number of participants included in the analyses of each trial.

Appendix 6. Glycemic Control Measures in Diabetics and Non-Diabetics in 2 Randomized Controlled Trials*

				Fasting Glucose	Fasting Insulin	HOMA	HbA1c
Study	**N†**	**Status**	**Follow-Up, mo**	**Mean Change, mmol/L**	**Mean Change, μU/mL**	**Mean Change**	**Mean Change, %**
Shai 2008[1]‡							
Mediterranean Diet	13	Diabetic	24	-1.82‖	-4.0	-2.3‖	NR
Low-Fat Diet	11	Diabetic		0.67	-1.5	-0.3	
Low-Carbohydrate Diet	12	Diabetic		0.07	-2.2	-1.0	
Mediterranean Diet	79	Non-diabetic	24	0.17	-1.8	-0.3	NR
Low-Fat Diet	79	Non-diabetic		0.17	-1.4	-0.2	
Low-carbohydrate Diet	69	Non-diabetic		0.07	-3.7	-0.8	
Tuttle 2008[4]§							
Mediterranean Diet	– #	Diabetic	12	-0.89	0	NR	NR
Low-Fat Diet		Diabetic		-0.44	-14		
Mediterranean Diet	– #	Non-diabetic	12	-0.11	3	NR	NR
Low-Fat Diet		Non-diabetic		-0.06	2		
Mediterranean Diet	– #	Diabetic	24	-1.10	5	NR	NR
Low-Fat Diet		Diabetic		-0.60	-16		
Mediterranean Diet	– #	Non-diabetic	24	0.11	0	NR	NR
Low-Fat Diet		Non-diabetic		-0.17	4		

Abbreviations: HOMA=Homeostatic model assessment; HbA1c=glycated hemoglobin.
* Studies are listed in descending order of number of participants included in the analyses of each trial.
† N is the number of participants analyzed for each arm of the trial at a specific point of follow-up (shown in Table 1).
‡ Standard deviation could not be discerned (values were presented graphically).
§ Mean change was calculated as difference of means from baseline to follow-up from data of the publication.
‖ $p<0.05$ vs. low-fat diet.
There were n=10 diabetics in the Mediterranean diet group and n=10 diabetics in the low-fat diet group at baseline. The number of diabetics and non-diabetics represented at this point of follow-up was not reported.

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