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## Central obesity and the Mediterranean diet: A systematic review of intervention trials

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### ABSTRACT

Central obesity is associated with chronic low-grade inflammation, and is a risk factor for cardiometabolic syndrome. The Mediterranean diet pattern has a convincing evidence-base for improving cardiometabolic health. This review investigated the impact of Mediterranean diet interventions on central obesity, specifically. A systematic literature search was conducted in the MEDLINE, CINAHL, EMBASE and Cochrane library databases. Search terms included: 'Mediterranean Diet', 'Mediterranean dietary pattern', 'central obesity' and 'visceral fat'. The search was limited to English language and humans  $\geq 18$  years. Eighteen articles met the eligibility criteria and reported at least one outcome measure of central obesity with Mediterranean diet intervention. Central obesity measures included waist circumference (16 studies), waist-hip ratio (5 studies) and visceral fat (2 studies). Thirteen (72%) of the studies, totaling 7186 subjects (5168 subjects assigned to a Mediterranean Diet), reported a significant reduction in central obesity with a Mediterranean-type diet. However, seven out of these 13 interventions employed energy restriction, and only three showed a statistically significant favorable effect of the Mediterranean diet relative to a control group. This systematic review highlights the potential for a Mediterranean diet intervention to reduce central obesity and in turn reduce obesity-related chronic disease risk and associated public health burden.

**Abbreviations:** T2DM, Type 2 diabetes mellitus; CVD, Cardiovascular disease; PAI-1, Plasminogen Activator Inhibitor-1; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; IL-6, Interleukin-6; PUFAs, Polyunsaturated fatty acids; MUFAs, Monounsaturated fatty acids; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HIV, Human Immunodeficiency Virus; EVOO, Extra virgin olive oil; BMI, Body mass index; Med diet, Mediterranean diet

### KEYWORDS

Mediterranean diet; central obesity; visceral fat; waist circumference

### Introduction

Obesity is considered to be one of the greatest public health challenges, with the worldwide prevalence of obesity doubling between 1980 and 2014 (World Health Organisation, 2016). In 2014, more than 1.9 billion adults, aged 18 years and older, were overweight and of these, over 600 million were obese (World Health Organisation, 2016). At present, most of the world's population live in countries where overweight and obesity kills more people than those who are underweight (World Health Organisation Western Pacific Region, 2016), thus exemplifying the significant health concerns behind this preventable health condition.

Lifestyle changes towards consumption of an energy-dense diet and a lack of physical activity are major determinants of the increased prevalence of obesity worldwide (Chan and Jean, 2010; Popkin, 2001). Specifically, the energy imbalance between an energy-dense diet and low physical activity leads to the accumulation of fat around the abdomen, which is referred to as central obesity (Bertoli et al., 2015). Fat stored in these areas can be particularly deleterious and increases the risk of type II diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Prasad, Kabir, Dash, and Das, 2011).

Anatomically, abdominal fat accumulates in three major areas: (i) subcutaneous fat, (ii) retro-peritoneal fat and (iii) visceral fat (Prasad et al., 2011). The deposit of visceral fat, which is situated around the vital organs, is considered to be the most detrimental (Prasad et al., 2011). Excess abdominal tissue is associated with insulin resistance, the precursor for T2DM, and creates an atherogenic pro-inflammatory environment characterized by elevated levels of C-reactive protein and other inflammatory markers such as fibrinogen, plasminogen activator inhibitor-1 (PAI-1), cytokines and adhesion molecules (Haffner, 2007). Adipose tissue also secretes biologically active molecules, termed adipokines, such as adiponectin, resistin, leptin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) (Sowers, 2003). Inflammatory markers and adipokines impact on the inflammatory process and increase risk for thrombosis at the vascular endothelium, hence contributing to the pathogenesis of atherosclerosis and increasing the risk of CVD (Sowers, 2003). This physiological process highlights the specific concern for the accumulation of central obesity, rather than simply body weight, and if not addressed, the potential for obesity-related diseases will continue to rise. Lifestyle

interventions, particularly targeting diet, could reduce abdominal adiposity and are non-invasive and cost-effective (Dalziel and Segal, 2007; Matsuzawa, Guddeti, Kwon, Lerman, and Lerman, 2015).

It has been well documented that the traditional Mediterranean diet pattern is cardioprotective, and this has been attributed to its antioxidant and anti-inflammatory properties (Dontas, Zerefos, Panagiotakos, and Valis, 2007; Esposito and Giugliano, 2002). The Mediterranean diet is characterized by an abundance of plant-based foods such as green-leafy vegetables, herbs, fruits, nuts and legumes, moderate to high intake of fish and seafood, low intake of red meat, low to moderate intake of dairy foods, the use of extra virgin olive oil (EVOO) as the main source of dietary fat and consumption of red wine with meals (if already consuming alcohol). Indeed, it is the increased consumption of these foods which exemplifies the antioxidant and anti-inflammatory nature of this diet pattern (Trichopoulos and Lagiou, 1997). Despite its high fat content, Mediterranean diet interventions do not lead to weight gain, rather the evidence supports modest weight loss (Esposito, Kastorini, Panagiotakos, and Giugliano, 2011; Mancini, Filion, Atallah, and Eisenberg, 2016). However, it is still unclear if a Mediterranean diet affects adipose tissue or central obesity, specifically.

Emerging evidence indicates that a Mediterranean diet can counterbalance the detrimental effects of central obesity associated with chronic low-grade inflammation (Rallidis et al., 2009). Furthermore, the high intake of polyunsaturated and monounsaturated fatty acids (PUFAs and MUFAs) compared to low intake of saturated fatty acids (SFAs) in a traditional Mediterranean diet could be beneficial for central adipose tissue distribution. Analysis of human cadavers has highlighted that visceral abdominal tissue is comprised of the deposit of saturated fats, whereas subcutaneous tissue is mostly comprised of the deposit of PUFAs and MUFAs (Calder, Harvey, Pond, and Newsholme, 1992). Garaulet and colleagues (2011) confirmed this finding in a Mediterranean-based population, showing subcutaneous abdominal fat was rich in PUFAs and MUFAs. There is however inconsistent epidemiological evidence regarding the association between the Mediterranean diet and abdominal adiposity.

Published literature in this field indicates that a greater adherence to a Mediterranean diet (assessed by a validated Mediterranean diet score) is associated with lower abdominal adiposity in a Mediterranean population (Bertoli et al., 2015; Boghossian et al., 2013; Romaguera et al., 2009). Prospective cohort studies have also determined that there is an inverse relationship between the development of central obesity and adherence to the Mediterranean diet (Funtikova et al., 2014; Kesse-Guyot et al.; Li et al., 2015; Roswall et al., 2014). As such, observational data is suggestive of an inverse relationship between adherence to a Mediterranean diet and lower levels of central obesity. At present, two systematic reviews have collated evidence to suggest that a Mediterranean-type diet intervention supports modest weight loss (Esposito et al., 2011; Mancini et al., 2016), however these reviews did not consider central obesity as an outcome. A review published in 2011 evaluated the effect of Mediterranean diet interventions on metabolic syndrome and its components, with waist circumference as a secondary outcome (Kastorini et al., 2011). Meta-analysis

demonstrated a modest significant reduction in waist circumference with Mediterranean diet (Kastorini et al., 2011). There has been no systematic review regarding specifically the effects of the Mediterranean diet on central obesity outcomes. Thus, the purpose of this review was to synthesize data from existing intervention trials, with or without a control group, studying the effect of the Mediterranean diet (with or without an energy restriction) on any measure of central obesity in an adult population.

## Methods

### Literature search

The methods of this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, and Altman, 2009) (Table S1). A systematic literature search conducted on electronic databases: MEDLINE, EMBASE, CINAHL and Cochrane library identified relevant studies for articles published between 1946 and August 2016. The first systematic search was completed in March 2016 and the last and final searches of databases were completed in August 2016. Relevant keywords relating to diet in combination as Medical Subject Headings (MeSH) terms and text words ('Mediterranean Diet' or 'Diet, Mediterranean' or 'Mediterranean dietary pattern' or 'Med Diet') were used in combination with words relating to central obesity ('visceral fat' or 'abdominal fat' or 'body fat distribution' or 'abdominal adiposity' or 'central adiposity' or 'visceral adiposity' or 'central obesity' or 'intra-abdominal fat' or 'waist circumference' or 'waist-to-hip ratio' or 'obesity' or 'abdominal circumference' or 'overweight'). The search was limited to human subjects, adults ( $\geq 18$  years of age) and English language. See Table S2 for the full electronic search strategy.

### Eligibility criteria

In order to be eligible for inclusion, intervention trials studying the effect of a Mediterranean diet on central obesity in adults, both with and without a control group, were included in this systematic literature review. No publication date or publication status restrictions were imposed. Letters, conference proceedings and reviews were excluded. At minimum, the Mediterranean diet intervention had to include a high consumption of plant-based foods such as vegetables, fruits, nuts or legumes. This level of dietary information needed to be specifically reported in the manuscript. Diet patterns that either did or did not involve an energy restriction were eligible for inclusion. Studies that solely focused on single-food items (such as olive oil or nuts) or macronutrients (such as a diet high in MUFAs without Mediterranean diet principles considered) or supplementation trials were excluded. Studies must have included participants  $\geq 18$  years of age, and reported on at least one measure of central obesity, such as waist circumference, waist-hip ratio or visceral fat, in order to be included. Studies were deemed eligible if they included healthy participants or participants with a chronic condition that related directly to central obesity (e.g. CVD, or T2DM). Comparator dietary interventions (e.g. those with a dietary control group) were also

included. Where a study employed a multiple treatment-arm design (e.g. diet and exercise vs. diet), the results from the condition considered most comparable to other studies were included.

Only dietary interventions without a co-intervention were included. For example, studies were excluded if they employed an exercise intervention or pharmacological intervention in combination with the dietary intervention, as these co-interventions would have made it difficult to determine the true effect of diet. Studies were deemed ineligible if participants were pregnant and/or breastfeeding women, <18 years of age, animal studies, if participants had a malignancy or were undergoing cancer treatment or had a human immunodeficiency virus (HIV). These exclusion criteria were established to omit studies that did not report on the specific outcomes of central obesity, while, those comprising participants with a cancer malignancy, had HIV or were pregnant and/or breast-feeding women were excluded as these conditions could have been considered as confounding factors. No criteria were set for the minimum and maximum number of participants in each study or length of intervention period.

### Study selection

To prevent duplication and allow for a distinctive analysis, any duplicate references found in the initial search were excluded. The reference lists of systematic reviews and meta-analyses were searched in order to obtain additional potentially eligible original articles. Using the inclusion and exclusion criteria citations were screened for eligibility based on titles and abstracts by one review author (CLB). If deemed potentially eligible the full text publication was retrieved and reviewed by two review authors (CLB and HLM) independently to determine eligibility for inclusion of articles for the final analysis. Contrasting opinions regarding eligibility were resolved by consensus.

### Data extraction

Data were extracted from included studies and details are presented in Table 1 using the following parameters: author, year, country of origin, population, eligibility criteria, length of follow-up, Mediterranean diet intervention, control group, intervention intensity, study aims, primary outcome, central obesity measure, and study results.

### Quality assessment criteria

The quality of included studies was evaluated using quality criteria recommended by the Academy of Nutrition and Dietetics (Academy of Nutrition and Dietetics, 2012). This checklist for primary research includes criteria for assessment of selection bias, randomization methods, study retention, study design, intention to treat methods, withdrawals/drop out methods, publication and funding bias and methods of blinding (see Figure S1). Each study was assessed as having either a positive, neutral or negative method quality rating (Table 2). Papers were not excluded based on the quality criteria. All studies received a score out of 10 (Table 2). A score of 8 or above was rated positive (+).

However, to achieve a positive rating, studies needed to meet the criteria of Sections 2, 3, 6 and 7 (Figure S1). A score of 5–7 was rated neutral ( $\Phi$ ). A score of below 5 was rated negative (-), indicating that these criteria were not adequately addressed or reported within the study.

### Summary measures

Data is presented as mean change (pre- vs. post- effect) of the central obesity measure under investigation for all studies. Where available, mean  $\pm$  standard deviation (SD) or mean  $\pm$  standard error of the mean (SEM) is presented which allowed for effect size calculation between the Mediterranean diet intervention group and the control group. Effect size of a decline to measures of central obesity between control and intervention was the primary measure of treatment effect. The Cohen's  $d$  effect size was used to determine this value. The effect size was classified as small ( $<0.20$ ), medium (2.0 to 0.50) or large (0.5 to 0.80) (Thalheimer and Cook, 2002). Data were considered statistically significant if  $p < 0.05$ . This systematic literature review uses a narrative approach, as a meta-analysis was not conducted in the present review due to heterogeneity in Mediterranean diet interventions and control groups across the studies.

## Results

### Study selection

Figure 1 shows the results of the study selection process. Briefly, the original search yielded 2242 citations, of which 1008 were excluded as duplicate references. One additional article was identified through screening of reference lists of relevant review papers. Based on title and abstract screening of the remaining 1235 records, 1168 were excluded for not meeting the inclusion criteria. The remaining 67 articles were reviewed in full text and 49 were excluded. Incorrect target outcome ( $n = 27$ ), incorrect study design ( $n = 9$ ) and no Mediterranean diet intervention ( $n = 7$ ) were the main reasons for exclusion. Thus, in total 18 intervention trials were included in this systematic literature review.

### Study and sample characteristics

Characteristics of included studies are summarized in Table 1. Of the eighteen included publications, four studies each were conducted in Spain (Corbalán et al., 2009; de la Puebla et al., 2003; Estruch et al., 2016; Fernández et al., 2012) and Italy (Buscemi, Verga, Tranchina, Cottone, and Cerasola, 2009; Esposito et al., 2009; Esposito, Marfella, Ciotola, and et al., 2004; Schiavo et al., 2015), two studies each were conducted in Canada (Bedard, Dodin, Corneau, and Lemieux, 2012; Richard, Couture, Desroches, and Lamarche, 2013), Israel (Elhayany, Lustman, Abel, Attal-Singer, and Vinker, 2010; Shai et al., 2008) and the United States of America (Jones. et al., 2011; McManus, Antinoro, and Sacks, 2001) and one study each was conducted in Australia (Ryan et al., 2013), Greece (Kolomvotsou et al., 2013), Sweden (Lindeberg et al., 2007) and the Netherlands (Bos et al., 2010). The eighteen studies included in this review represent a total of 7186 participants, with sample

Table 1. Characteristics and results of Mediterranean Diet interventions.

Author, year Country	Population, eligibility criteria	Intervention, sample size	Intensity, frequency, delivery/follow-up length	Details of diet intervention, dietary components	Comparison group, sample size	Primary aim	Relevant outcomes	Results	Method of presenting results
Bedard <i>et al.</i> , 2012 Canada	69 (31 non-abdominally obese, 38 abdominally obese) men and women, 24–53 years.	Isoenergetic Med diet in non-abdominally obese $n = 31$ Isoenergetic Med diet in abdominally obese $n = 38$	There was a 4-week 'run in' period. After completion, Med diet intervention began. Food was prepared and provided to participants with a 7-day cyclic menu. Meals were consumed under supervision. /4 weeks	High intake of EVOO, wholegrains, fruit and vegetables, legumes, nuts, fish, cheese and yoghurt. Moderate intake of red wine. Low intake of red meat and sweets.	No comparison group	Whether guidelines to adhere to a Med diet lead to similar beneficial CV effects in abdominally obese and in non-abdominally obese.	Waist circumference Waist-hip ratio	<b>Waist circumference Med diet group</b> (abdominally obese): significant mean decline in waist circumference in abdominally obese individuals ( $-1.20 \pm$ $0.49$ cm) ( $p = 0.03$ ). <b>Waist-hip ratio Med</b> <b>diet group</b> (abdominally obese) (NS) Decrease in waist-hip ratio in abdominally obese individuals ( $-0.01 \pm 0.01$ cm) ( $p >$ $0.05$ ). <b>Waist circumference Med diet</b> <b>group</b> (non-abdominally obese): (NS) Mean increase in waist circumference in non-abdominally obese individuals ( $+0.31$ $\pm 0.32$ cm) ( $p > 0.05$ ). <b>Waist-hip ratio</b> <b>Med diet group</b> (non-abdominally obese) (NS) Mean increase in waist-hip ratio in non-abdominally obese individuals ( $+0.01$ $\pm 0.01$ cm) ( $p > 0.05$ ). Effect size: N/A	Mean $\pm$ SEM
Bos <i>et al.</i> , 2010 Netherlands	59 men and women with BMI $\geq 25$ kg/m <sup>2</sup> or waist circumference $\geq 94$ cm for men and $\geq 80$ cm for women, 40– 65 years, without diabetes or CVD	Med diet $n = 20$	Subjects received Western-style diet for two weeks run-in period then subjects allocated to one of the three groups. Mediterranean diet was implemented as a 2-week menu cycle with 90% of foods provided. Instructed how to prepare take-home meals. /8 weeks	Dietary composition included: CHO 41%, fat 40%, 11% SFA, 21% MUFA, 7% PUFA, protein 15%. High intake of EVOO and vegetables. Low intake of meat and dairy products.	High MUFA-diet (refined olive oil) $n$ = 19 High SFA- diet $n = 20$	To compare the effects of a high MUFA- diet with a high SFA-diet and the additional effect of a Mediterranean diet on insulin sensitivity and serum lipids.	Waist circumference Waist-hip ratio	<b>Waist circumference Med diet group</b> (NS) decrease from baseline ( $98.8 \pm 3.8$ cm) to end of intervention ( $96.4 \pm 2.7$ cm) (mean change: decrease $2.4$ cm) ( $p > 0.05$ ). <b>High</b> <b>MUFA-diet</b> (NS) decrease from baseline ( $97.3 \pm 3.1$ cm) to end of intervention ( $96.6 \pm 3.1$ cm) (mean change: decrease $0.7$ cm) ( $p > 0.05$ ). <b>High SFA-diet</b> significant decrease from baseline ( $94.5 \pm$ $2.2$ cm) to end of intervention ( $92.6 \pm$ $2.1$ cm) (mean change: decrease $1.9$ cm) ( $p$ $< 0.05$ ). No significant difference between groups after the 8-week intervention period ( $p > 0.05$ ) (effect size for Med diet vs high MUFA-diet: 0.07; effect size for Med Diet vs high SFA-diet: NA due to significant baseline differences).	Mean $\pm$ SD
Buscemi <i>et al.</i> , 2009 Italy	20 overweight-obese non- pregnant women, 30–50 years, BMI $27$ – $40$ kg/m <sup>2</sup> , otherwise healthy.	Med hypocaloric diet, $n = 10$	Subjects met with a registered dietitian weekly to receive nutritional counseling. /8 weeks	Dietary composition included: CHO 55%, fat 25% (20% SFA, 67% MUFA, and 13% PUFA), protein 20%, fiber 30 g and cholesterol 250 mg. Foods provided: fatty fish (3 servings/week), unrefined-grain products, nuts (15 g/day), legumes (40 g/ day), and red wine (1 glass/day).	Very low carbohydrate diet, $n = 10$	To examine the effect on endothelial function, measured by flow-mediated dilation, of low carbohydrate diet compared to that of an equally hypocaloric Med diet.	Waist circumference Waist-hip ratio Rectus-aorta thickness	<b>Waist Circumference: Med diet group</b> Significantly decreased from baseline ( $102.2 \pm 2.2$ cm) to end of intervention ( $97 \pm 2$ cm) (mean change: decrease $5$ cm) ( $p < 0.05$ ). <b>Very low carbohydrate diet</b> <b>(control)</b> Significantly decreased from baseline ( $102 \pm 4$ cm) to end of intervention ( $94 \pm 5$ cm) (mean change: decrease $8$ cm) ( $p < 0.05$ ). No significant difference between groups ( $p > 0.05$ ) (effect size: 1.5). <b>Rectus-aorta thickness</b> <b>Med diet group</b> Significantly decreased from baseline ( $73 \pm 4$ mm) to end of intervention ( $64 \pm 6$ mm) (mean change: decrease $9$ mm) ( $p < 0.05$ ). <b>Very low</b> <b>carbohydrate diet (control)</b> Significantly decreased from baseline ( $71 \pm 13$ mm) to end of intervention ( $48 \pm 10$ mm) (mean change: decrease $28$ mm) ( $p < 0.001$ ). No significant difference between groups ( $p > 0.05$ ) (effect size: 1.9). <b>Waist-hip ratio</b> <b>Med diet group</b> : (NS.) Decrease from baseline ( $0.90 \pm 0.01$ ) to end of intervention ( $0.87 \pm 0.02$ ) (mean change: decrease $0.03$ ) ( $p > 0.05$ ). <b>Very low</b> <b>carbohydrate diet (control)</b> (NS) Decreased from baseline ( $0.86 \pm 0.01$ ) to end of intervention ( $0.84 \pm 0.02$ ) (mean change: decrease $0.02$ ) ( $p > 0.05$ ). No significant difference between groups ( $p >$ $0.05$ ) (effect size: 1.5).	Mean $\pm$ SD





Corbalán <i>et al.</i> , 2009 Spain	1406 obese men and women, 20–65 years, BMI 25–40 kg/m <sup>2</sup>	Med-type diet + cognitive behavioral therapy, n = 1550	Education surrounding the intervention diet was used. Sessions involved: 1) nutritional education, 2) physiological sessions; 3) behavioral/ cognitive sessions and 4) practical shopping plans / 12 months	Unrestricted vegetables, 250–300 g of fruit; Olive oil as main fat, 100 g of legumes three times per week, 100 g rice once per week, 100 g wheat and pasta once per week, 2 serves of fish	No comparison group	To assess the effectiveness of behavioral based therapy on Med diet for the treatment of obesity	Waist circumference Waist-hip ratio	<b>Waist circumference Med diet group</b> Significant decrease in waist circumference from baseline (103±13 cm) to end of intervention (96±13 cm) (mean change: 7 cm) ( <i>p</i> < 0.001). <b>Waist-hip ratio:</b> <b>Med diet group:</b> Significant decrease in waist to hip ratio from baseline (0.91± 0.08 cm) and end of intervention (0.89± 0.08 cm) ( <i>p</i> < 0.001) (mean change: 0.02 cm) Effect size: N/A	Mean ± SD
de la Puebla <i>et al.</i> , 2003 Spain	34 hypercholesterolemic males 18–63 years, without chronic disease	Med-type diet n = 17	Subjects followed high SFA-diet for four week run-in period then allocated to one of the two groups. Twenty menus were prepared using the most common foodstuffs and administered on a rotational basis. Meals provided. / 4 weeks	Dietary composition included: 47% carbohydrates and 38% fat (<10% SFA, 22% MUFA, 75% of which provided EVOO and 6% PUFA). High in vegetables and nuts and EVOO used to cook the meals, dress the salads and put on toast.	Carbohydrate-rich diet n = 17	To determine whether body composition is modified by the isocaloric substitution of a SFA-rich diet by a MUFA-rich (Mediterranean) diet or a CHO-rich diet in overweight subjects with hypercholesterolemia.	Waist-to-hip ratio	<b>Waist-hip ratio Med diet group (NS)</b> No change in waist-hip ratio from end of run- in (0.98) to end of intervention (0.98) ( <i>p</i> > 0.05) <b>CHO-rich diet (NS)</b> Small decrease in waist-hip ratio from end of run in period to (0.98) to end of intervention (0.97) (mean change: decrease 0.01) ( <i>p</i> > 0.05) No differences between groups ( <i>p</i> > 0.05) (effect size: NA as no SDs reported)	Mean
Ehlayany <i>et al.</i> , 2010 Israel	259 men and women, 30– 65 years, BMI 27–34 kg/m <sup>2</sup> , T2DM within 1–10 years.	Traditional Med diet, n = 89 Low carbohydrate Med diet, n = 85	Prior to randomization, participants entered a 2-week maintenance period. The same dietitian followed up patients every 2 weeks for 1 year. All dietitians had a strict protocol for the 24 scheduled meetings. / 12 months	Traditional Med diet: 50% CHO, fiber 30 g, 30% fats (10% MUFA, 12% PUFA, 7% SFA), 20% protein Low-carb Med diet: 35% CHO, 30 g fiber, 45% fat (23% MUFA, 15% PUFA, 7% SFA), 20% protein	American Diabetes Association diet, n = 85	To determine the effectiveness of a low-carbohydrate Med diet, traditional Med diet, and the 2003 American Diabetes Association diet on health parameters.	Waist circumference	<b>Waist circumference: Traditional Med diet group</b> Significant decrease from baseline (110.9 ± 8.9 cm) to end of intervention (101.6 ± 8.0 cm) (mean change: decrease 9.3 cm) ( <i>p</i> < 0.001). <b>Low carbohydrate Med diet group:</b> Significantly decrease from baseline (112.6 ± 9.7 cm) to end of intervention (102.2 ± 10.2 cm) (mean change: decrease 10.4 cm) ( <i>p</i> < 0.01). <b>American Diabetes diet (control) (NS)</b> Decrease in waist circumference from baseline (113.1 ± 9.7 cm) to end of intervention (104.0 ± 10.2 cm) (mean change: decrease 9.1 cm), ( <i>p</i> > 0.05). No significant difference between groups after the 12-month intervention period ( <i>p</i> = 0.388) (effect size for traditional Med diet vs control: 0.26; effect size for low- carbohydrate Med Diet vs control: 0.18).	Mean ± SD
Esposito <i>et al.</i> , 2004 Italy	180 sedentary men and women with metabolic syndrome without CVD	Med-style diet, n = 90	Education in reducing calories, personal goal-setting, and self- monitoring using food diaries in small-group sessions with Nutritionist monthly the first year and bimonthly thereafter. Behavioral and psychological counseling offered. / 24 months	Dietary composition included 50% to 60% CHO, 15% to 20% protein; < 30% fats (<10% SFA) and <300 mg cholesterol. Daily consumption 250 to 300 g fruits, 125 to 150 g vegetables, 25 to 50 g walnuts, 400 g of whole grains (legumes, rice, maize, and wheat) and increase olive oil.	Prudent diet, n = 90	To assess the effect of a Mediterranean- style diet on endothelial function and vascular inflammatory markers in patients with the metabolic syndrome	Waist circumference	<b>Waist circumference: Med diet group</b> Significant decrease from baseline (92 ± 9 cm) to end of intervention (90 ± 8 cm) (mean change: decrease 2 cm) ( <i>p</i> = 0.01). <b>Prudent (control) (NS)</b> No change from baseline (93 ± 10 cm) to end of intervention (93 ± 10 cm) (mean change: 0 cm) ( <i>p</i> < 0.74). Significant difference between groups after the 24-month intervention period ( <i>p</i> = 0.01) (effect size for Med diet vs control: 0.33)	Mean ± SD
Esposito <i>et al.</i> , 2009 Italy	215 newly diagnosed T2DM, overweight men and women, 30–75 years, BMI > 25 kg/m <sup>2</sup>	Low carbohydrate Med diet n = 108	Nutritionists and Dietitians gave dietary advice to participants in both groups in monthly sessions in the first years and bimonthly sessions thereafter. / 4 years	Vegetables and whole grains. Reduce red meat and replace with poultry and fish. 30–50 g of olive oil. Energy intake was restricted to 1500 kcal/d (women) and 1800 kcal/d (men)	Low-fat diet n = 107	To compare the effects of a low- carbohydrate Med diet or low-fat diet on the need for drug therapy in newly diagnosed T2DM patients	Waist circumference	<b>Waist circumference (1-year post intervention) Med diet group</b> Significant decrease –4.8(3.0) cm in waist circumference ( <i>p</i> < 0.05) <b>Low-fat (control)</b> (NS) decrease –3.5 (2.8) cm in waist circumference ( <i>p</i> > 0.05). → No significant differences between Med Diet and Control after 1-year post intervention ( <i>p</i> > 0.05) <b>Waist circumference (4-years post intervention) Med diet group (NS)</b> decrease –3(1.7) cm in waist circumference ( <i>p</i> > 0.05) <b>Low-fat (control)</b> (NS) decrease –2.6(2.0) cm in waist circumference ( <i>p</i> > 0.05) No significant difference between Med Diet and Control 4-year post intervention ( <i>p</i> > 0.05) (effect size: N/A)	Mean change (95% CI)

(Continued on next page)

Table 1. Characteristics and results of Mediterranean Diet interventions. (Continued)

Author, year Country	Population, eligibility criteria	Intervention, sample size	Intensity, frequency, delivery/follow-up length	Details of diet intervention, dietary components	Comparison group, sample size	Primary aim	Relevant outcomes	Results	Method of presenting results
Estruch <i>et al.</i> , 2016 Spain	3985 high-cardiovascular risk men and women, 55–80 years, BMI >25 kg/m <sup>2</sup> , have T2DM or 3 CV risk factors, no CVD at baseline.	Med diet enriched with EVOO, n = 1501 Med diet enriched with mixed nuts, n = 1241	Personalized advice was given to participants in both Med Diet groups. Dietitians gave individual and group training sessions to provide information on typical Mediterranean foods, seasonal shopping lists, meal plans and recipes / 5 years	Abundant olive oil, >2–3 vegetables and fresh fruits servings, >3 weekly serving of fish or seafood (at least one serving of fatty fish), >1 weekly serving of nuts or seeds, select white meats instead of red meats. Cook regularly with tomato, garlic and onion. Limit intake of cream, butter, cold meat, carbonated and/or sugared beverages, and pastries. Red wine consumed with meals (150 ml for males and 100 ml for females).	Low-fat diet n = 1243	To assess long-term changes in body weight and waist circumference in the PREDIMED trial.	Waist circumference	<b>Waist circumference (1-year post intervention) Med diet with EVOO:</b> Significant decrease in waist circumference, −0.659 (−0.898 to −0.419 cm) ( <i>p</i> < 0.05). <b>Med diet with nuts:</b> Significant decrease in waist circumference, −0.406 (−0.655 to −0.157 cm) ( <i>p</i> < 0.05). <b>Low-fat (control)</b> (NS) Decrease in waist circumference, −0.447 (−0.729 to −0.166 cm) ( <i>p</i> > 0.05). <b>Waist circumference (5-years post intervention) Med diet with EVOO Small</b> significant increase in waist circumference, 0.851 (0.427 to 1.275) cm, ( <i>p</i> < 0.05). <b>Med diet with nuts:</b> (NS, <sup>1</sup> ) Increase in waist circumference, 0.372 (−0.123 to 0.868) cm, ( <i>p</i> > 0.05). <b>Low-fat (control):</b> (NS) Increase in waist circumference, 1.198 (0.677 to 1.719) cm, ( <i>p</i> > 0.05). No significant difference between the three groups after 1-year. Significant difference between Med diet + EVOO and control diet ( <i>p</i> = 0.048) and Med diet + nuts and control diet ( <i>p</i> = 0.006) 5-years post intervention for change in waist circumference. (effect size: N/A).	Mean change (95% CI)
Fernández <i>et al.</i> , 2012 Spain	40 men and women with Metabolic Syndrome, 50– 60 years.	Hypocaloric Med diet n = 24	All participants were provided with information about the Med Diet, all were counseled on food groups and specific dietary pattern items. Participants were asked to follow daily and weekly food plans. / 12 weeks	Daily consumption of olive oil, red wine, whole-wheat grains, low-fat dairy products, salads, mixed fruits and whole raw almonds. Elimination of deep-fried foods, processed meats, confectionary, soft drinks, pies and sugars.	Hypocaloric Med diet with high intensity exercise (data not reported) n = 21	To investigate the effect of a hypocaloric Med diet alone, or combined with training, on CV risk factors in sedentary adults.	Waist circumference	<b>Waist circumference Med diet group (no exercise)</b> Significant decrease in waist circumference from baseline (114.0 ± 2.56 cm) to end of intervention (110.69 ± 2.71) (mean change: decrease 4 cm) ( <i>p</i> < 0.05) Effect size: N/A	Mean change ± SD
Jones <i>et al.</i> , 2011 USA	89 women, 20–75 years, BMI 25– 45 kg/m <sup>2</sup> ; met two of the four criteria for Metabolic Syndrome.	Med diet n = 44	Participants consumed a modified Med diet and came on-site for a baseline visit and returned at weeks 2, 4, 6, 8, 10 and 12 weeks. / 12 weeks	Emphasis on intake of grains, fish and lean meats, 1 serving/day of grains, 1 serving/ day of alcohol, Natural and artificial sweeteners excluded from the diet.	Med diet plus medical food beverage (data not reported) n = 45	To evaluate the impact of a Med-style, low glycaemic (GI) index diet on Metabolic Syndrome characteristics	Waist circumference	<b>Waist circumference Med diet group:</b> (NS) Decrease in waist circumference from baseline (107.9 ± 11.7 cm) to end of intervention (101.4 ± 12.3 cm) (mean change: decrease 6.5 cm) ( <i>p</i> > 0.05); Effect size: N/A	Mean ± SD
Kolomvoutsou <i>et al.</i> , 2013 Greece	82 men and women with abdominal obesity, waist circumference > 102 cm for men; > 88 cm for women.	Med diet n = 46	Participants familiarized with meal plan at first study appointment with a dietitian. Participants were required to return empty food packets and meet with the dietitian weekly. / 8 weeks	Consumption of wholegrains, 2–3 portions of low-fat dairy products, 2 salads a day (one should contain ≥1 tomato), ≥3 fruits, 5 mL of olive oil based margarine / EVOO, 6 whole raw almonds, 250 mL red wine ≥1 portion of fish, 1 portion of red meat.	Control diet with brief Med Diet counseling, n = 44	To assess the influence of a Med-type diet on total dietary antioxidant intake and plasma total antioxidant capacity.	Waist circumference	<b>Waist circumference Med diet group</b> Significant decrease in waist circumference from baseline (106.1 ± 9.1) cm to end of intervention (103.9 ± 9.3 cm) (mean change: decrease 2.2 cm) ( <i>p</i> < 0.001). <b>Control group</b> Significant decrease from baseline (106.1 ± 9.5) to end of intervention (105.7 ± 10.2) (mean change: decrease 0.4 cm) ( <i>p</i> = 0.007). No significant difference between the groups, ( <i>p</i> = 0.34) (effect size: 0.18).	Mean ± SD
Lindeberg <i>et al.</i> , 2007 Sweden	29 males with ischemic heart disease (IHD), waist circumference > 94 cm, excluded diabetics on hypoglycemic agents	Med-like diet, n = 14	During two 1 hour sessions were given written dietary advice and food recipes with use of a dietary questionnaire for nutrition counseling. Med-like diet considered standard care diet. / 12 weeks	Based on whole-grain cereals, low-fat dairy products, potatoes, legumes, vegetables, fruits, fatty fish and refined fats rich in MUFAs and alpha-linolenic acid	Paleolithic diet n = 15	The effect of a Paleolithic diet model on glucose tolerance and post challenge insulin response in glucose- intolerant IHD patients compared with Mediterranean-like diet.	Waist circumference	<b>Waist circumference Med diet group</b> Significant decrease in waist circumference from baseline (105.8 ± 7.6) cm to end of intervention (100.2 ± 7.7 cm) (mean change: decrease 5.6 cm; 95% CI: −7.2 to −3.9) ( <i>p</i> < 0.001). <b>Paleolithic diet</b> Significant decrease in waist circumference from baseline (106.6 ± 8.0) cm to end of intervention (103.6 ± 8.6 cm) (mean change: decrease 2.9 cm; 95% CI: −4.8 to −1.1) ( <i>p</i> = 0.004). Significant difference between the groups, ( <i>p</i> = 0.03) (effect size of Paleolithic diet compared to Med diet: 0.42).	Mean change (95% CI)

McManus <i>et al.</i> , 2001 USA	101 overweight men and women 18–70 years, BMI 26.5–46 kg/m <sup>2</sup> without chronic disease	Moderate fat Med-style diet <i>Baseline</i> <i>n</i> = 50	Dietitian delivered weekly group education for 1 hour. Meal plan developed, sample menus given. / 18 months	Limit daily energy intake to 1200 kcal for women and 1500 kcal for men with 35% as fat. Increase vegetables, nuts and olive oil.	Low-fat diet <i>Baseline</i> <i>n</i> = 51	To evaluate a moderate fat Mediterranean based diet compared to a standard low-fat diet for weight loss when both controlled for energy	Waist circumference Waist-hip ratio	<b>Waist circumference</b> Med diet group (of <i>n</i> = 31 at 18 months). Significant decrease in waist circumference, $-6.9 \pm 9.1$ cm ( $p < 0.001$ ) <b>Low-fat</b> (control): (of <i>n</i> = 30 at 18 months) (NS) Increase in waist circumference, $2.6 \pm 10.5$ cm ( $p > 0.05$ ) Significant difference between groups after the 18-month intervention period in participants available for measurement ( $p < 0.01$ ) (effect size: NA). <b>Waist-hip ratio</b> Med diet group (of <i>n</i> = 24 at 18 months) Significant decrease in waist-hip ratio, $-0.02 \pm 0.05$ ( $p < 0.05$ ) <b>Low-fat</b> (control) (of <i>n</i> = 10 at 18 months) (NS) No change in waist-hip ratio, $0 \pm 0.06$ ( $p > 0.05$ ) Between group difference not reported.	Mean change $\pm$ SD
Richard <i>et al.</i> , 2013 Canada	26 non-smoking males, 18–65 years, without previous history of CVD or T2DM.	Isocaloric Med diet, <i>n</i> = 26 Hypocaloric Med diet, <i>n</i> = 26	Subject's diet was first a standardized North American Control diet that they consumed for 5 weeks under isocaloric, weight-maintaining conditions. Participants then consumed the Med diet for 5 weeks under isocaloric, weight-maintaining conditions. / 35 weeks	Energy kcal/d 3169.0 $\pm$ 443.4 Lipids g/day 112.7 $\pm$ 15.8 (32%) (SFA g/day (%) 23.7 $\pm$ 3.3 (6.7%), MUFA, g/day (5) 63.8 $\pm$ 8.9 (18.1%), PUFA 16.7 $\pm$ 2.3 (4.7%) Carbohydrates g/day 396.4 $\pm$ 55.5 (50%), Protein g/day 134.7 $\pm$ 18.8 (17%) Alcohol, g/day 22.7 $\pm$ 3.2 (5%).	North American diet <i>n</i> = 26	To examine the impact of the Med diet consumed in controlled feeding conditions in the absence of weight-loss on markers of inflammation in men with Metabolic Syndrome.	Waist circumference	<b>Waist circumference</b> Isocaloric Med diet group (NS, <sup>1</sup> ) decrease in waist circumference from end of control diet (111.5 $\pm$ 12.0 cm) to end of intervention (110.9 $\pm$ 11.1 cm) (mean change: decrease 0.6 cm) ( $p > 0.05$ ). <b>Hypocaloric Med diet group</b> Significant decrease in waist circumference from end of Isocaloric Med diet (110.9 $\pm$ 11.1 cm) to end of Hypocaloric Med Diet (104.3 $\pm$ 13.4 cm) (mean change: 6.6 cm) ( $p < 0.05$ ). <b>Control diet</b> End measure reported only and compared to end of Isocaloric Med diet. (effect size: 0.05).	Mean $\pm$ SD
Ryan <i>et al.</i> , 2013 Australia	12 non-diabetic men and women, Med diet group <i>n</i> = 12	Med diet group <i>n</i> = 12	Participants were required to crossover after a 6-week wash out period. There was an hour of dietary instruction from a dietitian who provided recipes and a 2-weekly meal plan. / 6 weeks	Recreation of the traditional Cretan Med diet: olives, dried fruit, nuts, Greek yoghurt, fish and extra virgin olive oil.	Australian National Heart Foundation diet, <i>n</i> = 12	To examine the effect of Med diet on steatosis and insulin sensitivity.	Waist circumference	<b>Waist circumference</b> Med diet group (NS, <sup>1</sup> ) Small decrease in waist circumference from baseline (104.8 $\pm$ 9.0 cm) to end of intervention (102.7 $\pm$ 6.0 cm) (mean change: decrease 2.1 cm) ( $p > 0.05$ ) <b>Australian National Heart Foundation group</b> (NS) Small decrease in waist circumference from baseline (103.7 $\pm$ 8.6 cm) to end of intervention (102.2 $\pm$ 8.2 cm) (mean change: decrease 1.5 cm) ( $p > 0.05$ ). No significant differences between the groups after the intervention period ( $p > 0.05$ ) (effect size: 0.07).	Mean $\pm$ SD
Schiavo <i>et al.</i> , 2015 Italy	37 obese males, 25–65 years, BMI $> 40$ kg/m <sup>2</sup>	Protein-enriched Med diet <i>n</i> = 37	A week prior to beginning the intervention, each candidate was counseled individually about the dietary intervention. Each participant was provided with 4 meal plans that they were required to follow for the duration of the intervention / 8 weeks	Included fruits and vegetables, no bread or pastries; pasta (whole or multigrain, made from any non-refined grains) dairy products (reduced fat), herbs and spices, meat and fish (with strong emphasis on white meats).	No comparison group	To evaluate the effects of 8-week protein-enriched Med diet on weight, liver size, visceral fat, fat mass and fat-free mass in obese patients.	A scale measure of visceral fat	<b>Visceral fat Med diet group</b> Significant decrease in the scale measure of visceral fat from baseline (9.2 $\pm$ 0.9) to end of intervention (6.7 $\pm$ 1.2) ( $p < 0.01$ ) (mean change: 2.52) (effect size: N/A).	Mean $\pm$ SD
Shai <i>et al.</i> , Israel	322 moderately obese men and women, 40–65 years, BMI $> 27$ kg/m <sup>2</sup> , or presence of T2DM or CHO.	Traditional Med diet, <i>n</i> = 109	Dietary groups and subgroups were made. Subgroups met with dietitian in weeks 1, 3, 5 and 7 and at 6-week intervals. Dietary strategies differed. / 2 years	Rich in vegetables; low in red meat, with poultry and fish replacing beef and lamb. The diet was restricted to 1500 kcal per day for women and 1800 kcal for men.	Low-fat diet <i>n</i> = 104 Low-carbohydrate diet <i>n</i> = 109	To compare the effectiveness and safety of three nutritional protocols.	Waist circumference	<b>Waist circumference</b> (NS) Mean decrease in the traditional Mediterranean diet group (3.5 $\pm$ 5.1 cm), the low-carbohydrate groups (2.8 $\pm$ 4.3 cm) and the low-fat Control group (2.8 $\pm$ 4.3 cm). No significant difference between the groups across the 8-week intervention period ( $p = 0.33$ ) (effect size between Med diet and low-fat: 0.15; Med diet and low carbohydrate diet: 0.14).	Mean $\pm$ SD

\*Statistically significant; NS: not statistically significant;

<sup>1</sup>results greater in Med diet arm compared to Control.

Abbreviations: BMI: body mass index, Med diet: Mediterranean diet, T2DM: type II diabetes mellitus, CVD: cardiovascular disease, CHD: coronary heart disease, EVOO: extra virgin olive oil, CV: cardiovascular, CI: confidence intervals, CHO: carbohydrate, SFA: saturated fatty acid, MUFA, monounsaturated fatty acid, SD: standard deviation, SEM: standard error of the mean and PUFA: polyunsaturated fatty acid.

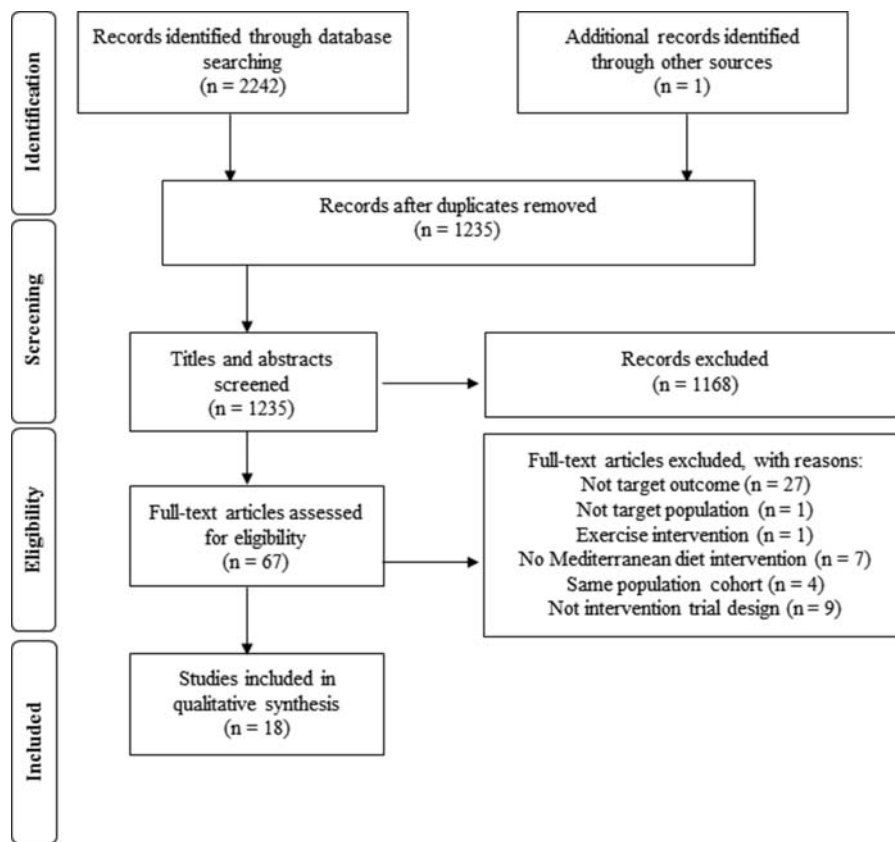


Table 2. Quality criteria assessment for each included study.

Author, Year	1.0 Clear research question	2.0 Selection of subjects free from bias	3.0 Study groups comparable	4.0 Described handling withdrawals	5.0 Blinding adequately described	6.0 Intervention adequately described	7.0 Outcome measures valid and reliable	8.0 Statistical analyses appropriate	9.0 Conclusions valid	10.0 Bias due to funding or sponsorship unlikely	TOTAL (out of 10) Rating (+, -, $\phi$ )
Bedard <i>et al.</i> , 2012	Y	Y	N	Y	N	Y	Y	?	Y	Y	(7/10) $\phi$
Bos <i>et al.</i> , 2010	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9/10 +
Buscemi <i>et al.</i> , 2009	Y	Y	N	Y	N*	Y	Y	N	Y	Y	(7/10) $\phi$
Corbalán <i>et al.</i> , 2009	Y	Y	N	Y	N	Y	Y	N	Y	Y	(7/10) $\phi$
de la Puebla <i>et al.</i> , 2003	Y	Y	?	N	N	?	Y	?	Y	Y	(5/10) $\phi$
Elhayany <i>et al.</i> , 2010	Y	Y	Y	Y	N	Y	Y	N	Y	?	(7/10) $\phi$
Esposito <i>et al.</i> , 2004	Y	Y	Y	Y	N*	Y	Y	Y	Y	Y	(9/10) +
Esposito <i>et al.</i> , 2009	Y	Y	Y	Y	N*	Y	Y	Y	Y	Y	(9/10) +
Estruch <i>et al.</i> , 2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	(9/10) +
Fernández <i>et al.</i> , 2012	Y	Y	Y	N	N	Y	Y	N	Y	Y	(7/10) $\phi$
Jones <i>et al.</i> , 2011	Y	Y	?	N	N	Y	Y	Y	Y	Y	(7/10) $\phi$
Kolomvotsou <i>et al.</i> , 2013	Y	Y	Y	N	N	Y	Y	Y	N	Y	(7/10) $\phi$
Lindeberg <i>et al.</i> , 2007	Y	Y	Y	?	N	Y	Y	?	Y	Y	(7/10) $\phi$
McManus <i>et al.</i> , 2001	Y	N	Y	?	N	N	Y	Y	Y	Y	(6/10) $\phi$
Richard <i>et al.</i> , 2013	Y	Y	N	N	N	Y	Y	Y	?	Y	(6/10) $\phi$
Ryan <i>et al.</i> , 2013	Y	Y	Y	Y	N*	Y	Y	N	Y	Y	(8/10) +
Schiavo <i>et al.</i> , 2015	Y	Y	N	N	N	Y	Y	N	Y	Y	(6/10) $\phi$
Shai <i>et al.</i> , 2008	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	(9/10) +

Numbers in column headings correspond to Quality Criteria checklist number (as per Figure S1). Y, yes; N, no; ?, Unclear; (+), positive of high method quality with score  $\geq 8$  and yes to 2, 3, 6 and 7; ( $\phi$ ), neutral of moderate method quality with score 5 to 7 or  $\geq 8$  without yes to 2, 3, 6 and 7; (-), negative of low method quality with score  $< 5$ .

\*Blinding was used for assessment of primary outcome measure.



**Figure 1.** Flowchart illustrating the literature search and selection process. “Same population cohort” refers to three PREDIMED group preliminary studies and an earlier publication for the Kolomvotsou et al., study.

sizes ranging from 26 to 5801 participants. Length of follow-up ranged from 4 weeks to 5 years, with the most common length of follow-up 8 weeks ( $n = 5$ ) and 12 weeks ( $n = 3$ ).

All studies reported on the presence of co-morbidities such as metabolic syndrome, T2DM, high CVD risk or obesity (Table 1). Only one study targeted non-abdominally obese versus abdominally obese adults (Bedard et al., 2012). Ten studies recruited participants who were overweight or obese (Bos et al., 2010; Buscemi et al., 2009; Corbalán et al., 2009; Elhayany et al., 2010; Jones et al., 2011; Kolomvotsou et al., 2013; Lindeberg et al., 2007; McManus et al., 2001; Schiavo et al., 2015; Shai et al., 2008), four studies recruited participants with Metabolic Syndrome (Esposito et al., 2004; Fernández et al., 2012; Richard et al., 2013; Ryan et al., 2013), one study recruited participants at high risk of developing CVD (Estruch et al., 2016), one study recruited participants with diagnosed ischemic heart disease but without medicated T2DM (Lindeberg et al., 2007) and one study recruited participants with newly diagnosed T2DM (Esposito et al., 2009). Two studies each included females only (Buscemi et al., 2009; Jones et al., 2011) or males only (Richard et al., 2013; Schiavo et al., 2015). Ten studies excluded participants with T2DM (Bedard et al., 2012; Bos et al., 2010; Buscemi et al., 2009; Corbalán et al., 2009; de la Puebla et al., 2003; Fernández et al., 2012; Kolomvotsou et al., 2013; McManus et al., 2001; Richard et al., 2013; Ryan et al., 2013) and nine studies excluded participants with a history CVD (Buscemi et al., 2009; Corbalán et al., 2009; de la Puebla et al., 2003; Esposito et al., 2004; Estruch et al., 2016; Jones

et al., 2011; Kolomvotsou et al., 2013; Lindeberg et al., 2007; McManus et al., 2001).

### Mediterranean diet intervention

All studies used a whole-of-diet approach (Table 1). Eight out of the eighteen studies delivered an energy-restricted or weight-loss condition as a part of their Mediterranean diet intervention (Buscemi et al., 2009; Corbalán et al., 2009; Esposito et al., 2009; Fernández et al., 2012; McManus et al., 2001; Richard et al., 2013; Schiavo et al., 2015; Shai et al., 2008). All studies promoted increased fruit and vegetable consumption ( $n = 18$ ) and nearly all promoted increased use of olive oil ( $n = 16$ ). Other common food recommendations included increased consumption of wholegrains ( $n = 12$ ) or nuts ( $n = 8$ ), or moderate consumption of red wine ( $n = 7$ ). Delivery style differed across the Mediterranean diet interventions. These included, nutrition counseling delivered by a dietitian or nutritionist ( $n = 8$ ), structured meal plans or menus ( $n = 7$ ), or staple foods provided to participants ( $n = 4$ ). Whilst all studies employed a Mediterranean-style diet, some interventions had characteristics that were not typical of a traditional Mediterranean diet pattern. These included a protein-enriched Mediterranean diet (Schiavo et al., 2015) and prescriptions of low contribution to energy from fat ( $<30\%$ ) (Buscemi et al., 2009; Esposito et al., 2004; Schiavo et al., 2015). Three studies employed two alternative styles of Mediterranean diet interventions in their design; an

isocaloric versus hypocaloric Mediterranean diet (Richard et al., 2013), a traditional versus low carbohydrate Mediterranean diet (Elhayany et al., 2010), and a Mediterranean diet enriched with EVOO versus mixed nuts (Estruch et al., 2016).

### Control groups

Of the eighteen studies, thirteen had at least one diet-related control group (Table 1). These control groups included low fat (Elhayany et al., 2010; Esposito et al., 2009; Esposito et al., 2004; Estruch et al., 2016; McManus et al., 2001; Ryan et al., 2013; Shai et al., 2008), high fat (Bos et al., 2010), low carbohydrate (Buscemi et al., 2009; Shai et al., 2008), high carbohydrate (de la Puebla et al., 2003), standard North American (Richard et al., 2013) or Paleolithic (Lindeberg et al., 2007) diets. One study had a Mediterranean diet intervention plus an exercise intervention (Fernández et al., 2012), while another study had a Mediterranean-style diet plus a soy protein beverage (Jones et al., 2011). These two study arms were not analyzed in this literature review due to the nature of their co-interventions. The remaining three studies did not have a control group (Bedard et al., 2012; Corbalán et al., 2009; Schiavo et al., 2015).

### Risk of bias

Results of the quality assessment criteria are summarized in Table 2. Twelve studies received a neutral quality rating and were considered to be of moderate methodological quality ( $\Phi$ ), while the remaining six studies were considered to be of high methodological quality, receiving a positive rating (+). No studies received a negative (-) rating. All studies set a clear research question and all but one study (McManus et al., 2001) presented selection of subjects which was deemed to be free from bias. Seven studies failed to indicate their method of randomization or did not have a method of randomization based on study design (Buscemi et al., 2009; Corbalán et al., 2009; de la Puebla et al., 2003; Elhayany et al., 2010; Jones et al., 2011; Ryan et al., 2013; Schiavo et al., 2015). The remaining eleven studies identified their method of randomization, which was completed by a computer-based randomization method. Six studies did not indicate sufficient characteristics of withdrawals such as dropouts and loss to follow up (de la Puebla et al., 2003; Jones et al., 2011; Lindeberg et al., 2007; McManus et al., 2001; Richard et al., 2013; Schiavo et al., 2015), while the remaining studies provided details in this area. A lack of blinding of participants, assessors and data collectors was the main source of bias with no study adhering completely to the three components of this criteria. Nine studies had unclear or inappropriate statistical analyses, largely due to not performing intention-to-treat analyses, not controlling for confounding variables or failing to account for baseline differences between groups (Bedard et al., 2012; Buscemi et al., 2009; Corbalán et al., 2009; de la Puebla et al., 2003; Elhayany et al., 2010; Fernández et al., 2012; Lindeberg et al., 2007; Ryan et al., 2013; Schiavo et al., 2015). Two of these nine studies also provided insufficient detail regarding their dietary interventions and study procedure (de la Puebla et al., 2003; McManus et al., 2001). Only one study failed to mention their source of funding or if there was any conflict of interest (Elhayany et al., 2010).

### Central obesity outcomes

Table 1 provides details of all measures of central obesity for each study. The most common measure of central obesity reported was waist circumference ( $n = 16$ ). Other central obesity measurements included waist-hip ratio ( $n = 5$ ) and visceral fat ( $n = 2$ ). Three studies reported on a combination of central obesity outcomes (Bedard et al., 2012; Corbalán et al., 2009; McManus et al., 2001).

### Waist circumference

Sixteen out of eighteen studies reported on waist circumference (Table 1). Of these sixteen studies, thirteen studies reported a statistically significant change in waist circumference with a Mediterranean diet (range of mean change pre to post intervention across studies:  $-10.4$  cm to  $+0.85$  cm). Twelve of these thirteen studies reported a statistically significant decline in waist circumference (range of mean change pre to post intervention across studies:  $-10.4$  cm to  $-0.41$  cm), five of which had an energy restricted diet. The magnitude of effect among these positive studies ranged from a very small to large effect size, 0.07 to 0.78 (Cohen's  $d$ ). Four studies reported no significant effect of the diet on waist circumference (Bos et al., 2010; Jones et al., 2011; Ryan et al., 2013; Shai et al., 2008); three of these studies had a non-energy restricted diet and one employed energy restriction. Finally, one study, which reported an initial reduction at one year, had a small ( $+0.85$  cm) but statistically significant increase in waist circumference over long-term follow up of five years in its Mediterranean diet with EVOO, but not in the Mediterranean diet with mixed nuts (Estruch et al., 2016).

### Waist-hip ratio

Four of the studies which evaluated waist circumference also evaluated the effect of Mediterranean diet on waist-hip ratio (Bedard et al., 2012; Buscemi et al., 2009; Corbalán et al., 2009; McManus et al., 2001), while one study reported waist-hip ratio as its only measure of central obesity (de la Puebla et al., 2003) (Table 1). One of these studies found that the Mediterranean diet significantly reduced waist-hip ratio ( $-0.02$  cm) over 18 months ( $p < 0.01$ ) (McManus et al., 2001). The remaining three studies found no significant effect of the Mediterranean diet on waist-hip ratio, however two of these reported a small decline (Bedard et al., 2012; Buscemi et al., 2009).

### Visceral fat

Two of the thirteen studies evaluated the effect of Mediterranean diet on visceral fat (Table 1). One study used bioelectrical impedance analysis and converted visceral fat measures to a score on a scale ranging from 1 to 12 (Buscemi et al., 2009). It was not specified how the score was calculated. The other study used ultrasound to measure rectus-aorta thickness as a surrogate measure of visceral abdominal fat (Schiavo et al., 2015). Both studies found that the Mediterranean diet significantly reduced visceral fat. Buscemi and colleagues (2009) reported a significant decline in rectus-aorta thickness by 9 mm after

8 weeks ( $p = 0.001$ ). Schiavo and colleagues (2015) reported a significant decrease in visceral fat rating by an average of 2.5 after 8 weeks ( $p < 0.01$ ). The magnitude of effect compared to control group could be calculated for the study measuring rectis-aorta thickness only (Buscemi et al., 2009), which demonstrated a very large effect size of 1.9 in favor of the very low carbohydrate diet compared to Mediterranean diet.

### Energy-restricted / weight loss studies

Eight studies focused on weight loss or provided an energy-restricted Mediterranean diet intervention (Table 1). Apart from one, each of these studies reported that participants had a significant reduction in a measure of central obesity. Two studies reported a significant decrease in waist circumference alone (Corbalán et al., 2009; Fernández et al., 2012). Another study reported a significant decrease in waist circumference with Mediterranean diet and weight loss, but a non-significant decrease in waist circumference with Mediterranean diet without weight loss (Richard et al., 2013). One study reported a significant decrease in both waist circumference and waist-hip ratio (McManus et al., 2001). Another intervention reported a significant reduction in waist circumference and visceral fat, but not waist-hip ratio (Buscemi et al., 2009). One study demonstrated a significant reduction in waist circumference 1-year post intervention, however the effect was no longer significant after 4 years (Esposito et al., 2009). One study each reported a significant decrease in waist-hip ratio (Corbalán et al., 2009) and visceral fat (Schiavo et al., 2015). The final study reported no effect on waist circumference with its calorie restricted intervention (Shai et al., 2008).

### Non-energy restricted studies

Of the ten studies that did not focus on weight loss or energy-restricted intervention, six studies had a significant reduction in measures of central obesity, all of which reported a decline in waist circumference (Bedard et al., 2012; Esposito et al., 2004; Estruch et al., 2016; Jones et al., 2011; Kolomvotsou et al., 2013; Lindeberg et al., 2007) (Table 1). Despite a decline in waist circumference, one of these studies reported no effect on waist-hip ratio in abdominally obese participants (Bedard et al., 2012). This study also demonstrated no effect of the Mediterranean diet on waist circumference or waist-hip ratio in non-abdominally obese participants (Bedard et al., 2012). One study demonstrated no change in waist-hip ratio, however no measures for waist circumference were reported (de la Puebla et al., 2003). For one study, the decline in waist circumference was recorded at 1-year follow-up in participants from both of its Mediterranean diet intervention groups (supplemented with EVOO or nuts). However, at 5-year follow-up, this effect was attenuated and a small significant increase in waist circumference was seen in the Mediterranean diet group with EVOO (Estruch et al., 2016). In terms of intervention style for the studies which saw reduced central obesity without energy restriction, three studies provided both dietetic counseling and meal plans (Estruch

et al., 2016; Kolomvotsou et al., 2013; McManus et al., 2001), one had behavioral counseling with a nutritionist (Esposito et al., 2004), another a 7-day cyclic menu (Bedard et al., 2012) and the remaining study provided no dietetic support or meal plans to their participants (Lindeberg et al., 2007).

### Discussion

The aim of this systematic literature review was to synthesize the findings from existing intervention trials investigating the impact of a Mediterranean diet on central obesity. Overall, the present review of eighteen intervention trials revealed that a Mediterranean diet intervention can significantly reduce measures of central obesity as determined by waist circumference, waist-hip ratio or visceral fat. Thirteen out of 18 studies showed a reduction in central obesity measurements with Mediterranean diet intervention, with at least one time-point of follow up (4966 participants, or 96% of the Mediterranean diet group participants). The most consistent reductions were in waist circumference and visceral fat. However, it remains unclear whether the dietary pattern itself resulted in reduction in central obesity or whether the Mediterranean diet is more effective than other styles of dietary intervention as a number of the effective interventions were hypocaloric ( $n = 7$ ) and only three studies showed a statistically significant favorable effect of the diet relative to a control diet. Where a control or comparator group was employed, interventions generated an effect size for central obesity outcomes between 0.05 and 1.9, which indicates a small effect size to a very large effect size, highlighting the broad range of results identified in this review.

Whilst thirteen studies reported a significant change in measures of central obesity, there was inconsistency in some of the findings and characteristics of these studies. Two studies reported a significant reduction in waist circumference with Mediterranean diet but not waist-hip ratio (Bedard et al., 2012; Buscemi et al., 2009). This could have been due to a mirrored reduction in hip circumference or the smaller scale of this measure. Each of the four studies that did not employ a control or comparator diet group reported a significant reduction in central obesity measure with the Mediterranean diet. The absence of a control group makes it difficult to conclude that the improvement in central obesity was due to the diet rather than potential confounding variables, or more effective than standard care diets. However, none of the studies that employed a control group reported a statistically significant improvement in central obesity measure relative to the Mediterranean diet group.

The study with the largest cohort of participants, a sub study of the PREDIMED intervention trial, reported a small increase in waist circumference at long-term follow up of five years (Estruch et al., 2016). This study employed two alternative *ad libitum* Mediterranean diets supplemented with EVOO or nuts with no energy restriction. It may be that over a longer time frame, the putative beneficial effect of olive oil or nuts on CVD in reducing waist circumference are negated by additional calories ingested. However, the available scientific evidence suggests that olive oil and nut consumption in the context of a Mediterranean dietary pattern is not related to weight gain, and this is



explained by intrinsic biological mechanisms (Bes-Rastrollo et al., 2006; Martinez-Gonzalez and Bes-Rastrollo, 2011). Moreover, this small increase in waist circumference may not necessarily be associated with an increase in deposition of visceral fat. MUFAs are known to deposit as subcutaneous fat (Calder et al., 1992), which is not associated with increased cardiometabolic disease risk compared to visceral fat (Haffner, 2007; Prasad et al., 2011). Finally, it is important to note that both the Mediterranean diet groups had a statistically significant lower increase in waist circumference compared to the low fat diet control group.

Of those studies with successful outcomes, it was evident that no one specific Mediterranean diet style resulted in a change to central obesity measurements. There was a range of Mediterranean dietary patterns, including both energy-restricted and *ad libitum* approaches that resulted in a reduction to central obesity measures. Despite the different styles of Mediterranean diet intervention employed, commonalities between interventions included dietary changes such as; increasing MUFA consumption through EVOO, and increasing vegetables, fruit, fish, nuts and legumes. These foods are key components of a traditional Mediterranean diet (Trichopoulou and Lagiou, 1997). However, some of the Mediterranean diets did employ recommendations for macronutrients that were not typical of the traditional pattern, such as low carbohydrate or protein-enriched. Nine of the thirteen studies which reported an improvement in central obesity were conducted in Mediterranean populations and four of the five studies which had no improvement were in non-Mediterranean populations. Hence, the positive results could in part be reflective of ease of dietary compliance in countries where the diet is their traditional cuisine.

Seven out of the thirteen trials that reported a significant reduction in a central obesity measure, employed a weight-loss or energy-restricted Mediterranean diet. This makes it difficult to determine whether the benefits in reducing central obesity resulted from the diet *per se* or due to energy restriction. However, six of the ten studies that did not have a weight-loss or energy-restricted focus also reported reductions in waist circumference. It is plausible to suggest that these significant reductions in central obesity were a result of the implementation of the Mediterranean dietary pattern, demonstrating its potential effect in reducing central obesity in the absence of weight loss. The trials with interventions which produced reductions in central obesity measurements shared similar participant characteristics, such as being overweight/obese or at high CVD risk, highlighting the homogeneity of these study participants.

The findings from the present review imply that a Mediterranean diet could be used as a treatment strategy to reduce central obesity. These findings support earlier epidemiological studies that have shown a Mediterranean diet can reverse or reduce central obesity (Funtikova et al., 2014; Romaguera et al., 2009). Epidemiological evidence supports that the incidence of a range of cardiometabolic risk factors is reduced significantly with waist circumference reductions of  $\geq 3$  cm (Balkau, Picard, Vol, Fezeu, and Eschwege, 2007). Therefore, mean changes for waist circumference for most studies included in this review are likely to represent clinically significant reductions. Notably, one

non-energy restricted Mediterranean diet intervention reported a mean 9.3 cm decline in waist circumference with 12-month intervention. Due to its higher fat content, particularly in comparison to prudent diet patterns, there remains a stigma attached to the Mediterranean diet pattern: that it will lead to increased weight or adiposity (Mozaffarian, 2016). This review suggests that the opposite is true, that a Mediterranean diet high in fat, specifically MUFAs, is more likely to lead to a reduction in central adiposity. This review adds to the existing literature that supports a Mediterranean diet lead to modest weight loss (Esposito et al., 2011; Mancini et al., 2016) and a reduction in waist circumference (Kastorini et al., 2011).

The reduction in central obesity, outside of energy restriction, could be related to the high content of MUFAs in the Mediterranean diet. Other studies have reported changes to anthropometry, weight, fat mass and specifically waist circumference with a high MUFA diet (Jones, Ridgen, Phang, and Birmingham, 1992; Piers, Walker, Stoney, Soares, and O'Dea, 2003; Soares, Cummings, Mamo, Kenrick, and Piers, 2004). Changes to these parameters could be explained by the higher post-prandial fat oxidation rate and higher thermic effect following high MUFA meals (Piers et al., 2003). Furthermore, it appears that certain types of fats are favorably oxidized, such as oleic acid (the predominant MUFA in olive oil), while others are favorably stored, such as saturated fats (Clandinin et al., 1995; Jones et al., 1992; Soares et al., 2004). Therefore, a Mediterranean diet that is high in MUFAs is more likely to be oxidized and utilized for energy as opposed to being stored as fat. This was however not completely supported by the PREDIMED study which, despite a reduction in weight, saw a small increase in waist circumference with increased intake of EVOO and nuts at long-term follow up (Estruch et al., 2016).

Improvement in central obesity may in part explain other known health benefits of a Mediterranean diet. It is well established that greater adherence to a Mediterranean diet can significantly reduce the risk of overall mortality, mortality from CVD, incidence of T2DM, and incidence of and mortality from cancer (Sofi, Abbate, Gensini, and Casini, 2010). Since central obesity is a known risk factor for each of these health outcomes, it is likely that an improvement in or prevention of central obesity is part of the mechanism by which the Mediterranean diet reduces chronic disease and mortality risk. Furthermore, central obesity leads to chronic low-grade inflammation (Samaras, Botelho, Chisholm, and Lord, 2010) which is an established risk factor for metabolic diseases including T2DM (Esser, Legrand-Poels, Piette, Scheen, and Paquot, 2014) and CVD (Hansson, 2005). Indeed, there is already strong evidence to indicate that a low-grade inflammatory state can be counteracted with the implementation of the Mediterranean diet (Chrysohooou, Panagiotakos, Pitsavos, Das, and Stefanadis, 2004; Esposito et al., 2004; Salas-Salvado et al., 2007; Urpi-Sarda et al., 2012). This impact on inflammation has been linked to both the high MUFA (Kennedy, Martinez, Chuang, LaPoint, and McIntosh, 2009; Milanski et al., 2009) and polyphenol content (Medina-Remón et al., 2016) of the diet. It must be noted that the cardioprotective benefits of a Mediterranean diet may not always be mediated via a reduction in central adiposity. As noted above, there was no reduction in waist



circumference in a subset of the PREDIMED study in the Mediterranean diet arms, despite the impressive 30% relative risk reduction in CVD events on these diets compared to control (Estruch et al., 2013).

To our knowledge, this is the first systematic literature review to investigate specifically the effect of a Mediterranean diet on central obesity. A strength of the review is that it only included intervention trials and no study received a low quality rating for methodological approach. The search strategy applied was comprehensive and the methods of the study selection and inclusion criteria were determined *a priori*, before commencement of the review. The combined sample size of the study populations is sufficient to determine if a change in central obesity is a true effect. However, due to the heterogeneity of the diet interventions and control groups, it is difficult to determine if this was the true effect of a traditional Mediterranean diet. Furthermore, not all intervention trials employed randomization, nor did all of the studies have a control or comparison group.

Some studies did not provide thorough information regarding techniques used to achieve dietary compliance (e.g. administering adherence scores via validated Mediterranean dietary score or validated food frequency questionnaire). Of those studies that employed techniques to measure adherence of dietary intake and dietary compliance, most studies used validated tools. The majority of studies included either 3- to 7-day food diaries ( $n = 7$ ), validated food frequency questionnaires ( $n = 4$ ) and/or a Mediterranean dietary adherence score ( $n = 4$ ). 3- and 7-day food records are considered to be a 'gold-standard' measurements of dietary assessment in an overweight/obese cohort (Johnson, 2002). Nonetheless, it is recognized that methods which rely on self-reported measures can be subject to measurement errors, which can result in bias. One way to combat this is by inclusion of nutritional biomarkers from serum or urine samples, which provide an objective measure of dietary intake (Bach-Faig, Geleva, Carrasco, Ribas-Barba, and Serra-Majem, 2006). Unfortunately, nutritional biomarkers are not commonly used due to their cost. One study in the present review reported such biochemical data with measurements of fatty acids in cholesterol esters at the end of the dietary interventions by means of gas chromatography (de la Puebla et al., 2003).

It is also recognized that the use of anthropometrical techniques to measure central obesity is not considered to be a gold-standard measurement. These techniques can lead to measurement errors and increase the risk for bias. Additionally, waist circumference does not differentiate between visceral and subcutaneous fat. Ideally, the use of imaging techniques which have been validated to measure visceral adiposity such as magnetic resonance imaging, computerized tomography, ultrasound or dual-energy x-ray absorptiometry would be encouraged in a research setting. Only one study in this review used a validated imaging technique with ultrasound measurement and one study utilized bioelectrical impedance analysis to estimate visceral fat.

Some methodological limitations of the reviewed studies impact the strength of the present review. Nine of the 13 studies which demonstrated a significant improvement in central obesity with Mediterranean diet were conducted in a

Mediterranean country. Consequently, the findings from this review may not be generalizable to a non-Mediterranean population group. Additionally, a small number of studies failed to identify their source of funding or declare if any conflict of interest existed. Hence, there is the possibility for a source of funding or publication bias in those studies.

## Conclusion

This review evaluated whether the Mediterranean diet could be used as a dietary approach to reduce central obesity. Despite the high level of heterogeneity between the Mediterranean diet interventions, the present review identified that a Mediterranean-type diet has the potential to reduce different measures of central obesity. It cannot be confirmed however that this dietary pattern is superior to alternative diets for improvement in central obesity. Although the findings of the present review are encouraging, future research in this area is warranted. In particular, future studies should focus on randomized control trials evaluating the impact of a traditional Mediterranean dietary pattern versus standard care diets in non-Mediterranean populations and utilize objective measures of dietary compliance. Nonetheless, recommending a Mediterranean-type diet could be incorporated in treatment strategies for reducing central obesity considering there are few to negligible risks involved with consumption of this healthy eating pattern.

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## Conflict of interest

There are no conflicts of interest to report.

## Disclosures

The authors have no disclosures to make.

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