NUTRITION RESEARCH 36 (2016) 391–401

Available online at www.sciencedirect.com

ScienceDirect

www.nrjournal.com

Review Article

Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis

E.P. Neale[a,*], M.J. Batterham[b], L.C. Tapsell[a]

[a] Smart Foods Centre, School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, NSW, Australia, 2522
[b] Statistical Consulting Service, School of Mathematics and Applied Statistics, Faculty of Engineering and Information Sciences, University of Wollongong, NSW, Australia, 2522

ARTICLE INFO

Article history:
Received 17 November 2015
Revised 17 February 2016
Accepted 19 February 2016

Keywords:
Meta-analysis
Mediterranean diet
Biomarkers
C-reactive protein
Adiponectin

ABSTRACT

Consumption of healthy dietary patterns has been associated with reduced risk of cardiovascular disease and metabolic syndrome. Dietary intervention targets disease prevention, so studies increasingly use biomarkers of underlying inflammation and metabolic syndrome progression to examine the diet-health relationship. The extent to which these biomarkers contribute to the body of evidence on healthy dietary patterns is unknown. The aim of this meta-analysis was to determine the effect of healthy dietary patterns on biomarkers associated with adiposity, insulin resistance, and inflammation in adults. A systematic search of Scopus, PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (all years to April 2015) was conducted. Inclusion criteria were randomized controlled trials; effects of dietary patterns assessed on C-reactive protein (CRP), total adiponectin, high-molecular-weight adiponectin, tumor necrosis factor–α, adiponectin:leptin, resistin, or retinol binding protein 4. Random effects meta-analyses were conducted to assess the weighted mean differences in change or final mean values for each outcome. Seventeen studies were included in the review. These reflected research on dietary patterns associated with the Mediterranean diet, Nordic diet, Tibetan diet, and the Dietary Approaches to Stop Hypertension diet. Consumption of a healthy dietary pattern was associated with significant reductions in CRP (weighted mean difference, –0.75 [–1.16, –0.35]; $P = .0003$). Non-significant changes were found for all other biomarkers. This analysis found evidence for favorable effects of healthy dietary patterns on CRP, with limited evidence for other biomarkers. Future research should include additional randomized controlled trials incorporating a greater range of dietary patterns and biomarkers.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; HMW, high molecular weight; MetS, metabolic syndrome; RCT, randomized controlled trial; RBP4, retinol binding protein 4; TNF-α, tumor necrosis factor-alpha; WMD, weighted mean difference.

* *Corresponding author at:* Research Fellow, School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, NSW, Australia, 2522. Tel.: +61 242215961, +61 242214844.
E-mail address: elizan@uow.edu.au (E.P. Neale).

http://dx.doi.org/10.1016/j.nutres.2016.02.009
0271-5317/

1. Introduction

The study of the diet-disease relationship has seen a major shift in focus from single nutrients to that of healthy dietary patterns [1]. The shift recognizes that individual foods or nutrients are not eaten in isolation, and there are potential synergistic effects of multiple components within the diet [2]. This shift is reflected in dietary guidance, with recent reviews by the 2015 US Dietary Guidelines Advisory Committee identifying healthy cuisine-based dietary patterns, such as the Mediterranean diet, to be associated with reduced risk of chronic disease [3]. Likewise, disease risk is being examined in a more integrated fashion. For example, the metabolic syndrome (MetS) represents a cluster of risk factors including abdominal obesity, raised blood pressure, insulin resistance, and dyslipidemia [4]. The known relationship between MetS, and cardiovascular disease and type 2 diabetes [5] highlights the importance of understanding the effects of dietary patterns on disease progression. Of particular relevance is the state of chronic, low-grade inflammation indicative of ongoing pathology, which underpins the MetS (Fig. 1).

A suite of biomarkers has emerged in the literature to indicate changes in this underlying low grade inflammation which characterizes the components of the MetS (Fig. 1). For example, tumor necrosis factor–α (TNF-α), secreted by adipocytes, is a pro-inflammatory cytokine which propagates the inflammatory response and is associated with low insulin sensitivity [6]. Pro-inflammatory cytokines stimulate the hepatic production of C-reactive protein (CRP), another marker of inflammation [7] and an independent predictor of cardiovascular events [8–11]. The inclusion of CRP in prediction models based on traditional risk markers improves the prediction of cardiovascular events [12]. Another adipokine, resistin, increases the expression of pro-inflammatory cytokines including TNF-α thus stimulating the inflammatory response [13] and serves as a biomarker of atherosclerotic risk [14]. Retinol binding protein 4 (RBP4), an adipokine associated with increased body mass index and visceral adipose tissue, may serve as an early detection biomarker for type 2 diabetes mellitus [15]. In contrast, adiponectin is a hormone with anti-inflammatory [16] and insulin sensitizing effects [17,18], making it a potential biomarker of health, with the high-molecular-weight (HMW) form the most physiologically active [19]. The ratio of adiponectin to leptin has also been proposed as biomarker of the metabolic syndrome [20], and has also been suggested as a method of assessing insulin resistance [21].

These biomarkers provide insight into the progression and amelioration of MetS, so they are increasingly used as indicators of the effect of dietary interventions on health. For example, the Mediterranean diet (a healthy, cuisine-based dietary pattern) has been associated with a reduced incidence of MetS [22,23], and meta-analyses show effects on markers of inflammation [24,25]. These need to be updated with the latest results from the landmark PREDIMED study [26,27]. Moreover, given the emergence of dietary guidance surrounding dietary patterns, the effects of healthy dietary patterns in general needs to be explored, as well as considerations of novel biomarkers of inflammation such as HMW adiponectin. The aim of this meta-analysis was to determine the effect of interventions targeting healthy dietary patterns on a range of biomarkers associated with underlying adiposity, insulin resistance, and inflammation in adults. It was hypothesized that consumption of a healthy dietary pattern characterized by higher consumption of vegetables, fruit, wholegrains, and lower consumption of red meat would result in favorable changes in these biomarkers.

2. Approach for the meta-analysis

This systematic literature review and meta-analysis followed the requirements of the PRISMA statement [28] (Supplemental

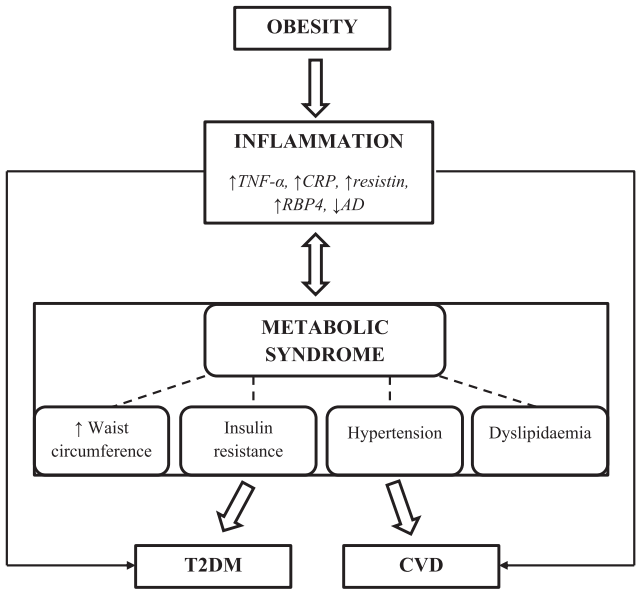

Fig. 1 – The metabolic syndrome is associated with increased risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD), underpinned by a chronic state of low-grade inflammation. The relationships with the suite of biomarkers included in this review are indicated (AD, adiponectin).

Table 1). The review was registered in PROSPERO, the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42015019236).

2.1. Study selection

One study author (EN) conducted a systematic search of the databases Scopus, PubMed, Web of Science and Cochrane Central Register of Controlled Trials (all years to 17 April 2015). Search terms included ("diet* pattern*" OR "food pattern*" OR "Mediterranean diet" OR "prudent diet" OR "western diet" OR "diet* score*" OR "diet* index*"), in combination with ("biomarker*" AND ("metabolic syndrome" OR "metabolic health")) OR ("tumour necrosis factor" OR "tumor necrosis factor" OR TNF*) OR ("retinol binding protein 4" OR "RBP4") OR ("leptin" OR "leptin:adiponectin" OR "leptin/adiponectin") OR ("CRP" OR "hsCRP" OR "high sensitivity C-reactive protein") OR ("resistin") OR ("adiponectin" OR "high molecular weight adiponectin"). An example of the search strategy is shown in Supplemental Terms. Articles were restricted to those published in English.

To be included in this review, studies were limited to randomized controlled trials (including both parallel and cross-over study designs) to ensure the effects of healthy dietary patterns on outcomes could be identified compared to control diets. Studies were further required to meet the following inclusion criteria: (1) studies conducted in humans aged 18 years or older; (2) studies which identified a specific cuisine-based dietary pattern (for example the Mediterranean diet); (3) studies assessing the effect of dietary patterns on an outcome of interest (CRP, total and HMW adiponectin, TNF-α, ratio of adiponectin to leptin, resistin, or RBP4), where the effect of the dietary pattern could be isolated. In addition, the following exclusion criteria were applied: (1) studies involving pregnant or breastfeeding women; (2) studies published as conference abstracts only; (3) studies reporting only postprandial effects of dietary patterns.

Articles were initially screened based on title and abstract, with the full text sought if an abstract was not available or did not provide sufficient information to draw a conclusion regarding inclusion in the current review. In addition, reference lists of articles were reviewed to identify additional relevant articles. Where multiple articles reported results from the same study, the article reporting the longest follow-up period was included, to avoid duplication of study populations.

2.2. Data extraction

The following data were extracted from each study: citation, details of study population (including age, gender, and body mass index), study duration, study design, sample size, details of the intervention, and outcomes of interest measured. Where possible mean change in outcomes was extracted, however where this data was not provided mean final values were extracted for further use, in accordance with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions [29]. Where the required data were not provided in the published article, study authors were contacted for additional details. Where a study involved more than one intervention group meeting the inclusion criteria, data for the two intervention groups were combined as recommended by the Cochrane Handbook [29].

2.3. Quality assessment

Risk of bias in each study was assessed using the Cochrane Collaboration's tool for assessing risk of bias [29]. The quality of the body of evidence was then appraised using the GRADE approach [30]. GRADEproGDT software (GRADEpro. [Computer program on www.gradepro.org]. Version April 2015. McMaster University, 2014) was utilized to facilitate this process.

2.4. Statistical analyses

Data for each study outcome were pooled using Review Manager (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Random effects meta-analyses were conducted to assess the weighted mean differences (WMD) (with 95% confidence intervals) in change or final mean values for each outcome. The consistency of the weighted mean differences for each outcome was assessed using the chi-squared test, with I^2 calculated using the formula: $I^2 = 100\% \times (Q - df)/Q$ (where Q is the chi-squared statistic, and df is the degrees of freedom) [31]. In line with the recommendations by Higgins et al [31], an I^2 value of 75% or greater was deemed to indicate a high level of inconsistency. Funnel plots were then generated to assist in the identification of publication bias, and Egger's test was conducted to determine the degree of funnel plot asymmetry [32].

Additionally, sub-group analyses were conducted based on the type of dietary pattern, final versus change values, duration of intervention (less than three months versus three months or greater), and the risk of bias. Studies were also compared based on whether significant differences in weight loss were found between the intervention and control groups. Sensitivity analyses were also conducted by excluding studies with participants with chronic renal failure [33], asymptomatic asthma [34] and rheumatoid arthritis [35].

3. Findings of dietary pattern and health

3.1. Description of the included studies

A total of 737 articles were assessed for eligibility in the review. Following application of the exclusion criteria, 18 articles describing 17 studies were included in the review. Fig. 2 displays the process of study selection [28].

Included studies assessed the effects of dietary patterns such as the Mediterranean diet (n = 13), the Nordic diet (n = 2), the Tibetan diet (n = 1), and the Dietary Approaches to Stop Hypertension (DASH) diet (n = 1) on outcomes, with studies grouped according to dietary pattern classification from the original study. Characteristics of included studies, including key components of intervention and control diets are displayed in Table 1. The study duration ranged from 28

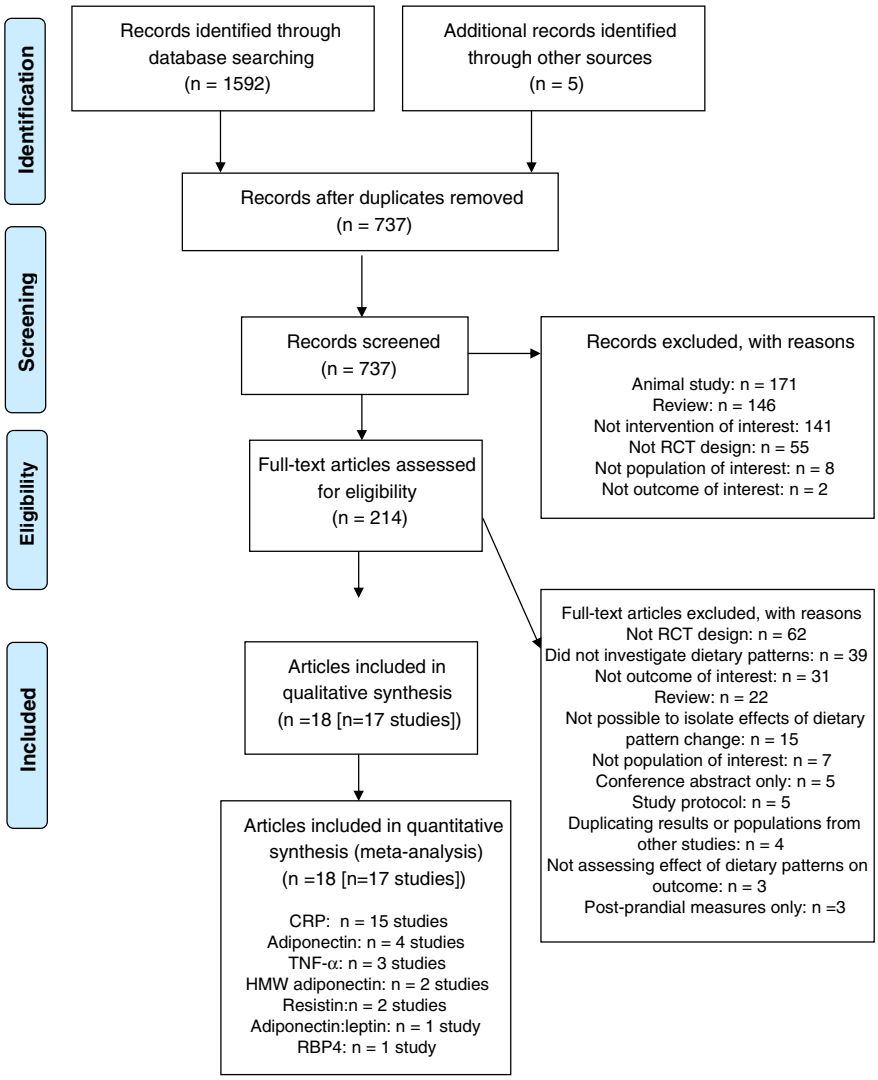

Fig. 2 – Flow chart of study selection.

days to 2 years. Studies were conducted in range of countries including: the United States of America [36,37], Israel [38], Spain [26,27,39], Sweden [35,40], Greece [41], Italy [42–44], Algeria [33], Australia [45], New Zealand [34], Denmark [46], Germany [47], and, in the case of Uusitupa et al [48], across multiple European countries (Finland, Sweden, Denmark, and Iceland). Studies involved both males and females [26,27,33–36,38–41,43,45–48], or females only [37,42,44] and participant's mean body mass index (BMI) ranged from 24 kg/m^2 [37] to 34.9 kg/m^2 [44].

3.2. *Effect of dietary patterns on study outcomes*

Consumption of a healthy dietary pattern was associated with a significant greater reduction in CRP compared to control diets (WMD, –0.75 mg/L (95% CI –1.16, –0.35), P = .0003, I^2= 90%) (Fig. 3).

Compared to control, non-significant increases in total and HMW adiponectin, TNF-α, and resistin were found following consumption of healthy dietary patterns (Table 2, Supplemental Fig. 1a-d). The availability of one study each for RBP4 and adiponectin:leptin meant that meta-analyses could not be conducted for these outcomes. Non-significant changes between groups were found for RBP4 (Mediterranean diet: –8.85 ± 35.87 μg/mL, low-fat diet: –4.78 ± 36.19 μg/mL [38]), and adiponectin:leptin (Mediterranean diet + olive oil: 8.1 ± 21.9, Mediterranean diet + nuts: 7.4 ± 19.8, low-fat diet: 6.7 ± 25 [27]). The results of the risk of bias assessment are shown in Fig. 4 and Supplemental Fig. 2. The quality of the evidence for CRP and HMW adiponectin was downgraded to low due to the level of inconsistency found between studies. In comparison, the quality of the evidence for other outcomes was moderate (Table 2, Supplemental materials).

3.3. *Subgroup analyses, sensitivity analyses, and assessment of publication bias*

Sub-group analyses based on final versus change values, diet type, risk of bias, and duration of intervention are shown in Supplemental Fig. 4a-i. Significant reductions in CRP were only found for trials investigating the Mediterranean diet, those with a low risk of bias, or those which ran for three months or more. There was no evidence of sub-group

differences when studies with significant differences in weight loss between groups were compared to studies without differences in weight loss (test for subgroup differences: χ^2 = 0.28, df = 1 (P = .60), I^2 = 0%, data not shown). Sensitivity analyses which involved excluding studies with participants with chronic renal failure, asymptomatic asthma, and rheumatoid arthritis did not change the interpretation of the significance of the effect of dietary patterns on CRP levels (WMD, –0.56 (95% CI, –0.88 to –0.23); P < .0001) (Supplemental Fig. 5).

Due to the small number of studies available for most outcomes, funnel plots were only generated for CRP (Fig. 5). Egger's test did not indicate the presence of asymmetry in the funnel plot (bias = 0.66 (95% CI = –1.80 to 3.12), P = .57), suggesting publication bias was not detected.

4. Discussion

The dietary patterns identified in this review were characterized as plant food based (mostly fruit, vegetables, and wholegrains and with little red meat). CRP was the only biomarker to emerge with substantial evidence for a relationship with healthy dietary patterns, namely that healthy dietary patterns reduced CRP levels compared to control diets. Sub-group analysis showed the effect was demonstrated with the Mediterranean diet, and in studies with intervention duration of three months or more. Significant effects of healthy dietary patterns were not found for other defined biomarkers, although there were trends for increases in total and HMW adiponectin. The lack of evidence may have reflected the small number of available studies for the analysis, highlighting the need for additional randomized controlled trials assessing the effects of cuisine-based dietary patterns on emerging biomarkers including total and HMW adiponectin, TNF-α, resistin, adiponectin:leptin and RBP4.

The finding for CRP is consistent with the concept of healthy diets affording protective effects from a number of different perspectives; given the delivery of multiple compounds in the forms of foods and nutrients. CRP acts in a number of ways that promote the development of atherosclerosis: prompting oxidation of low-density lipoprotein and the production of cell adhesion molecules, and decreasing production of nitric oxide [7]. The results of large prospective cohort studies suggest that CRP is an independent predictor of cardiovascular events [8–11]. In the present analysis, significant reductions in CRP following consumption of healthy dietary patterns suggest an attenuation of the inflammatory process, and thereby improved cardiovascular health. Even so, substantial inconsistency amongst the results of these studies meant the quality of the body of evidence was "low". The inconsistency was somewhat attenuated in sensitivity analyses when studies involving participants with chronic renal failure, asymptomatic asthma, and rheumatoid arthritis were excluded, suggesting that underlying levels of inflammation in other disease entities create a more complex scenario. Other reasons for this inconsistency could not be identified, however the level of inconsistency is similar to that reported in a previous analysis of the effects of the Mediterranean diet on CRP [24].

Sub-group analyses suggested that the effect may be time-dependent, as a significant pooled effect was only found for those studies with duration of three months or more. Grouping patterns by diet type limited the finding to the Mediterranean diet, suggesting that drawing conclusions on the effects of other healthy dietary patterns (for example DASH, Nordic or Tibetan) requires more studies. The results were consistent with that of observational studies showing adherence to a Mediterranean dietary pattern is associated with reduced inflammation [49–51], reduced incidence of the metabolic syndrome [22,23] and a reduced risk of cardiovascular disease [52,53].

Despite the relative lack of studies on other healthy dietary patterns, examining the food components of the Mediterranean diet may build links with other patterns. Olive oil is a key component of most of the Mediterranean diet research. Compared to a Western diet, consumption of a Mediterranean diet rich in olive oil reduces activation of nuclear transcription factor κB, a transcription factor heavily involved in the inflammation process, in peripheral blood mononuclear cells [54]. The PREDIMED trial showed that a Mediterranean diet rich in olive oil attenuated the expression of pro-inflammatory genes cyclooxygenase-2 and monocyte chemoattractant protein-1, compared to a Mediterranean diet supplemented with nuts, or a control diet [55]. The consumption of fish may attenuate inflammation via its long chain omega-3 polyunsaturated fatty acid content, which, amongst other effects, decrease the production of prostaglandins, thromboxanes and leukotrienes associated with inflammation, and act as ligands for PPARγ, thus regulating the expression of inflammatory genes [56]. There is likely to be an additive effect of these and other foods contained in healthy dietary patterns. Focusing on individual foods helps to identify key food components which may be present in other dietary patterns.

Despite indications that adiponectin may be a useful biomarker of protective dietary effects, there were not enough studies to draw conclusions from our review. The consumption of healthy dietary patterns was associated with non-significant increases in total adiponectin from an evidence base of four studies [27,39,42,44], and in high molecular weight adiponectin from only two studies [38,48]. A single study reported non-significant increases in the adiponectin:leptin ratio [27]. Adiponectin has been proposed as a metabolic biomarker due to its diverse anti-inflammatory, insulin sensitizing and anti-obesity effects [57]. Observational evidence has linked adherence to healthier dietary patterns with increased adiponectin levels [58–60]. A limited number of studies which assessed the effect of dietary patterns on total and HMW adiponectin were available in the current analysis, and the lack of a significant effect may have been the result of changes in body weight overpowering the effects of dietary pattern change [38], or the absence of large dietary differences between the control and intervention groups as seen in the PREDIMED study [61]. These results appear to contrast with a previous meta-analysis [24], but that did not include results for adiponectin in PREDIMED [27] published afterwards. Our analysis, which also considered

Table 1 – Characteristics of studies examining the effect of dietary patterns on biomarkers of metabolic health

Citation and location	Population	Study design	Dietary pattern	Sample size	Duration (wk)	Intervention	Control diet	Outcomes measured
Roussell et al (2012) [36] USA	Adults (aged 30-65 years) elevated LDL cholesterol, mean body mass index (BMI): 27.5 kg/m^2	RCT (crossover)	DASH	35 (DASH arm) 33 (Healthy American Diet arm)	5	Dietary approaches to stop hypertension (DASH): rich in fruit, vegetables, lower fat dairy, lean meat, and wholegrains	Healthy American diet: including full-fat cheese and dairy, more oil and butter, and refined grains	CRP
Bluher et al (2012) [38] Israel	Adults (aged 40–60 years), with either a minimum BMI of 27 kg/m^2 or type 2 diabetes, mean BMI: 30.9 kg/m^2	RCT (parallel)	Mediterranean	204 (in Mediterranean and low fat groups)	104	Moderate fat, restricted calorie Mediterranean diet: 1500 kcal/d for women and 1800 kcal/d for men (no more than 35% calories from fat). The diet was rich in vegetables, olive oil and nuts and low in red meat with poultry and fish replacing beef and lamb.	Low fat, restricted calorie diet: isocaloric with intervention, with 30% calories from fat, 10% calories from saturated fat and 300 mg cholesterol/day. Diet included low-fat grains, vegetables, fruits and legumes, and limit consumption of additional fats, sweets and high-fat snacks	HMW adiponectin, leptin, CRP, RBP4
Lasa et al (2014) [27] Casas et al (2014) [26] Spain	Adults (aged 55-80 years), with type 2 diabetes or 3 or more CHD risk factors, mean BMI: 29.8 kg/m^2 (Lasa et al, 2014) 28.1 kg/m^2 (Casas et al, 2014)	RCT (parallel)	Mediterranean	191 (all outcomes other than CRP) 164 (CRP)	52	1. Mediterranean diet supplemented with olive oil 2. Mediterranean diet supplemented with mixed nuts Advised to increase consumption of fruit, vegetables, legumes and fish, reduce consumption of meat (particularly red and processed meat), prepare home-made tomato sauces, avoid butter, cream, fast food, sweets, pastries and sugar-sweetened beverages, and to consume moderate amounts of red wine Groups 1 and 2 combined for analysis	Low-fat diet (control)	Total adiponectin, TNF-α, leptin, resistin, adiponectin: leptin ratio, CRP
Ambring et al (2006) [40] Sweden	Healthy adults (mean age 43 years), mean BMI: 25.9 kg/m^2	RCT (crossover design)	Mediterranean	22	4	Mediterranean-inspired diet (MID) MID contained fruit, vegetables, fish, plant sterols and slow-release carbohydrates, and was higher in fibre, antioxidants, long chain omega-3 polyunsaturated fatty acids than the Ordinary Swedish Diet	Ordinary Swedish diet	CRP
Athyros et al (2011) [41] Greece	Adults with mild hypercholesterolaemia (total cholesterol: 5.2-6.4 mmol/L), mean BMI: 27.6 kg/m^2	RCT (parallel design)	Mediterranean	100 (in groups 2 and 3)	16	Advised to adhere to a Mediterranean diet	Step I hypolipidemic diet plus spread without plant sterol esters	CRP
Buscemi et al (2009) [42] Italy	Overweight and obese women (age range, 30–50 years), mean BMI: 34.3 kg/m^2	RCT (parallel design)	Mediterranean	20	8	Mediterranean diet: composition: 55% carbohydrate, 25% lipids (20% saturated fatty acids, 67% monounsaturated fatty acids, 13% polyunsaturated fatty acids), 20% protein, 30 g fibre, 250 mg cholesterol) All participants were instructed to consume 20 kcal/kg weight daily.	Atkins low-carbohydrate diet (composition: 20% carbohydrate, 55% lipids (25% saturated fatty acids, 60% monounsaturated fatty acids, 15% polyunsaturated fatty acids), 25% protein, 15 g fibre, 400 mg cholesterol)	Total adiponectin, TNF-α
Djuric et al (2009) [37] USA	Adult women (aged 25–65 years), generally healthy, mean BMI: 24 kg/m^2	RCT (parallel)	Mediterranean	60	26	Mediterranean intervention: given dietary advice to increase fruit and vegetable intake to 7–9 servings per day, and to achieve a polyunsaturated fatty acid/saturated fatty acid/ monounsaturated fatty acid ratio of 1:2:5	Given general written advice (National Cancer Institute's Action Guide to Healthy Eating),	CRP
Esposito et al (2003) [44] Italy	Premenopausal obese women (20 – 46 years), without diabetes, hypertension or hypercholestaemia, mean BMI: 34.9 kg/m^2	RCT (parallel design)	Mediterranean	120	104	Mediterranean diet: Given detailed lifestyle advice including behavioural and physical activity advice and were prescribed a Mediterranean-style diet (50-60% carbohydrate, 15-20% protein, <30% fat, <10% saturated fat, 10-15% monounsaturated fat, 5-8% polyunsaturated fat, and 18 g of fibre per 1000 kcal), including wholegrain products, legumes, fruit, vegetables, fish and olive oil	Received general information about healthy food choices and exercise	CRP, total adiponectin

Esposito et al (2004) [43] Italy	Adults with the metabolic syndrome (as defined by Adult Treatment Panel III), mean BMI: 28 kg/m^2	RCT (parallel design)	Mediterranean	180	104	Mediterranean diet: Given detailed lifestyle advice including behavioural and physical activity advice and were prescribed a Mediterranean-style diet (50-60% carbohydrate, 15-20% protein, <30% fat, <10% saturated fat, <300 mg/d cholesterol). Intervention participants were instructed to consume at least 250-300 g fruit, 125-150 g vegetables, 25-50 g walnuts, 400 g wholegrains per day and increase consumption of olive oil	Received general information about healthy food choices and exercise (recommended dietary composition was: 50-60% carbohydrate, 15-20% protein, <30% fat)	CRP
Itsiopoulos et al (2011) [45] Australia	Adults (aged 47-77 years) with well-controlled type 2 diabetes, mean BMI: 30.2 kg/m^2	RCT (crossover)	Mediterranean	26	12	Mediterranean diet: majority of meals provided to participants, including traditional cooked meals, wholegrain bread, olives, dried fruit, nuts, Greek coffee, herbal tea, extra virgin olive oil. Participants were also advised to consume 3 serves of fruit per day.	Habitual diet	CRP
Mekki et al (2010) [33] Algeria	Adults (mean age 61 years), with chronic renal failure (undialyzed), mean BMI: 26.1 kg/m^2	RCT (parallel)	Mediterranean	40	12	Nutritional advice based on the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative adapted to a Mediterranean diet. Participants were encouraged to consume olive oil and nuts, wholegrains, fruit, vegetables and fish	Nutritional advice based on the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative	CRP
Paniagua et al (2007) [39] Spain	Overweight adults (mean age 62 years) with insulin resistance, mean BMI: 32.6 kg/m^2	RCT (crossover)	Mediterranean	11	4	Mediterranean diet: high fat, monounsaturated fat rich diet (47% carbohydrate, 38% fat (9% saturated fat, 23% monounsaturated fat (75% of which was provided as extra virgin olive oil), 6% polyunsaturated fat) 3. high saturated fat diet (47% carbohydrate, 15% protein, 38% fat (23% saturated fat, 9% monounsaturated fat, 6% polyunsaturated fat)	low-fat, high carbohydrate diet (65% carbohydrate, 20% fat (6% saturated fat, 8% monounsaturated fat, 6% polyunsaturated fat)	Total adiponectin, resistin
Sexton et al (2013) [34] New Zealand	Adults with symptomatic asthma, mean BMI: 25.6 kg/m^2	RCT (parallel)	Mediterranean	23 (in Groups 1 and 3)	12	High-intervention Mediterranean diet group (received intensive advice from a dietitian (41 hours total) and supplied with olive oil and vouchers for the purchase of appropriate foods)	Received one session with dietitian, recipes and free food at the end of the study	CRP, TNF-α
Skoldstam et al (2003) [35] Sweden	Adults with diagnosed rheumatoid arthritis (stable and under adequate control), mean BMI: 27 kg/m^2	RCT (parallel)	Mediterranean	48	12	Cretan Mediterranean diet (adapted for Swedish participants): encouraging the use of olive and canola oil, lower amounts of dairy, or reduced fat dairy products, green or black tea (to provide polyphenols). Olive and canola oil, liquid margarine, spreadable margarine, frozen vegetables and tea were provided to participants	Habitual diet	CRP
Poulsen et al (2014) [46] Denmark	Adults (aged 20-66 years) with central adiposity (≥80 cm for females, ≥94 cm for males), mean BMI: 30.2 kg/m^2	RCT (parallel)	Nordic	146	26	New Nordic Diet: based on fruits, vegetables, potatoes, fresh herbs, plants, mushrooms, nuts, wholegrains, meats from livestock and game, fish and shellfish, seaweed. Foods and beverages were provided in a study shop	Average Danish Diet: including refined grains, meat, dairy and cheese, sugary products, convenience foods, low-fibre vegetables and imported fruits	CRP
Uusitupa et al (2013) [48] Finland, Sweden, Denmark, Iceland	Adults (mean age 55 years), with features of the metabolic syndrome, mean BMI: 31.6 kg/m^2	RCT (parallel)	Nordic	154 (CRP) 156 (HMW adiponectin)	18-24	Healthy Nordic diet (emphasizing wholegrain products, use of berries, fruit, vegetables, rapeseed oil, fish (3 times per week), low-fat dairy products and avoidance of sugar sweetened products. Participants were provided with wholegrain products, berry products and rapeseed oil. Fish was either provided or cost of consuming fish was covered.)	Control (including refined cereal products, 200-250 g fruit and vegetables per day, butter, dairy products, ≤ fish meal per week, with no limitations on meat or beverages. Participants were provided with low-fibre cereal products and dairy fat-based spread)	CRP, HMW adiponectin
von Haehling et al (2013) [47] Germany	Adults with significant coronary artery disease, who were overweight or obese with at least two other metabolic syndrome components, mean BMI: 30.4 kg/m^2	RCT (parallel)	Tibetan	489	26	Tibetan diet, including focusing on high protein and vitamin rich food	Western diet, based on standard diet and lifestyle advice issued by the American Heart Association and the German Academy and Society of Nutritional Medicine	CRP

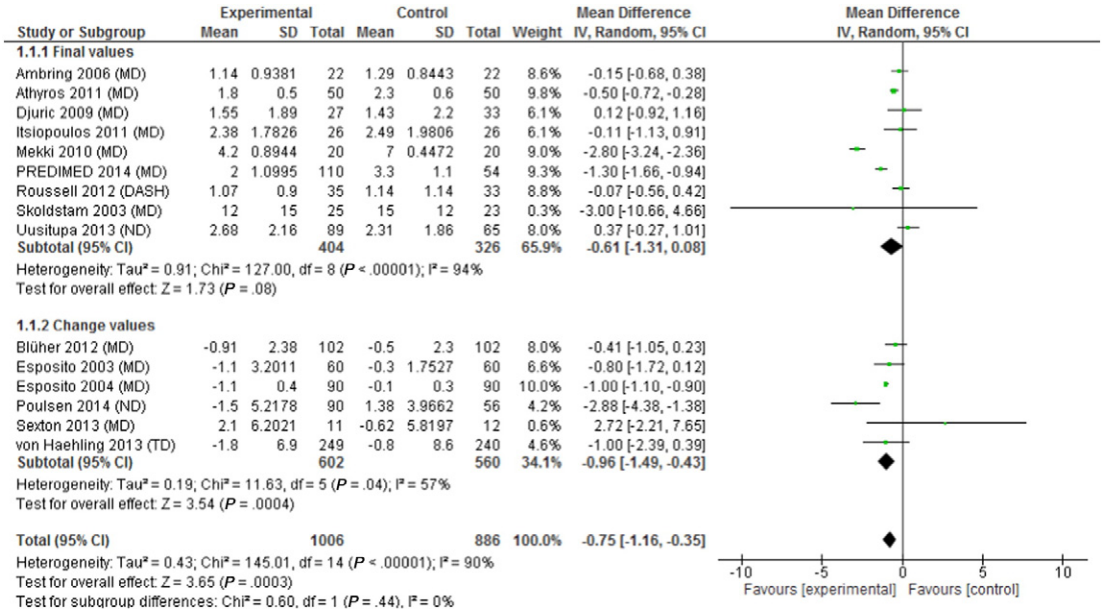

Fig. 3 – Change in C-reactive protein (mg/L) between dietary patterns and control (presented as sub-groups based on mean final or change values for readability). Diamond indicates weighted mean difference with 95% confidence intervals. MD, Mediterranean diet; ND, Nordic diet; TD, Tibetan diet.

total and HMW adiponectin as separate outcomes, updates the evidence base in this regard.

Our analysis found the consumption of healthy dietary patterns was associated with non-significant increases in TNF-α and resistin levels. These results contrast with those found in observational research [59], although there were few studies available for our purposes, and in most cases the studies had small sample sizes [34,39,42]. The effect of a healthy dietary pattern on RBP4, a potential biomarker for the development of type 2 diabetes, was only assessed in one study [38], where a non-significant reduction in RBP4 was reported. There are clearly gaps in the evidence base which require more studies.

This meta-analysis was the first to explore the effects of multiple healthy dietary patterns on a range of biomarkers associated with the development of MetS, including changes to the inflammatory state, with implications for glucose metabolism, and the development of atherosclerosis. We considered a range of healthy dietary patterns, explored possible markers of health protection in HMW and total adiponectin, and included the most recent results from the PREDIMED trial. We attempted to broaden the scope of investigation by considering dietary patterns associated with multiple cultural backgrounds, and found research beyond the Mediterranean diet quite minimal.

Our analysis was limited by the small number of studies assessing the effect of dietary patterns on biomarkers of interest, including TNF-α, HMW adiponectin, adiponectin: leptin, resistin, and RBP4. As a result, the findings for these outcomes should be interpreted with caution. Studies involving pregnant or breastfeeding woman were also excluded from the analysis. Whilst this is in line with other systematic literature reviews assessing the effects of dietary interventions on biomarkers of inflammation [62–65], it should be noted that the findings of the present review may not apply to pregnant or breastfeeding women. Even though care was taken to restrict studies to those identified as using cuisine-based dietary patterns, patterns were grouped based on classifications by study authors, meaning variations existed between studies in regards to the types and quantities of foods, as well as the degree of compliance to dietary targets, which may have accounted for differences in results.

Table 2 – Changes in CRP, total and HMW adiponectin, adiponectin:leptin, TNF-α and resistin following consumption of healthy dietary patterns, compared to control

Outcome	No. of analyses	No. of participants	Effect estimate	Inconsistency (I^2)	GRADE quality of evidence
CRP (mg/L)	15	1892	–0.75 (–1.16, –0.35), P = .0003	90%	Low
Total adiponectin (<mu>g/mL)	4	353	0.59 (–0.82, 2.00), P = .41	25%	Moderate
TNF-α (pg/mL)	3	234	0.17 (–0.38, 0.72), P = .54	0%	Moderate
HMW adiponectin (<mu>g/L)	2	360	0.39 (–0.53, 1.32), P = .41	58%	Low
Resistin (ng/mL)	2	213	0.04 (–0.08, 0.16), P = .53	0%	Moderate

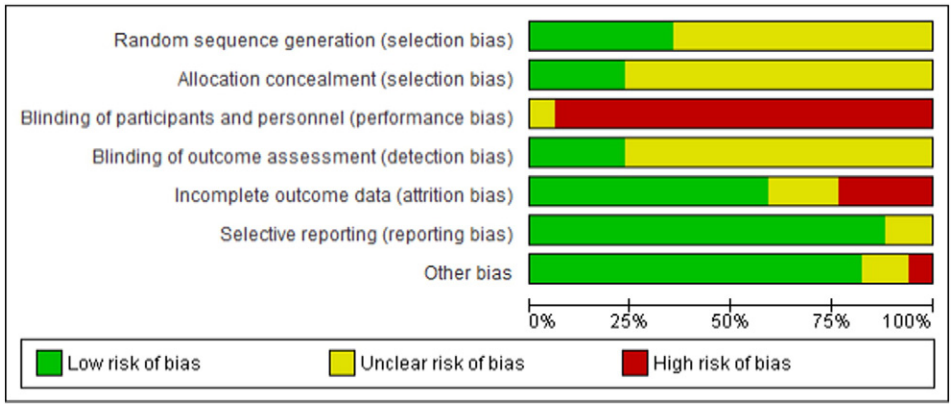

Fig. 4 – Risk of bias assessment as proportion of total studies.

Although variations in smoking status, co-morbidities and physical activity prescriptions did exist between studies, no differences in these factors were reported between treatment groups in individual studies, allowing the effect of the dietary pattern to be isolated. Differences in study results for CRP were also not attributable to whether significant differences in weight loss were achieved, suggesting these effects were not only due to weight loss.

This meta-analysis of the effects of healthy dietary patterns on biomarkers of inflammation, adiposity, and insulin resistance suggests that consumption of dietary patterns rich in fruits, vegetables, wholegrains and with reduced intakes of red meat resulted in decreases in levels of CRP, suggesting attenuation of the inflammatory state. Non-significant increases in total and HMW adiponectin were found with consumption of healthy dietary patterns, although the results should be interpreted with caution due to the small number of studies available. Similarly, the body of evidence for the effect of dietary patterns on TNF-α, resistin, adiponectin:leptin and RBP4 was small and often limited by studies with small sample sizes. In order to further elucidate the effects of dietary patterns on these emerging biomarkers of health, future research should include additional randomized controlled trials with appropriate dietary comparator groups, and should focus on a greater range of dietary patterns and study outcomes.

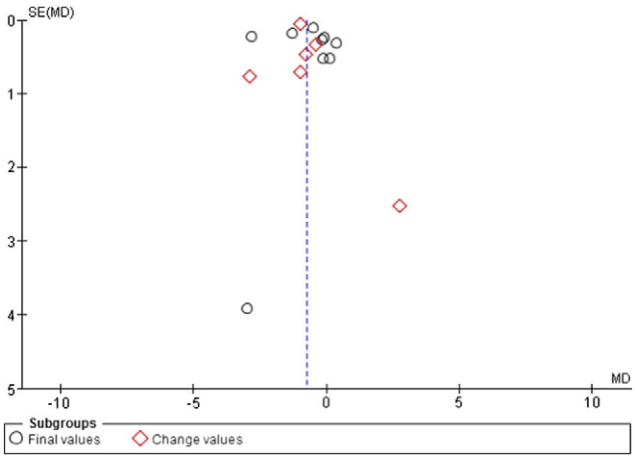

Fig. 5 – Funnel plot of studies investigating the effects of consuming healthy dietary patterns on CRP.

Disclosure statement

The authors declare they have no conflict of interest

Acknowledgment

This study was supported by the Smart Foods Centre, School of Medicine, University of Wollongong.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nutres.2016.02.009.

REFERENCES

[1] Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
[2] Jacobs DRJ, Tapsell LC. Food synergy: the key to a healthy diet. Proc Nutr Soc 2013;72:200–6.
[3] US Department of Agriculture, US Department of Health & Human Services. Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Health & Human Services and the Secretary of Agriculture; 2015.
[4] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3143–421.
[5] Ford ES. Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome: A summary of the evidence. Diabetes Care 2005;28:1769–78.
[6] Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 2003;14:447–55.

[7] Silva D, de Lacerda AP. High-sensitivity C-reactive protein as a biomarker of risk in coronary artery disease. Rev Port Cardiol 2012;31:733–45.
[8] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. Circulation 2003;107:391–7.
[9] Ridker PM, Glynn RJ, Hennekens CH. C-Reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 1998;97:2007–11.
[10] Pradhan AD, Manson JE, Rossouw JE, Siscovick DS, Mouton CP, Rifai N, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease – Prospective analysis from the Women's Health Initiative observational study. J Am Med Assoc 2002;288:980–7.
[11] Boekholdt SM, Hack CE, Sandhu MS, Luben R, Bingham SA, Wareham NJ, et al. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: The EPIC-Norfolk prospective population study 1993–2003. Atherosclerosis 2006;187:415–22.
[12] Cook NR, Buring JE, Ridker PM. The Effect of Including C-Reactive Protein in Cardiovascular Risk Prediction Models for Women. Ann Intern Med 2006;145:21–9.
[13] Jiang CY, Wang W, Tang JX, Yuan ZR. The adipocytokine resistin stimulates the production of proinflammatory cytokines TNF-α and IL-6 in pancreatic acinar cells via NF-κB activation. J Endocrinol Investig 2013;36:986–92.
[14] Codoñer-Franch P, Alonso-Iglesias E. Resistin: Insulin resistance to malignancy. Clin Chim Acta 2015;438:46–54.
[15] Kotnik P, Fischer-Posovszky P, Wabitsch M. RBP4: a controversial adipokine. Eur J Endocrinol 2011;165:703–11.
[16] Robinson K, Prins J, Venkatesh B. Clinical review: Adiponectin biology and its role in inflammation and critical illness. Crit Care 2011;15:221.
[17] Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, et al. A Transgenic Mouse with a Deletion in the Collagenous Domain of Adiponectin Displays Elevated Circulating Adiponectin and Improved Insulin Sensitivity. Endocrinology 2004;145:367–83.
[18] Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 2001;108:1875–81.
[19] Liu ML, Liu F. Regulation of adiponectin multimerization, signaling and function. Best Pract Res Clin Endocrinol Metab 2014;28:25–31.
[20] Mirza S, Qu HQ, Li Q, Martinez PJ, Rentfro AR, McCormick JB, et al. Adiponectin/leptin ratio and Metabolic Syndrome in a Mexican American population. Clin Invest Med 2011;34: E290–7.
[21] Inoue M, Yano M, Yamakado M, Maehata E, Suzuki S. Relationship between the adiponectin-leptin ratio and parameters of insulin resistance in subjects without hyperglycemia. Metabolism 2006;55:1248–54.
[22] Steffen LM, Van Horn L, Daviglus ML, Zhou X, Reis JP, Loria CM, et al. A modified Mediterranean diet score is associated with a lower risk of incident metabolic syndrome over 25 years among young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Br J Nutr 2014;112: 1654–61.
[23] Kesse-Guyot E, Ahluwalia N, Lassale C, Hercberg S, Fezeu L, Lairon D. Adherence to Mediterranean diet reduces the risk of metabolic syndrome: A 6-year prospective study. Nutr Metab Cardiovasc Dis 2013;23:677–83.
[24] Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: Asystematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis 2014;24:929–39.
[25] Nordmann AJ, Suter-Zimmermann K, Bucher HC, Shai I, Tuttle KR, Estruch R, et al. Meta-Analysis Comparing Mediterranean to Low-Fat Diets for Modification of Cardiovascular Risk Factors. Am J Med 2011;124:841–51 [e2].
[26] Casas R, Sacanella E, Estruch R. The Immune Protective Effect of the Mediterranean Diet against Chronic Low-grade Inflammatory Diseases. Endocr Metab Immune Disord Drug Targets 2014;14:245–54.
[27] Lasa A, Miranda J, Bullo M, Casas R, Salas-Salvado J, Larretxi I, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. Eur J Clin Nutr 2014:767–72.
[28] Moher D, Liberati A, Tetzlaff J, Altman DG, P.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097.
[29] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. Cochrane Collaboration 2011.
[30] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations; 2008.
[31] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.
[32] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315: 629–34.
[33] Mekki K, Bouzidi-bekada N, Kaddous A, Bouchenak M. Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. Food Funct 2010:110–5.
[34] Sexton P, Black P, Metcalf P, Wall CR, Ley S, Wu L, et al. Influence of Mediterranean diet on asthma symptoms, lung function, and systemic inflammation: A randomized controlled trial. J Asthma 2013;50:75–81.
[35] Skoldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:208–14.
[36] Roussell MA, Hill AM, Gaugler TL, West SG, Vanden Heuvel JP, Alaupovic P, et al. Beef in an Optimal Lean Diet study: Effects on lipids, lipoproteins, and apolipoproteins. Am J Clin Nutr 2012;95:9–16.
[37] Djuric Z, Ren J, Blythe J, VanLoon G, Sen A. A Mediterranean dietary intervention in healthy American women changes plasma carotenoids and fatty acids in distinct clusters. Nutr Res 2009;29:156–63.
[38] Blüher M, Rudich A, Klöting N, Golan R, Henkin Y, Rubin E, et al. Two patterns of adipokine and other biomarker dynamics in a long-term weight loss intervention. Diabetes Care 2012;35:342–9.
[39] Paniagua González JA, Gallego De La Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, et al. Monounsaturated fat-rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. Diabetes Care 2007;30:1717–23.
[40] Ambring A, Johansson M, Axelsen M, Gan L, Strandvik B, Friberg P. Mediterranean-inspired diet lowers the ratio of serum phospholipid n-6 to n-3 fatty acids, the number of leukocytes and platelets, and vascular endothelial growth factor in healthy subjects. Am J Clin Nutr 2006;83:575–81.
[41] Athyros VG, Kakafika AI, Papageorgiou AA, Tziomalos K, Peletidou A, Vosikis C, et al. Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. Nutr Metab Cardiovasc Dis 2011:213–21.
[42] Buscemi S, Verga S, Tranchina MR, Cottone S, Cerasola G. Effects of hypocaloric very-low-carbohydrate diet vs. Mediterranean diet on endothelial function in obese women*. Eur J Clin Investig 2009;39:339–47.
[43] Esposito K, Marfella R, Ciotola M, Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-style diet on endothelial

dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004:1440–6.
[44] Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women – A randomized trial. J Am Med Assoc 2003;289:1799–804.
[45] Itsiopoulos C, Brazionis L, Kaimakamis M, Cameron M, Best JD, O'Dea K, et al. Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. Nutr Metab Cardiovasc Dis 2011;21:740–7.
[46] Poulsen SK, Due A, Jordy AB, Kiens B, Stark KD, Stender S, et al. Health effect of the New Nordic Diet in adults with increased waist circumference: a 6-mo randomized controlled trial. Am J Clin Nutr 2014;99:35–45.
[47] von Haehling S, Stellos K, Qusar N, Gawaz M, Bigalke B. Weight reduction in patients with coronary artery disease: Comparison of Traditional Tibetan Medicine and Western diet. Int J Cardiol 2013;168:1509–15.
[48] Uusitupa M, Hermansen K, Savolainen MJ, Schwab U, Kolehmainen M, Brader L, et al. Effects of an isocaloric healthy Nordic diet on insulin sensitivity, lipid profile and inflammation markers in metabolic syndrome – a randomized study (SYSDIET). J Intern Med 2013;274:52–66.
[49] Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, et al. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2005;82:163–73.
[50] Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults – The ATTICA study. J Am Coll Cardiol 2004;44:152–8.
[51] Carter SJ, Roberts MB, Salter J, Eaton CB. Relationship between Mediterranean Diet Score and atherothrombotic risk: Findings from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Atherosclerosis 2010;210:630–6.
[52] Panagiotakos DB, Georgousopoulou EN, Pitsavos C, Chrysohoou C, Skoumas I, Pitaraki E, et al. Exploring the path of Mediterranean diet on 10-year incidence of cardiovascular disease: The ATTICA study (2002–2012). Nutr Metab Cardiovasc Dis 2015;25:327–35.
[53] Dominguez LJ, Bes-Rastrollo M, de la Fuente-Arrillaga C, Toledo E, Beunza JJ, Barbagallo M, et al. Similar prediction of total mortality, diabetes incidence and cardiovascular events using relative-and absolute-component Mediterranean diet score: The SUN cohort. Nutr Metab Cardiovasc Dis 2013;23:451–8.
[54] Perez-Martinez P, Lopez-Miranda J, Blanco-Colio L, Bellido C, Jimenez Y, Moreno JA, et al. The chronic intake of a Mediterranean diet enriched in virgin olive oil, decreases nuclear transcription factor κB activation in peripheral blood mononuclear cells from healthy men. Atherosclerosis 2007; 194:e141–6.
[55] Llorente-Cortés V, Estruch R, Mena MP, Ros E, González MAM, Fitó M, et al. Effect of Mediterranean diet on the expression of pro-atherogenic genes in a population at high cardiovascular risk. Atherosclerosis 2010;208:442–50.
[56] Calder PC. Long-chain fatty acids and inflammation. Proc Nutr Soc 2012;71:284–9.
[57] Kishida K, Funahashi T, Shimomura I. Adiponectin as a routine clinical biomarker. Best Pract Res Clin Endocrinol Metab 2014;28:119–30.
[58] Mantzoros CS, Williams CJ, Manson JE, Meigs JB, Hu FB. Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women. Am J Clin Nutr 2006;84:328–35.
[59] Fargnoli JL, Fung TT, Olenczuk DM, Chamberland JP, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. Am J Clin Nutr 2008; 88:1213–24.
[60] Guo H, Niu K, Monma H, Kobayashi Y, Guan L, Sato M, et al. Association of Japanese dietary pattern with serum adiponectin concentration in Japanese adult men. Nutr Metab Cardiovasc Dis 2012;22:277–84.
[61] Appel LJ, Van Horn L. Did the PREDIMED Trial Test a Mediterranean Diet? N Engl J Med 2013;368:1353–4.
[62] von Frankenberg AD, Silva FM, de Almeida JC, Piccoli V, do Nascimento FV, Sost MM, et al. Effect of dietary lipids on circulating adiponectin: a systematic review with meta-analysis of randomised controlled trials. Br J Nutr 2014;112: 1235–50.
[63] Buyken AE, Goletzke J, Joslowski G, Felbick A, Cheng G, Herder C, et al. Association between carbohydrate quality and inflammatory markers: systematic review of observational and interventional studies. Am J Clin Nutr 2014;99:813–33.
[64] Wu JHY, Cahill LE, Mozaffarian D. Effect of Fish Oil on Circulating Adiponectin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Endocrinol Metab 2013;98:2451–9.
[65] Labonté M-È, Couture P, Richard C, Desroches S, Lamarche B. Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults. Am J Clin Nutr 2013;97:706–17.