Special Article

The effect of dietary intervention, with or without co-interventions, on inflammatory markers in patients with Non-Alcoholic Fatty Liver Disease: A Systematic Literature Review

Keywords: Non-alcoholic fatty liver disease, dietary intervention, inflammatory markers

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Abstract

Context

Non-Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum of liver disorders ranging from simple steatosis to Non-Alcoholic Steatohepatitis (NASH) with inflammation acting as a key driver in its pathogenesis and progression. Diet has the potential to mediate the release of inflammatory markers, however little is known about the effects of various diets.

Objective

This systematic review aimed to evaluate the effect of dietary interventions on cytokines and adipokines in patients with NAFLD.

Data sources

Electronic databases MEDLINE, EMBASE, CINAHL and Cochrane Library were searched for clinical trials investigating dietary interventions, with or without supplementation, on cytokines and adipokines in NAFLD patients.

Data Extraction

Basic characteristics of populations, dietary intervention protocol, cytokines and adipokines were extracted for each study. Quality of evidence was assessed using the American Dietetic Association criteria.

Data Analysis

Nineteen studies with a total of 874 participants were included. The most frequently reported inflammatory outcomes were C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), adiponectin and leptin. Hypocaloric, isocaloric or low-fat diets significantly lowered levels of CRP, TNF-α and adiponectin. The addition of nutraceutical or pharmacological supplementation to dietary interventions appeared to elicit additional benefits to all of the most frequently reported inflammatory markers.

Conclusions

Hypo- or iso-caloric diets alone, or with co-interventions including a nutraceutical or pharmacological supplementation appear to improve the inflammatory profile in patients with NAFLD. Thus, anti-inflammatory diets may have the potential to relieve underlying chronic inflammatory pathophysiological mechanisms of NAFLD through the improvement in circulating inflammatory markers. In the absence of any known liver-sensitive markers, the usefulness of cytokines and adipokines as a surrogate marker of liver disease should be further investigated in well controlled trials.

Keywords: Non-alcoholic fatty liver disease, dietary intervention, inflammatory markers, cytokines, adipokines

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of liver disease in developed countries [1] affecting at least 25% of adults [2] Rates of NAFLD parallel the obesity epidemic and are present in up to 80% of obese individuals and 75% in people with type 2 diabetes.[3,4]

Although the pathogenesis of NAFLD is not well understood, Tilg and Moschen (2010) propose a "multiple parallel hit" hypothesis suggesting that inflammatory mediators derived from various tissues, specifically from adipose tissue and the gut, play a central role in the cascade of inflammation and fibrosis.[5] Adipose tissue itself can produce and secrete pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as adipokines; adiponectin and leptinwhich are both implicated in the development of insulin resistance (IR) and metabolic dysregulation in NAFLD.[6,7] In contrast to leptin, adiponectin secretion is often diminished in obesity and acts to increase insulin sensitivity.[6] In response to the secretion of cytokines, extrahepatic production of the acute phase protein high sensitivity C-reactive protein (hs-CRP) exacerbates a pro-inflammatory milieu and drives further hepatic and cardiometabolic damage.[8,9]

There is currently no proven, safe and effective pharmacotherapy for the treatment of NAFLD.[10] Current recommendations emphasise weight loss which may be achieved through management of lifestyle including diet .[11] Dietary intakes of individuals with NAFLD have been reported to be high in saturated fat, refined carbohydrates, fructose and cholesterol, and low in antioxidants and omega-3 fatty acids.[12] These diets are known to exacerbate inflammatory cytokine and adipokine production, release free fatty acids (FFAs), stimulate oxidative stress and influence disease progression in metabolic diseases.[8] Furthermore,

85 over-feeding can cause impaired energy homeostasis, appetite dysregulation and weight
86 fluctuation, which is regulated by the pro-inflammatory cytokine, Leptin.[13] One of the main
87 physiological roles of Leptin is to prevent lipid accumulation in nonadipose sites, including
88 the liver.[14] Although Leptin is not commonly reported in existing studies, patients with
89 NAFLD tend to have increased serum leptin concentrations.[15]
90 Low-fat diets, though well-researched in chronic disease management, show variable results
91 for the effects on inflammatory markers and seem to be dependent on weight loss.[16]
92 Hypocaloric diets typically provided an energy deficit of 500-1000 kcal/d aimed at inducing a
93 total body weight loss of ~5-10%,[17] that may ameliorate hepatic and metabolic outcomes
94 via a reduction in adiposity and improvement of glucose and lipid metabolism.[18]
95 However, weight loss can be difficult to achieve and maintain and thus isocaloric diets which
96 aim for energy balance focus on dietary componenets that are anti-inflammatory in
97 nature.[19] This includes the Mediterranean Diet which is predominantly plant-based, high in
98 fibre, high in monounsaturated and polyunsaturated fats and has anti-inflammatory
99 properties, [11,12] and thus may alleviate hepatic and cardiometabolic stress irrespective of
100 weight loss.[20-24]
101 Alternative therapies, including nutraceuticals (i.e. substances derived from biologically
102 active isolated nutrients or functional foods) are being increasingly considered in the
103 treatment of NAFLD.[25-27] Presently, there is not enough substantial evidence to make any
104 recommendations for the use of nutraceutical agents in the management of NAFLD.
105 Despite the number of trials that have assessed varying diet and supplementation
106 approaches, there is currently no consensus regarding the optimal dietary intervention(s) to
107 improve the inflammatory milieu within the liver that is responsible for hepatocyte injury
108 and fibrosis in individuals with NAFLD. Hence, the present systematic review aims to assess

the current literature and to determine the effect of dietary interventions on cytokines and adipokines in adults diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD).

Method

This systematic review adheres to the relevant criteria of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Appendix S1 in the Supporting Information online),[28] and the Cochrane Handbook for Systematic Reviews of Interventions.[29] The review was registered in PROSPERO, the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42017055921).

Search Strategy

A search for all relevant articles was performed by one researcher (AJR) using the electronic databases MEDLINE Ovid (1946-present), EMBASE Ovid (1947-present), CINAHL (EBSCO) and the Cochrane Library (Wiley Online Library). The last search was run on January 15th, 2018. English language limits were applied. The search strategy used combinations of the terms *Non-Alcoholic Fatty Liver Disease, NAFLD, Non-Alcoholic Steatohepatitis (NASH), cirrhosis, diet,* and *nutrition* as both Medical Subject Headings (MeSH) and subject headings specific to each database and key- or free-text words, and included a wide range of derivations to ensure an extensive search strategy was performed (Appendix S2 in the Supporting Information online). The search was not limited to specific outcomes to ensure all relevant literature investigating cytokines and adipokines was captured. Citation tracking and hand searching of the reference lists of relevant reviews and articles that were retrieved in searches was also undertaken. Conference abstracts and reports were also screened and the full articles of potentially eligible studies were retrieved.

Eligibility Criteria

The inclusion and exclusion criteria were developed using the Patient, Intervention, Comparators, Outcome and Study Design (PICOS)[30] method (Table 1).

References were imported into a bibliographic database to automatically exclude duplicates (EndNote X7.4). References were screened in duplicate by two researchers (AJR, ESG) by title and abstract and full publications of potentially eligible references were obtained.

Quality Assessment and Data Extraction

Once eligible studies were identified, two independent researchers (AJR, ESG) assessed the methodological quality of each using the American Dietetic Association Quality Criteria Checklist for Primary Research.[31] The criteria checklist for validity assessment contained ten questions. A study was considered negative (-) if six or more validity questions were answered 'no'; a study was considered neutral (ɷ) if four specific validity questions were answered and a study was considered positive (+) if most validity questions were answered 'yes'.

The process of extracting data from eligible articles was then completed independently by one researcher (AJR), after which a second reviewer (ESG) cross-checked all extracted data. When articles contained insufficient information to perform quality assessment or extract relevant data, the corresponding author was contacted for further information. This occurred for five articles.[32-36] Two authors responded.[35,36] Disagreements regarding eligibility, quality assessment and data extraction were resolved through discussion and consensus.

Data analysis

A meta-analysis was not undertaken due to the heterogeneity of the dietary interventions, study designs, and participants within the included studies, as well as inconsistent control and experimental intervention groups, including co-interventions. Due to this variability,

researchers were unable to group dietary interventions for analysis. Where numerical values for inflammatory markers were presented in different units (e.g. mmol/L versus mg/dL); measures were converted into the same unit to allow comparisons to be made. The difference in means and level of significance were extracted from each study, and change was calculated as a percentage.

Results

A total of 3,855 articles were retrieved from the database search and after duplicates were removed 2,993 remained. Following a review of titles and abstracts, 79 were deemed potentially eligible. Full-text articles were examined and 20 fulfilled the inclusion criteria. One article was excluded as it contained no result tables or figures with numerical values and no response was obtained after contacting the authors.[37] Nineteen studies were therefore included. Reference lists of all eligible studies and relevant reviews were checked for potential inclusions, however no additional articles were retrieved. The study selection process is summarised in Figure 1.

All nineteen included studies were RCTs; three were non blinded,[33,38,39] two were single-blinded,[34,40] three were double-blinded,[32,36,41] seven were double-blind placebo controlled,[42-48] three were open label-parallel arm RCTs[35,49,50] and one study was a prospective single-blinded random order controlled dietary feeding study.[51]

<u>Study Characteristics and Participants</u>

Studies included in this review were published between 2003 and 2018; there were a total of 874 participants with NAFLD and the length of interventions ranged from 2 weeks to 12 months. Of the overall sample, 488 (56%) were males and 386 (44%) were females. The age of participants ranged from 36 to 65 years and BMI ranged between 23 kg/m² and 35 kg/m². Three of the nineteen studies used the gold standard liver biopsy (Bx) to diagnose

NAFLD,[34,38,45] three used Magnetic Resonance Spectroscopy (^{1}H-MRS),[35,40,51] two used abdominal ultrasound alone,[32,42] one used Fibroscan alone,[50] two used a combination of Fibroscan and liver enzymes,[46,47] one used a combination of ultrasound and Fibroscan,[49] and seven used a combination of ultrasound and liver enzymes.[33,36,39,41,43,44,48] Characteristics of each study, patient population and study design are presented in Table 2.[32-36,38-51]

Intervention Characteristics

Of the nineteen studies included in this review, two compared a hypocaloric diet to a hypocaloric diet plus a co-intervention (a cholesterol absorption inhibitor and an oral hypoglycaemic agent).[32,40] One study compared a hypocaloric diet to a Dietary Approaches to Stop Hypertension (DASH) diet [41] and one compared an isocaloric diet to an isocaloric diet plus the addition of Corinthian currants.[49] Two studies compared an energy-balanced diet to an energy-balanced diet with the addition of a synbiotic supplement [44,46] and four studies compared an energy-balanced diet to an energy-balanced diet plus supplementation (prebiotic, probiotic, ginger, green coffee bean extract (GCBE), or flaxseed).[43,47,48,50] Four studies used a Low-Fat Diet (LFD) intervention (American Diabetes Association guide for weight-management diet,[42] National Cholesterol Education Program (NCEP) Adult Treatment Panel III therapeutic lifestyle-change diet,[45] and Step One American Heart Association (AHA) Diet)[34,39] compared to the same LFD plus supplementation (soy isoflavone,[42] L-carnitine,[45] Vitamin E,[34] and n-3 PUFA).[39] One study compared a LFD to a High-Fat Diet (HFD),[51] another study compared a Plant Protein Isocaloric Diet to an Animal Protein Isocaloric Diet,[35] and another compared a Mediterranean Diet to an identical diet plus olive oil enriched with n-3 PUFA.[36] A trial with three intervention arms compared a low-calorie diet, a low-calorie and low carbohydrate diet and a soy containing – low-calorie, low carbohydrate diet.[33]

Protocols for the dietary interventions were diverse; the nutrient composition and caloric intake targets, major food sources and physical activity (PA) recommendations are detailed in Table 3.[32-36,38-51] Definitions for the calorie-restricted diets ranged from unspecified,[40] a 250kcal per day deficit to 700kcal per day deficit,[41] for which most caloric requirements were calculated on an individual basis and were dependent on baseline BMI. The energy-balanced diet and PA recommendations implemented in six studies [43,44,46-48,50] were according to Clinical Guidelines for the Study of Obesity.[52] The Mediterranean Diet protocol was unspecified.[36]

Inflammatory Markers

Cytokines

The most commonly analysed cytokines in the included studies were hs-CRP, TNF-alpha and IL-6 which were reported in twelve,[33,38,40,41,44-51] eleven,[35,39,40,42,44-50] and six studies respectively.[35,38,40,42,49,51] Data extracted for intervention effects of cytokines within each study are presented in Table 4.[33,35,38-42,44-51]

hs-CRP

Of the twelve studies that evaluated hs-CRP, eleven studies reported significant improvements from pre- to post-intervention and one study reported non-significant improvements (Table 4). Kaliora *et al.*[49] conducted a 24-week RCT which found that participants who received isocaloric dietary advice alone and participants who received isocaloric dietary advice with additional 35g Corinthian currents both significantly improved hs-CRP (P =0.023 and 0.002, respectively). No significant differences were seen between treatment groups (P =0.748). After an 8-week intervention comparing a hypocaloric diet to a DASH diet there was a significant reduction in hs-CRP for the DASH diet group only (P =0.08 and 0.004, respectively).[41] Another 8-week intervention saw a reduction in hs-CRP following

a low-calorie, low-carbohydrate, soy containing diet (P =0.01).[33] Both a food-based and meal replacement very low energy diet significantly reduced hs-CRP (P =0.007 and 0.004, respectively).[38] Of the studies intervening with diet plus supplementation, Chan *et al.*[40] reported significant improvements following a hypocaloric, low-fat diet plus a cholesterol lowering supplement (P <0.05) in comparison to a hypocaloric, low-fat diet alone which resulted in a non-significant increase in hs-CRP (NS). Similarly, a NCEP diet plus L-carnitine supplement significantly reduced hs-CRP (P <0.05) in comparison to the non-significant reduction seen in the NCEP diet alone (NS).[45] Significant reductions in hs-CRP occurred after both an energy-balanced diet alone and an energy-balanced diet alongside ginger supplementation (P =0.005 and 0.007, respectively).[47] In contrast, Shahmohammadi *et al.*[48] found an energy-balanced diet alone did not change levels of hs-CRP whereas an energy-balanced diet plus GCBE supplement improved hs-CRP (P =0.846 and <0.001, respectively). Two studies compared an energy balanced diet alone with an energy-balanced diet plus synbiotic supplement and a third study compared an energy balanced diet with or without flaxseed supplementation; all studies reported a decrease in hs-CRP for all groups, though the mean decrease in supplementation groups were significantly greater (P <0.001).[44,46,50] Overall, dietary interventions such as a DASH, isocaloric or energy-balanced diet significantly improved hs-CRP. Interestingly, a co-intervention which supplemented Corinthian currents alongside an isocaloric diet significantly improved hs-CRP. Pharmacological agents including a cholesterol lowering supplement alongside a hypocaloric, low-fat diet and L-carnitine supplement alongside NCEP diet significantly lowered hs-CRP, as did nutraceutical supplements of ginger, GCBE, synbiotic and flaxseed with energy-balanced diets.

TNF-α

Ten of the eleven studies that analysed TNF-α reported significant improvements with dietary interventions, and one study reported beneficial change in the supplementation group only, albeit without statistical significance (Table 4). Of the diet alone studies, Kaliora *et al.*[49] found that TNF-α significantly decreased following an isocaloric diet alone (P =0.004) whereas adversely increased following an isocaloric diet with the addition of Corinthian currents (P =0.063). Markova *et al*.[35] found significant reductions in TNF-α following a plant protein isocaloric diet and no increase following an animal protein isocaloric diet (P =0.016 and 0.925, respectively). Of the studies implementing a diet alongside supplementation, Chan *et al.*[40] reported significant improvement in TNF-α for the hypocaloric, low-fat diet plus cholesterol lowering supplement (P < 0.05) in comparison to the hypocaloric, low-fat diet alone (NS). Similarly, the NCEP diet plus L-carnitine supplementation significantly reduced TNF-α (P <0.001) compared to the NCEP diet alone (NS).[45] Likewise, Amanat *et al.*[42] found significant reductions of TNF-α following a weight-management diet plus soy isoflavone supplement and no change following a weight-management diet alone (P =0.01 and 0.99, respectively). One study investigating an energy-balanced diet alone compared with an energy-balanced diet plus synbiotic supplementation [44] and one study investigating an energy-balanced diet alone compared with an energy-balanced diet plus flaxseed supplement [50] reported a decrease in TNF-α for all groups, although the mean decrease in supplementation groups were significantly greater (P <0.001). Furthermore, both an energy-balanced diet alone and an energy-balanced diet alongside ginger supplementation significantly reduced levels of TNF-α (P =0.003 and <0.001, respectively).[47]

Dietary interventions including; a plant-protein isocaloric diet, isocaloric diet and an energy-balanced diet significantly improved TNF-α. A healthy weight-management diet plus soy

isoflavone supplement significantly improved TNF- α, whilst nutraceutical supplements of ginger, synbiotics and flaxseed all alongside energy-balanced diets significantly improved TNF- α. Pharmacological agents including a cholesterol lowering supplement alongside a hypocaloric, low-fat diet and L-carnitine supplement alongside NCEP diet lowered hs-CRP significantly.

IL-6

Six studies reported on the effects of a dietary intervention on levels of IL-6, with four studies reporting significant improvements and two studies reporting non-significant improvements (Table 4). Of the diet studies, a 24-week study conducted by Kaliora *et al*.[49] found significant reductions in IL-6 with the isocaloric diet plus Corinthian currants group compared to a non-significant reduction with isocaloric diet alone (P =0.009 and 0.322, respectively). Of the diet and supplementation studies investigating IL-6, Amanat *et al*.[42] reported significant reductions in IL-6 following a weight-management diet plus soy isoflavone supplement compared to a weight-management diet alone where no change was seen (P =0.01 and 0.80, respectively). Chan *et al.*[40] reported significant changes for IL-6 in the hypocaloric, low-fat diet plus cholesterol lowering supplement group (P <0.05) in comparison to the hypocaloric, low-fat diet alone (NS). Kugelmas *et al.*[34] compared an AHA diet with an AHA diet plus Vitamin E supplementation and merged these groups for data analysis (due to a small and similar intervention groups), reporting a significant decrease in IL-6 concentration (data not presented in table as numerical values were not provided). No dietary intervention alone significantly improved IL-6, however, a short-term low-energy meal replacement diet; a hypocaloric, low-fat diet plus cholesterol lowering agent; an isocaloric diet plus Corinthian current supplementation and a weight-management diet plus soy isoflavone significantly improved IL-6.

Other cytokines

Interleukins 4, 8, 10, 12 and 18,[35,51] Monocyte Chemoattractant Protein-1 (MCP-1),[35] Interferon Gamma (IFNγ),[51] Visfatin [49] and Retinol binding protein-4 (RBP-4) [40] were each reported in one study (Table S1 in the Supporting Information online). Nuclear Factor-κB (NF-κB) [44,46] and Fetuin-A [38,40] were reported in two studies. An animal protein isocaloric diet resulted in significantly decreased IL-18.[35] NF-κB decreased following an energy-balanced diet with and without synbiotic and flaxseed supplementation,[44,46] although the mean decrease in supplementation groups pre versus post intervention were significantly greater than diet alone (P <0.001). A hypocaloric, low fat diet alone and a hypocaloric, low fat diet plus cholesterol lowering supplement significantly lowered both RBP-4 (P <0.05) and Fetuin-A (P <0.05).[40] VLED's in the form of FD and MRP both reduced Fetuin-A significantly.[38] No significant changes were reported for all other markers.

Adipokines

The effects of a dietary intervention on adiponectin were investigated in six studies [32,35,36,40,43,51] and three studies reported on leptin.[43,49,51] Data extracted for intervention effects of adipokines within each study are presented in Table 5.[32,35,36,40,43,49,51]

Adiponectin

Of the six studies evaluating adiponectin, five reported a significant increase in serum adiponectin levels suggesting improvement in inflammatory status and one study showed no significant change (Table 5). Of the diet alone studies, Markova *et al.*[35] reported a significant improvement in adiponectin following a plant protein isocaloric diet (P =0.003) but not an animal protein isocaloric diet (NS). Moreover, Sofi *et al.*[36] observed a significant increase of adiponectin levels in the Mediterranean diet enriched with n-3 PUFA olive oil (P =0.04), while a non-significant increase was reported for the Mediterranean diet alone (NS).

Of the dietary intervention plus supplementation studies, Behrouz *et al.*[43] reported a significant increase in adiponectin for each of the energy-balanced diets alone, the energy-balanced diet plus probiotic and the energy-balanced diet plus prebiotic groups (P =0.005, <0.001 and 0.001, respectively). A hypocaloric, low-fat diet plus placebo and a hypocaloric, low-fat diet plus cholesterol lowering agent, reported that adiponectin increased significantly in both groups (P <0.05).[40] Garinis *et al.*[40] showed that a hypocaloric diet alone compared to a hypocaloric diet plus oral hypoglycaemic supplement increased adiponectin for both groups; although the increase reached statistical significance in the hypocaloric diet plus oral hypoglycaemic agent group (P <0.005) and not in the hypocaloric diet only group (P <0.17).

Adiponectin improved significantly following a plant-protein isocaloric diet and an energy balanced diet. Significant improvements were also observed following hypocaloric diets. Supplements which improved adiponectin were n-3 PUFA olive oil, probiotics and prebiotics. Pharmacological agents which improved adiponectin include both a cholesterol lowering agent and an oral hypoglycaemic agent.

Leptin

Behrouz *et al.*[43] reported significant reductions in leptin following both an energy-balanced diet plus probiotic supplement (P <0.001) and an energy-balanced diet plus prebiotic supplement (P <0.001), although no significant changes were seen following the diet alone group.

Dietary intervention alone did not improve leptin significantly, however energy–balanced diet supplemented with probiotics, or prebiotics, significantly improved leptin.

Liver Imaging and Histology

Five studies assessed liver imaging and histology post-intervention using abdominal ultrasound,[32,36,39,41,48] one study used ultrasound and TE Fibroscan™,[49] four studies used TE Fibroscan™ only,[44,46,47,50] three utilised ^{1}H-MRS,[35,40,51] and two performed liver biopsy.[38,45] Of the nineteen studies, four did not assess post-intervention liver imaging or histology. Data extracted for each of these measures is presented in Table S2 in the Supporting Information online. Most significant changes occurred following a hypocaloric diet with and without an oral hypoglycaemic agent ($p<0.029$ and $p<0.0001$),[32] hypocaloric diet with and without a cholesterol lowering agent ($p<0.05$),[40] hypocaloric and DASH diet(s) alone ($p<0.001$),[41] isocaloric diet with and without current supplementation ($p<0.05$),[49] or energy-balanced dietary intervention alone or with synbiotic,[44,46] ginger,[47] or flaxseed[50] supplementation. The Mediterranean[36] and AHA[39] diets (with or without n-3 PUFA supplement) have also achieved significant reductions in hepatic steatosis and insulin resistance in a NAFLD population, although p-values were not reported. Using liver biopsy, the NCEP diet alone significantly reduced NASH-activity scores ($p<0.001$), as did the NCEP diet plus L-carnitine supplementation group ($p<0.001$).[45]

Quality assessment of studies

The quality assessment of studies using the American Dietetic Association (ADA) quality assessment tool for primary studies [31] is presented in Table 2, and the assessment of internal and external biases of each study is shown in Figure 2.[32-36,38-51] All studies were, overall, found to be of positive (+) quality, with seven of the twenty studies ranking positive in all sections.[33,41,43-47] Ten studies ranked negative (-) or unclear (ø) due to inadequate blinding of participants or research personnel.[32,34-36,38-40,49-51] Blinding is often not possible in dietary intervention trials however blinding of outcome assessors, technicians, and laboratory staff enhances research rigour if applied to all trials. This intent was not clear in

the above studies that ranked negative for this domain. Of the aforementioned eleven studies, six ranked negative (-) or unclear (ø) in the way they described withdrawals [34-36,42,48,51] and a further two had groups that were considered non-comparable and may affect interpretation of outcome measures due to significant differences at baseline.[34,51]

Of the nineteen included studies, only seven studies [33,36,38,39,41-43] calculated sample size using statistical power generated to see a significant change, although these outcomes were not specific to inflammatory markers. Furthermore, it was unclear in most studies whether the inflammatory marker(s) were examined as a primary or secondary outcome.

Discussion

This systematic review provides evidence that dietary interventions implemented in RCTs can lower levels of circulating serum inflammatory cytokines and increase levels of circulating adiponectin in individuals with NAFLD. Although the effects of dietary interventions on inflammatory markers varied, diets which demonstrated more favourable change were calorie restricted, isocaloric and diets adhering to DASH or NCEP dietary guidelines . Dietary interventions with the addition of a co-intervention – specifically nutraceuticals or a pharmacological supplementation demonstrated added benefits compared to diet alone in a NAFLD population.

In this review, the most effective studies were calorie restricted dietary interventions which resulted in significant weight loss. Typically in the treatment of NAFLD weight loss is considered a primary focus as restriction of energy intake induces rapid adipose tissue reduction thus lowering IR and hepatic steatosis.[53,54] Adipokine and cytokine production is inhibited subsequent to the decrease in adiposity.[55] While clinical trials investigating calorie-restricted diets report inflammatory changes following weight loss, due to their restrictive

394 nature these diets are often unsustainable in NAFLD patients and may result in portal
395 fibrosis or necroinflammation following rapid weight loss.[56]
396 This review also highlighted the effects of the NCEP diet; advocated in NAFLD to balance
397 macronutrient intake and anti-inflammatory foods, and DASH eating plan; for a low-
398 glycaemic-index and low energy-dense diet with an emphasis on sodium intake. The NCEP
399 diet has been successful in trials lowering CRP,[53] as well as hepatic steatosis and fibrosis.[45]
400 The DASH diet has also reduced CRP levels in adults with NAFLD,[41] adolescents with MetS,[57]
401 and patients with polycystic ovary syndrome (PCOS)[58] – chronic disease in which insulin
402 resistance, obesity and abdominal fat accumulation are underlying pathophysiological
403 contributors. These changes have been attributed to weight loss, considering a reduction in
404 adipocytes accompanied by a reduction in IL-6 is likely to be responsible for the reduction in
405 CRP.[59]
406 One small study included in this review investigated the Mediterranean diet, in which
407 researchers did not find a significant effect for diet alone in a NAFLD population.[36] This study
408 however; resulted in an improvement in adiponectin following a Mediterranean Diet with n-
409 3 enriched olive oil supplementation.[36] Adhering to a diet rich in antioxidants and phenolic
410 compounds from wholegrains, fruits, vegetables, nuts and extra virgin olive oil may
411 decrease hs-CRP, as well as circulating levels of free radicals and pro-inflammatory cytokines
412 IL-6, IL-18, and TNF-α.[19] These dietary components, typical of the Mediterranean diet, are
413 extensively investigated in the treatment of IR and MetS.[19,23] Moreover, Kaliora *et al.*[49]
414 found that within a Greek population, adherence to a Mediterranean diet supplemented
415 with Corinthian currents as a regular dietary snack, there was an associated improvement in
416 levels of hs-CRP and IL-6. This was not unprecedented as authors noted recent studies

identifying bioactive phytochemicals and phenolic compounds in currents could potentially ameliorate fasting glucose, inflammation and fibrosis stage.[49]

A diet receiving considerable attention in recent RCT's for NAFLD populations and within this review was an energy-balanced diet - implementing "general tips for healthy eating", low-fat cooking methods and moderate PA recommendations;[52] this diet improved hs-CRP, TNF- α and adiponectin. Improvements in these inflammatory markers were further enhanced when an energy-balanced diet was combined with prebiotic,[43] probiotic,[43] synbiotic,[44,46] ginger,[47] flaxseed [50] or GBCE [48] supplements. Although the efficacy of dietary intervention was partially assessed in these studies, the effect of supplementation was considered the primary outcome and found to elicit superior benefits than diet alone. Hence the diet alone group was used as a control rather than as an experimental group, though significant effects were seen following diet only. Shahmohammadi *et al.*[48] attributed a significant decrease in hs-CRP to the anti-inflammatory and anti-oxidant activities of a GCBE supplement. Similarly, Rahimlou *et al.*[47] found their results to be in line with previous studies reporting that ginger supplementation exhibited anti-diabetic, anti-cancer and anti-inflammatory properties, leading to a significant decrease in serum levels of TNF- α and hs-CRP.[60,61] Flaxseed oil, a supplement that has been shown to have potential health benefits for cardiovascular disease, MetS and dyslipidaemia,[62-64] is thought to improve weight management, lipid profile, IR and inflammatory cytokines; hs-CRP and TNF-α.[50] Given that flaxseed is a rich source of n-3 fatty acids, it's mechanism of action is to ameliorate hepatic lipid accumulation and oxidative stress. This review found improvements in both leptin and adiponectin following prebiotic, probiotic and synbiotic supplementation.[43] Few studies have investigated the effects of prebiotics and probiotics in adipokines in humans, though evidence is mounting for potential use synbiotic supplements to protect the liver from

damage. It is thought that synbiotic supplements retard inflammation, resulting in down-regulating of insulin signalling in adipose tissue thereby decreasing fat accumulation. Animal models have displayed the benefits of probiotics on leptin.[65] Moreover, a recent meta-analysis found that microbial therapies of prebiotic, probiotic and synbiotic supplementation did not improve levels of CRP and TNF- α.[66] L-Carnitine supplementation was seen to have beneficial effects on inflammatory cytokines hs-CRP and TNF-α;[45] although this has been confirmed animal model,[27] human studies in a NAFLD population are yet to prove L-carnitine as convincing as a therapeutic option.[25]

Alternatively, Kuglemas *et al.*[34] concluded that lifestyle modification and exercise were associated with improvement in liver enzymes and cholesterol in patients with NASH, whereas vitamin E supplementation provided no apparent added benefit. Previous studies in NAFLD have shown the potential benefits effects of Vitamin E [67] and nutraceutical supplementation on hepatic outcomes when administered alongside diet,[45] however additional evidence is required before prescription can be recommended for the alleviation of inflammatory outcomes. Whether participants in supplement arms of trials adhere better to the intervention is difficult to determine, as is the efficacy of these therapies alongside diet. The effect of nutraceutical intervention in NAFLD has potential to be further investigated in a short- to medium-term capacity. However, in this review supplements were only included if they were within an intervention that had a stand-alone dietary intervention arm.

PA, although not a primary outcome of this review, also plays a central role in the alleviation of hepatic and inflammatory outcomes and may independently reduce disease severity.[68] The majority of studies in this review recommended that all study participants, regardless of their assigned intervention group, engage in moderate PA for 30 minutes,

more than three times per week. Recommendations were brief and generally advised low to moderate intensity aerobic exercise and routine stretching. Although PA recommendations were given, adherence to this parameter was not recorded or reported hence these changes could not be assessed. In future studies, PA should be monitored and/or controlled for in future dietary intervention trials in this population, so that the true impact of dietary intervention can be assessed.

The use of pharmaceuticals is also emerging in NAFLD. Chan *et al.*[40] showed that Ezetimibe, a potent cholesterol absorption inhibitor, improved adiponectin, hs-CRP, TNF-α, and IL-6. The underlying mechanism of ezetimibe is to reduce LDL cholesterol concentrations and therefore improve dyslipidaemia. For this reason, it was thought to be an optimal approach in the clinical setting, as well as to moderate weight loss. Additional studies have found improvement in weight-loss when ezetimibe was combined with statins.[34,69,70] Definitive conclusions for Ezetimibe cannot be drawn as yet, due to insufficient evidence surrounding their effects for short- and long-term use.

Whilst it was not a primary outcome of this review, noteworthy changes in liver histology were evident following; hypocaloric,[32,41,45] isocaloric,[49] energy-balanced,[44,46,47,50] DASH,[41] AHA,[39] NCEP,[45] and Mediterranean[36] diets. The addition of various co-interventions achieved significant changes in markers of steatosis and fibrosis, as defined by abdominal ultrasound, ^{1}H-MRS, Transient Elastography (TE) Fibroscan™ and/or liver biopsies. Changes in liver severity were difficult to compare between studies due to the various liver imaging and histology tools, though findings are relatively consistent with previous literature. Although liver biopsy remains the gold-standard approach in confirming NAFLD severity, the approach remains too invasive particularly in large dietary intervention cohorts of patients with simple steatosis. Therefore, additional large studies of this disease cohort are required

to elucidate the specificity of cytokines and adipokines as surrogate markers of disease. Given the pathophysiology and underlying mechanisms of the chronic inflammatory state of NAFLD, it is important to consider the inflammatory markers presented in this review and the role they place in disease progression in the absence of any known liver-sensitive markers.

This review highlights the limited evidence that is currently available to assess the impact of an optimal dietary composition on pro-inflammatory cytokines and adipokines in a NAFLD population. A pooled estimate of effect, or meta-analysis, was not possible given the heterogeneity of control and experimental groups within each study. The populations across the studies were diverse and the impact of habitual diets and genetics may influence the extent of response to dietary interventions. Other limitations of this review included the small sample size of included studies reducing statistical power for inflammatory markers as a primary outcome, especially when some inflammatory markers may be more susceptible to change with diet and other external factors. Two studies [40,51] included in this review focused on recruiting obese individuals from which 10 participants did not have NAFLD (IHTG<5%). Some studies did not report a macronutrient breakdown of the recommended diets and therefore it was difficult to make comparisons or pool together dietary prescriptions. Dietary compliance was often not monitored or reported, and there was inconsistency between cytokines and adipokines studied.

Still this systematic review study has important strengths in that the overall population within the included studies - age, gender, anthropometry and general characteristics were reflective of and therefore generalisable to the NAFLD population. Moreover, liver biopsy, US, magnetic resonance spectroscopy and transient elastography, and/or liver chemistries were used in the diagnosis and reporting of NAFLD in all included studies.

To determine whether dietary interventions, with or without co-interventions are effective at improving inflammatory outcomes in individuals with NAFLD and more widely assess liver outcomes future research should involve large, statistically powered cohorts with specific pro-inflammatory cytokines and adipokines as primary outcome measures in patients with biopsy or ultrasound proven NAFLD.[16] Dietary interventions should consist of an experimental diet in comparison to a control (or habitual) diet for the same duration of time. To determine if dietary interventions are effective at improving inflammatory outcomes supplementation should not be administered in either group, as it will allow the dietary interventions with quality of diet or active nutrients of interest to be adequately assessed. It will also be beneficial, from a mechanistic and clinical standpoint, to distinguish between the effect of diet on serum cytokines and adipokines in the absence if weight loss.

Conclusions

Dietary interventions including hypocaloric, isocaloric or diets which adhere to DASH or NCEP dietary guidelines appear to demonstrate improvements in circulating serum inflammatory cytokines and adipokines in a NAFLD population. However, these effects were predominantly driven by weight loss. Dietary interventions including nutraceutical or a pharmacological supplementation appear to elicit superior outcomes compared to diet alone in patients with NAFLD.

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Author contributions

AJR and ACT conceptualised and designed this review. AJR and ESG conducted the search process and data extraction. AJR, ESG and ACT contributed to data analysis and

interpretation. AJR drafted the manuscript and all authors reviewed approved the final manuscript.

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Declaration of interest

There are no conflicts of interest to disclose for all authors.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1: PRISMA checklist

Appendix S2: Search strategy

Table S1: Data extracted for intervention effects of other cytokines

Table S2: Data extracted for intervention effects on liver histology and imaging

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Figure 1. PRSIMA Flow Chart for study selection

Figure 2. Individual quality assessment of studies according to ADA quality checklist.

Table 1. PICOS criteria for inclusion and exclusion of studies

PICOS	Inclusion/Exclusion	Data Extracted
Population	Inclusion: Adults ≥18 years old, diagnosed with NAFLD using one or more of the following diagnostic criteria: (i) histological examination of biopsies; (ii) magnetic resonance imaging (MRI) and/or magnetic resonance spectroscopy (^{1}H-MRS); (iii) computed tomography (CT); (iv) ultrasound (US); and (v) blood concentrations of liver enzymes alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). Exclusion: Any animal, paediatric or pregnancy studies	Location (country), method of NAFLD diagnosis, number of participants, age, gender, body mass index.
Intervention	Inclusion: Studies that compared a dietary intervention with an alternative diet or control. Studies where supplementation was provided alongside a dietary intervention, as long as there was an independent dietary intervention group (for example, supplementation plus dietary intervention vs. dietary intervention alone). Interventions that included a dietary intervention alongside a co-intervention such as physical activity, behaviour training or other lifestyle interventions were eligible if the control or other diet arm were stand alone (i.e. dietary intervention only). Studies that suggested physical activity reccomendations alongside both dietary intervention and control groups were included if these reccomendations were consistent between groups and not a primary outcome. Exclusion: Studies that intervened only with supplements or pharmacological drugs, or investigated only postprandial effects of a dietary or meal intervention.	Intervention length, type of dietary intervention, dietary intervention protocol. The addition of supplementation or co-intervention.
Comparators	Inclusion: Control group or standalone diet. Exclusion: Studies without a comparator group.	Intervention length, type of dietary intervention, dietary intervention protocol.
Outcomes	Inclusion: Studies which reported outcomes of inflammatory cytokines and/or adipokines. Exclusion: Studies that did not present results as numerical values for inflammatory cytokines and/or adipokines.	Type of inflammatory marker. Pre- and post-intervention results of each inflammatory marker.
Study Design	Inclusion: The current review included only randomised controlled trials (RCTs). Publications were eligible if they were published in peer-reviewed scientific journals, written in English language or had English versions of foreign language studies available. Exclusion: Reviews, cohort studies, cross-sectional studies, case control studies, conference abstracts,	Type of study design. Level of evidence of each study, as determined using the NHMRC Evidence Hierarchy (ref). Methodological quality of each study using the American Dietetic Association Quality Criteria Checklist for Primary Research (ref).

	editorials, letters, and reviews. Non-English language only papers.

Where 2 reports relate to the same patient group, the most complete report was included to avoid duplication of patient numbers.

Table 2. Characteristics of studies included for the systematic review investigating the effects of randomised controlled dietary intervention(s) on inflammatory markers in adults with NAFLD.

Reference	Country	NAFLD Diagnostic Method	Sample, n (M/F)	Study Type/NHMRC LOE and Quality Ax	Diet of Interest	2º Diet of Interest	3º Diet of Interest	Intervention length	Inflammatory Biomarkers measured
Amanat et al. (2017)[42]	Iran	US	Enrolled (n = 82), analysed (n = 78), M61/F21	RCT/Level II Positive	Weight-management diet plus placebo	Weight-management diet plus soy isoflavone supplement		8 weeks	TNF-α, IL-6
Baldry et al. (2017)[38]	United Kingdom	Liver Bx	Total (n = 54), M44/F10	RCT/Level II Positive	Very Low Energy Diet (VLED) in the form of standard pre-bariatric surgery food-based diet	Very Low Energy Diet (VLED) in the form of a meal-replacement plan		2 weeks	hs-CRP, IL-6, fetuin-A
Behrouz et al. (2017)[43]	Iran	US and ALT (>1.5 x upper limit of normal)	Total (n = 89), M63/F26	RCT/ Level II Positive	Energy-balanced diet plus prebiotic and probiotic placebo	Energy-balanced diet plus probiotic supplement and prebiotic placebo	Energy-balanced diet plus prebiotic supplement and probiotic placebo	12 weeks	Adiponectin, Leptin
Chan et al. (2010)[40]	Australia	MR-S (IHTG %)	Total Obese and T2DM (n = 25), M15/F10	RCT/Level II Positive	16-week hypocaloric, Low-Fat diet**,** followed by 6-week isocaloric diet plus placebo supplement consumed for 22-weeks.	16-week hypocaloric, Low-Fat diet, followed by 6-week isocaloric diet plus 10mg/d ezetimibe consumed for 22-weeks.		22 weeks	Adiponectin, hs-CRP, TNF-α, IL-6, RBP-4, Fetuin-A,
Eslamparast et al. (2014)[42]	Iran	US and ALT (>60 U/L)	Total (n = 52), M25/F27	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus synbiotic supplement		28 weeks	hs-CRP, TNF-α, NF-κB

Garinis et al. (2010)[38]	Italy	US	Total (n = 45), M7/F38	RCT/Level II Positive	Hypocaloric diet	Hypocaloric diet plus metformin 1000mg/d		6 months	Adiponectin
Kaliora et al. (2016)[49]	Greece	US	Total (n = 55), M23/F32	RCT/Level II Positive	Isocaloric diet	Isocaloric diet plus Corinthian currants		24 weeks	hs-CRP, TNF-α, IL-6, Leptin, Visfatin
Kani et al. (2014)[33]	Iran	US, ALT and AST (M >30 U/L, F >20 U/L)	Total (n = 45), M21/F24	RCT/Level II Positive	Low calorie diet	Low-calorie, low carbohydrate diet	Low-calorie, low carbohydrate soy-diet	8 weeks	hs-CRP
Kugelmas et al. (2003)[44]	USA	Liver Bx	Total (n = 16), M7/F9	RCT/Level II Positive	Step One American Heart Association (AHA) diet	Step One American Heart Association (AHA) diet plus Vitamin E 800IU p/d		12 weeks	TNF-α, IL-6, IL-8
Malaguarnera et al. (2010)[32]	Italy	Liver Bx	Total (n = 74), M40/F34	RCT/Level II Positive	National Cholesterol Education Program (NCEP) diet plus placebo.	National Cholesterol Education Program (NCEP) diet plus L-Carnitine.		24 weeks	hs-CRP, TNF-α
Marina et al. (2014)[49]	USA	MR-S	Total Obese sample (n = 13), M10/F3	Random order, comparative study with concurrent controls/Level III-2 Positive	Low-Fat Diet (LFD)	High-Fat Diet (HFD)		4 weeks	Adiponectin, Leptin, hs-CRP, IL-6, IL-10, IL-12, Gamma-Inferon (IFNγ)
Markova et al. (2016)[33]	Germany	MR-S	Total (n = 37), M24/F13	RCT/Level II Positive	Plant protein Isocaloric Diet	Animal protein Isocaloric Diet		6 weeks	Adiponectin, TNF-α, IL-4, IL-6, IL-8, IL-18, MCP-1
Mofidi et al. (2017)[34]	Iran	Fibroscan and ALT (>60 U/L)	Total (n = 42), M23/F19	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus synbiotic supplement		28 weeks	hs-CRP, TNF-α, NF-κB

Rahimlou et al. (2016)[45]	Iran	Fibroscan and ALT (>1.5 x upper limit of normal)	Total (n = 44), M20/F24	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus ginger supplement	12 weeks	hs-CRP, TNF-α
Razavi Zade et al. (2016)[51]	Iran	US and ALT (M >30 U/L, F >19 U/L	Total (n = 60), M30/F30	RCT/Level II Positive	Hypocaloric Diet	Dietary Approaches to Stop Hypertension (DASH) Diet	8 weeks	hs-CRP
Shahmohammadi et al. (2017)[35]	Iran	US and ALT (M >30 U/L, F >19 U/L	Total (n = 44), M22/F22	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus green coffee bean extract (GCBE) supplement	8 weeks	hs-CRP, TNF-α
Sofi et al. (2010)[46]	Italy	US and ALT (M >30 U/L, F >20 U/L)	Total (n = 11), M9/F2	RCT/Level II Positive	Mediterranean Diet	Mediterranean diet + olive oil enriched with n-3 PUFA	12 months	Adiponectin
Spadaro et al. (2008)[47]	Italy	US and ALT (M >30 U/L, F >20 U/L)	Total (n = 36), M19/F17	RCT/Level II Positive	American Heart Association (AHA) Diet Plus placebo	American Heart Association (AHA) Diet plus n-3 PUFA capsule.	6 months	TNF-α
Yari et al. (2016)[41]	Iran	Fibroscan	Total (n = 50), M25/F25	RCT/Level II Positive	Energy-balanced diet	Energy-balanced diet plus flaxseed supplement	12 weeks	hs-CRP, TNF-α

Abbreviations: ns, not specified; MR-S, Magnetic Resonance-Spectroscopy; IHTG%, Intra-Hepatic Triglyceride percent; US, Ultrasound; ALT, Alanine transaminase; AST, Aspartate transaminase; Bx, Biopsy; M, Male; F, Female; RCT, Randomised Controlled Trial; PUFA, Polyunsaturated Fatty Acid; n-3, Omega-3; hs-CRP, high sensitivity C-reactive protein, TNF-α, tumour necrosis factor-alpha; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; IL-12, Interleukin-12; IL-18, Interleukin-18; RPB-4, Retinol Binding Protein-4; NF-κB, Nuclear Factor-kappa B; MCP-1, Monocyte Chemoattractant Protein-1.

Table 3. Dietary intervention protocol data extracted from each study

Ref.	Diet Label	Nutrient Composition Targets	Caloric Intake Recommendations	Main food sources:	Physical Activity recommendations
Amanat et al. (2017)[48]	American Diabetes Association Guidelines or "Weight-management Diet"	<25-30% of total energy as fat (<7% as SFAs, 20% as MUFAs, and 10% as PUFAs), 15% as protein, 50-60% as carbohydrate, <200 mg/d as dietary cholesterol, and 20–30g fibre/d.	Energy intake goal to achieve a 500–1,000 kcal/day energy deficit.	A variety of fruits, vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry, and lean meats. Limit foods high in saturated fat, trans fatty acids, and cholesterol; substitute unsaturated fat from vegetables, fish, legumes, and nuts. Emphasize a diet rich in fruits, vegetables, and low-fat dairy products. Limit salt to 6 g/day (2,400 mg sodium) by choosing foods low in salt. Limit alcohol intake to <2 drinks per day (men) and 1 drink per day (women).	Initial physical activity recommendations of 30 – 45 min of moderate aerobic activity, 3–5 days per week, when possible. Greater activity levels of at least 1 h per day of moderate (walking) or 30 min per day of vigorous (jogging) activity to achieve successful long-term weight loss.
Baldry et al. (2017)[36]	Very Low Energy Diet (VLED); pre-bariatric surgery food-based diet	ns	800kcal/d	Standard pre-bariatric surgery food-based diet using LighterLife Nutritional supplements	ns
	Very Low Energy Diet (VLED); pre-bariatric surgery meal replacement plan	ns	800kcal/d	Standard pre-bariatric surgery meal replacement plan using LighterLife Nutritional supplements	ns
Behrouz et al. (2017)[39]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.
Chan et al. (2010)[50]	Hypocaloric, LF	ns	ns	ns	ns
	Isocaloric	ns	ns	ns	ns
Eslamparast et al. (2014)[42]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.
	Hypocaloric	ns	1,300 kcal consumed per day	ns	ns

Garinis et al. (2010)[38]					
Kaliora et al. (2016)[43]	Isocaloric	30% of the total energy as fat (<10% as SFAs, ~10% as MUFAs, and ~10% as PUFAs), 20% as protein, 50% as carbohydrate, 300 mg d−1 as dietary cholesterol, and 20–30 g fibre per d.	Daily energy needs were determined according to the basic metabolic rate equation of Harris–Benedict and sedentary lifestyle.	Participants in both diet groups received the same dietary counselling. The Current arm incorporated in their daily diet the consumption of 36 g of Corinthian currants equal to two fruit servings replacing snacks of alike nutritional value (low fat yogurt, mini crackers, or bread with low fat cheese).	Aim of nutritional counselling was a weight loss of approximately 5% of the initial BW within 6 months.
Kani et al. (2014)[40]	Low-calorie	55% of calories were supplied by carbohydrates, 30% by fats, and 15% by proteins.	Calorie restriction was considered according to participant's BMI category. A 200-calorie reduction was considered for overweight individuals and up to a 500-calorie reduction for obese participants.	ns	Recommended that all participants engage in moderate physical activity for 30 min a day.
	Low-calorie, low carbohydrate	45% of the calories were supplied by carbohydrates, 35% by fats, and 20% by proteins.		ns	
	Low-calorie, low carbohydrate soy containing	Composition of the macronutrients was similar to the low calorie, low carbohydrate group except in this diet 30 g of soy nut was incorporated instead of 30 g of red meat.		Soy nut was provided in suitable amounts in a separated box with a small glass showing 30 g.	
Kugelmas et al. (2003)[44]	AHA	ns	ns	ns	ns
Malaguarnera et al. (2010)[32]	NCEP	50-60% of total energy as carbohydrates, 15% as protein and 25-35% as fat.	Patients in both the groups were given the same 1,600-calorie diet.	ns	Both the groups were prescribed an exercise plan and a 30-min home-based whole-body stretching routine to perform three times per week.
Marina et al. (2014)[49]	Low-Fat	20% total energy as fat (8% saturated fat) and 62% as carbohydrates.	Caloric needs were estimated using the average of the Mifflin-St. Jeor and Harris-Benedict equations, adjusted for physical activity.	Major sources of fats in both diets included butter and high oleic safflower oil. Vegetable content was matched. Because fructose was limited on the HFD due to the low carbohydrate content, fructose was limited in both diets to <30 g/day based on a 2000 kcal per day diet.	Subjects were instructed to maintain regular physical activity and to eat all of the food provided, not to eat any non-study food, and to report any deviations from the diet.
	High-Fat	55% total energy as fat (25% saturated fat) and 27% as carbohydrates.			

Markova et al. (2016)[33]	Plant Protein Isocaloric	30% of total energy as protein, 40% as carbohydrates and 30% as fat (10% SFA, 10% MUFA, 10% PUFA).	Energy intake of participants was estimated using reports on daily intake and physical activity and resting energy expenditure measured by indirect calorimetry.	Foods enriched with pea proteins especially developed for this study (e.g., noodles, a pea protein drink, a mash potato, a pea protein bread, and cookies).	ns
	Animal Protein Isocaloric	30% of total energy as protein, 40% as carbohydrates and 30% as fat (10% SFA, 10% MUFA, 10% PUFA).		Dairy products, meat and fish.	ns
Mofidi et al. (2017)[34]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.
Rahimlou et al. (2016)[45]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.
Razavi Zade et al. (2016)[51]	Hypocaloric	52-55% of total energy as carbohydrates, 16-18% as protein and 30% as fat.	Both diets designed to be calorie-restricted (350–700 kcal deficit) depending on the BMI of the individual. Calorie requirements of each patient estimated based on resting energy expenditure (by use of Harris-Benedict equation) and physical activity levels.	Higher intake of whole grains and simple sugar than DASH diet. Moderate fruit, vegetable and meat, poultry and fish intake. Low dairy, nuts and legume intake.	Researchers requested participants not to change their routine physical activity and not to consume any supplements and medications that might influence related markers.
	DASH	52-55% of total energy as carbohydrates, 16-18% as protein and 30% as fat.		Rich in fruits, vegetables, whole grains, and low-fat dairy products and low in saturated fats, cholesterol, refined grains, and sweets. Suggested sodium was <2400mg/day.	
Shahmohammadi et al. (2017)[35]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.
Sofi et al. (2010)[46]	Mediterranean	ns	ns	Dietary recommendations and a package of olive oil not enriched with n-3 PUFA.	Participants were asked to indicate their usual pattern of physical activity.
	Mediterranean diet + olive oil enriched with n-3 PUFA	ns	ns	Dietary recommendations and a package of olive oil enriched with n-3 PUFA at the dosage of 6.5ml per day (0.83g n-3 PUFA, of which 0.47g Eicosapentaenoic acid (EPA)	

				and 0.24g Docosahexaenoic acid (DHA)).	
Spadaro et al. (2008)[47]	AHA	50% of total energy as carbohydrates, 20% as protein and 30% as fat.	All obese and overweight patients were advised to lose weight with a restriction of daily caloric intake to 25–30 kcal/kg per day.	ns	Initially, engaging in a moderate level of physical activity for 30-45 minutes recommended. Subsequent increases to 30-60 minutes on most/all days of the week need to be individualized and are targeted to expend a total of 100-200kcal.
Yari et al. (2017)[41]	Energy-balanced	<30% of total energy as fat (10% as SFAs, 15% as MUFAs, and 5% as PUFAs), 15–18% as protein, 52–55% as carbohydrate, <300 mg/d as dietary cholesterol, and 20–30g fibre/d.	Approximately 500 to 1,000 kcal/day reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week.

Abbreviations: ns, not specified; LF, Low-Fat; AHA, American Heart Association; NCEP, National Cholesterol Education Program; Ex, Exercise; DASH, Dietary Approaches to Stop Hypertension.

Table 4. Data extracted for intervention effects of cytokines

High sensitivity C-reactive protein							
Ref.	**Diet**	**Pre- ($mg\ L^{-1}$)**	**Post- ($mg\ L^{-1}$)**	**p value**	**%Change**	**Mean Change (95% CIs) ($mg\ mL^{-1}$)**	**Mean change ± SD ($mg\ L^{-1}$)**
		Dietary Intervention Alone					
Baldry et al. (2017)[48]	Very low energy diet; food based-diet	8.2 (42.8)[a]	5.1 (21.7)[a]	0.007*	-37.8%		
	Very low energy diet; meal-replacement plan	9.6 (29.1)[a]	6.4 (21.8)[a]	0.004*	-33.3%		
Kani et al. (2014)[36]	Low calorie	nd	nd	nd			-1.0 ± 0.6
	Low calorie, low carbo	nd	nd	nd			-1.1 ± 0.6
	Low calorie, low carbo, soy containing	nd	nd	0.01*			-8.0 ± 1.0
Marina et al. (2014)[39]	LF	3.3 ± 2.8	2.8 ± 2.5	ns	-15.1%		
	HF	2.3 ± 1.9	2.2 ± 1.2	ns	-4.3%		
Razavi Zade et al. (2016)[50]	Hypocaloric	4.9 ± 3.4	4.6 ± 2.8	0.08	-6.1%		
	DASH	4.8 ± 3.3	3.6 ± 2.7	0.004*	-25.0%		
		Dietary Intervention plus co-intervention					
Chan et al. (2010)[38]	Hypocaloric, LF	2.2 ± 1.3	2.4 ± 1.6	nd	+9.1%		
	Hypocaloric, LF + chol. lowering agent	3.9 ± 3.8	2.2 ± 2.7	<0.05*	-43.6%		
Kaliora et al, (2016)[33]	Isocaloric	2.4 ± 3.0	0.84 ± 1.1	0.023*	-65.0%		
	Isocaloric + Corinthian currants	2.1 ± 1.8	0.82 ± 0.7	0.002*	-60.9%		
Malaguarnera et al. (2010)[51]	NCEP	8.7 ± 3.4	7.4 ± 3.2	ns	-14.9%		
	NCEP + L-carnitine	9.1 ± 3.2	5.2 ± 3.1	<0.001*	-42.9%		
		Dietary Intervention plus supplementation					
Eslamparast et al. (2014)[41]	Energy-balanced	nd	nd			-1.04 (-1.5, -0.6)	
	Energy-balanced + synbiotic supp.	nd	nd			-2.30 (-3.0, -1.5)	
Mofidi et al. (2017)[40]	Energy-balanced	nd	nd				-0.42 ± 0.1[c]
	Energy-balanced + synbiotic supp.	nd	nd				-1.16 ± 0.4[c]
	Energy-balanced	4.8 ± 0.2	2.8 ± 0.2	0.005*	-41.7%		

Rahimlou et al. (2016)[49]	Energy-balanced + ginger supp.	4.6 ± 0.1	3.4 ± 0.1	0.007*	-26.1%	
Shahmohammadi et al. (2017)[45]	Energy-balanced	1.5 (0.4, 2.7)[b]	1.5 (0.4, 3.0)[b]	0.846	0.0%	
	Energy-balanced + GCBE supp.	1.4 (0.4, 3.4)[b]	1.1 (0.5, 2.3)[b]	<0.001*	-21.4%	
Yari et al. (2016)[44]	Energy-balanced	nd	nd			-1.02 (-1.6, -0.5)
	Energy-balanced + Flaxseed supp.	nd	nd			-2.05 (-2.6, 1.5)
TNF-alpha						
Ref.	**Diet**	**Pre- (ng mL^{-1})**	**Post- (ng mL^{-1})**	**p value**	**%Change**	**Mean Change (95% Cis) (ng mL^{-1})**
		Dietary Intervention Alone				
Markova et al. (2016)[46]	Plant protein Isocaloric	4.5 ± 2.6	3.8 ± 2.4	0.016*	-15.6%	
	Animal protein Isocaloric	4.3 ± 2.8	4.4 ± 2.2	0.925	+2.3%	
		Dietary Intervention plus co-intervention				
Chan et al. (2010)[47]	Hypocaloric, LF	5.4 ± 1.6	5.4 ± 1.9	ns	0.0%	
	Hypocaloric, LF + chol. lowering agent	6.3 ± 1.9	5.4 ± 2.3	<0.05*	-14.3%	
Kaliora et al. (2010)[48]	Isocaloric	1.3 ± 1.0	0.8 ± 0.5	0.004*	-38.5%	
	Isocaloric diet + Corinthian currants	0.9 ± 1.0	1.3 ± 1.4	0.063	+44.4%	
Malaguarnera et al. (2010)[50]	NCEP	1.4 ± 0.2	1.3 ± 0.2	ns	-7.1%	
	NCEP + L-carnitine	1.4 ± 0.3	1.1 ± 0.1	<0.001*	-21.4%	
		Dietary Intervention plus supplementation				
Amanat et al. (2017)[35]	Weight-management	1.8 ± 2.6	1.8 ± 2.6	0.99	0.0%	
	Weight-management + soy isoflavone	1.8 ± 2.5	1.6 ± 2.4	0.01*	-11.1%	
Eslamparast et al. (2014)[40]	Energy Balanced	nd	nd			-0.59 (-0.8, -0.3)
	Energy Balanced + synbiotic supp.	nd	nd			-1.40 (-1.7, -1.1)
Yari et al. (2016)[49]	Energy-balanced					-0.14 (-0.07, -0.2)
	Energy-balanced + Flaxseed supp.					-1.30 (-0.4, 2.2)
Mofidi et al. (2017)[45]	Energy Balanced					-0.30 ± 0.2[a]
	Energy Balanced + synbiotic supp.					-1.22 ± 0.8[a]

Rahimlou et al. (2016)[42]	Energy-balanced	3.0 ± 0.2	2.8 ± 0.2	0.003	-6.7%
	Energy-balanced + ginger supp.	4.7 ± 0.4	3.5 ± 0.4	0.00	-25.5%
Shahmoham-madi et al. (2017)[44]	Energy-balanced	8.2 ± 3.2	8.8 ± 4.1	0.279	+7.3%
	Energy-balanced + GCBE supp.	9.6 ± 3.9	8.6 ± 5.0	0.161	-10.4%
Spadaro et al. (2008)[50]	AHA	3.1 ± 0.4	3.0 ± 0.7	ns	-3.2%
	AHA + n-3 PUFA supp.	3.3 ± 0.5	2.7 ± 0.5	<0.05	-18.2%
Interleukin-6					
Ref.	**Diet**	**Pre- (pg mL^{-1})**	**Post- (pg mL^{-1})**	**p value**	**%Change**
Dietary Intervention Alone					
Baldry et al. (2017)[46]	Very low energy diet; food based-diet	3.7 (10.4)[a]	3.7 (25.4)[a]	0.175	0.0%
	Very low energy diet; meal-replacement plan	4.5 (42.6)[a]	3.7 (25.4)[a]	0.040*	-17.8%
Marina et al. (2014)[47]	LF	1.08 (1.09)[a]	1.01 (1.14)[a]	ns	-6.5%
	HF	0.91 (1.4)[a]	0.83 (2.4)[a]	ns	-8.8%
Markova et al. (2016)[48]	Plant protein Isocaloric	1.4 ± 1.4	1.4 ± 1.5	0.816	-1.4%
	Animal protein Isocaloric	1.1 ± 1.1	0.9 ± 0.7	0.166	-21.7%
Dietary Intervention plus co-intervention					
Chan et al. (2010)[39]	Hypocaloric, LF	0.8 ± 0.2	0.9 ± 0.4	ns	+12.5%
	Hypocaloric, LF + chol. lowering agent	1.1 ± 0.4	0.9 ± 0.5	<0.05*	-18.2%
Kaliora et al. (2010)[38]	Isocaloric	1.7 ± 3.2	1.3 ± 1.4	0.322	-23.5%
	Isocaloric diet + Corinthian currants	1.6 ± 1.4	0.9 ± 0.5	0.009*	-43.7%
Dietary Intervention plus supplementation					
Amanat et al. (2017)[51]	Weight-management	18.2 ± 3.4	18.1 ± 1.8	0.80	0.5%
	Weight-management + soy isoflavone	18.8 ± 3.1	16.6 ± 2.5	0.01*	-11.7%

Data presented as mean ± SD or %Change (calculated from mean values). [a]Median (range); [b]Mean (minimum, maximum); [c]Mean change ± SEM. *Statistically significant. p<0.05 significant. Abbreviations: Pre-, pre-intervention; Post-, post-intervention; nd, no data; ns, not significant; Chol., Cholesterol; LF, Low-Fat, HF, High-Fat; AHA, American Heart Association; NCEP, National Cholesterol Education Program; DASH, Dietary Approaches to Stop Hypertension; supp., supplement; GCBE, green coffee bean extract; carbo, carbohydrate; n-3, omega-3; PUFA, Polyunsaturated Fatty Acids.

Table 5. Data extracted for intervention effects of adipokines

Adiponectin					
Ref.	**Diet**	**Pre- (ug mL^{-1})**	**Post- (ug mL^{-1})**	**p-value**	**Change**
	Dietary Intervention Alone				
Marina et al. (2014)[35]	LF	3.4 ± 0.94	4.1 ± 3.8	ns	+20.6%
	HF	4.2 ± 2.8	4.6 ± 3.8	ns	+9.5%
Markova et al. (2016)[40]	Plant protein Isocaloric	4.2 ± 1.7	3.6 ± 1.3	0.003	-14.3%
	Animal protein Isocaloric	4.1 ± 3.5	3.6 ± 3.0	ns	-12.2%
Sofi et al. (2010)[49]	Mediterranean	1.17 ± 0.08	1.25 ± 0.06	nd	+6.8%
	Mediterranean plus olive oil enriched with n-3 PUFA	1.14 ± 0.02	1.48 ± 0.09	0.04*	+29.8%
	Dietary Intervention plus co-intervention				
Chan et al. (2010)[42]	Hypocaloric, LF	5.9 ± 2.2	6.8 ± 2.5	<0.05*	+15.2%
	Hypocaloric, LF + cholesterol lowering agent	4.9 ± 2.7	6.1 ± 3.5	<0.05*	+24%
Garinis et al. (2010)[51]	Hypocaloric	7.9 ± 4.4	8.5 ± 4.6	0.17	+7.6%
	Hypocaloric + oral hypoglycaemic agent	5.8 ± 2.7	7.0 ± 3.3	0.005*	+20.7%
	Dietary Intervention plus supplementation				
Behrouz et al. (2017)[35]	Energy-balanced	25.8 ± 9.4	39.4 ± 24.2	0.005*	+52.7%
	Energy-balanced + probiotic supp.	24.4 ± 11.1	40.7 ± 24.1	<0.001*	+66.8%
	Energy-balanced + prebiotic supp.	27.8 ± 10.4	43.9 ± 15.6	<0.001*	+57.9%
Leptin					
Ref.	**Diet**	**Pre- (ng mL^{-1})**	**Post- (ng mL^{-1})**	**p value**	**Change**
	Dietary Intervention Alone				
Marina et al. (2014)[36]	LF	13.9 ± 10.4	15.1 ± 10.4	ns	+8.6%
	HF	17.3 ± 11.1	16.8 ± 12.6	ns	-2.9%
	Dietary Intervention plus co-intervention				
Kaliora et al. (2016)[40]	Isocaloric	63.5 ± 48.6	55.2 ± 39.4	0.09	-13.1%
	Isocaloric diet + Corinthian currants	95.9 ± 81.6	85.2 ± 76.8	0.19	-11.16%
	Dietary Intervention plus supplementation				
	Energy-balanced	75.8 ± 26.9	74.4 ± 26.2	0.629	-1.8%

Behrouz et al. (2017)[71]	Energy-balanced + probiotic supp.	73.1 ± 26.8	48.6 ± 13.6	<0.001*	-33.5%
	Energy-balanced + prebiotic supp.	80.3 ± 29.7	56.8 ± 22.8	<0.001*	-29.3%

Data presented as mean ± SD or %Change (calculated from mean values). *Statistically significant. p<0.05 significant. Abbreviations: Pre-, pre-intervention; Post-, post-intervention; nd, no data; ns, not significant; LF, Low-Fat; HF, High-Fat; n-3, omega-3; PUFA, Polyunsaturated Fatty Acids