Special Article

Effect of dietary intervention, with or without co-interventions, on inflammatory markers in patients with nonalcoholic fatty liver disease: a systematic literature review

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Context: *Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver disorders, ranging from simple steatosis to nonalcoholic 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:*** *The 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 ($P < 0.05$) lowered levels of CRP, TNF-α, and adiponectin. The addition of nutraceutical or pharmacological supplementation to dietary interventions appeared to elicit additional benefits for all of the most frequently reported inflammatory markers.* ***Conclusions:*** *Hypo- or isocaloric diets alone, or with co-interventions that included a nutraceutical or pharmacological supplementation, appear to improve the inflammatory profile in patients with NAFLD. Thus, anti-inflammatory diets may have the potential to improve underlying chronic inflammation that underpins the pathophysiological mechanisms of NAFLD. In the absence of any known liver-sensitive markers, the use of cytokines and adipokines as a surrogate marker of liver disease should be further investigated in well-controlled trials.*

INTRODUCTION

Nonalcoholic 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% of people with type 2 diabetes.[3,4]

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Although the pathogenesis of NAFLD is not well understood, Tilg and Moschen have proposed a "multiple parallel hit" hypothesis, suggesting that inflammatory mediators derived from various tissues, specifically 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 tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), as well as adipokines and adiponectin and leptin, which are both implicated in the progression of insulin resistance (IR) and metabolic dysregulation in NAFLD.[6,7] In contrast with 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 emphasize 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, overfeeding can cause impaired energy homeostasis, appetite dysregulation, and weight fluctuation, which is regulated by the pro-inflammatory cytokine, leptin.[13] One of the main physiological roles of leptin is to prevent lipid accumulation in nonadipose sites, including the liver.[14] Although leptin is not commonly reported in existing studies, patients with NAFLD tend to have increased serum leptin concentrations.[15]

Low-fat diets, although well-researched in chronic disease management, show variable results for the effects on inflammatory markers and seem to be dependent on weight loss.[16] Hypocaloric diets typically provide an energy deficit of 500–1000 kcal/day and are aimed at inducing a total body weight loss of approximately 5%–10%,[17] which may ameliorate hepatic and metabolic outcomes via a reduction in adiposity and improvement of glucose and lipid metabolism.[18]

However, weight loss can be difficult to achieve and maintain, and thus isocaloric diets that aim for energy balance focus on dietary components that are anti-inflammatory in nature.[19] This includes the Mediterranean diet, which is predominantly plant-based, high in fiber, high in monounsaturated and polyunsaturated fats, and has anti-inflammatory properties[11,12] and thus may alleviate hepatic and cardiometabolic stress irrespective of weight loss.[20–24]

Alternative therapies, including nutraceuticals (ie, substances derived from biologically active isolated nutrients or functional foods) are being increasingly considered in the treatment of NAFLD.[25–27] Presently, there is not enough substantial evidence to make any recommendations for the use of nutraceutical agents in the management of NAFLD.

Despite the number of trials that have assessed varying diet and supplementation approaches, there is currently no consensus regarding the optimal dietary intervention(s) to improve the inflammatory milieu within the liver that is responsible for hepatocyte injury 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 NAFLD.

METHOD

This systematic review adheres to the relevant criteria of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (see 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 no.: CRD42017055921).

Search strategy

A search for all relevant articles was performed 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 15, 2018. English language limits were applied. The search strategy used combinations of the terms "nonalcoholic fatty liver disease," "NAFLD," "nonalcoholic steatohepatitis (NASH)," "cirrhosis," "diet," and "nutrition" as both medical subject headings (MeSH) and subject headings specific to each database and keywords or free-text words and included a wide range of derivations to ensure an extensive search was performed (see 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 were 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 2 researchers by title and abstract, and full publications of potentially eligible references were obtained.

Quality assessment and data extraction

Once eligible studies were identified, 2 independent researchers 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 10 questions. A study was considered negative (−) if >6 validity questions were answered "no"; a study was considered unclear (∅) if 4 specific validity questions were answered "yes"; 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 1 researcher, after which a second reviewer 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 5 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 (eg, mmol/L vs 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 3855 articles were retrieved from the database search, and after duplicates were removed 2993 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 because 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 summarized in Figure 1.

All 19 included studies were randomized controlled trials (RCTs): 3 were nonblinded[33,38,39]; 2 were single-blinded[34,40]; 3 were double-blinded[32,36,41]; 7 were double-blind, placebo-controlled[42–48]; 3 were open-label, parallel-arm[35,49,50]; and 1 study was a prospective, single-blinded, random-order, controlled dietary feeding study.[51]

Study characteristics and participants

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 body mass index (BMI) ranged 23–35 kg/m^2. Three of the 19 studies used the gold-standard liver biopsy (Bx) to diagnose NAFLD,[34,38,45] 3 used magnetic resonance spectroscopy (^{1}H-MRS),[35,40,51] 2 used abdominal ultrasound alone,[32,42] 1 used Fibroscan alone,[50] 2 used a combination of Fibroscan and liver enzymes,[46,47] 1 used a combination of ultrasound and Fibroscan,[49] and 7 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.d[32–36,38–45,47–51]

Intervention characteristics

Of the 19 studies included in this review, 2 compared a hypocaloric diet with a hypocaloric diet plus a co-intervention (a cholesterol absorption inhibitor and an oral hypoglycemic agent).[32,40] One study compared a hypocaloric diet with a Dietary Approaches to Stop Hypertension (DASH) diet,[41] and 1 compared an isocaloric diet with an isocaloric diet plus the addition of Corinthian currants.[49] Two studies compared an energy-balanced diet with an energy-balanced diet with the addition of a synbiotic supplement,[44,46] and 4 studies compared an energy-balanced diet with an energy-balanced diet plus supplementation (prebiotic,

Table 1 **PICOS criteria for inclusion and exclusion of studies**

PICOS	Inclusion/exclusion criteria[a]	Data extracted
Population	Inclusion: Adults aged ≥18 y, diagnosed with NAFLD using >1 of the following diagnostic criteria: 1) histological examination of biopsies; 2) magnetic resonance imaging and/or magnetic resonance spectroscopy; 3) computed tomography; 4) ultrasound; and 5) blood concentrations of liver enzymes alanine aminotransferase and/or aspartate aminotransferase Exclusion: Any animal, pediatric, or pregnancy studies	Location (country), method of NAFLD diagnosis, no. of participants, age, sex, 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 (eg, supplementation plus dietary intervention vs dietary intervention alone) Interventions that included a dietary intervention alongside a co-intervention such as physical activity, behavior training, or other lifestyle interventions were eligible if the control or other diet arm was stand-alone (ie, dietary intervention only). Studies that suggested physical activity recommendations alongside both dietary intervention and control groups were included if these recommendations were consistent among 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 stand-alone diet Exclusion: Studies without a comparator group	Intervention length, type of dietary intervention, dietary intervention protocol
Outcomes	Inclusion: Studies that 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 randomized controlled trials. 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, editorials, letters, and reviews. Non-English language only papers	Type of study design Level of evidence of each study, as determined using the NHMRC Evidence Hierarchy Methodological quality of each study using the American Dietetic Association Quality Criteria Checklist for Primary Research[31]

[a]Where 2 reports relate to the same patient group, the most complete report was included to avoid duplication of patient numbers.
Abbreviations: NAFLD, nonalcoholic fatty liver disease; NHMRC, National Health and Medical Research Council.

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 with the same LFD plus supplementation (soy isoflavone,[42] L-carnitine,[45] vitamin E,[34] and n-3 polyunsaturated fatty acid [PUFA]).[39] One study compared an LFD with a high-fat diet (HFD),[51] another study compared a plant protein isocaloric diet with an animal protein isocaloric diet,[35] and another compared a Mediterranean diet with an identical diet plus olive oil enriched with n-3 PUFA.[36] A trial with 3 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] to a 250-kcal-per-day deficit to 700-kcal-per-day deficit[41]; in most cases, caloric requirements were calculated on an individual basis and were dependent on baseline BMI. The energy-balanced diet and PA recommendations implemented in 6 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 analyzed cytokines in the included studies were hs-CRP, TNF-α, and IL-6, which were reported in 12,[33,38,40,41,44–51] 11,[35,39,40,42,44–50] and 6 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]

Table 2 **Characteristics of studies included for the systematic review investigating the effects of randomized controlled dietary intervention(s) on inflammatory markers in adults with nonalcoholic fatty liver disease**

Reference	Country	NAFLD diagnostic method	Sample (n), M/F	Study type/ NHMRC LOE and Quality Ax	Diet of Interest	2° diet of interest	3° diet of interest	Intervention length	Inflammatory biomarkers measured
Amanat et al (2017)[42]	Iran	US	Enrolled (n=82), analyzed (n=78), 61/21	RCT/Level II Positive	Weight-management diet plus placebo	Weight-management diet plus soy isoflavone supplement	—	8 wk	TNF-α, IL-6
Baldry et al (2017)[38]	United Kingdom	Liver Bx	Total (n=54), 44/10	RCT/Level II Positive	Very-low-energy diet 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 wk	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), 63/26	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 wk	Adiponectin, leptin
Chan et al (2010)[40]	Australia	MR-S (IHTG %)	Total obese and T2DM (n=25), 15/10	RCT/Level II Positive	16-wk hypocaloric, low-fat diet, followed by 6-wk isocaloric diet plus placebo supplement consumed for 22 wk	16-wk hypocaloric, low-fat diet, followed by 6-wk isocaloric diet plus 10 mg/d ezetimibe consumed for 22 wk	—	22 wk	Adiponectin, hs-CRP, TNF-α, IL-6, RBP-4, fetuin-A
Eslamparast et al (2014)[44]	Iran	US and ALT (>60 U/L)	Total (n=52), 25/27	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus synbiotic supplement	—	28 wk	hs-CRP, TNF-α, NF-κB
Garinis et al (2010)[32]	Italy	US	Total (n=45), 7/38	RCT/Level II Positive	Hypocaloric diet	Hypocaloric diet plus metformin 1000 mg/d	—	6 mo	Adiponectin
Kaliora et al (2016)[49]	Greece	US	Total (n=55), 23/32	RCT/Level II Positive	Isocaloric diet	Isocaloric diet plus Corinthian currants	—	24 wk	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), 21/24	RCT/Level II Positive	Low-calorie diet	Low-calorie, low-carbohydrate diet	Low-calorie, low-carbohydrate soy diet	8 wk	hs-CRP
Kugelmas et al (2003)[34]	United States	Liver Bx	Total (n=16), 7/9	RCT/Level II Positive	Step One American Heart Association diet	Step One American Heart Association diet plus vitamin E 800 IU p/d	—	12 wk	TNF-α, IL-6, IL-8

(continued)

Table 2 **Continued**

Reference	Country	NAFLD diagnostic method	Sample (n), M/F	Study type/ NHMRC LOE and Quality Ax	Diet of Interest	2° diet of interest	3° diet of interest	Intervention length	Inflammatory biomarkers measured
Malaguarnera et al (2010)[45]	Italy	Liver Bx	Total (n=74), 40/34	RCT/Level II Positive	National Cholesterol Education Program diet plus placebo	National Cholesterol Education Program diet plus L-carnitine	—	24 wk	hs-CRP, TNF-α
Marina et al (2014)[51]	United States	MR-S	Total obese sample (n=13), 10/3	Random order, comparative study with concurrent controls/ Level III-2 Positive	Low-fat diet	High-fat diet	—	4 wk	Adiponectin, leptin, hs-CRP, IL-6, IL-10, IL-12, IFN-γ
Markova et al (2016)[35]	Germany	MR-S	Total (n=37), 24/13	RCT/Level II Positive	Plant protein isocaloric diet	Animal protein isocaloric diet	—	6 wk	Adiponectin, TNF-α, IL-4, IL-6, IL-8, IL-18, MCP-1
Mofidi et al (2017)[46]	Iran	Fibroscan and ALT (>60 U/L)	Total (n=42), 23/19	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus synbiotic supplement	—	28 wk	hs-CRP, TNF-α, NF-κB
Rahimlou et al (2016)[47]	Iran	Fibroscan and ALT (>1.5 x upper limit of normal)	Total (n=44), 20/24	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus ginger supplement	—	12 wk	hs-CRP, TNF-α
Razavi Zade et al (2016)[41]	Iran	US and ALT (M >30 U/L, F >19 U/L)	Total (n=60), 30/30	RCT/Level II Positive	Hypocaloric diet	Dietary Approaches to Stop Hypertension diet	—	8 wk	hs-CRP
Shahmohammadi et al (2017)[48]	Iran	US and ALT (M >30 U/L, F >19 U/L)	Total (n=44), 22/22	RCT/Level II Positive	Energy-balanced diet plus placebo	Energy-balanced diet plus green coffee bean extract supplement	—	8 wk	hs-CRP, TNF-α
Sofi et al (2010)[36]	Italy	US and ALT (M >30 U/L, F >20 U/L)	Total (n=11), 9/2	RCT/Level II Positive	Mediterranean diet	Mediterranean diet + olive oil enriched with n-3 PUFA	—	12 mo	Adiponectin
Spadaro et al (2008)[39]	Italy	US and ALT (M >30 U/L, F >20 U/L)	Total (n=36), 19/17	RCT/Level II Positive	American Heart Association diet plus placebo	American Heart Association diet plus n-3 PUFA capsule	—	6 mo	TNF-α
Yari et al (2016)[50]	Iran	Fibroscan	Total (n=50), 25/25	RCT/Level II Positive	Energy-balanced diet	Energy-balanced diet plus flaxseed supplement	—	12 wk	hs-CRP, TNF-α

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; Ax, assessment; Bx, biopsy; F, female; hs-CRP, high sensitivity C-reactive protein; IFN-γ, interferon gamma; IHTG%, intrahepatic triglyceride percent; IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-12, interleukin 12; IL-18, interleukin 18; LOE, level of evidence; M, male; MCP-1, monocyte chemoattractant protein 1; MR-S, magnetic resonance–spectroscopy; n-3, omega 3; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor kappa B; NHMRC, National Health and Medical Research Council; PUFA, polyunsaturated fatty acid; RPB-4, retinol binding protein 4; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-alpha; US, ultrasound.

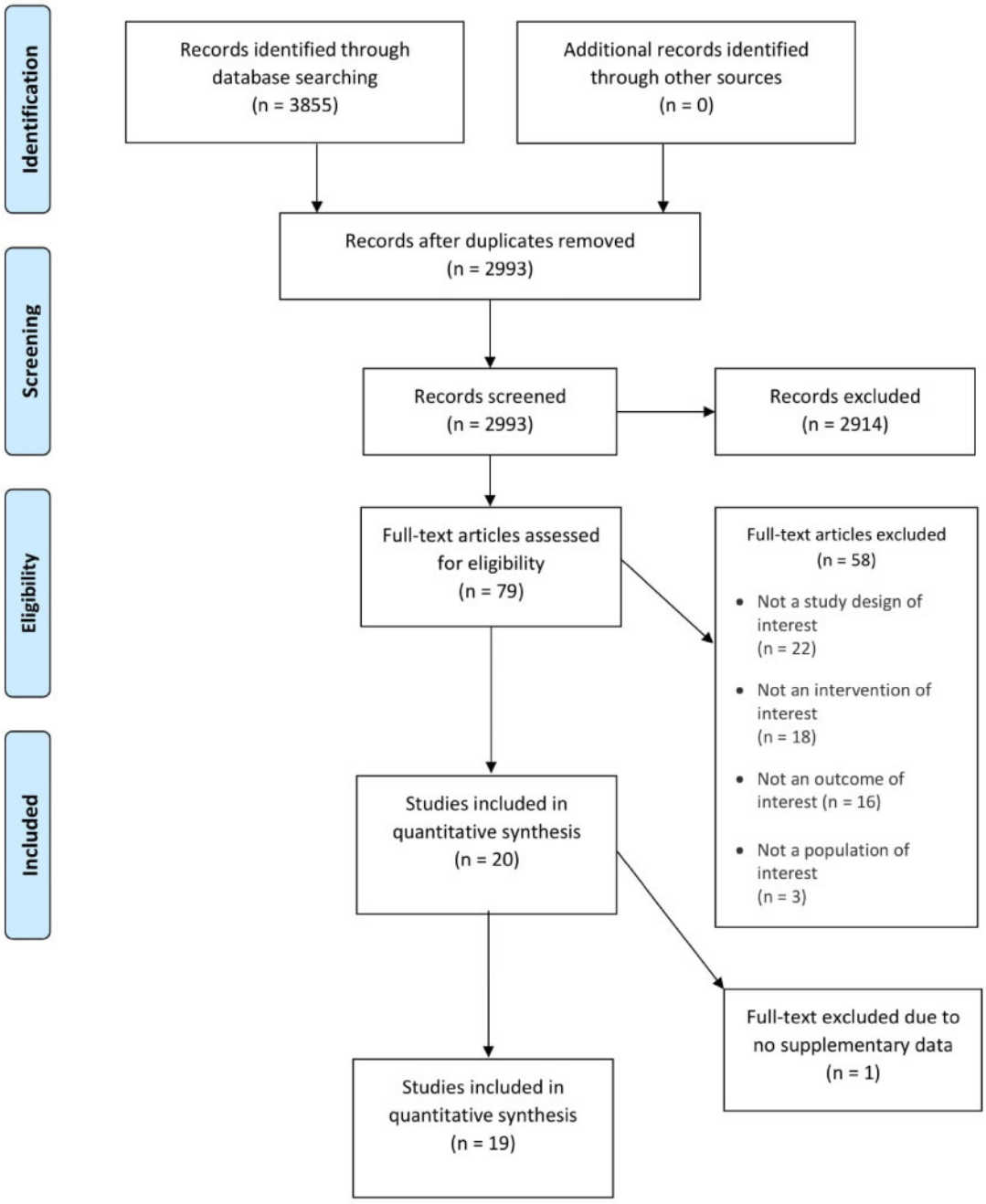

Figure 1 **PRISMA flow chart for study selection**

High-sensitivity C-reactive protein. Of the 12 studies that evaluated hs-CRP, 11 studies reported significant ($P < 0.05$) improvements from pre- to post-intervention, and 1 study reported nonsignificant ($P > 0.05$) improvements (Table 4).[33,35,38–42,44–51] Kaliora et al[49] conducted a 24-week RCT that found that participants who received isocaloric dietary advice alone and participants who received isocaloric dietary advice with an additional 35 g of 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 with 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 a meal replacement very-low-energy diet (VLED) 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

Table 3 **Dietary intervention protocol data extracted from each study**

Reference	Diet label	Nutrient composition targets	Caloric intake recommendations	Main food sources	Physical activity recommendations
Amanat et al (2017)[42]	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 20–30 g fiber/d	Energy intake goal to achieve a 500–1000 kcal/d energy deficit	A variety of fruits, vegetables, grains, low-fat or nonfat 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/d (2400 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 d 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)[38]	Very-low-energy diet; pre-bariatric surgery food-based diet	ns	800 kcal/d	Standard pre-bariatric surgery food-based diet using LighterLife Nutritional supplements	ns
	Very-low-energy diet; pre-bariatric surgery meal replacement plan	ns	800 kcal/d	Standard pre-bariatric surgery meal replacement plan using LighterLife Nutritional supplements	ns
Behrouz et al (2017)[43]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week
Chan et al (2010)[40]	Hypocaloric, LF	ns	ns	ns	ns
	Isocaloric	ns	ns	ns	ns
Eslamparast et al (2014)[44]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week

(continued)

Table 3 **Continued**

Reference	Diet label	Nutrient composition targets	Caloric intake recommendations	Main food sources	Physical activity recommendations
Garinis et al (2010)[32]	Hypocaloric	ns	1300 kcal consumed per day	ns	ns
Kaliora et al (2016)[49]	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 as dietary cholesterol, and 20–30 g fiber/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 counseling. The Current arm incorporated in their daily diet the consumption of 36 g of Corinthian currants equal to 2 fruit servings replacing snacks of like nutritional value (low-fat yogurt, mini crackers, or bread with low-fat cheese)	Aim of nutritional counseling was a weight loss of ≈5% of the initial BW within 6 mo
Kani et al (2014)[33]	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)[34]	AHA	ns	ns	ns	ns
Malaguarnera et al (2010)[45]	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 1600-calorie diet	ns	Both the groups were prescribed an exercise plan and a 30-min home-based whole-body stretching routine to perform 3 times per week
Marina et al (2014)[51]	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/d based on a 2000 kcal per day diet	Participants 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			

(continued)

Table 3 **Continued**

Reference	Diet label	Nutrient composition targets	Caloric intake recommendations	Main food sources	Physical activity recommendations
Markova et al (2016)[35]	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 specially developed for this study (eg, 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)[46]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week
Rahimlou et al (2016)[47]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week
Razavi Zade et al (2016)[41]	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 <2400 mg/d	
Shahmohammadi et al (2017)[48]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week

(continued)

Table 3 **Continued**

Reference	Diet label	Nutrient composition targets	Caloric intake recommendations	Main food sources	Physical activity recommendations
Sofi et al (2010)[36]	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 6.5 mL/d (0.83 g n-3 PUFA, of which 0.47 g eicosapentaenoic acid and 0.24 g docosahexaenoic acid)	
Spadaro et al (2008)[39]	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 min recommended. Subsequent increases to 30–60 min on most/all days of the week need to be individualized and are targeted to expend a total of 100–200 kcal
Yari et al (2016)[50]	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 20–30 g fiber/d	≈500 to 1000 kcal/d reduction from usual intake	ns	Patients were also advised to exercise >30 min, 3 times per week

Abbreviations: AHA, American Heart Association; BMI, body mass index; BW, body weight; DASH, Dietary Approaches to Stop Hypertension; HFD, high-fat diet; LF, low fat; MUFA, monounsaturated fatty acid; NCEP, National Cholesterol Education Program; ns, not specified; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Table 4 **Data extracted for intervention effects of cytokines**

High sensitivity C-reactive protein							
Reference	Diet	Pre-intervention, mg/L	Post-intervention, mg/L	*P* value	Change	Mean change (95%CI), mg/mL	Mean change ± SD. mg/L
Dietary intervention alone							
Baldry et al (2017)[38]	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)[33]	Low calorie	nd	nd	nd			−1.0 ± 0.6
	Low calorie, low carbohydrate	nd	nd	nd			−1.1 ± 0.6
	Low calorie, low carbohydrate, soy containing	nd	nd	0.01*			−8.0 ± 1.0
Marina et al (2014)[51]	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)[41]	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)[40]	Hypocaloric, LF	2.2 ± 1.3	2.4 ± 1.6	nd	+9.1%		
	Hypocaloric, LF + cholesterol-lowering agent	3.9 ± 3.8	2.2 ± 2.7	<0.05*	−43.6%		
Kaliora et al (2016)[49]	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)[45]	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)[44]	Energy-balanced	nd	nd			−1.04 (−1.5 to −0.6)	
	Energy-balanced + synbiotic supplement	nd	nd			−2.30 (−3.0 to −1.5)	
Mofidi et al (2017)[46]	Energy-balanced	nd	nd				−0.42 ± 0.1[c]
	Energy-balanced + synbiotic supplement	nd	nd				−1.16 ± 0.4[c]
Rahimlou et al (2016)[47]	Energy-balanced	4.8 ± 0.2	2.8 ± 0.2	0.005*	−41.7%		
	Energy-balanced + ginger supplement	4.6 ± 0.1	3.4 ± 0.1	0.007*	−26.1%		
Shahmoham-madi et al (2017)[48]	Energy-balanced	1.5 (0.4, 2.7)[b]	1.5 (0.4, 3.0)[b]	0.846	0.0%		
	Energy-balanced + GCBE supplement	1.4 (0.4, 3.4)[b]	1.1 (0.5, 2.3)[b]	<0.001*	−21.4%		
Yari et al (2016)[50]	Energy-balanced	nd	nd			−1.02 (−1.6 to −0.5)	
	Energy-balanced + Flaxseed supplement	nd	nd			−2.05 (−2.6 to 1.5)	

(continued)

Table 4 **Continued**

Tumor necrosis factor alpha

Reference	Diet	Pre-intervention, ng/mL	Post-intervention, ng/mL	*P* value	Change	Mean change (95%CI), ng/mL
Dietary intervention alone						
Markova et al (2016)[35]	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)[40]	Hypocaloric, LF	5.4 ± 1.6	5.4 ± 1.9	ns	0.0%	
	Hypocaloric, LF + cholesterol-lowering agent	6.3 ± 1.9	5.4 ± 2.3	<0.05*	−14.3%	
Kaliora et al (2016)[49]	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)[45]	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)[42]	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)[44]	Energy balanced	nd	nd			−0.59 (−0.8 to −0.3)
	Energy balanced + synbiotic supplement	nd	nd			−1.40 (−1.7 to −1.1)
Yari et al (2016)[50]	Energy-balanced					−0.14 (−0.07 to −0.2)
	Energy-balanced + flaxseed supplement					−1.30 (−0.4 to 2.2)
Mofidi et al (2017)[46]	Energy balanced					−0.30 ± 0.2[a]
	Energy balanced + synbiotic supplement					−1.22 ± 0.8[a]
Rahimlou et al (2016)[47]	Energy-balanced	3.0 ± 0.2	2.8 ± 0.2	0.003	−6.7%	
	Energy-balanced + ginger supplement	4.7 ± 0.4	3.5 ± 0.4	0.00	−25.5%	
Shahmoham-madi et al (2017)[48]	Energy-balanced	8.2 ± 3.2	8.8 ± 4.1	0.279	+7.3%	
	Energy-balanced + GCBE supplement	9.6 ± 3.9	8.6 ± 5.0	0.161	−10.4%	
Spadaro et al (2008)[39]	AHA	3.1 ± 0.4	3.0 ± 0.7	ns	−3.2%	
	AHA + n-3 PUFA supplement	3.3 ± 0.5	2.7 ± 0.5	<0.05	−18.2%	

Interleukin 6

Reference	Diet	Pre-intervention, pg/mL	Post-intervention, pg/mL	*P* value	Change
Dietary intervention alone					
Baldry et al (2017)[38]	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%

(continued)

Table 4 **Continued**

Interleukin 6

Reference	Diet	Pre-intervention, pg/mL	Post-intervention, pg/mL	*P* value	Change
Marina et al (2014)[51]	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)[35]	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)[40]	Hypocaloric, LF	0.8 ± 0.2	0.9 ± 0.4	ns	+12.5%
	Hypocaloric, LF + cholesterol- lowering agent	1.1 ± 0.4	0.9 ± 0.5	<0.05*	−18.2%
Kaliora et al (2016)[49]	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)[42]	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).

Abbreviations: AHA, American Heart Association; DASH, Dietary Approaches to Stop Hypertension; GCBE, green coffee bean extract; HF, high fat; LF, low fat; nd, no data; ns, not significant; NCEP, National Cholesterol Education Program; PUFA, polyunsaturated fatty acid.

[a]Median (range);

[b]Mean (minimum, maximum);

[c]Mean change ± SEM.

*Statistically significant. $P < 0.05$ significant.

Table 5 **Data extracted for intervention effects of adipokines**

Adiponectin

Reference	Diet	Pre-intervention, ug/mL	Post-intervention, ug/mL	*P* value	Change
Dietary intervention alone					
Marina et al (2014)[51]	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)[35]	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)[36]	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)[40]	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)[32]	Hypocaloric	7.9 ± 4.4	8.5 ± 4.6	0.17	+7.6%
	Hypocaloric + oral hypoglycemic agent	5.8 ± 2.7	7.0 ± 3.3	0.005*	+20.7%
Dietary intervention plus supplementation					
Behrouz et al (2017)[43]	Energy-balanced	25.8 ± 9.4	39.4 ± 24.2	0.005*	+52.7%
	Energy-balanced + probiotic supplement	24.4 ± 11.1	40.7 ± 24.1	<0.001*	+66.8%
	Energy-balanced + prebiotic supplement	27.8 ± 10.4	43.9 ± 15.6	<0.001*	+57.9%

Leptin

Reference	Diet	Pre-intervention, ng/mL	Post-intervention, ng/mL	*P* value	Change
Dietary intervention alone					
Marina et al (2014)[51]	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)[49]	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					
Behrouz et al (2017)[43]	Energy-balanced	75.8 ± 26.9	74.4 ± 26.2	0.629	−1.8%
	Energy-balanced + probiotic supplement	73.1 ± 26.8	48.6 ± 13.6	<0.001*	−33.5%
	Energy-balanced + prebiotic supplement	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: HF, high fat; LF, low fat; nd, no data; ns, not significant; PUFA, polyunsaturated fatty acid.

hypocaloric, low-fat diet plus a cholesterol-lowering supplement ($P < 0.05$) in comparison with a hypocaloric, low-fat diet alone, which resulted in a nonsignificant increase in hs-CRP (NS). Similarly, an NCEP diet plus L-carnitine supplement significantly reduced hs-CRP ($P < 0.05$) in comparison with the nonsignificant 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, although the mean decrease in supplementation groups were significantly greater ($P < 0.001$).[44,46,50]

Tumor necrosis factor alpha. Ten of the 11 studies that analyzed TNF-α reported significant improvements with dietary interventions, and 1 study reported beneficial change in the supplementation group only, albeit

	RELEVANCE				VALIDITY										
Study (Ref)	1	2	3	4	1	2	3	4	5	6	7	8	9	10	RANK
Amanat et al (2017)[42]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	+
Baldry et al (2017)[38]	Y	Y	Y	Y	Y	Y	Y	Y	N	Ø	Y	Y	Y	Y	+
Behrouz et al (2017)[43]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Chan et al (2010)[40]	Y	Y	Y	Y	Y	Y	Y	Y	Ø	N	Y	Y	Y	Y	+
Eslamparast et al (2014)[44]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Garinis et al (2010)[32]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Ø	+
Kaliora et al (2016)[49]	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	+
Kani et al (2014)[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Kugelmas et al (2003)[34]	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	+
Malaguaranera et al (2010)[45]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Marina et al (2014)[51]	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	+
Markova et al (2016)[35]	Y	Y	Y	Y	Y	Y	Y	Ø	N	Y	Y	Y	Y	Y	+
Mofidi et al (2017)[46]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Rahimlou et al (2016)[47]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Razavi Zade et al (2016)[41]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Shahmohammadi et al (2017)[48]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	+
Sofi et al (2010)[36]	Y	Y	Y	Y	Y	Y	Y	Ø	Ø	Y	Y	Y	Y	Y	+
Spadaro et al (2008)[39]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Ø	+
Yari et al (2016)[50]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	+

Abbreviations: Y; Yes, N; No, Ø; Unclear

Figure 2 **Individual quality assessment of studies according to American Dietetic Association quality checklist.**

without statistical significance (Table 4).[33,35,38–42,44–51] Of the diet-alone studies, Kaliora et al[49] found that TNF-α significantly decreased following an isocaloric diet alone (P=0.004) but 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 with the hypocaloric, low-fat diet alone (NS). Similarly, the NCEP diet plus L-carnitine supplementation significantly reduced TNF-α ($P < 0.001$) compared with 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 1 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]

Interleukin 6. Six studies reported on the effects of a dietary intervention on levels of IL-6, with 4 studies reporting significant improvements and 2 studies reporting nonsignificant improvements (Table 4).[33,35,38–42,44–51] 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 compared with a nonsignificant 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 with a weight-management diet alone, for which 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 with 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 small and similar intervention groups), reporting a significant decrease in IL-6 concentration (data not presented in table because numerical values were not provided).

Other cytokines. Interleukins 4, 8, 10, 12, and 18,[35,51] monocyte chemoattractant protein 1 (MCP-1),[35] interferon gamma (IFN-γ),[51] visfatin,[49] and retinol binding protein 4 (RBP-4)[40] were each included in 1 study (see Table S1 in the Supporting Information online). Nuclear factor κB (NF-κB)[44,46] and fetuin A[38,40] were included in 2 studies. An animal protein isocaloric diet resulted in significantly decreased IL-18 ($P < 0.05$).[35] Nuclear factor κB decreased following an energy-balanced diet with and without synbiotic and flaxseed supplementation,[44,46] although the mean decrease in supplementation groups before versus after intervention were significantly greater than for 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] Very-low-energy diets in the form of a food-based diet and meal-replacement plan both reduced fetuin A significantly ($P < 0.05$).[38] No significant changes were reported for all other markers ($P > 0.05$).

Adipokines.

The effects of a dietary intervention on adiponectin were investigated in 6 studies,[32,35,36,40,43,51] and 3 studies included 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 6 studies evaluating adiponectin, 5 reported a significant ($P < 0.05$) increase in serum adiponectin levels, suggesting improvement in inflammatory status, and 1 study showed no significant ($P > 0.05$) change (Table 5).[32,35,36,40,43,49,51] 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), whereas a nonsignificant 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 study of a hypocaloric, low-fat diet plus placebo and a hypocaloric, low-fat diet plus cholesterol-lowering agent found that adiponectin increased significantly in both groups ($P < 0.05$).[40] Garinis et al[40] showed that a hypocaloric diet alone compared with a hypocaloric diet plus oral hypoglycemic supplement increased adiponectin for both groups, although the increase reached statistical significance in the hypocaloric diet plus oral hypoglycemic agent group ($P < 0.005$) and not in the hypocaloric diet-only group ($P < 0.17$).

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 ($P > 0.05$).

Liver imaging and histology

Five studies assessed liver imaging and histology after intervention using abdominal ultrasound,[32,36,39,41,48] 1 study used ultrasound and transient elastography (TE) Fibroscan,[49] 4 studies used TE Fibroscan only,[44,46,47,50] 3 used ^{1}H-MRS,[35,40,51] and 2 performed liver biopsy.[38,45] Of the 19 studies, 4 did not assess postintervention liver imaging or histology. Data extracted for each of these measures are presented in Table S2 (see Table S2 in the Supporting Information online). Most significant changes occurred following a hypocaloric diet with and without an oral hypoglycemic 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 an 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 ($P < 0.001$).[45]

Quality assessment of studies

The quality assessment of studies using the American Dietetic Association Quality Criteria Checklist for Primary Research[31] is presented in Table 2[32–36,38–45,47–51], 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 7 of the 20 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 rigor if applied to all trials. This intent was not clear in the above studies that ranked negative for this domain. Of the aforementioned 11 studies, 6 ranked negative (−) or unclear (ø) in the way they described withdrawals,[34–36,42,48,51] and a further 2 had groups that were considered noncomparable and may affect interpretation of outcome measures due to significant ($P < 0.05$) differences at baseline.[34,51]

Of the 19 included studies, only 7 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 that demonstrated more favorable change were those that were calorie restricted, those that were isocaloric, and those that adhere 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 with diet alone in an NAFLD population.

In this review, the most effective studies were calorie-restricted dietary interventions that resulted in significant ($P < 0.05$) weight loss. Typically in the treatment of NAFLD weight loss is considered a primary focus because 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] Although clinical trials investigating calorie-restricted diets report inflammatory changes following weight loss, due to their restrictive nature these diets are often unsustainable in NAFLD patients and may result in portal fibrosis or necroinflammation following rapid weight loss.[56]

This review also highlighted the effects of the NCEP diet, which is advocated in NAFLD to balance macronutrient intake and anti-inflammatory foods, and the DASH eating plan, recommended as a low-glycemic-index, low energy-dense diet with an emphasis on reduced sodium intake. In trials, the NCEP diet has been successful in lowering CRP,[53] as well as hepatic steatosis and fibrosis.[45] The DASH diet has also reduced CRP levels in adults with NAFLD,[41] adolescents with metabolic syndrome,[57] and patients with polycystic ovary syndrome[58]—chronic diseases in which insulin resistance, obesity, and abdominal fat accumulation are underlying pathophysiological contributors. These changes have been attributed to weight loss, considering a reduction in adipocytes accompanied by a reduction in IL-6 is likely to be responsible for the reduction in CRP.[59]

One small study included in this review investigated the Mediterranean diet; researchers did not find a substantial effect for diet alone in an NAFLD population.[36] In this study, however, an improvement in adiponectin was seen following a Mediterranean diet with n-3 enriched olive oil supplementation.[36] Adhering to a diet rich in antioxidants and phenolic compounds from whole grains, fruits, vegetables, nuts, and extra-virgin olive oil may decrease hs-CRP, as well as circulating levels of free radicals and pro-inflammatory cytokines IL-6, IL-18, and TNF-α.[19] These dietary components, typical of the Mediterranean diet, are extensively investigated in the treatment of IR and metabolic syndrome.[19,23] Moreover, Kaliora et al[49] found that within a Greek population, adherence to a Mediterranean diet supplemented with Corinthian currents as a regular dietary snack was associated with an improvement in levels of hs-CRP and IL-6. This was not unprecedented as the authors noted recent studies identifying bioactive phytochemicals and phenolic compounds in currents could potentially ameliorate fasting glucose, inflammation, and the fibrosis stage.[49]

A diet receiving considerable attention in recent RCTs 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, although noteworthy effects were seen following diet only. Shahmohammadi et al[48] attributed a significant ($P < 0.05$) decrease in hs-CRP to the anti-inflammatory and antioxidant 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 antidiabetic, anticancer, and anti-inflammatory properties, leading to a significant ($P < 0.05$) 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, metabolic syndrome, and dyslipidemia,[62–64] is thought to improve weight management, lipid profile, IR, and the 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, although evidence is mounting for potential use of synbiotic supplements to protect the liver from damage. It is thought that synbiotic supplements retard inflammation, resulting in downregulation of insulin signaling 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 the inflammatory cytokines hs-CRP and TNF-α[45]; although this has been confirmed in an animal model,[27] human studies in an NAFLD population have yet to prove L-carnitine as a convincing 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 beneficial 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 the 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.

Physical activity, 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 >3 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 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 low-density lipoprotein cholesterol concentrations and therefore improve dyslipidemia. For this reason, it was thought to be an optimal approach in the clinical setting, as well as for moderation of 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 yet due to insufficient evidence surrounding the effects for short- and long-term use.

Although 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 resulted in prominent changes in markers of steatosis and fibrosis, as defined by abdominal ultrasound, ^{1}H-MRS, TE Fibroscan, and/or liver biopsies. Changes in liver severity were difficult to compare among studies due to the various liver imaging and histology tools, although 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 optimal dietary composition on pro-inflammatory cytokines and adipokines in an 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 include 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, of whom 10 participants did not have NAFLD intrahepatic triglyceride content $< 5\%$. Some studies did not report a macronutrient breakdown of the recommended diets; therefore it was difficult to make comparisons or pool together dietary prescriptions. Dietary compliance was often not monitored or reported, and there was inconsistency in regards to cytokines and adipokines studied.

Still this systematic review study has important strengths in that the overall population within the included studies—age, sex, anthropometry, and general characteristics—were reflective of and therefore generalizable to the NAFLD population. Moreover, liver biopsy, ultrasound, magnetic resonance spectroscopy, TE, 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 to 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 with a control (or habitual) diet for the same duration of time. To determine whether dietary interventions are effective at improving inflammatory outcomes, supplementation should not be administered in either group because 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 of weight loss.

CONCLUSION

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

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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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