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Review

Effect of Dietary Intervention, with or without Cointerventions, on Inflammatory Markers in Patients with Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

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A B S T R A C T

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease from simple steatosis to nonalcoholic steatohepatitis, with inflammatory cytokines and adipokines identified as drivers of disease progression. Poor dietary patterns are known to promote an inflammatory milieu, although the effects of specific diets remain largely unknown. This review aimed to gather and summarize new and existing evidence on the effect of dietary intervention on inflammatory markers in patients with NAFLD. The electronic databases MEDLINE, EMBASE, CINAHL, and Cochrane were searched for clinical trials which investigated outcomes of inflammatory cytokines and adipokines. Eligible studies included adults ≥18 y with NAFLD, which compared a dietary intervention with an alternative diet or control (no intervention) group or were accompanied by supplementation or other lifestyle interventions. Outcomes for inflammatory markers were grouped and pooled for meta-analysis where heterogeneity was allowed. Methodological quality and risk of bias were assessed using the Academy of Nutrition and Dietetics Criteria. Overall, 44 studies with a total of 2579 participants were included. Meta-analyses indicated intervention with an isocaloric diet plus supplement was more effective in reducing C-reactive protein (CRP) [standard mean difference (SMD): 0.44; 95% CI: 0.20, 0.68; $P = 0.0003$] and tumor necrosis factor-alpha (TNF-α) (SMD: 0.74; 95% CI: 0.02, 1.46; $P = 0.03$) than an isocaloric diet alone. No significant weighting was shown between a hypocaloric diet with or without supplementation for CRP (SMD: 0.30; 95% CI: −0.84, 1.44; $P = 0.60$) and TNF-α (SMD: 0.01; 95% CI: −0.43, 0.45; $P = 0.97$). In conclusion, hypocaloric and energy-restricted diets alone or with supplementation, and isocaloric diets with supplementation were shown to be most effective in improving the inflammatory profile of patients with NAFLD. To better determine the effectiveness of dietary intervention alone on a NAFLD population, further investigations of longer durations, with larger sample sizes are required.

Keywords: adipokines, cytokines, dietary patterns, diet, inflammation, inflammatory markers, nonalcoholic fatty liver disease, nutrition

Statement of Significance

This comprehensive synthesis of high-level evidence will help to inform the dietary management of nonalcoholic fatty liver disease by targeting key pathophysiological mechanism—inflammation—via nutrition. This review establishes an extensive evidence base and identifies evidence gaps that may inform practitioners and scientists, whereby guiding future treatments and research.

Abbreviations: AHA, American Heart Association; α-LA, alpha-lipoic acid; ALT, alanine transaminase; Ax, assessment; Bx, biopsy; FLIO, Fatty Liver in Obesity; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; NF-κB, nuclear factor kappa B; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHLBI-EB, National Heart Lung and Blood Institute-Energy Balanced; NHMRC, National Health and Medical Research Council; NIHFN, National Institute of Health & Food & Nutrition; RCT, randomized controlled trial; TNF-a, tumor necrosis factor-alpha; US, ultrasound.

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Introduction

The global prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated to be ~25%, with rates as high as 42% in Asian countries [1]. The prevalence and incidence of NAFLD have rapidly risen alongside the obesity epidemic, adding to the global burden of the disease [2]. A meta-analysis of studies from >22 countries involving 8.5 million subjects indicated that individuals with NAFLD are also commonly overweight or obese (80%), have high LDL cholesterol and/or triglycerides (72%) and are also diagnosed with type II diabetes mellitus (44%) [1]. NAFLD encompasses a spectrum of disease ranging from simple steatosis "accumulation of fat in the liver," affecting >5% of hepatocytes in the absence of excessive alcohol consumption [3]. The more progressed form involving inflammation is referred to as nonalcoholic steatohepatitis (NASH), and if left untreated can progress to liver cirrhosis and hepatocellular carcinoma [4–6]. Approximately 10–20% of patients with NAFLD will develop NASH, increasing the risk of liver related and other mortality, however, can be reversed through diet and lifestyle modification [7].

Multiple factors, including toxic accumulation of fatty acids in adipose tissue; impaired microbial functioning of the gut; and an imbalance of inflammatory mediators, contribute to a progressed inflammatory state in the liver [7]. More recent studies have now recognized that adipose tissue may produce multiple inflammatory cytokines and adipokines that have been implicated in the development of NAFLD [8]. Polyzos et al. [9] describe the underlying dynamic between adipokines and cytokines related to the progression of NAFLD as an antagonistic one, where pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) work in opposition to adipokines such as adiponectin, known to suppress the release of those pro-inflammatory cytokines and to stimulate the release of anti-inflammatory cytokines such as interleukin-10 (IL-10) [10,11]. In the liver, the pro-inflammatory adipokine leptin has been shown to interfere with regulation of glucose metabolism, fatty acid, and lipid production and is associated with increased severity of NAFLD [9,11]. Elevated levels of high-sensitivity C-reactive protein (hs-CRP) have been significantly correlated with liver steatosis and severity of NAFLD, as well as risk of cardiovascular disease (CVD) [12]. It has been suggested that hs-CRP may be used as a surrogate marker for disease severity in NAFLD [13]. Unhealthy dietary patterns, in particular high fructose and fat intake, have been evidenced to support an inflammatory milieu by increasing the production and release of proinflammatory cytokines [11,14].

As there is currently no safe, proven pharmacological treatment for NAFLD, diet and lifestyle intervention, aimed to induce 7%–10% total body weight loss is the recommended therapeutic strategy, in which hypocaloric diet is indicated [15,16]. Although weight-loss diets have been shown to improve metabolic and liver outcomes by a reduction in adipose tissue, weight loss can be difficult to achieve and maintain in an overweight/obese population and indeed with metabolic risk factors [14,15,17]. Instead, diets that are energy-balanced or "isocaloric" in nature and focus on specific dietary components, which produce anti-inflammatory health benefits may be a more feasible option [14]. The Mediterranean diet has been recommended as the superior diet for the improvement of cardio-metabolic and liver-associated risks of NAFLD even in the absence of weight loss and may also induce weight loss. Benefits associated with Mediterranean diet are attributed via the anti-inflammatory components of the diet [14–16]. George et al. [18] concurred that a Mediterranean diet, rich in antioxidants; mono-unsaturated fats, and fiber; and low in saturated fat, may provide an anti-inflammatory and protective benefit against risk factors related to NAFLD.

Alternative therapies and nutraceuticals "food-derived alternatives to pharmaceuticals, which may provide a health benefit" have increasingly been used alongside diet to assist with the improvement of NAFLD and its associated risk factors [19]. Cicero et al. [19] refer to vitamin E, vitamin D, omega-3 polyunsaturated fatty acids (n-3 PUFA), resveratrol, and probiotics, as being among the few supplements to be investigated in clinical studies. Although some supplements have been shown to improve liver or metabolic outcomes alongside diet, heterogeneity of supplements, doses, length of studies, change independent of weight loss, and measurement tools used to assess outcomes, prohibits the ability to conclusively state that are the most superior to use in conjunction with diet in therapeutic treatment of NAFLD [20]. As with pharmacological interventions, there is no current consensus regarding the use of supplementation for the management of NAFLD [15,16].

In 2019, Reddy et al. [20] conducted a systematic literature review to investigate the effect of dietary interventions (with or without cointerventions) on changes in cytokines and adipokines in adults with NAFLD. The review included 19 randomized controlled trials (RCTs) (n = 874 participants) and reported markers most prevalent in the literature; hs-CRP, TNF-α, IL-6, adiponectin, and leptin. Authors concluded that dietary intervention alone (either hypo- or isocaloric), or diet in combination with a nutraceutical or pharmacological supplement in the form of a prebiotic, probiotic, ginger, flaxseed, green coffee bean extract, or ezetimibe, provided a significant improvement to the inflammatory profile of patients with NAFLD, although these improvements appeared to be mostly driven by weight loss but remained undetermined [20]. Authors concluded that further investigation into the use of inflammatory markers as a potential surrogate marker of liver disease was warranted but, required more specific and sensitive investigations in response to diet. Since the publication of this review, a considerable number of clinical trials intervening with diet or supplement(s) have been published investigating inflammatory outcomes in NAFLD. The aim of the present study was therefore, to conduct a meta-analysis, where feasible, to assess the cumulative effect of evidence regarding the effect of dietary intervention, with or without cointerventions, on the inflammatory profile of adults diagnosed with NAFLD.

Methods

This systematic literature review followed the relevant criteria of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [21]. The review was registered as an update to an existing review in PROSPERO, the international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/; registration no.: CRD42017055921).

Search strategy

The electronic databases MEDLINE Ovid (1946–present), EMBASE Ovid (1947–present), CINAHL (EBSCO), and the Cochrane Library (Wiley Online Library) were searched for all

relevant articles. The last search was run on 12 January, 2022. Year of publication limits was not applied, to capture any potential studies that may have been missed in the original review [20]. Searches were limited to English language and adult human subjects. The search strategy consisted of variations of the terms "nonalcoholic fatty liver disease," "NAFLD," "nonalcoholic steatohepatitis (NASH)," "cirrhosis," "diet," and "nutrition" as both medical subject headings and subject headings specific to each database and keywords or free-text words that included a wide range of derivations to ensure an extensive search was performed. **Supplemental Data 1** provides search strategies for all databases. Outcomes were not specified in the search strategy, to ensure all relevant literature relating to cytokines and adipokines was retrieved. Hand-searching of reference lists of included papers was completed to retrieve any additional relevant literature, as were conference abstracts and reports, however, there were no potentially eligible studies retrieved from these sources.

Eligibility criteria

The eligibility for inclusion/exclusion was determined using the Patient, Intervention, Comparators, Outcome, and Study Design (PICOS) method [22] and is presented in Table 1. In summary, inclusion criteria were studies of adults aged $\geq$ 18 y, diagnosed with NAFLD, where diagnosis of NAFLD was by a specified method; studies that compared a dietary intervention with an alternative diet or control, or were accompanied by supplementation or other lifestyle interventions; studies that reported outcomes of inflammatory cytokines and/or adipokines; study designs that were a RCT; publications that were published in peer-reviewed scientific journals. Exclusion criteria included: Any animal, pediatric, or pregnancy studies; studies that intervened only with supplements or pharmacological drugs; studies without a comparator group; studies that did not present numerical values in the results for cytokines and/or adipokines; studies that were not conducted as RCTs; or were deemed to have not met the inclusion criteria.

Databases were searched by 1 reviewer (R.L.H.) and references were imported into a bibliographic database (EndNote 20) to automatically exclude duplicates. All references were then exported to Covidence.org (review management program software), where additional duplicates were removed, and references were screened by title and abstract by 1 researcher (R.L.H.). Full-text publications of potentially eligible references were then obtained and screened independently by 2 researchers (R.L.H. and A.R.). Disputes relating to eligibility or inclusion were resolved by discussion and consensus.

Data extraction and quality assessment

Once eligible studies were identified, 2 researchers (R.L.H. and A.J.R.) independently assessed each article for methodological quality and risk of bias using the Academy of Nutrition and Dietetics Quality Criteria Checklist – Primary Research [23] that was uploaded to Covidence program. The validity assessment criteria checklist contained 10 questions. A study received a negative ranking (-) if >6 validity questions were answered as "no"; a study received an unclear ranking (ø) if validity questions 2, 3, 6, and 7 did not indicate that the study was exceptionally strong; and a study received a positive ranking (+) if most validity questions were answered "yes" (including questions 2, 3, 6, 7, and at least 1 additional "Yes"). Extraction of relevant data from studies deemed eligible was completed independently by 1 researcher (R.L.H.). Extracted information included: location (country); diagnosis method of NAFLD; number of participants; age and sex; body mass index; intervention length; type of dietary intervention; dietary intervention protocol; the addition of supplementation or cointervention, and description of same; type of inflammatory marker; pre- and postintervention results of each inflammatory marker; type of study design; level of evidence of each study, as determined using the NHMRC Evidence Hierarchy [24]; methodological quality of each study using the Academy of Nutrition and Dietetics Quality Criteria Checklist—Primary Research [23]. Authors were contacted to provide

TABLE 1
PICOS criteria applied for inclusion/exclusion of studies

PICOS	Inclusion/exclusion criteria
Population	Inclusion: Adults aged $\geq$18 y, diagnosed with NAFLD, where diagnosis of NAFLD by one of the following; histological examination of biopsies; magnetic resonance imaging and/or magnetic resonance spectroscopy; computed tomography; ultrasound; transient elastography (FibroScan); and blood concentrations of liver enzymes alanine aminotransferase and/or aspartate aminotransferase. Exclusion: Any animal, pediatric, or pregnancy studies
Intervention	Inclusion: Studies comparing a dietary intervention with an alternate diet or control group (no intervention); studies in which supplementation was provided alongside a dietary intervention, so long as there was an independent dietary intervention group; interventions that included a dietary intervention alongside a cointervention including physical activity, behavior training, or other lifestyle interventions (only eligible if the control or other diet arm was stand-alone; 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; studies that reported outcomes of inflammatory cytokine and/or adipokine markers. Exclusion: Studies that intervened only with supplementation or pharmacological drugs or investigated only postprandial effects of a dietary or meal intervention
Comparators	Inclusion: Control or stand-alone diet group Exclusion: Studies without control or stand-alone diet group
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
Study design	Inclusion: Study designs that were a randomized controlled trial; publications that were published in peer-reviewed scientific journals, written in English language, or had English versions of foreign language studies available; were published since the previous review (2018 onward), or identified as eligible but overlooked for the previous review. Exclusion: Study designs that are reviews, cohort studies, cross-sectional studies, case-control studies, conference abstracts, editorials, letters, and reviews; non-English language only papers; studies that were included in the previous review or were published prior to 2018 and deemed to have not met the inclusion criteria.

NAFLD, nonalcoholic fatty liver disease. Reprinted from reference 20.

additional data when articles contained insufficient information. This occurred for 12 articles [25–36]. No responses were received from the authors that were contacted; therefore the aforementioned articles were excluded from the review. Disputes relating to quality assessment or data extractions were resolved through discussion and consensus. Whereby the first 2 reviewers could not resolve conflict, a third independent reviewer (E.G.) was consulted.

Data analysis

Data were synthesized by grouping outcomes of inflammatory markers by dietary intervention and the difference in end-intervention means between groups, change between groups, and level of significance was extracted from each study and percentage change was then calculated. Reporting of this data was dependent on the analysis reported for individual studies. Meta-analysis was considered appropriate only when studies were homogenous both from a clinical and methodological standpoint [37]. Heterogeneity of data allowed outcomes hs-CRP and TNF-α to be grouped by dietary intervention for data analysis, data were pooled using Review Manager (RevMan, Version 5.4. The Cochrane Collaboration, 2020). To calculate the overall treatment effect, the differences between the control and intervention groups' outcomes at end-intervention were analyzed using a random-effects model. Continuous outcome data were calculated using the inverse variance test as mean differences (MDs) for studies that used the same measurement. Where numerical values for inflammatory markers were reported in different units, they were converted, where possible, into the same unit (e.g., pg/mL to ng/mL and an MD was calculated. Where heterogeneity of data did not allow for data to be included for meta-analysis, narrative synthesis was presented instead.

Results of meta-analyses were inspected for heterogeneity, tested using the χ^2 test, and assessed by the I^2 statistic. A P value of <0.05 provides evidence of statistical heterogeneity for the χ^2 test, as recommended by the Cochrane Collaboration [38]. The I^2 statistic (0%–100%), the percentage of total variation across studies due to heterogeneity, were defined as low (I^2 = 0%–33%), moderate (I^2 = 34%–66%), and high (I^2 = 67%–100%). When heterogeneity was high, the data were examined to determine, which studies were responsible for the heterogeneity. The data were then re-analyzed without the studies contributing heterogeneity by setting the weighting for those studies to zero. Sensitivity analysis was performed to detect whether a single study with high overall risk of bias or which scored negatively for random sequence generation, selection, and allocation bias significantly affected the pooled result by removing 1 study in each turn. The possibility of publication bias was estimated by visual inspection of the funnel plot and the "fill and trim" method was used to further evaluate the possible effect of publication bias [39].

Results

A total of 5729 records were retrieved from database searches, and after removal of duplicates, 4462 remained. Titles and abstracts were screened, and 81 articles were deemed to be potentially eligible. Overall, 81 full-text articles were screened independently in duplicate, of which 56 fulfilled the inclusion criteria. Overall, 12 articles were excluded during data extraction because of a lack of dietary information provided and no response from authors when contacted [25–36]. Overall, 44 articles were therefore included in the present review, 19 of which comprised the first publication/iteration of this review and 25 new articles retrieved from the present search, which met the eligibility criteria. The reference lists of all included papers were hand searched for any additional relevant literature, however, there were no additional studies retrieved. The study selection process is summarized in Figure 1.

The study design of all 44 included articles were RCTs: 8 were nonblinded [40–47]; 5 were single blinded [48–52]; 3 were double blinded [53–55]; 22 were double blinded, placebo controlled [56–77]; 5 were open-label parallel-arm [78–82]; and 1 was a prospective, single blinded, random order controlled dietary feeding study [83].

Study characteristics and participants

Overall 44 studies included in this updated systematic literature review were published between 2003 and 2021. A total of 2579 participants with NAFLD were enrolled in the studies, of whom 2497 participants were analyzed. Of the participants included for analysis, 1333 (53%) were male and 1164 (47%) were female. The age of participants ranged from 18 to 80 y, and BMI ranged from 23 to 40 kg/m^2. Intervention length ranged from 2 wk to 2 y. Overall, 27 studies took place in Iran [40,41,45,48,52,55,56,58,60–68,70–73,75–79,82], 7 in Italy [47,49,53,54,57,69,74], 2 in Spain [42,43], 2 in the United States [50,83], and 1 each, respectively, in Australia [51], Germany [80], Greece [81], India [59], Serbia [44], and the United Kingdom [46]. Two of the included studies reported results drawn from the same cohort, where Marin-Alejandre et al. [42], reported a 6-mo intervention and the same group [43] a 2-y intervention, that analyzed different biomarkers in each of the studies. Another study conducted by Behrouz et al. [56] reported results from the same cohort as included in the original review [67]; however, Behrouz et al. [67] also analyzed different biomarkers in the 2 published studies.

Assessment tools for characterizing NAFLD varied across the 44 studies. Four studies used the gold-standard liver biopsy (Bx) [46,49,50,69], 1 study used a combination of Bx and ultrasound (US) [59], 18 used US alone [40–44,48,52,53,61,63–66,75–78,81], 11 used a combination of US and liver enzymes [45,47,54–57,60,62,67,68,72], 3 used magnetic resonance spectroscopy (MR-S) [51,80,83], and 7 used Fibroscan alone [58,70,71,73,74,79,82]. The characteristics of all included studies are presented in Table 2.

Intervention characteristics

The dietary interventions in each study varied with regard to caloric content and macronutrient distribution. Comparison diets and cointerventions were also widely diverse. Of the 44 studies, 17 studies intervened with a hypocaloric diet and compared that diet with: a hypocaloric Mediterranean diet [42–44]; a hypocaloric soy-containing diet [40,41]; the Dietary Approaches to Stop Hypertension (DASH) diet [55]; a hypocaloric diet plus supplementation in the form of a probiotic [59], a probiotic and prebiotic combination [49], the addition of olive oil [64], flaxseed [65], L-carnitine [69], soy isoflavone [66], hydroxy-citric acid [52], *Camelina sativa* oil (CSO), and prebiotic [75]; a hypocaloric diet plus cointervention of hesperidin, hesperidin and flaxseed and flaxseed alone [79]; a cholesterol

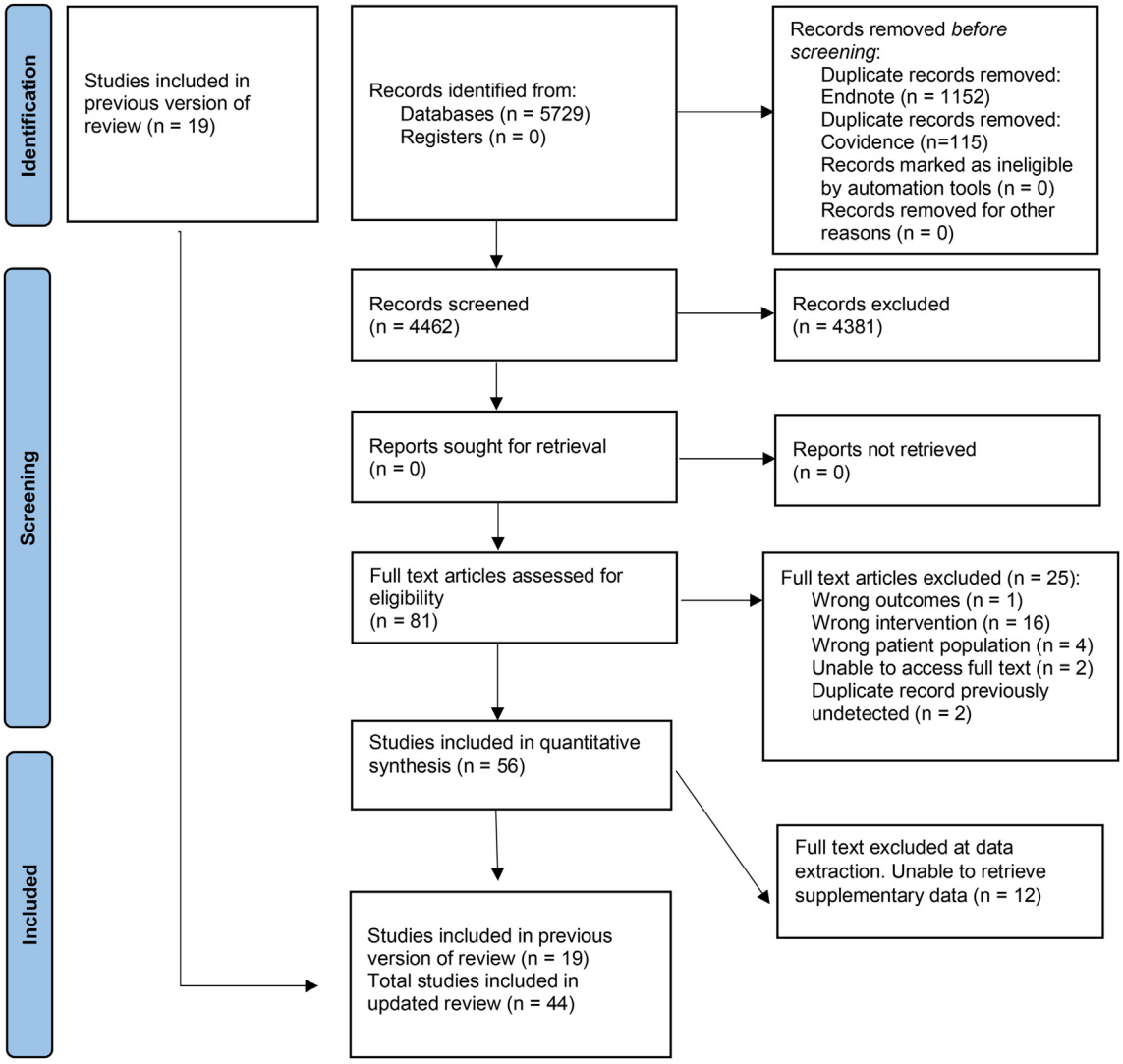

FIGURE 1. PRISMA flow chart for study selection.

absorption inhibitor (ezetimibe) [51]; and an oral hypoglycemic agent (metformin) [53]. Four studies reported interventions with an energy-restricted (ER) diet that was compared with the same-diet plus: a low-carbohydrate diet and a low-carbohydrate/soy-containing diet; a very-low-energy diet (VLED) meal-replacement plan; a conjugated linoleic acid (CLA) supplement; and a β-Cryptoxanthin (BCX) supplement, an ER-high protein diet and an ER-high protein diet plus BCX supplement, respectively [45,46,48,61].

Overall, 23 studies intervened with an energy-balanced or isocaloric diet and compared that diet with: the same energy-balanced diet in a low-fat and high-fat form [83]; the same diet with yogurt and then yogurt with a symbiotic [78]; the same diet with a probiotic and then a prebiotic [56,67]; a plant-protein based diet to an animal protein-based diet [80]; the same diet plus supplementation in the form of *Nigella sativa* seed [58], trans-resveratrol [60], ginger [62,71], alpha-lipoic acid (α-LA) [63], symbiotic [68,70,73], coffee bean extract [72], Corinthian currants [81], vitamin E [50], chromium picolinate [76], n-3 PUFA [47], saffron [77], flaxseed [82], bergamot polyphenolic fraction (BPF), and *Cynara Cardunculus* extract (CyC) [74], a nutraceutical mix (containing fish oil, phosphatidylcholine, silymarin, choline bitartrate, curcumin, D-α-tocopherol) [57], and olive oil enriched with n-3 PUFA [54].

Of the 44 included studies, all but 8 [46,50,51,53,61,74,75,80] made recommendations for physical activity. Physical activity recommendations ranged from ≥30 min of exercise, 3 times per week for the 14 studies adhering to the National Heart Lung and Blood Institute-Energy Balanced (NHLBI-EB) diet [56,58,60,62,63,67,68,70–73,78,79,82] to ≥30 min of exercise ≥5 d per week, for 9 studies that intervened with a hypocaloric diet, where weight loss was intended [40–44,59,64,65,79]. The dietary and physical activity intervention information extracted from each study is presented in Supplemental Table 1.

Inflammatory markers

Results have been reported per inflammatory marker (cytokines followed by adipokines) and then further assessed based on diet alone plus any cointerventions.

Cytokines

The most commonly reported cytokines in the included studies were hs-CRP, reported by 29 studies [40, 42,44–46,48,49,51,52,55–58,60–62,68–73,75–77,79,81–83]; TNF-α,

TABLE 2
Characteristics of studies included for the updated systematic review investigating the effects of randomized controlled dietary intervention(s) and/or cointervention on inflammatory markers in adults with nonalcoholic fatty liver disease

Study	Country	Diagnostic Method	Sample, *n* (M/F)	Study type, NHMRC LOE, Quality Ax	Diet of Interest	2nd Diet of Interest	3rd Diet of Interest	4th Diet of Interest	Int. Duration	Inflammatory Biomarker
Abedi et al. (2018) [48]	Iran	US	Total (n = 38) 5/33	RCT/Level II. Neutral	Energy-restricted diet plus Vitamin E supplement	Energy-restricted diet plus conjugated linoleic acid (CLA) and Vitamin E supplement			8 wk	IL-6, IL-10, TNF-α, hs-CRP
Abhari et al. (2020) [73]	IranTABLE	Fibroscan (CAP >270 dB/m)	Total (n = 46) 25/20	RCT/II. Positive	Energy balanced (NHLBI-EB) plus placebo	Energy balanced (NHLBI) plus synbiotic (*B. coagulans*)			12 wk	hs-CRP, TNF-α, NF-κB
Amanat et al. (2017) [66]	Iran	US	Enrolled (n = 82), analyzed (n = 78), 61/21	RCT/II. Positive	Weight-management diet plus placebo	Weight-management diet plus soy isoflavone supplement			8 wk	TNF-α, IL-6
Baldry et al. (2017) [46]	United Kingdom	Liver bx.	Total (n = 54), 44/10	RCT/II. Positive	Very-low energy diet, in the form of standard prebariatric surgery food-based diet	Very-low energy diet (VLED) in the form of meal-replacement plan			2 wk	hs-CRP, IL-6, fetuin-A
Bakhshimoghaddam et al. (2018) [78]	Iran	US	Total (n = 102) 50/52	RCT/Level II. Positive	Weight-management diet (NHLBI-EB)	Weight-management diet (NHLBI-EB) plus conventional yogurt	Weight-management diet plus conventional yogurt containing synbiotic		24 wk	CTRP-5
Behrouz et al. (2017) [67]	Iran	US and ALT (>1.5 x upper limit of normal)	Total (n = 89) 63/26	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus prebiotic and probiotic placebo	Energy-balanced diet (NHLBI-EB) plus probiotic supplement and prebiotic placebo	Energy-balanced diet plus prebiotic supplement and probiotic placebo		12 wk	adiponectin, leptin
Behrouz et al. (2020) [56]	Iran	US (steatosis > grade II) and ALT (>1.5×upper limit of normal)	Enrolled (n = 111). Analyzed (n = 89) 63/26	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo	Energy-balanced diet (NHLBI-EB) plus probiotic and prebiotic placebo	Energy-balanced diet plus prebiotic and probiotic placebo		12 wk	hs-CRP
Chan et al. (2010) [51]	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 10mg/d ezetimibe consumed for 22-wk			22 wk	Adiponectin, hs-CRP, TNF-α, IL-6, RBP-4, fetuin-A

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Cerletti et al. (2020) [57]	Italy	US, AST & ALT	Enrolled (n = 126). Analyzed (n = 113) 74/39	RCT/Level II. Positive	Mediterranean diet plus placebo	Mediterranean diet plus nutraceutical			12 wk	hs-CRP
Darand et al. (2019) [58]	Iran	Fibroscan with CAP (score > 263 (dB/m)	Enrolled (n = 50). Analyzed (n = 43) 22/21	RCT/Level II. Positive	Energy balanced diet (NHLBI-EB) plus placebo.	Energy balanced diet (NHLBI-EB) plus *Nigella sativa* seed powder supplement			12 wk	hs-CRP, TNFα, NF-κB
Duseja et al. (2019) [59]	India	US and Liver Bx	Enrolled (n = 39) 28/11. Analyzed (n = 30)	RCT/Level II. Neutral	Hypocaloric diet	Hypocaloric diet plus multistrain probiotic preparation			12 mo	Leptin, adiponectin, TNF-a, IL-1β, IL-6
Eslami et al. (2019) [40]	Iran	US	Enrolled (n = 70). Analyzed (n = 64) 19/55	RCT/Level II. Neutral	Hypocaloric diet	Hypocaloric diet plus soy milk			8 wk	hs-CRP
Eslamparast et al. (2014) [68]	Iran	UL and ALT >30 IU/L	Total (n = 52) 25/27	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo	Energy-balanced diet (NHLBI-EB) plus synbiotic supplement			28 wk	hs-CRP, TNF-α, NF-κB
Faghihzadeh et al. (2014) [60]	Iran	US and ALT >30 IU/L (M); >19 IU/L (F)	Total (n = 50) 35/15	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo	Energy balanced diet(NHLBI-EB) plus trans-resveratrol supplement			12 wk	hs-CRP, IL-6, TNF-α, NF-κB, CK-18
Ferro et al. (2020) [74]	Italy	Fibroscan	Total (n = 86) 52/34	RCT/Level II. Positive	MedDiet plus placebo (maltodextrin)	MedDiet plus bergamot polyphenolic fraction (BPF) and Cynara Cardunculus extract (CyC).			12 wk	IL-1β, IL-6, TNF-α
Garinis et al. (2010) [53]	Italy	US	Total (n = 45) 7/38	RCT/Level II. Positive	Hypocaloric diet	Hypocaloric diet plus Metformin 1000mg/d			6 mo	Adiponectin
Haidari et al. (2020) [61]	Iran	US	Total (n = 92) 44/48	RCT/Level II. Positive	Energy-restricted normal-protein diet plus placebo	Energy-restricted normal-protein diet plus β-Cryptoxanthin (BCX) supplement	Energy-restricted High Protein Diet plus placebo	Energy-restricted High Protein Diet plus β-Cryptoxanthin (BCX) supplement	12 wk	hs-CRP, IL-6, CK18-M65, adiponectin
Kaliora et al. (2016) [81]	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) [45]	Iran	US, AST & ALT (M>30 IU/L, F>20 IU/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
Kavyani et al. (2021) [75]	Iran	US	Total (n = 44) 19/17	RCT/Level II. Positive	Low-calorie diet plus placebo	Low-calorie diet plus *Camelina sativa* oil (CSO) &			12 wk	hs-CRP

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TABLE 2 (*continued*)

Study	Country	Diagnostic Method	Sample, *n* (M/F)	Study type, NHMRC LOE, Quality Ax	Diet of Interest	2nd Diet of Interest	3rd Diet of Interest	4th Diet of Interest	Int. Duration	Inflammatory Biomarker
						prebiotic (resistant dextrin)				
Kugelmas et al. (2003) [50]	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 Vit. E 800 IU/d			12 wk	TNF-α, IL-6, IL-8
Malaguarnera et al. (2010) [69]	Italy	Liver bx.	Total (*n* = 74) 40/34	RCT/Level II. Positive	Hypocaloric (NCEP-ATPIII) diet PLUS placebo	Hypocaloric diet (NCEP-ATPIII) plus L-carnitine			24 wk	hs-CRP, TNF-α
Malaguarnera et al. (2012) [49]	Italy	Liver bx.	Total (*n* = 66) 33/33	RCT/Level II. Neutral	Hypocaloric (NCEP-ATPIII) diet PLUS placebo	Hypocaloric diet (NCEP-ATPIII) plus probiotic and prebiotic supplement			24 wk	hs-CRP, TNF-α
Maleki et al. (2019) [41]	Iran	US	Enrolled (*n* = 66), Analyzed (*n* = 62) 19/43	RCT/Level II. Positive	Hypocaloric diet	Hypocaloric diet plus soy milk			8 wk	Fibrinogen
Marin-Alejandre et al. (2019) [42]	Spain	US	Total (*n* = 98) 51/47	RCT/Level II. Positive	Hypocaloric diet (AHA)	Hypocaloric Mediterranean diet (FLIO)			6 mo	Leptin, adiponectin, hs-CRP
Marin-Alejandre et al. (2021) [43]	Spain	US	Enrolled (98) 55/43	RCT/Level II. Positive	Hypocaloric diet (AHA)	Hypocaloric Mediterranean diet (FLIO)			2 y	Leptin, adiponectin
Marina et al. (2014) [83]	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, IFN-γ
Markova et al. (2016) [80]	Germany	MR-S	Total (*n* = 37) 24/13	RCT/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) [70]	Iran	Fibroscan & ALT (>60 IU/L)	Total (*n* = 42) 23/19	RCT/II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo	Energy-balanced diet (NHLBI-EB) plus synbiotic supplement			28 wk	hs-CRP, TNF-α, NF-κB
Moradi et al. (2021) [76]	Iran	US	Enrolled (*n* = 46) 26/17	RCT/II. Neutral	Energy-restricted diet (AHA) plus placebo	Energy-restricted diet (AHA) plus Chromium Picolinate			12 wk	Fetuin-A, hs-CRP, TNF-α, IL-6
Nomi-Golzar et al. (2020) [52]	Iran	US	Total (*n* = 40) 0/40	RCT/II. Neutral	Low-calorie diet plus Hydroxy-citric acid supplement	Low-calorie diet			8 wk	hs-CRP
	Iran	US							12 wk	

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Pour et al. (2020) [77]			Total (n = 76) 43/33	RCT/II. Positive	Healthy diet plus placebo	Healthy diet plus 100 mg/d saffron supplement				hs-CRP, TNF-α, adiponectin, leptin
Rafie et al. (2020) [62]	Iran	US and ALT	Enrolled (n = 50). analyzed (n = 46) 20/26	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo.	Energy-balanced diet (NHLBI-EB)plus ginger supplement			12 wk	hs-CRP, TNF-a, adiponectin, Fetuin-A
Rahimlou et al.(2016) [71]	Iran	Fibroscan and ALT (>1.5 x upper limit of normal)	Total (n = 44) 20/24	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB) plus placebo	Energy-balanced diet (NHLBI-EB) plus ginger supplement			12 wk	hs-CRP, TNF-α
Rahmanabadi et al. (2019) [63]	Iran	US	Total (n = 50) 27/23	RCT/Level II. Positive	Weight-control diet (NHLBI-EB) plus placebo	Weight-control diet (NHLBI-EB) plus α-LA supplement			12 wk	Adiponectin, leptin, resistin, irisin
Razavi Zade et al. (2016) [55]	Iran	US and ALT (M>30 IU/L, F>19IU/L)	Total (n = 60) 30/30	RCT/Level II. Positive	Hypocaloric diet	Dietary Approaches to Stop Hypertension diet			8 wk	hs-CRP
Rezaei et al. (2019) [64]	Iran	US	Total (n = 66) 29/37	RCT/Level II. Positive	Hypocaloric diet plus sunflower oil (control).	Hypocaloric diet plus olive oil			12 wk	IL-6
Rezaei et al. (2020) [65]	Iran	US	Total (n = 68) 33/35	RCT/Level II. Positive	Hypocaloric diet plus sunflower oil (control)	Hypocaloric diet plus flaxseed oil			12 wk	IL-6
Ristic-Medic et al. (2021) [44]	Serbia	US	Enrolled (n = 27). analyzed (n = 24) 24	RCT/Level II. Positive	Hypocaloric (Board of the US NIHFN)	Hypocaloric Mediterranean diet. (Board of the US NIHFN)			12 wk	hs-CRP
Shahmohammadi et al. (2017) [72]	Iran	US and ALT (M>30 IU/L, F>19IU/L)	Total (n = 44) 22/22	RCT/Level II. Positive	Energy-balanced (NHLBI-EB) plus placebo	Energy-balanced (NHLBI-EB) plus green coffee bean extract supplement			8 wk	hs-CRP, TNF-α
Sofi et al. (2010) [54]	Italy	US and ALT (M>30 IU/L, F>20 IU/L)	Total (n = 11) 9/2	RCT/Level II. Positive	Mediterranean diet	Mediterranean diet plus olive oil enriched with n-3 PUFA			12 mo	Adiponectin
Spadaro et al. (2008) [47]	Italy	US and ALT (M>30 IU/L, F>20 IU/L)	Total (n = 36) 19/17	RCT/Level II. Positive	AHA diet plus placebo	AHA diet plus n-3 PUFA capsule			6 mo	TNF-α
Yari et al. (2016) [82]	Iran	Fibroscan	Total (n = 50) 25/25	RCT/Level II. Positive	Energy-balanced diet (NHLBI-EB)	Energy-balanced diet (NHLBI-EB) plus flaxseed supplement			12 wk	hs-CRP, TNF-α
Yari et al. (2021) [79]	Iran	Fibroscan + CAP≥260	Enrolled (n = 100). analyzed (n = 92) 49/43	RCT/Level II. Neutral	Hypocaloric diet (NHLBI-EB)	Hypocaloric diet (NHLBI-EB) plus hesperidin	Hypocaloric diet plus flaxseed	Hypocaloric diet plus hesperidin and flaxseed	12 wk	hs-CRP, TNF-a, NF-κB

AHA, American Heart Association; α-LA, alpha-lipoic acid; ALT, alanine transaminase; AST, aspartate transaminase; Ax, assessment; Bx, biopsy; CK-18, cytokeratin-18; CK18-M65, total cytokeratin-18; CTRP-5, C1q/TNF-related protein 5; F, female; FLIO, Fatty Liver in Obesity; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; Interv., intervention; LOE, level of evidence; M, male; NF-κB, nuclear factor kappa B; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NHLBI-EB, National Heart Lung and Blood Institute-Energy Balanced; NHMRC, National Health and Medical Research Council; NIHFN, National Institute of Health & Food & Nutrition; RCT, randomized controlled trial; TNF-a, tumor necrosis factor-alpha; US, ultrasound.

reported by 22 studies [47–49,51,58–60,62,66,68–74,76,77,79–82]; and IL-6 reported by 14 studies. [46, 48,51,59–61,64–66,74,76,80,81,83]. Table 3 presents the data extracted for the intervention effects on cytokines.

High-sensitivity C-reactive protein

Of the 29 included studies that analyzed hs-CRP (Table 3), 23 reported a significant ($P \leq 0.05$) improvement from pre- to postintervention [40,42,44–46,48,49,51,55,56,58,60–62,69,71,72,75–77,79,81]. Overall, 23 of the studies investigated hs-CRP following dietary intervention plus cointervention or supplementation [40,48,49,51,52,56–58,60–62,68–73,75–77,79,81,82], of which 17 reported statistically significant positive changes following diet and a cointervention or supplementation [40,48,49,51,56,58,60–62,69,71,72,75–77,79,81].

Effect of diet alone. Of the 6 studies that investigated the effect of diet alone on hs-CRP, 2 studies reported significant ($P \leq 0.05$) improvements for both intervention groups [44,46], 3 studies reported significant ($P \leq 0.05$) improvements for 1 intervention arm only [42,45,55] and 1 study reported nonsignificant ($P \geq 0.05$) improvements for both intervention groups [83]. Baldry et al. [46] conducted a 2-wk intervention that compared a very-low energy diet (VLED), prebariatric surgery, food based with a VLED meal-replacement plan and reported a significant improvement for both intervention groups ($P = 0.007$ and $P = 0.004$, respectively). Similarly, a hypocaloric MedDiet and a hypocaloric National Institute of Health and Food and Nutrition (NIHFN) diet, provided a significant improvement to hs-CRP for both intervention groups ($P = 0.000$ and $P = 0.008$, respectively) [44]. A 6-mo hypocaloric MedDiet significantly improved hs-CRP ($P = 0.001$) compared with a hypocaloric American Heart Association (AHA) diet ($P = 0.250$) [42]. An 8-wk DASH diet was superior to an unspecified hypocaloric diet for reducing hs-CRP, in a study by Razavi Zade et al. ($P = 0.004$ vs. $P = 0.08$, respectively) [55].

Effect of diet vs. combined diet and cointervention, including supplements. Of the 17 studies that reported statistically significant positive changes following dietary intervention plus cointervention or supplementation, 5 of those studies reported significant ($P \leq 0.05$) improvement for both study arms [48,56,61,71,81] and 12 studies reported significant ($P \leq 0.05$) improvement for the diet plus cointervention or supplementation group only [40,49,51,58,60,62,69,72,75–77,79]. An isocaloric or energy-balanced diet provided significant improvement to hs-CRP when used alone or with the addition of Corinthian currants ($P = 0.023$ and $P = 0.002$, respectively) [81]; alone or with the addition of a probiotic supplement and prebiotic placebo and the addition of a prebiotic supplement and probiotic placebo ($P = 0.03$, $P = 0.001$, and $P = 0.001$, respectively) [56]; and, alone or with the addition of a ginger supplement ($P = 0.005$ and $P = 0.007$, respectively) [71]. An energy-restricted (ER) or low-calorie diet provided significant improvement to hs-CRP when used alone or with the addition of CLA supplement ($P = 0.008$ and $P = 0.001$, respectively) [48]; and as a ER-normal protein or ER-high protein diet alone or with the addition of a BCX supplement to each diet groups ($P < 0.001$) [61]. An ER or hypocaloric diet provided significant improvement to hs-CRP when used in conjunction with: a cholesterol-lowering agent ($P \leq 0.05$) [51]; soy milk ($P < 0.001$) [40]; *CSO* and prebiotic supplement ($P \leq 0.05$) [75]; a probiotic and prebiotic supplement ($P < 0.001$) [49]; a chromium picolinate supplement ($P = 0.04$) [76]; hesperidin or hesperidin and flaxseed ($P = 0.005$ and $P < 0.001$, respectively) [79]; but not when used alone. An energy-balanced, NHLBI-EB or healthy diet provided significant improvement to hs-CRP when used in conjunction with: a trans-resveratrol supplement ($P = 0.011$) [60]; a saffron supplement ($P < 0.01$) [77]; a ginger supplement ($P = 0.001$) [62]; a GCBE supplement ($P < 0.001$) [72], but not when used alone.

Interleukin 6

Of the 14 studies investigating IL-6 as an outcome, 9 studies reported significant improvements [46,48,51,59–61,66,76,81] and 3 studies reporting nonsignificant improvements [64,65,83] (see Table 3). Overall, 7 of the 9 studies reporting significant improvements administered dietary intervention in comparison to dietary intervention plus supplementation [48,59–61,66,74,76].

Effect of diet alone. Baldry et al. [46] tested a VLED with meal-replacement vs. an *ad libitum* VLED, finding that IL-6 significantly improved in the VLED meal-replacement group only ($P = 0.04$).

Effect of diet vs. combined diet and cointervention, including supplements. Of the 7 studies that reported significant ($P \leq 0.05$) improvements following dietary intervention plus a cointervention or supplement, 2 of those studies reported significant improvements to all study arms [61,74]. A hypocaloric, weight management, or ER diet provided significant improvement to IL-6 when used in conjunction with: a cholesterol-lowering agent ($P \leq 0.05$) [51]; a CLA and Vitamin E supplement ($P = 0.042$) [48]; a soy isoflavone supplement ($P = 0.01$) [66]; a multistrain probiotic ($P = 0.041$) [59]; a chromium picolinate supplement ($P = 0.02$) [76]; but not when used alone. A NHLBI-EB or isocaloric diet provided significant improvement to IL-6 when used in conjunction with: Corinthian currants ($P = 0.009$) [81]; a trans-resveratrol supplement ($P = 0.034$) [60]; but not when used alone.

Tumor necrosis factor-alpha

Overall, 22 studies analyzed TNF-α, of which 13 studies reported significant improvements [47–49,51,58,66,69,71,73,74,77,79,81] and 5 studies reported nonsignificant improvement only in the intervention group [59,60,62,72,76] (Table 3). Overall, 18 studies reported on dietary intervention plus supplement [47–49,58–60,62,66,68,70–74,76,77,79,82], of which 10 studies reported statistically significant changes following diet and supplementation [47–49,58,66,71,73,74,77,79].

Effect of diet alone. Markova et al. [80] tested a plant-protein isocaloric diet vs. an animal protein isocaloric diet, finding that TNF-α significantly improved in the plant-protein isocaloric diet group only ($P = 0.016$).

Effect of diet vs. combined diet and cointervention, including supplements. Of the 10 studies that reported significant ($P \leq 0.05$) improvements following dietary intervention plus a cointervention or supplement, 5 studies reported significant improvements to both study arms [48,58,71,74,77], 6 studies reported significant improvements to the diet plus supplement or cointervention arm only [47,49,51,66,69,73], 1 study reported significant improvements to 3 of 4 study arms [79], and 1 study reported significant improvement to the diet-only arm of the study [81]. A NHLBI-EB diet, an ER diet, a Mediterranean diet, and a healthy diet provided significant improvements to TNF-α when used alone or in conjunction with: a CLA and Vitamin E

TABLE 3
Data extracted from studies included for the updated systematic review investigating the effects of randomized controlled dietary intervention(s) and/or cointervention on inflammatory markers in adults with nonalcoholic fatty liver disease for the intervention effects of cytokines

High-sensitivity C-reactive protein

Reference	Diet	Unit	Preintervention serum concentration	Postintervention serum concentration	*P* value	Computed change	Mean change conc. (95% CI), mg/mL
Dietary intervention alone							
Baldry et al. (2017) [46]	Very-low energy diet; food-based diet	mg/L	8.2 (42.8)	5.1 (21.7)	0.007	−37.8%	
	Very-low energy diet; meal-replacement plan		9.6 (29.1)	6.4 (21.8)	0.004	−33.3%	
Kani et al. (2014) [45]	Low calorie	mg/L	nd	nd	nd	−1.0 ± 0.6[b]	
	Low calorie, low carbohydrate		nd	nd	nd	−1.1 ± 0.6[b]	
	Low calorie, low carbohydrate, soy containing		nd	nd	0.01	−8.0 ± 1.0[b]	
Marin-Alejandre et al. (2019) [42]	Hypocaloric diet (AHA)	mg/L	6.5 ± 1.9	3.2 ± 0.4	0.250	−51.0%	
	Hypocaloric Mediterranean diet (FLIO)		4.0 ± 0.60	1.8 ± 0.20	0.001	−55.0%	
Marina et al. (2014) [83]	Low-fat diet	mg/L	3.3 ± 2.8	2.8 ± 2.5	ns	−15.1%	
	High-fat diet		2.3 ± 1.9	2.2 ± 1.2	ns	−4.3%	
Razavi Zade et al. (2016) [55]	Hypocaloric diet	mg/L	4.9 ± 3.4	4.6 ± 2.8	0.08	−6.1%	
	DASH diet		4.8 ± 3.3	3.6 ± 2.7	0.004	−25.0%	
Ristic-Medic et al. (2020) [44]	Hypocaloric (NIHFN)	mg/L	2.10 (0.98,3.20)[a]	0.77 (0.54,1.27)[a]	0.008	−63.0%	
	Hypocaloric Mediterranean diet (NIHFN)		1.02 (0.75,2,23)[a]	0.81 (0.34,1.40)[a]	0.000	−21.0%	
Dietary intervention plus cointervention							
Chan et al. (2010) [51]	Hypocaloric diet, Low fat	mg/L	2.2 ± 1.3	2.4 ± 1.6	nd	9.1%	
	Hypocaloric diet, Low fat + cholesterol-lowering agent		3.9 ± 3.8	2.2 ± 2.7	<0.05*	−43.6%	
Kaliora et al. (2016) [81]	Isocaloric diet	mg/L	2.4 ± 3.0	0.84 ± 1.1	0.023	−65.0%	
	Isocaloric diet + Corinthian currants		2.1 ± 1.8	0.82 ± 0.7	0.002	−60.9%	
Malaguarnera et al. (2010) [69]	NCEP-ATPIII	mg/L	8.7 ± 3.4	7.4 ± 3.2	≥ 0.05	−14.9%	
	NCEP-ATPIII + L-carnitine		9.1 ± 3.2	5.2 ± 3.1	<0.001*	−42.9%	
Dietary intervention plus supplementation							
Abedi et al. (2018) [48]	Energy-restricted diet plus Vitamin E supplement	mg/L	4.1 ± 4.6	3.4 ± 4.1	0.008	−17.0%	
	Energy-restricted diet plus CLA and Vitamin E supplement		3.6 ± 4.6	2.6 ± 3.8	0.001	−28.0%	
Abhari et al. (2020) [73]	Energy-balanced (NHLBI-EB) plus placebo	mg/L	5797.3 ± 3497.5	6049.7 ± 4740.0	0.459	259.67 ± 1274.55[b]	
	Energy-balanced (NHLBI-EB) plus synbiotic (*B. coagulans*)		5183.9 ± 3497.1	4397.5 ± 3616.0	0.119	−793.38 ± 2174.87[b]	
Behrouz et al. (2020) [56]	Energy-balanced diet (NHLBI-EB) plus placebo	pg/ml	9.2 ± 4.5	6.9 ± 3.7	0.03	−25.0%	
	Energy-balanced diet (NHLBI-EB) plus probiotic and prebiotic placebo		9.3 ± 4.3	6.3 ± 4.9	0.001	−32.0%	
	Energy-balanced diet (NHLBI-EB) plus prebiotic and probiotic placebo		9.9 ± 5.8	6.1 ± 5.0	0.001	−38.0%	
Cerletti et al. (2020) [57]	Mediterranean diet	mg/L	2.97 (0.36, 4.67)[a]	2.52 (1.39, 4.30)[a]	0.420	−15.0%	
	Mediterranean diet plus nutraceutical		2.20 (1.40, 4.00)[a]	17.1 (1.80, 3.20)[a]	0.120	−19.0%	

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TABLE 3 (*continued*)

High-sensitivity C-reactive protein							
Reference	Diet	Unit	Preintervention serum concentration	Postintervention serum concentration	*P* value	Computed change	Mean change conc. (95% CI), mg/mL
Darand et al. (2019) [58]	Energy balanced diet (NHLBI-EB) plus placebo.	mg/L	5057.53 ± 3,291.26	4509.86 + 3,288.4	0.480	−11.0%	
	Energy balanced diet (NHLBI-EB) plus *Nigella sativa* seed powder supplement		4959.63 ± 3,391.89	3514.22 ± 3982.89	0.000	−29.0%	
Eslami et al. (2019) [40]	Hypocaloric diet	mg/L	3.51 ± 1.3	3.14 ± 1.4	0.18	−11.0%	
	Hypocaloric diet plus soy milk		3.68 ± 1.82	2.34 ± 1.59	<0.001*	−36.0%	
Eslamparast et al. (2014) [68]	Energy-balanced diet (NHLBI-EB)	mg/L	nd	nd			−1.04 (−1.5 to −0.6)
	Energy-balanced diet (NHLBI-EB) + synbiotic supplement		nd	nd			−2.30 (−3.0 to −1.5)
Faghihzadeh et al. (2014) [60]	Energy-balanced diet (NHLBI-EB)	mg/L	3.20 ± 1.85	3.4 ± 2.13	0.861	6.0%	
	Energy balanced diet (NHLBI-EB) plus trans-resveratrol supplement		3.02 ± 1.04	2.11 ± 0.96	0.011	−30.0%	
Haidari et al. (2020) [61]	Energy-restricted normal-protein diet	mg/L	4.9 ± 1.5	3.5 ± 0.1	<0.001**	−29.0%	
	Energy-restricted normal-protein diet plus BCX		5.0 ± 1.9	3.2 ± 0.1	<0.001**	−36.0%	
	Energy-restricted High Protein Diet		4.7 ± 1.5	2.6 ± 0.1	<0.001**	−45.0%	
	Energy-restricted High Protein Diet plus BCX		4.8 ± 1.9	2.4 ± 0.1	<0.001**	−50.0%	
Kavyani et al. (2021) [75]	Low calorie diet plus placebo	ng/mL $^{-1}$	11.66 ± 2.90	10.23 ± 2.37	nd	−12.0%	
	Low calorie diet plus *Camelina Sativa* oil & prebiotic		10.49 ± 1.58	8.81 ± 2.29	<0.05	−16.0%	
Malaguarnera et al. (2012) [49]	Hypocaloric (NCEP-ATPIII) diet	mg/L	6.7 ± 3.1	6.0 ± 3.0	≥ 0.05	−10.0%	
	Hypocaloric diet (NCEP-ATPIII) plus probiotic and prebiotic supplement		7.0 ± 3.4	4.1 ± 3.1	<0.001*	−41.0%	
Mofidi et al. (2017) [70]	NHLBI-EB Diet	mg/L	nd	nd		−0.42 ± 0.1[b]	
	NHLBI-EB Diet plus synbiotic supplement		nd	nd		−1.16 ± 0.4[b]	
Moradi et al. (2021) [76]	Energy-restricted diet (AHA) plus placebo	mg/L	5.20 ± 2.73	4.75 ± 1.04	0.425	−9.0%	
	Energy-restricted diet (AHA) plus Chromium Picolinate supplement		4.32 ± 1.42	3.61 ± 1.36	0.004	−16.0%	
Nomi-Golzar et al. (2021) [52]	Low-calorie diet	ng/mL	5.0 ± nd	5.1 ± nd	>0.05	2.0%	
	Low-calorie diet plus Hydroxy-citric acid supplement		4.9 ± nd	5.1 ± nd	>0.05	4.0%	
Pour et al. (2020) [77]	Healthy diet plus placebo	ng/mL	5.48 ± 5.17	4.37 ± 3.90	0.248	−20.0%	
	Healthy diet plus saffron supplement		5.30 ± 4.48	2.49 ± 2.25	<0.01	−53.0%	
Rahimlou et al. (2016) [71]	NHLBI-EB Diet	mg/L	4.8 ± 0.2	2.8 ± 0.2	0.005	−41.7%	
	NHLBI-EB Diet plus ginger supplement		4.6 ± 0.1	3.4 ± 0.1	0.007	−26.1%	
Rafie et al. (2020) [62]	NHLBI-EB Diet	mg/L	2.26 (1.16,3.98)[a]	2.12 (0.98,3.78)[a]	0.128	−-6.0%	
	NHLBI-EB Diet plus ginger supplement		2.40 (1.14,3.58)[a]	1.82 (0.88,3.18)[a]	0.001	−24.0%	
Shahmoham-madi et al. (2017) [72]	NHLBI-EB Diet	mg/L	1.5 (0.4, 2.7)[a]	1.5 (0.4, 3.0)[a]	0.846	0.0%	
	NHLBI-EB Diet plus GCBE supplement		1.4 (0.4, 3.4)[a]	1.1 (0.5, 2.3)[a]	<0.001*	−21.4%	

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TABLE 3 (*continued*)

High-sensitivity C-reactive protein							
Reference	Diet	Unit	Preintervention serum concentration	Postintervention serum concentration	*P* value	Computed change	Mean change conc. (95% CI), mg/mL
Yari et al. (2016) [82]	NHLBI-EB Diet	mg/L	nd	nd			−1.02 (−1.6 to −0.5)
	NHLBI-EB Diet plus flaxseed supplement		nd	nd			−2.05 (−2.6 to 1.5)
Yari et al. (2021) [79]	Hypocaloric diet	mg/L	3.81 ± 3.30	3.04 ± 2.67	0.388	−20.0%	
	Hypocaloric diet plus hesperidin		4.17± 2.62	2.98 ± 2.34	0.005	−28.0%	
	Hypocaloric diet plus flaxseed		4.68 ± 2.04	4.80 ± 6.72	0.992	2.0%	
	Hypocaloric diet plus hesperidin and flaxseed		6.19 ± 5.50	4.62 ± 4.93	<0.001*	−25.0%	

Interleukin-6							
Reference	Diet	Unit	Pre-	Post-	*P* value	Computed change	Mean change (95%CI), mg/mL
Dietary intervention alone							
Baldry et al. (2017) [46]	Very-low energy diet; food-based diet	pg/	3.7 (10.4)[c]	3.7 (25.4)[c]	0.175	0.0%	
	Very-low energy diet; meal-replacement plan	mL	4.5 (42.6)[c]	3.7 (25.4)[c]	0.04	−17.8%	
Marina et al. (2014) [83]	Low-fat diet	pg/	1.08 (1.09)[c]	1.01 (1.14)[c]	≥ 0.05	−6.5%	
	High-fat diet	mL	0.91 (1.4)[c]	0.83 (2.4)[c]	≥ 0.05	−8.8%	
Markova et al. (2016) [80]	Plant-protein isocaloric diet	pg/	1.4 ± 1.4	1.4 ± 1.5	0.816	−1.4%	
	Animal protein isocaloric	mL	1.1 ± 1.1	0.9 ± 0.7	0.166	21.7%	
Dietary intervention plus cointervention							
Chan et al. (2010) [51]	Hypocaloric diet, Low fat	pg/	0.8 ± 0.2	0.9 ± 0.4	≥0.05	12.5%	
	Hypocaloric diet, low fat + cholesterol-lowering agent	mL	1.1 ± 0.4	0.9 ± 0.5	<0.05*	−18.2%	
Kaliora et al. (2016) [81]	Isocaloric diet	pg/	1.7 ± 3.2	1.3 ± 1.4	0.322	−23.5%	
	Isocaloric diet + Corinthian currants	mL	1.6 ± 1.4	0.9 ± 0.5	0.009	−43.7%	
Dietary intervention plus supplementation							
Abedi et al. (2018) [48]	Energy-restricted diet plus Vitamin E	pg/	23.11 ± 16.80	22.10 ± 15.78	0.610	−4.0%	
	Energy-restricted diet plus CLA and Vitamin E	mL	16.18 ± 5.95	15.27 ± 5.5	0.042	−6.0%	
Amanat et al. (2017) [66]	Weight-management diet	pg/	18.2 ± 3.4	18.1 ± 1.8	0.8	0.5%	
	Weight management + soy isoflavone	mL	18.8 ± 3.1	16.6 ± 2.5	0.01	−11.7%	
Duseja et al. (2019) [59]	Hypocaloric diet	pg/	112.8 ± 83.7	141.4 ± 107.3	0.507	25.0%	
	Hypocaloric diet plus multistrain probiotic	mL	125.6 ± 95.3	100.6 ± 74.7	0.041	−20.0%	
Faghihzadeh et al. (2014) [60]	NHLB-EBI Diet	pg/dL	7.22 ± 4.73	6.65 ± 4.23	0.677	−8.0%	
	NHLBI-EB Diet plus trans-resveratrol supplement		5.49 ± 2.64	3.96 ± 1.91	0.034	−28.0%	
Ferro et al. (2020) [74]	Mediterranean diet plus placebo	pg/	1.68 ± 0.8	2.57 ± 1.3	<0.001	53.0%	
	Mediterranean diet plus BPF and CYC	mL	1.92 ± 0.9	3.03 ± 1.3	<0.001	58.0%	
Haidari et al. (2020) [61]	Energy-restricted normal-protein diet	pg/	6.1 ± 2.2	4.8 ± 0.3	<0.001**	−21.0%	
	Energy-restricted normal-protein diet plus BCX	mL	5.9 ± 2.2	4.0 ± 0.3		−32.0%	
	Energy-restricted High Protein Diet		6.6 ± 2.2	3.5 ± 0.3		−47.0%	
	Energy-restricted High Protein Diet plus BCX		6.4 ± 1.9	3.1 ± 0.3		−51.0%	
Moradi et al. (2021) [76]	Energy-restricted diet plus placebo	pg/	39.23 ± 16.29	39.57 ± 15.25	0.902	1.0%	
	Energy-restricted diet plus Chromium Picolinate supplement	mL	36.69 ± 17.70	28.76 ± 14.20	0.002	−22.0%	
Rezaei et al. (2019) [64]	Hypocaloric diet plus sunflower oil	pg/	8.5 ± 4.5	8.3 ± 3.3	0.400	−2.0%	
	Hypocaloric diet plus olive oil	mL	7.5 ± 1.6	7.7 ± 1.8	0.400	−3.0%	
Rezaei et al. (2020) [65]	Hypocaloric diet plus sunflower oil	pg/	8.4 ± 4.5	8.29 ± 3.27	0.430	−1.0%	
	Hypocaloric diet plus flaxseed oil	mL	7.63 ± 1.29	7.35 ± 0.89	0.100	−4.0%	

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TABLE 3 (*continued*)

Tumor necrosis factor-alpha							
Reference	Diet	Unit	Pre-	Post-	*P* value	Computed change	Mean change (95% CI), mg/mL
Dietary intervention alone							
Markova et al. (2016) [80]	Plant-protein isocaloric diet	ng/	4.5 ± 2.6	3.8 ± 2.4	0.016	−15.6%	
	Animal protein isocaloric diet	mL	4.3 ± 2.8	4.4 ± 2.2	0.925	2.3%	
Dietary intervention plus cointervention							
Chan et al. (2010) [51]	Hypocaloric, low-fat diet	ng/	5.4 ± 1.6	5.4 ± 1.9	≥ 0.05	0.0%	
	Hypocaloric, low-fat diet + cholesterol-lowering agent	mL	6.3 ± 1.9	5.4 ± 2.3	<0.05*	−14.3%	
Kaliora et al. (2016) [81]	Isocaloric diet	ng/ mL	1.3 ± 1.0	0.8 ± 0.5	0.004	−38.5%	
	Isocaloric diet + Corinthian currants		0.9 ± 1.0	1.3 ± 0.5	0.063	44.4%	
Malguarnera et al. (2010) [69]	NCEP-ATPIII diet	ng/	1.38 ± 0.22	1.30 ± 0.21	≥ 0.05	−5.8%	
	NCEP-ATPIII diet + L-carnitine	mL	1.44 ± 0.28	1.08 ± 0.15	<0.001*	−25.0%	
Dietary intervention plus supplementation							
Abedi et al. (2018) [48]	Energy-restricted diet plus Vitamin E supplement	pg/	26.59 ± 23.28	25.57 ± 22.83	0.020	−3.0%	
	Energy-restricted diet plus CLA and Vitamin E supplement	mL	64.25 ± 94.18	37.53 ± 51.13	0.010	−41.0%	
Abhari et al. (2020) [73]	NHLB-EB Diet plus placebo	pg/	18.4 ± 1.79	16.95 ± 2.37	0.054	−1.68 ± 2.82[b]	
	NHLB-EB Diet plus synbiotic (*B. coagulans*)	mL	17.35 ± 4.89	14.0 ± 1.29	0.010	−3.35 ± 5.24[b]	
Amanat et al. (2017) [66]	Weight-management diet	ng/	1.8 ± 2.6	1.8 ± 2.6	0.990	0.0%	
	Weight-management diet + soy isoflavone	mL	1.8 ± 2.5	1.6 ± 2.4	0.010	−11.1%	
Darand et al. (2019) [58]	NHLBI-EB Diet	pg/	18.68 ± 2.18	17.44 ± 1.77	0.010	−6.0%	
	NHLBI-EB Diet plus *Nigella sativa* seed powder	mL	17.71 ± 6.47	14.02 ± 1.91	0.010	−21.0%	
Duseja et al. (2019) [59]	Hypocaloric diet	pg/ mL	190.00 ± 131.10	243.15 ± 167.10	0.917	28.0%	
	Hypocaloric diet plus multistrain probiotic preparation		207.9 ± 102.2	107.8 ± 94.4	0.911	−48.0%	
Eslamparast et al. (2014) [68]	NHLBI-EB Diet	ng/	nd	nd			−0.59 (−0.8 to −0.3)
	NHLBI-EB Diet plus synbiotic supplement	mL	nd	nd			−1.4 (−1.7 to −1.1)
Faghihzadeh et al. (2014) [60]	NHLBI-EB Diet plus placebo	pg/	16.55 ± 4.79	20.62 ± 10.88	0.094	25.0%	
	NHLBI-EB Diet plus trans-resveratrol supplement	mL	19.96 ± 18.80	16.25 ± 5.47	0.317	−19.0%	
Ferro et al. (2020) [74]	Mediterranean diet plus placebo	pg/	3.08 ± 0.6	1.53 ± 0.8	<0.001	−50.0%	
	Mediterranean diet plus BPF and CYC	mL	3.56 ± 3.9	2.04 ± 2.4	0.002	−43.0%	
Malaguarnera et al. (2012) [49]	Hypocaloric (NCEP-ATPIII) diet plus placebo	ng/	1.24 ± 0.26	1.12 ± 0.31	≥ 0.05	−10.0%	
	Hypocaloric diet (NCEP-ATPIII) plus probiotic and prebiotic supplement	mL	1.28 ± 0.28	0.83 ± 0.36	<0.001*	−35.0%	
Mofidi et al. (2017) [70]	NHLBI-EB Diet	ng/				−0.3 ± 0.2[c]	
	NHLBI-EB Diet plus flaxseed supplement	mL				−1.22 ± 0.8[c]	
Moradi et al. (2021) [76]	Energy-restricted diet plus placebo	pg/	72.6 ± 34.2	77.2 ± 37.4	0.367	6.0%	
	Energy-restricted diet plus Chromium Picolinate supplement	mL	89.8 ± 40.8	70.2 ± 39.4	0.501	−22.0%	
Pour et al. (2020) [77]	Healthy diet plus placebo	pg/ mL	194.44 ± 99.45	181.60 ± 96.29	0.026	−7.0%	
	Healthy diet plus saffron supplement		207.31 ± 102.61	193.15 ± 95.10	0.019	−7.0%	
Rafie et al. (2020) [62]	NHLBI-EB Diet plus placebo	pg/	11.63 ± 1.77	11.57 ± 1.23	0.880	0.0%	
	NHLBI-EB Diet plus ginger supplement	mL	11.71 ± 1.02	11.40 ± 1.40	0.308	−3.0%	
Rahimlou et al. (2016) [71]	NHLBI-EB Diet	ng/	3.0 ± 0.2	2.8 ± 0.2	0.003	−6.7%	
	NHLBI-EB Diet plus ginger supplement	mL	4.7 ± 0.4	3.5 ± 0.4	0.00	−25.5%	
Shahmoham-madi et al. (2017) [72]	NHLBI-EB Diet	ng/	8.2 ± 3.2	8.8 ± 4.1	0.279	7.3%	
	NHLBI-EB Diet plus GCBE supplement	mL	9.6 ± 3.9	8.6 ± 5.0	0.161	−10.4%	
Spadaro et al. (2008) [47]	AHA diet	ng/	3.1 ± 0.4	3.0 ± 0.7	≥ 0.05	−3.2%	
	AHA diet + n-3 PUFA supplement	mL	3.3 ± 0.5	2.7 ± 0.5	<0.05	−18.2%	

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Yari et al. (2016) [82]	NHLBI-EB Diet	ng/mL					−0.14 (−0.07 to −0.2)
	NHLBI-EB Diet plus flaxseed supplement						−1.30 (−0.4 to 2.2)
Yari et al. (2021) [79]	Hypocaloric diet (NHLBI-EB)	pg/mL	22.36 + 5.61	20.16 ± 5.93	0.037	−10.0%	
	Hypocaloric diet plus hesperidin		27.87 ± 12.69	21.31 ± 6.95	0.001	−23.0%	
	Hypocaloric diet plus flaxseed		19.46 ± 5.41	18.97 ± 5.64	0.383	−2.0%	
	Hypocaloric diet plus hesperidin and flaxseed		26.18 ± 6.39	19.87 ± 4.66	<0.001*	−24.0%	

[1]Values are mean ± SD or % change (calculated from means) unless otherwise indicated.
[2] [a] Mean (minimum, maximum);
[b]Mean change + SEM.
[3]*Statistically significant. P<0.05 significant; ** Multivariable adjusted.
[4]AHA, American Heart Association; BCX, β-Cryptoxanthin; CLA, conjugated linoleic acid; FLIO, Fatty Liver in Obesity; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; NHLBI-EB, National Heart Lung and Blood Institute-Energy Balanced; NIHFN, National Institute of Health & Food & Nutrition; ns, nonsignificant.

supplement ($P = 0.020$ and $P = 0.010$, respectively) [48]; a *N. sativa* seed powder supplement ($P = 0.010$ and $P = 0.010$, respectively) [58]; a BPF and CYC supplement ($P < 0.01$ and $P = 0.002$, respectively) [74]; a saffron supplement ($P = 0.026$ and $P = 0.019$, respectively) [77]; and, a ginger supplement ($P = 0.003$ and $P = 0.00$, respectively) [71]. A NHLBI-EB diet or AHA diet provided significant improvements to TNF-α when used in conjunction with: a symbiotic of *Bacillus coagulans* ($P = 0.010$) [73]; and an n-3 PUFA supplement ($P \leq 0.05$) [47]; but not when used alone. A hypocaloric, NCEP-ATPIII or weight-management diet provided significant improvements to TNF-α when used in conjunction with: a L-carnitine supplement [$P < 0.001$] [69]; a soy isoflavone ($P = 0.010$) [66]; a probiotic and prebiotic supplement ($P < 0.001$) [49]; and a cholesterol-lowering agent ($P \leq 0.05$) [51]; but not when used alone. Yari et al. [79] reported significant improvements in TNF-α for 3 of 4 intervention arms, which were a hypocaloric diet alone ($P = 0.037$), the same diet with hesperidin ($P = 0.001$) and the same diet with hesperidin and flaxseed ($P < 0.001$), whereas the same diet plus flaxseed ($P = 0.383$) did not show improvement.

Other cytokines

Interleukin-1β was reported by 2 studies [59,74], interleukin-10 was reported by 2 studies [48,83], fetuin-A was reported by 3 studies [51,62,76], and nuclear factor κB (NF-κB) was reported by 4 studies (Supplemental Table 2) [58,60,73,79].

Adipokines. The adipokines that were reported by the included studies were adiponectin and leptin, and were reported by 13 [42,43,51,53,54,59,61–63,67,77,80,83] and 8 [42,43,59,63,67,77,81,83] studies, respectively. Table 4 presents the data extracted for intervention effects of adipokines.

Adiponectin. Of the 13 studies that reported adiponectin, 8 reported a significant improvement ($P \leq 0.05$) following the intervention [42,43,51,53,54,61,63,67] (Table 4).

Effect of diet alone. Of the 5 studies that examined the effect of diet alone on adiponectin, 1 study reported significant ($P \leq 0.05$) improvements for both intervention groups [43], 2 studies reported significant ($P \leq 0.05$) improvements for 1 intervention group only [42,54], and 1 study reported a statistically significant ($P \leq 0.05$) negative change for 1 intervention group only [80]. Following a 6-mo dietary intervention, a hypocaloric Mediterranean, Fatty Liver in Obesity (FLIO) diet significantly improved adiponectin ($P = 0.001$), in comparison to a hypocaloric AHA diet, which showed no significant improvement ($P = 0.118$) [42]. It was later reported that following a 2-y intervention, both AHA and FLIO hypocaloric diets provided significant improvement to adiponectin ($P < 0.01$ and $P < 0.001$, respectively) [43]. Another study that intervened with a Mediterranean diet reported a significant improvement for a Mediterranean diet plus olive oil enriched with n-3 PUFA group ($P = 0.04$), whereas no improvement was observed following diet alone ($P \geq 0.05$) [54].

Effect of diet vs. combined diet and cointervention, including supplements. Of the 5 studies that reported significant ($P \leq 0.05$) improvements following dietary intervention plus a cointervention or supplement, 3 studies reported significant improvements for all intervention groups [51,61,67], and 2 studies reported significant ($P \leq 0.05$) improvements to the dietary intervention plus cointervention or supplement group only [53,63]. A hypocaloric, ER, or weight-control diet provided significant

Table 4
Data extracted from studies included for the updated systematic review investigating the effects of randomized controlled dietary intervention(s) and/or cointervention on inflammatory markers in adults with nonalcoholic fatty liver disease for the intervention effects adipokines

Adiponectin

Reference	Diet	Unit	Pre-	Post-	*P* value	Computed change
Dietary intervention alone						
Marin-Alejandre et al. (2019) [42]	Hypocaloric diet (AHA)	μg/mL	6.7 ± 2.2	8.0 ± 3.0	0.118	19.0%
	Hypocaloric Mediterranean diet (FLIO)		6.6 ± 2.2	9.5 ± 3.7	0.001	44.0%
Marin-Alejandre et al. (2021) [43]	Hypocaloric diet (AHA)	μg/mL	6.7 ± 2.0	8.4 ± 3.0	<0.01*	25.0%
	Hypocaloric Mediterranean diet (FLIO)		6.6 ± 2.0	10.6 ± 3.0	<0.001*	61.0%
Marina et al. (2014) [83]	Low-fat diet	μg/mL	3.4 ± 0.94	4.1 ± 3.8	≥ 0.05	20.6%
	High-fat diet		4.2 ± 2.8	4.6 ± 3.8	≥ 0.05	9.5%
Markova et al. (2016) [80]	Plant-protein Isocaloric	μg/mL	4.2 ± 1.7	3.6 ± 1.3	0.003	-14.3%
	Animal-protein Isocaloric		4.1 ± 3.5	3.6 ± 3.0	≥ 0.05	-12.2%
Sofi et al. (2010) [54]	Mediterranean diet	μg/mL	1.17 ± 0.08	1.25 ± 0.06	≥ 0.05	6.8%
	Mediterranean diet + olive oil enriched with n-3 PUFA		1.14 ± 0.02	1.48 ± 0.09	0.04	29.8%
Dietary intervention plus cointervention						
Chan et al. (2010) [51]	Hypocaloric, LF diet	μg/mL	5.9 ± 2.2	6.8 ± 2.5	<0.05*	15.2%
	Hypocaloric, LF diet plus cholesterol-lowering agent		4.9 ± 2.7	6.8 ± 2.5	<0.05*	24.0%
Garinis et al. (2010) [53]	Hypocaloric diet	μg/mL	7.9 ± 4.4	8.5 ± 4.6	0.17	76.0%
	Hypocaloric + oral hypoglycemic agent		5.8 ± 2.7	7.0 ± 3.3	0.005	20.7%
Dietary intervention plus supplementation						
Behrouz et al. [2017) (67]	NHLBI-EB Diet	μg/mL	25.8 ± 9.4	39.4 ± 24.2	0.005	52.7%
	NHLBI-EB Diet plus probiotic supplement		24.4 ± 11.1	40.7 ± 24.1	<0.001*	66.8%
	NHLBI-EB Diet plus prebiotic supplement		27.8 ± 10.4	43.9 ± 15.6	<0.001*	57.9%
Duseja et al. [2019) (59]	Hypocaloric diet	μg/mL	4.8 ± 2.5	5.3 ± 2.2	0.917	10.0%
	Hypocaloric diet plus multistrain probiotic		5.0 ± 2.2	5.5 ± 2.2	0.866	10.0%
Haidari et al. [2020) (61]	Energy-restricted normal-protein diet	μg/mL	ns	ns	<0.001*	2.3 ± 0.2
	Energy-restricted normal-protein diet plus BCX		ns	ns		2.9 ± 0.2
	Energy-restricted High Protein Diet		ns	ns		3.3 ± 0.2
	Energy-restricted High Protein Diet plus BCX		ns	ns		4.2 ± 0.2

Adiponectin continued

Reference	Diet	Unit	Pre-	Post-	*P* value	Computed change
Dietary intervention plus supplementation *continued*						
Pour et al. (2020) [77]	Healthy diet plus placebo	ng/mL	15.63 ± 6.97	15.72 ± 6.36	0.853	1.0%
	Healthy diet plus saffron supplement		15.48 ± 6.94	15.82 ± 6.91	0.6	2.0%
Rafie et al. (2020) [62]	NHLBI-EB Diet	Not specified	1.2 (0.8,1.7)	1.3 (1.0,1.7)	0.161	8.0%
	NHLBI-EB Diet plus ginger		1.2 (0.8,1.7)	1.3 (0.9,1.6)	0.150	8.0%
Rahmanabadi et al. (2019) [63]	Weight-control diet (NHLBI-EB)	μg/mL	11.6 ± 6.1	10.7 ± 4.7	0.250	-7.0%
	Weight-control diet (NHLBI-EB) plus α-LA supplement		11.9 ± 5.9	14.4 ± 7	0.022	21.0%

Leptin

Reference	Diet	Unit	Pre-	Post-	*P* value	Computed change
Dietary intervention alone						
Marina et al. (2014) [83]	Low-fat diet	ng/mL	13.9 ± 10.4	15.1 ± 10.4	≥ 0.05	8.6%
	High-fat diet		17.3 ± 11.1	16.8 ± 12.6	≥ 0.05	−2.9%
Marin-Alejandre et al. (2019) [42]	Hypocaloric diet (AHA)	ng/mL	37.1 ± 27	20.8 ± 15.7	<0.001	−44.00%
	Hypocaloric Mediterranean diet (FLIO)		38.8 ± 30.1	22.3 ± 17.1	<0.001	−42.00%
Marin-Alejandre et al. (2021) [43]	Hypocaloric diet (AHA)	ng/mL	37.1 ± 27	27.1 ± 18	<0.05	−27.00%

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	Hypocaloric Mediterranean diet (FLIO)		38.8 ± 31	29.0 ± 17	<0.01	−25.00%
Dietary intervention plus cointervention						
Kaliora et al. (2016) [81]	Isocaloric diet	ng/mL	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	−11.2%
Dietary intervention plus supplementation						
Behrouz et al. (2017) [67]	NHLBI-EB Diet	ng/mL	75.8 ± 26.9	74.4 ± 26.2	0.629	−1.8%
	NHLBI-EB Diet plus probiotic supplement		73.1 ± 26.8	48.6 ± 13.6	<0.001*	−33.5%
	NHLBI-EB Diet plus prebiotic supplement		80.3 ± 29.7	56.8 ± 22.8	<0.001*	−29.3%
Duseja et al. (2019) [59]	Hypocaloric diet	ng/mL	5.1 ± 2.1	5.7 ± 2.4	0.972	12.00%
	Hypocaloric diet plus multistrain probiotic preparation		5.7 ± 2.1	4.0 ± 1.3	0.001	−30.00%
Pour et al. (2020) [77]	Healthy diet plus placebo	ng/mL	2.14 ± 1.85	1.74 ± 1.56	<0.001	−19.00%
	Healthy diet plus saffron supplement		2.49 ± 1.83	1.73 ± 1.65	<0.001	−31.00%
Rahmanabadi et al. (2019) [63]	Weight-control diet (NHLBI-EB) plus placebo	ng/mL	28.3 + 19.0	31.2 + 18.6	0.299	10.00%
	Weight-control diet (NHLBI-EB) plus α-LA supplement		30.7 + 19.8	24.9 + 16.3	0.042	−19.00%

[1]Values are mean ± SD or % change (calculated from means) unless otherwise indicated.
[2a] Mean (minimum, maximum);
[b]Mean change + SEM.
[3]*Statistically significant. P<0.05 significant; ** Multivariable adjusted.
[4]AHA, American Heart Association; α-LA, alpha-lipoic acid; BCX, β-Cryptoxanthin; FLIO, Fatty Liver in Obesity; nd, no data provided; NHLBI-EB, National Heart Lung and Blood Institute-Energy Balanced; NIHFN, National Institute of Health & Food & Nutrition; ns, nonsignificant.

improvement to adiponectin when used alone or in conjunction with: a cholesterol-lowering agent ($P \leq 0.05$) [51]; an oral hypoglycemic agent ($P = 0.005$) [53]; a ER NP diet, ER NP diet plus BCX, ER HP diet, or ER HP diet plus BCX ($P < 0.001$) [61]. An EB diet provided significant improvement to adiponectin when used alone ($P = 0.005$) or in conjunction with a probiotic supplement ($P < 0.001$) or a prebiotic supplement ($P < 0.001$) [67].

Leptin. Six studies reported a significant reduction of leptin levels following dietary intervention ($P \leq 0.05$) [42,43,59,63,67,77] (Table 4).

Effect of diet alone. Two articles reporting data from the same study found that a hypocaloric Mediterranean (FLIO) diet and a hypocaloric (AHA) diet both lowered leptin at 6-mo ($P < 0.001$ vs. $P < 0.001$, respectively) and 2-y ($P < 0.01$ vs. $P \leq 0.05$, respectively) intervention timepoints ($P \leq 0.05$) [42,43].

Effect of diet vs. combined diet and cointervention, including supplements. Of the 5 studies that reported significant ($P \leq 0.05$) improvements to leptin following dietary intervention plus a cointervention or supplement, 1 reported significant improvements to both intervention arms [77], 3 studies reported significant improvements to the dietary intervention plus supplement group only [59,63,67], and 1 study reported significant improvement to the diet-only intervention arm [81]. A hypocaloric or weight-control diet provided significant improvement to leptin when used in conjunction with: a multistrain probiotic supplement ($P = 0.001$) [59]; and α-LA supplement ($P = 0.042$) [63]; but not when used alone. An energy-balanced diet provided significant improvement to leptin when used in conjunction with a probiotic or prebiotic supplement ($P < 0.001$) [67], and a healthy diet provided significant improvement when used alone ($P < 0.001$) or with a saffron supplement ($P < 0.001$) [77].

Meta-Analysis Results

Two separate meta-analyses were conducted; the first assessed the effect of an isocaloric or hypocaloric diet vs. the same diet plus supplementation on hs-CRP (Figure 2); and the second assessed the effect of the same dietary interventions on TNF-α (Figure 3).

Effect of isocaloric or hypocaloric diet vs. diet plus supplementation on hs-CRP

A meta-analysis of 24 trial arms from 12 studies [48,49,61,71,75,76,79,56,58,60,73,77], with a total of 598 participants was conducted to assess the effect of dietary intervention with an isocaloric diet or a hypocaloric diet, alone or with supplementation, on hs-CRP (Figure 2). Meta-analysis favored the diet plus supplement group when an isocaloric diet (A) was the intervention (0.44; 95% CI: 0.20, 0.68; $P = 0.0003$) and no significant heterogeneity was detected ($I^2 = 0\%$, $P = 0.56$). Conversely, when a hypocaloric diet intervention (B) was used, the meta-analysis showed no significant weighting to either intervention (0.30; 95% CI: −0.84, 1.44; $P = 0.60$). Heterogeneity was significantly high ($I^2 = 95\%$, $P < 0.00001$).

Effect of isocaloric or hypocaloric diet alone vs. diet and supplementation on TNF-α

A meta-analysis of 30 trial arms from 15 studies [47–49,58–60,62,66,71–74,76,77,79], with a total of 773 participants was conducted to assess the effect of dietary interventions with an isocaloric diet or a hypocaloric diet, alone or with

supplementation, on TNF-α (Figure 3). Meta-analysis favored the diet plus supplement group when an isocaloric diet (A) was used for intervention (0.74; 95% CI: 0.02, 1.46; $P = 0.03$); however, heterogeneity was significantly high ($I^2 = 87\%$, $P < 0.00001$). Meta-analysis again showed no significant weighting to either intervention group when a hypocaloric diet was used for intervention (0.01; 95% CI: −0.43, 0.45; $P = 0.97$) and heterogeneity was significantly high ($I^2 = 83\%$, $P < 0.00001$).

Sensitivity analysis

To understand and report on the robustness of the choices made in setting up the meta-analyses, a sensitivity analysis was conducted. Removal of studies with high overall risk of bias or which scored negatively on random sequence generation, selection, and allocation bias, did not significantly impact results for meta-analyses.

Publication bias

Publication bias was checked via visual inspection of the funnel plot and the "fill and trim" method, though no indication of publication bias was detected.

Quality assessment of studies

The Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research [23] was used to assess the quality of studies included in this review (Table 2). The assessment of internal and external biases for each study is shown in Figure 4. Of the 44 included studies, a total of 37 studies were deemed to be of positive (+) quality [41–47,50,51,53–58,60–75,77,78,80–83] and 12 of those were rated positive in all sections [45,55,56,60,61,63, 65,67–71,77]. Seven studies were found to be of neutral (Ø) quality [40,48,49,52,59,76,79]. Twenty studies ranked negative (N) or unclear (Ø) because of inadequate or lack of blinding of participants or examiners [40–44,46–48,50–54,76,78–83]. Although it is often impossible to blind participants of dietary intervention trials, blinding outcome assessors where possible serves to strengthen the accuracy of results. The aforementioned studies that ranked negative for this section did not indicate any intention of blinding. Thirteen studies ranked negative (N) or unclear (Ø) for the method of handling withdrawals [42–44,48,50,54,57,59,72,78–80,83]. Eleven studies were ranked negative (N) or unclear (Ø) for inappropriate methods of statistical analysis [40,41,43,49,58,59,62,73,75,76,79], which included not reporting intention to treat analysis, not performing a power calculation, and not adjusting for confounding factors. Eleven studies did not adequately describe intervention, exposure factors and/or therapeutic regimens [40,41,44,46,48,51,52,58,59,74,76].

Discussion

This is the first meta-analysis and most comprehensive literature review to have evaluated the effect of dietary interventions, with or without supplementation, on the inflammatory profile of patients with nonalcoholic fatty liver disease. Meta-analysis showed a hypocaloric diet, when used alone or with supplementation, was the most effective dietary intervention for the improvement of NAFLD-implicated inflammatory markers hs-CRP, IL-6, TNF-α, adiponectin, and leptin. The findings further suggest that weight loss was a key driver of those improvements, with all but 2 of the studies that intervened with a hypocaloric diet and were included for meta-analysis, reporting significant ($P \leq 0.05$) weight loss in both dietary intervention groups [59,75]. Whereas, an isocaloric diet was found to be effective for improvement of the same inflammatory markers, only when used in combination with supplementation in the form of CLA [48], probiotic or prebiotic [56], *N. sativa* seed powder [58], ginger supplement [62,71], coffee bean extract [72], synbiotic (*B. coagulans*) [73], trans-resveratrol [60], and flaxseed [79]. These findings will be further explored in the discussion below.

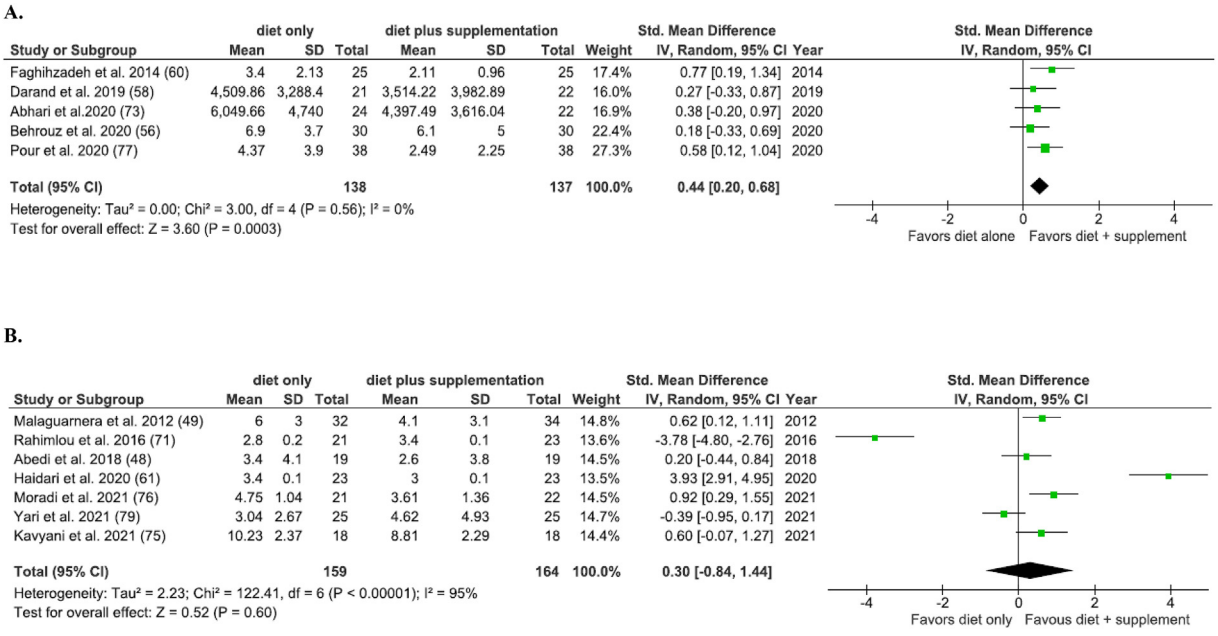

FIGURE 2. Meta-analyses for subgroup of selected studies assessing the effect of an isocaloric diet and isocaloric diet plus supplementation (A) and hypocaloric diet and hypo caloric diet plus supplement (B) on hs-CRP.

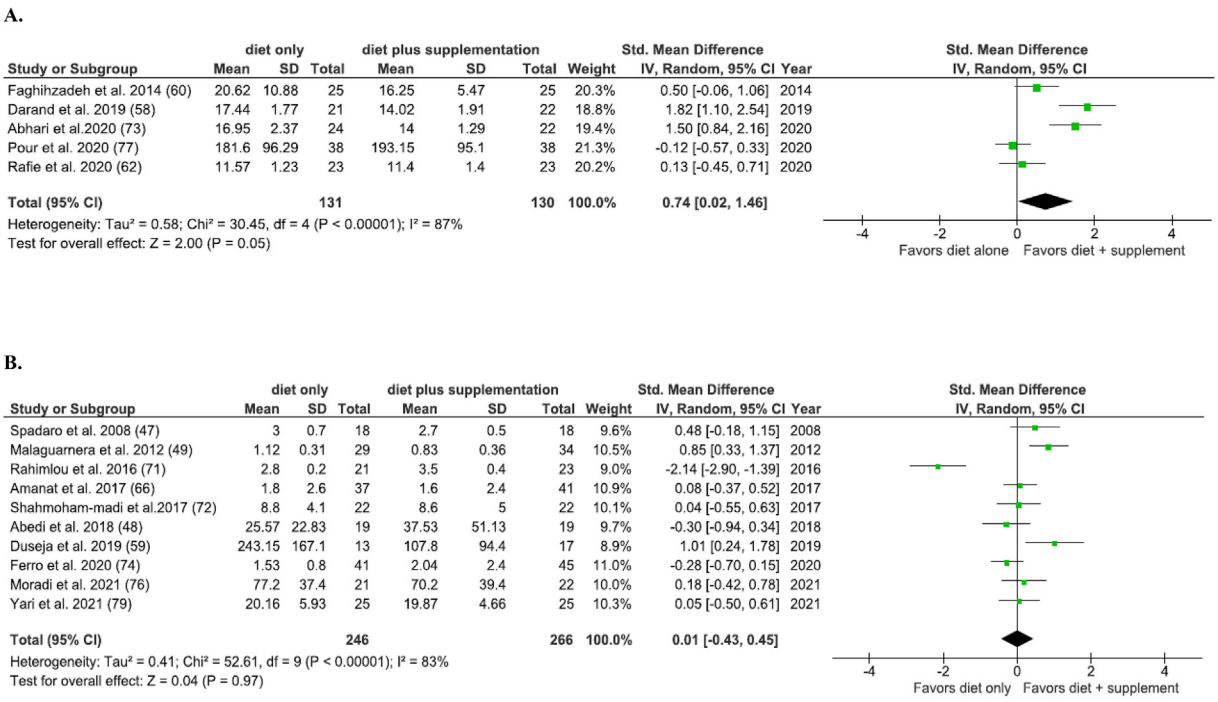

FIGURE 3. Meta-analysis by subgroup of selected studies on the effect of an isocaloric diet (A) or hypocaloric diet (B) on TNF-α when used alone or in conjunction with a supplement.

The effect of dietary interventions with the addition of supplementation was investigated by the majority of studies included in this review, with dietary intervention alone being the primary outcome of only 8 studies [42–46,54,55,80,83]. The meta-analysis demonstrated that hypocaloric diets provided significant ($P \leq 0.05$) improvements in hs-CRP and TNF-α when used alone or with supplementation. In contrast, an isocaloric diet provided significant ($P \leq 0.05$) improvements in hs-CRP and TNF-α only when combined with supplementation. Isocaloric diets alone did not elicit the same benefits. Noteworthy results included a multistrain probiotic used in combination with a hypocaloric diet that showed significant ($P \leq 0.05$) improvement to IL-6, TNF-α, and leptin, when the diet-only group showed no improvement of the same inflammatory markers [59]. The results were in agreement with previous research, where a potential benefit for probiotic supplementation for the improvement of leptin levels, had been initially identified in mouse models [84] and further supported in human clinical trials [67]. Malaguarnera et al. [49] reported a similar result for hs-CRP where a significant ($P \leq 0.05$) improvement was shown for a hypocaloric diet plus probiotic and prebiotic group, but not for the diet-only group. Indeed, synbiotic supplementation has gained a great deal of attention as a potential effective adjunct therapy to the dietary management of NAFLD, with minimal side effects. In 2019, a literature review and meta-analysis of 11 databases from 7 RCTs revealed that synbiotic supplementation had favorable effects on inflammatory markers hs-CRP and TNF-α, as well as liver enzymes, some anthropometric indices, lipid profiles, and glucose homeostasis parameters in patients with NAFLD [85], syn-, pre- and probiotics are proposed to exert a favorable effect via modulation of NAFLD-associated gut dysbiosis; promoting increased production of SCFAs; reduction in lipopolysaccharide (LPS) production; decreased activation of NF-κB pathway, resulting cytokine release and inflammatory response [86]. The beneficial effect of synbiotic supplementation was further supported in another review and meta-analysis that analyzed the effect of microbial therapy on markers of inflammation in NAFLD-diagnosed participants [87]. The review reported a significant ($P \leq 0.05$) improvement of hs-CRP and TNF-α that resulted from intervention with a synbiotic supplement that did not occur for the placebo groups [87]. This serves to highlight the critical role of gut microbiota in the pathogenesis of various metabolic diseases (including NAFLD) and the potential for use of syn/pre/probiotics as a supplementary approach for the future management of NAFLD. However, further studies of longer duration, with greater homogeneity between diet and supplementary interventions, are needed to inform the efficacy and role of synbiotic supplementation as an adjunct therapy for NAFLD over the long term [85,87].

An isocaloric diet (specifically, the NHLBI-EB diet recommendations), that was well represented within this and the original review, was shown to provide significant ($P \leq 0.05$) improvement to inflammatory cytokines hs-CRP, IL-6, and TNF-α, when combined with supplementation such as CLA [48], probiotic or prebiotic [56], *N. sativa* seed powder [58], ginger supplement [62,71], coffee bean extract [72], synbiotic (*B. coagulans*) [73], trans-resveratrol [60], and flaxseed [79]. Noteworthy results of those interventions with supplementation included a significant ($P \leq 0.05$) improvement of hs-CRP, IL-6, TNF-α, and NF-κB, that did not occur in the diet-only group of an intervention with NHLBI-EB diet plus trans-resveratrol supplement [60]. Resveratrol is a polyphenol whose primary benefit is its antioxidant properties, in addition, it has been purported to provide benefits such as neuro- and cardio-protection and has been shown in mouse models to ameliorate hepatic steatosis and insulin resistance in NAFLD [88]. However, the mechanisms

	RELEVANCE				VALIDITY										
Study (Ref)	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Rank**
Abedi et al. (2018)[45]	Y	Y	Y	Y	Y	Y	N	Ø	Ø	N	Y	Y	Y	Y	Ø
Abhari et al. (2020)[70]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Ø	Y	Y	+
Amanat et al. (2017)[63]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	+
Bakhshimoghaddam et al. (2018)[75]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	+
Baldry et al. (2017)[43]	Y	Y	Y	Y	Y	Y	Y	Y	N	Ø	Y	Y	Y	Y	+
Behrouz et al. (2017)[64]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Behrouz et al. (2020)[53]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Cerletti et al. (2020)[54]	Y	Y	Y	Y	Y	Y	Y	Ø	Y	Y	Ø	Y	Y	Y	+
Chan et al. (2010)[48]	Y	Y	Y	Y	Y	Y	Y	Y	Ø	N	Y	Y	Y	Y	+
Darand et al. (2019)[55]	Y	Y	Y	Y	Y	Y	Ø	Y	Y	Ø	Y	N	Y	Y	+
Duseja et al. (2019)[56]	Y	Y	Y	Y	Y	Y	Y	Ø	Y	Ø	Y	N	Y	N	Ø
Eslami et al. (2019)[37]	Y	Y	Y	Y	Y	Y	Y	Y	N	Ø	Ø	N	Y	Y	Ø
Eslamparast et al. (2014)[65]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Faghihzadeh et al. (2014)[57]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Garinis et al. (2010)[50]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Ø	+
Ferro et al. (2020)[71]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Ø	Y	Y	Y	Ø	+
Haidari et al. (2020)[58]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Kaliora et al. (2016)[78]	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	+
Kani et al. (2014)[42]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Kavyani et al. (2021)[72]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	+
Kugelmas et al. (2003)[47]	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	+
Malaguarnera et al. (2010)[66]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Malaguarnera et al. (2012)[46]	Y	Y	Y	Y	Y	Ø	Ø	Y	Y	Y	Y	N	N	Y	Ø
Maleki et al. (2019)[38]	Y	Y	Y	Y	Y	Y	Y	Y	N	Ø	Y	N	Y	Y	+
Marin-Alejandre et al. (2019)[39]	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	+
Marin-Alejandre et al. (2021)[40]	Y	Y	Y	Y	Y	Y	Y	N	Ø	Y	Y	N	Y	Y	+
Marina et al. (2014)[80]	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	+
Markova et al. (2016)[77]	Y	Y	Y	Y	Y	Y	Y	Ø	N	Y	Y	Y	Y	Y	+
Mofidi et al. (2017) [67]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Moradi et al. (2021) [73]	Y	Y	Y	Y	Y	Ø	Y	Y	N	Ø	Y	N	Y	Y	Ø
Nomi-Golzar et al. (2021) [49]	Y	Y	Y	Y	Y	Ø	N	Y	Ø	Ø	Y	Y	Y	Y	Ø
Pour et al. (2020)[74]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Rafie et al. (2020)[59]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	+
Rahmanabadi et al. (2019)[60]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+

FIGURE 4. Individual quality assessment of studies according to Academy of Nutrition and Dietetics Quality Criteria Checklist. [1]KEY: Category – Relevance: 1. Implementation; 2. Importance; 3. Common Concern; 4. Feasibility. Category – Validity: 1. Clarity of research question; 2. Selection bias; 3. Study groups comparable; 4. Attrition; 5. Blinding; 6. Transparent and parallel interventions; 7. Validity and reliability of outcomes; 8. Statistical analyses; 9. Conclusions, biases, and limitations adequately described; 10. Funding or sponsorship bias. [2]Y, yes; N, no; Ø, unclear

Rahimlou et al. (2016)[68]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Razavi-Zade et al. (2016)[52]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Rezaei et al. (2019)[61]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	+
Rezaei et al. (2020)[62]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	+
Ristic-Medic et al. (2021)[41]	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	+
Shahmohammadi et al. (2017)[69]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	+
Sofi et al. (2010)[51]	Y	Y	Y	Y	Y	Y	Y	Ø	Ø	Y	Y	Y	Y	Y	+
Spadaro et al. (2008)[44]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Ø	+
Yari et al. (2016)[79]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	+
Yari et al. (2021)[76]	Y	Y	Y	Y	Ø	Y	Ø	Ø	N	Y	Y	N	Y	Y	Ø

FIGURE 4. (*continued*).

underlying the reported benefits of resveratrol are not fully understood, and appear to be related mainly to its antioxidant and anti-inflammatory properties [60]. This is also true of the reported benefits for supplementation with CLA [48], *N. sativa* seed powder [58], ginger supplement [62,71], coffee bean extract [72], and flaxseed [79], with most proposing antioxidant, anti-inflammatory, antilipidemic and/or insulin sensitizing properties, without fully elucidating the underlying mechanisms or mode of action behind said properties. The NHLBI-EB diet independent of supplementation was reported to provide a significant ($P \leq 0.05$) improvement to hs-CRP in 2 studies only [56,71], and to TNF-α in 2 studies only [58,71]. There is still no consensus for the use of supplementation, or safe long-term dosage for specific outcomes related to treatment of NAFLD, or indeed the long-term effectiveness of those individual supplements [16,19]. The current review highlighted the heterogeneity between the included studies and the proposed mechanisms of action and/or pathways by which inflammation and hepatic steatosis are being mediated. Therefore, to better understand the complex pathophysiology of chronic inflammation in NAFLD, and to establish a benefit for supplementation that is distinguishable from that of the dietary intervention, more targeted approaches for longer-term clinical trials are required.

A hypocaloric Mediterranean diet was shown to significantly ($P \leq 0.05$) improve hs-CRP and leptin, as did a hypocaloric NIHFN diet alone [42–44]. Adiponectin levels increased more significantly ($P \leq 0.05$) with the hypocaloric Mediterranean diet than with the AHA diet [42,43]. The improvement shown to adiponectin and hs-CRP has previously been attributed to weight loss, believed to be driven by a decrease of adipocyte-released cytokines such as IL-6 and has been reported in other literature, and also in the original review [20,89]. However, 1 study included in the updated review investigated the effect of a Mediterranean diet independent of weight loss. The study by Cerletti et al. [57] reported a similar decrease to hs-CRP by both Mediterranean diet alone and with supplementation, albeit those results were nonsignificant. The beneficial effect of Mediterranean diet, independent of weight loss, on biomarkers of inflammation was further supported in a previous literature review and meta-analysis that analyzed the effect of various dietary patterns on key inflammatory cytokines and adipokines [14]. The review reported improvement of most inflammatory markers, but particularly hs-CRP, adiponectin, and IL-6, in those interventions that had applied a Mediterranean diet [14]. The recommendation for weight loss coupled with adherence to a Mediterranean diet is supported by the European Association for the Study of Liver (EASL) Clinical Practice Guidelines for the Management of Nonalcoholic Fatty Liver Disease [16]. The current updated review may provide reason to further investigate whether adherence to a Mediterranean diet will result in improvement to the aforementioned inflammatory markers that is independent of weight loss.

Physical activity of moderate intensity is recommended to attenuate weight gain in patients with NAFLD, with an inverse relationship being reported between more vigorous activity and severity of disease [90]. Physical activity of 150–200 min per week, of moderate-intensity exercise such as brisk walking is recommended by EASL guidelines, with vigorous exercise suggested to provide a greater benefit for NASH and fibrosis [16]. Of the studies included in the current updated review, those adhering to an energy-balanced diet were recommended to exercise for 30 min at least 3 times a week. For those reporting hypocaloric dietary intervention, the recommendation was increased to 30–45 min for ≥5 d per week; however, a number of included studies neglected to report exercise recommendations, or where they were reported, were missing detail. To distinguish the true impact of dietary intervention, it is recommended that future studies provide tighter controlled and better monitored recommendations for physical activity.

This meta-analysis and systematic review have several *strengths*. The review adhered to the inclusion criteria of the original literature review by Reddy et al. [20], and therefore, presented a population that was reflective of and generalizable to NAFLD. Furthermore, the method of diagnosis and reporting of NAFLD in all included studies was by validated methods. A final strength was that all included studies used a standalone comparison group of diet only to compare with the intervention group.

The current meta-analysis and systematic review have a number of *limitations*. The first being the heterogeneity of interventions of the included studies that limited the opportunity for further meta-analysis. The inclusion of studies that intervened with both diet and supplementation made it difficult to isolate the effect of dietary intervention from that of the dietary intervention with supplementation. Of the studies that

recommended an EB diet compared to an EB diet plus supplementation, many did not report dietary intake of the sample at the end-intervention to assess changes in diet alone. Moreover, some used inaccurate tools of measurement such as 24-h recall to assess dietary intake at each timepoint. Within this review, the diagnostic tools used to characterize NAFLD varied, and most studies did not employ the gold-standard liver biopsy. NAFLD is assessed in many ways across community and clinical settings, with the use of LFTs, US, MR-S, and the use of indexes or scores [91]. To conduct a review on this topic limiting to gold-standard biopsy would result in few papers being included. The many assessment methods used across the study is a limitation in the interpretation of findings but is reflective of this topic area.

The impact of physical activity was often vaguely reported or not reported, meaning its effect was indistinguishable from that of the dietary intervention or diet and supplementation. Length of intervention of 8 wk or less was a limitation of 11 included studies, where it was acknowledged that a longer intervention time was required to show the true effects of the intervention [40,41,45,46,48,52,55,66,72,80,83]. Sample size varied markedly across the included studies; however, was particularly noted for 9 of the included studies, where small numbers at baseline, together with patient attrition prevented the long-term follow-up of primary outcomes [44,47,48,50,51,54,59,80,83]. A significant number of scientific contributions to this topic came from Iran, evidenced by the 27 studies included in this review. Although the prevalence of NAFLD in Iran is consistent with the global estimated prevalence of disease [1], the high representation of individuals from the same country of origin may be considered an unconscious extrinsic bias [92]. Currently, it is challenging to draw conclusions regarding the extent to which geographic bias elicits skewed or improper results [92]. Despite the geographic imbalance present in this review, all 27 studies met the inclusion criteria, 22 studies received a positive quality assessment rating and only 5 studies were deemed neutral (indicating that the report was neither exceptionally strong nor exceptionally weak). Importantly, aside from studies published by the same author during different years, these studies were conducted by different departments, institutions, and/or healthcare facilities within Iran.

This meta-analysis and review is a comprehensive review of the literature including a meta-analysis, which highlights the likely role inflammation plays in NAFLD management. This review highlights the need for high quality, RCTs, of longer durations (≥6 mo), involving large cohorts of patients with NAFLD, and dietary interventions independent of supplementation, to assess the efficacy of dietary interventions alone on inflammatory outcomes in patients with NAFLD [93]. The assessment of dietary intervention independent of weight loss on adipokines and cytokines involved in the progression of NAFLD, is needed to further inform clinical practice.

Conclusion

Hypocaloric or ER diets, either Mediterranean, AHA, NIHFN or NCEP-ATPIII, with or without supplementation, demonstrated improvements in circulating levels of inflammatory cytokines and adipokines in a NAFLD population. However, weight loss appeared to be the key driver of those effects. Isocaloric or energy-balanced dietary interventions provided improvements to the same inflammatory cytokines and adipokines when coupled with supplementation but, did not elicit the same benefits from intervention with same diet alone.

Author disclosures

The authors report no conflicts of interest.

Acknowledgments

All authors conceptualized and designed this review. RLH and AJR conducted the search process and data extraction. RLH and AJR contributed to data analysis and interpretation. RLH drafted the manuscript, and all authors reviewed and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2023.01.001.

Registration and protocol

Update to original literature review (http://www.crd.york.ac.uk/PROSPERO; registration no.: CRD42017055921), Protocol may be viewed on request from author.

Data availability

Template data collection forms and extraction tables may be viewed upon request from the authors.

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