The effects of diet and lifestyle interventions on insulin resistance in patients with nonalcoholic fatty liver disease: a systematic review

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Nonalcoholic fatty liver disease (NAFLD) results from excessive fat accumulation in the liver in the absence of excessive alcohol consumption. Insulin resistance (IR) is proposed to be an underlying pathogenic factor in the development and progression of disease. There are currently no proven pharmacotherapies and weight loss is the only prescribed treatment despite a lack of evidence to support a specific diet or lifestyle therapy. The aim of this review is to evaluate the efficacy of dietary lifestyle interventions on IR measured by Homeostasis model assessment in patients with NAFLD. A systematic electronic search of Medline, Scopus, The Cochrane Library, CINAHL and PubMed databases (1999–2015) was performed by two independent reviewers. Randomized control trials evaluating the efficacy of diet and lifestyle interventions on IR in adults diagnosed with NAFLD were included. A total of 6441 articles were identified; eight randomized control trials fulfilled the inclusion criteria. Three studies involved dietary interventions and five incorporated diet and exercise. The majority of intervention groups resulted in significant reductions in IR, with no significant changes observed in the control groups. Lifestyle interventions compared with controls reduced IR measured by homeostasis model assessment. All diet and diet and lifestyle intervention trials were efficient in reducing IR in participants with NAFLD. A lack of literature and variation across interventions warrants the need for extensive research to establish firm dietary lifestyle recommendations. Eur J Gastroenterol Hepatol 29:867–878
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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, affecting ∼20–30% of adults in developed countries, with the prevalence increasing to 75% in obesity and 50–75% in those with type 2 diabetes (T2DM) [1–6]. The disease is defined as an accumulation of excess fat in the form of triglycerides in liver cells that occurs in the absence of excess alcohol consumption (>20 g/day) [7,8]. The disease progresses from simple steatosis to nonalcoholic steatohepatitis (NASH), where excess fat stores are associated with inflammation of the liver. This may progress to the development of liver fibrosis and cirrhosis with disruption to liver architecture and function [9,10]. Insulin resistance (IR) is a common pathogenic factor underlying the progression of NAFLD [11]. Epidemiological studies show a high prevalence of NAFLD in conditions associated with IR, such as abdominal obesity, T2DM, dyslipidaemia and the metabolic syndrome [12–14]. Indeed, NAFLD has been considered the hepatic manifestation of the metabolic syndrome. The pathogenesis of NAFLD and NASH is

incompletely understood and complex. One popular theory is that 'two hits' are involved [15]. The first 'hit' involves the development of hepatic steatosis (fatty liver), with IR being a major risk factor in the net retention of lipids within hepatic liver cells [16–18]. The second 'hit' is the progression of steatosis to NASH and fibrosis/cirrhosis and involves inflammatory mechanisms. Although these proposed theories have not been adequately defined, it is believed that diminished mitochondrial β-oxidation leads to decreased clearance of fatty acids [17].

IR is a disorder characterized by reduced responsiveness of peripheral tissues to the action of insulin secreted by pancreatic β-cells leading to relative hyperglycaemia and T2DM [19]. The euglycaemic clamp is the gold-standard technique for the measurement of IR; however, because of its impracticality, labour and duration, it is limited in its application in medical practice and clinical trials [20]. A number of surrogate methods have therefore been used to simplify and improve the determination of IR [21]. The homeostatic model assessment of insulin resistance (HOMA-IR) is an index that measures the functioning of beta cells releasing insulin by using a calculation of fasting glucose and insulin concentration levels in the blood [22]. HOMA-IR has proven to be a popular and efficient tool used to measure IR in many published clinical trials because of simplicity in its calculation [23]. HOMA-IR and the euglycaemic clamp have been compared and similar values for IR have been found [22].

The current literature suggests that dietary modifications resulting in weight loss are more effective than pharmacotherapies in the treatment of NAFLD [24,25]. Diet and diet and exercise resulting in weight loss significantly improves IR in patients with metabolic

syndrome [26]. With NAFLD becoming more prevalent and in the absence of meaningful therapy, monitoring IR could potentially be a noninvasive way to assess the severity of NAFLD advancement and monitor the effectiveness of diet and diet and lifestyle interventions in this patient group. To the author's knowledge, a systematic review investigating the effect of diet on IR as an outcome measure in NAFLD is yet to be performed. Therefore, the aim of this systematic review is to determine the effect of diet only and diet and lifestyle interventions on IR as measured by HOMA-IR in patients with diagnosed NAFLD.

Methods

Data sources

A systematic search of the electronic databases Medline, CINAHL, Scopus, PubMed and The Cochrane Library was performed in April 2015 and eligible studies were identified by the primary author. Limits were applied for the year of published articles (1999–2015) and language (English). If full-text articles were not available in English or if articles could not be retrieved, authors were contacted. An eligibility assessment of the articles was performed independently by two reviewers. Disagreements between reviewers were resolved by a third reviewer. Two reviewers also viewed search terms and article extraction data to ensure that they were correctly selected against inclusion and exclusion criteria.

Search terms

The following selected key search terms were used in all database searches including MEDLINE with truncations and MESH terms: ('NAFLD' or 'NASH' or 'fatty liver' or 'liver disease' or 'non-alcoholic fatty liver' or 'nonalcoholic fatty liver' or 'non-alcoholic steatosis' or 'nonalcoholic steatosis' or 'steatosis') AND ('nutrition counseling' or 'calorie restrict*' or 'lifestyle' or 'weight reduction' or 'weight loss' or 'dietary intake' or 'high carbohydrates' or 'low carbohydrates' or 'CHO' or 'low fat' or 'high fat' or 'saturated fat' or 'monounsaturated fat' or 'polyunsaturated fat' or 'PUFA' or 'MUFA' or 'diet*' or 'Mediterranean diet') AND ('Insulin resistance' or 'HOMA-IR' or 'metabolic syndrome' or 'fasting glucose' or 'insulin sensitivity' or 'hyperinsuline*' or 'euglyce*' or 'oral glucose').

Eligibility criteria

The review was restricted to published prospective interventions reporting the effects of diet and/or lifestyle modification on IR in participants with NAFLD/NASH/steatosis.

Types of studies

Randomized-controlled trials (RCTs) were selected for this review. Reviews, letters, editorials, commentaries, animal studies and duplicate articles were excluded. In addition, pilot studies, prospective cohort studies, nonrandomized interventions, case–control, cross sectional and case series were later excluded as these study designs did not compare the effects of a control and an intervention group. Full reports with sufficient information published in English were included to allow for the critical evaluation of the effects of the intervention on HOMA-IR in NAFLD.

Participants

Studies with participants diagnosed with NAFLD and older than 18 years of age were included. Articles were excluded if participants had liver diseases such as cirrhosis or hepatocellular carcinoma, conditions caused by excessive alcohol consumption and comorbidities without the presence of a diagnosis of NAFLD. It was considered sufficient if authors provided their own valid and justified diagnostic criteria for NAFLD or NASH. Diagnoses made with either histological examination of biopsies, proton magnetic resonance spectroscopy, computed tomography ultrasound and/or blood concentrations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were included.

Types of interventions

Dietary interventions alone and those that included diet as well as lifestyle interventions were included. Lifestyle interventions encompassed general lifestyle counselling by dietitians and/or the prescription of exercise. Diet and lifestyle interventions that incorporated nutritional supplements and/or pharmaceuticals were excluded. Studies focusing on supplements and/or pharmaceuticals alone were excluded. Exercise-only interventions were also excluded from this review.

Types of outcome measures

The primary metabolic outcome measure of interest was a reduction in IR measured using the HOMA-IR equation.

Articles were first excluded on the basis of title and abstract against inclusion and exclusion criteria. Studies that appeared eligible on the basis of their abstracts were obtained and full texts were read and assessed.

Data extraction and data items

Data extraction was carried out on the articles included in the systematic review. The information extracted from each trial included the following: (a) participants' characteristics (including the number of participants in the study, age, BMI, sex and the demographic location of the study); (b) the duration of the intervention and details of what the intervention and control groups were required to undertake (including the type of diet plan and exercise, frequency of physical activity, duration and intensity, nutritional intervention, dietary assessments); and (c) the methods used to record the diagnosis of NAFLD.

Risk of bias and study methodological quality assessment

The American Dietetic Association quality criteria checklist was used to assess the risk of bias and the studies' overall quality rating. Key questions address whether or not the selection of participants are free from bias, whether the groups were comparable, whether the intervention regimes were described in detail and whether the outcomes were clearly defined and the measurements are valid and

reliable. Positive scores obtain a yes answer for the questions addressed.

Data analysis

A meta-analysis was not carried out for studies in this review. This review is descriptive in nature. This review followed the PRISMA guidelines for reporting of systematic reviews [27].

Results

Study selection process

The initial search of the selected databases retrieved a total of 6441 citations. After excluding duplicates, a total of 5330 articles remained. Furthermore, 5170 were excluded as articles were reviews, animal interventions or cell studies, leaving 160 full-text articles to be assessed for eligibility. One hundred and fifty-two articles were excluded as the study population were not NAFLD participants, IR was not an outcome measure, articles were not in English, studies were not RCTs and/or diet and lifestyle interventions had nutritional and/or pharmaceutical supplementations. For full-text articles that were not available, authors were contacted. However, no replies were received and as such, these articles were then excluded [28–30]. A total of eight RCT were identified for inclusion in this review (Fig. 1).

The risk of bias and study methodology quality assessment scores

Two studies included in this systematic review received an overall neutral quality assessment rating [31,32]. This was because of the uncertainty as to whether or not the selection of the sample was free from bias and whether the participants were blinded to their group allocation. Six of the articles received a positive score in the quality assessment tool [33–38]. One study reported a limitation in that participants in the intervention group could make their own food choices and reported their own consumption of foods [33]. There was a lack of information on diet observations, physical activity measurement, a lack of follow-up and details on behavior change in two studies [31,34]. The duration of the intervention in two studies was perceived as inadequate [35,36]. Three studies did not measure the severity of histological liver injury [31,32,37]. In addition, various measures and diagnostic techniques were used for fatty liver assessment across the studies. One study had a small sample size and two studies only considered men (Table 1) [33–35].

Study findings – effects on homeostatic model assessment of insulin resistance diet-only interventions

Three of the eight studies included focused solely on dietary interventions for the improvement of HOMA-IR in patients with NAFLD [31,33,35] (Table 2 and Table 4). There were a total of 267 participants across the three studies, with an equal number of men and women. The age of the participants ranged between 37 and 55 years, with a BMI range of 27–38 kg/m^2. A variety of methods were used to diagnose NAFLD across the three studies including elevated ALT [31], liver biopsy [35] and ultrasonography [33]. The duration of the interventions ranged from 1.5 to 6 months. The prescribed diets within the intervention and control groups varied among the studies. The study by Nigam *et al.* [33] consisted of an intervention group consuming 20 g of olive oil, an intervention group consuming 20 g of canola oil and a control group consuming 20 g of soyabean oil. A 45-min brisk walk was recommended, but was not mandatory throughout the 6-month intervention. Similar improvements in IR were observed with canola (reduction of HOMA-IR score of 1.3, $P = 0.001$) and olive oil (reduction of HOMA-IR score of 1.5, $P = 0.001$) compared with the control group (reduction of HOMA-IR of 0.2, $P > 0.05$). Ryan *et al.* [35] conducted a randomized cross-over trial with a Mediterranean diet (MedD) intervention group and a low-fat/high-carbohydrate (CHO) diet control group. Each participant consumed both diets for 6 weeks, with a 6-week washout period. The MedD group showed significantly improved IR (reduction in HOMA-IR of 1.7, $P < 0.01$) compared with the low-fat/high-CHO diet (reduction in HOMA-IR of 0.2, $P < 0.05$). De Luis *et al.* [31] investigated the effects of two diets: a hypocaloric low-fat and a hypocaloric low-CHO diet. It was found that both diets were effective in improving IR; however, the low-fat diet showed greater improvements (reduction in HOMA-IR of 9, $P < 0.05$) compared with the low-CHO diet (reduction in HOMA-IR of 3.9, $P < 0.05$). Although all studies assessed IR, the primary outcome of each study varied. They involved either reducing the severity of liver steatosis, reducing body weight and decreasing liver enzymes [31,33,35]. The various dietary interventions resulted in significant reductions in HOMA-IR compared with control groups. An average reduction in HOMA-IR scores of 1.5–9 was observed across these studies. No significant differences were observed between
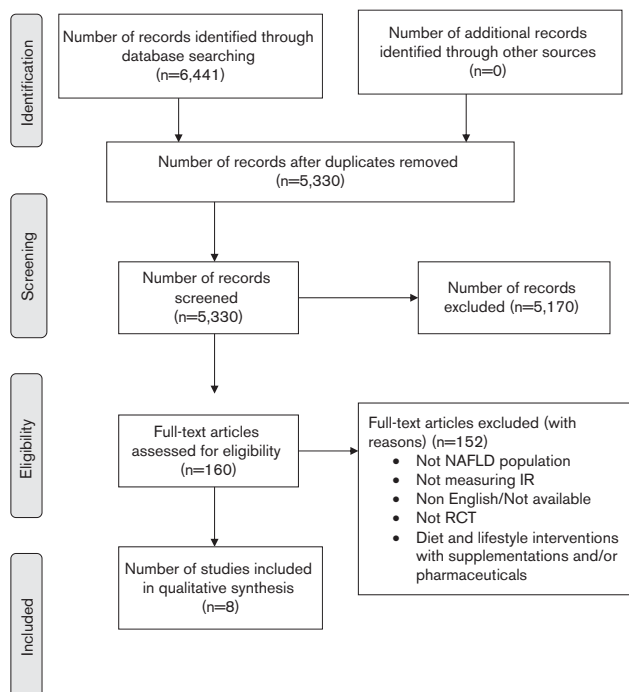
Fig. 1. PRISMA flowchart showing the process for the inclusion of studies. IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; RCT, randomized-controlled trial.

Table 1. Study methodological quality assessment American Dietetic Association quality rating tool

References	Research question clearly stated?	Study sample selection bias free?	Groups comparable?	Withdrawals described?	Blinding?	Were interventions described?	Outcomes defined and measurements reliable?	Were statistics appropriate for design and type of outcome indicators?	Conclusions supported by results, biases and limitations taken into consideration?
Ryan et al. [35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al-Jiffri et al. [34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nigam et al. [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Promrat et al. [38]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Sun et al. [36]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
St George et al. [37]	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes
Aller et al. [32]	Yes	Unclear	Yes	No withdrawal	No	Yes	Yes	Yes	Yes
De Luis et al. [31]	Yes	Unclear	Yes	No withdrawal	No	Yes	Yes	Yes	Yes

preintervention and postintervention for the control groups, with a reduction in the overall HOMA-IR score ranging between 0.2 and 3.9. Overall, the study by De Luis et al. [31] showed that a hypocaloric low-fat diet led to the greatest significant reduction in IR. In this study, both diet groups lost on average 4 kg in weight. In the study by Nigam et al. [33], participants who consumed olive oil achieved the greatest average weight reduction of 5 kg, those who consumed canola oil achieved an average weight loss of 4.2 kg, whereas the control group lost an average 1.6 kg. In the study by Ryan et al. [35], participants who consumed the MedD lost 1 kg in weight, albeit nonsignificant. Those who consumed the low-fat/high-CHO diet lost on average 2.4kg of weight.

Diet, exercise and counselling interventions

Five of the eight articles in this systematic review consisted of interventions that incorporated diet and exercise regimes (Table 3 and Table 4) [32,34,36–38]. There were a total of 1595 participants; the age of the participants ranged between 35 and 55 years and BMI ranged between 31 and 38 kg/m^2 across the studies. The study duration ranged from 2.5 to 12 months. The diagnosis of NAFLD was made by biopsy [38], high liver enzymes [32,34,37] and/or by ultrasonography [36]. The dietary interventions differed in macronutrient compositions, achieving either a general restrictive hypocaloric diet [34,37,38], a diet tailored to the individual's requirements (moderate CHO, protein and fats) [38], high in monounsaturated [34] or high polyunsaturated fat [32]. Exercise interventions involved jogging, walking, stair climbing, step tracking, cycling and/or strength training or a combination, ranging from three times per week to everyday for 20–60 min [32,34,38]. In two studies, participants were randomized in a 2 : 1 ratio to a lifestyle intervention or a control group [36,38]. The intervention group involved a tailored diet tailored on the basis of the individual's requirements (based on a fat-reduced and sugar-reduced diet) and increased physical exercise [36]. The control group received education on NAFLD and principles of healthy eating, physical activity and weight control [38]. The intervention group received a calorie goal on the basis of their starting weight (1000–1200 kcal/day if baseline weight was < 200 lb or 1200–1500/day if baseline weight > 200 lb) and a daily fat gram goal designed to meet 25% energy from fat (28–33 g for 1000–1200 kcal diet or 33–42 g for the 1200–1500 kcal diet) and moderate-intensity physical activity [38]. The control groups either attended nutrition classes, which provided information on health, lifestyle and education about NAFLD [36], or no treatment [38]. A study by Aller et al. [32] applied a hypocaloric diet high in monounsaturated fat in one group and a hypocaloric diet high in polyunsaturated fat in the other group. In the study by Al-Jiffri et al. [34], the participants in the intervention group followed a low-calorie diet with on average 15% energy as protein, 30–35% as fat and 50–55% as CHO to provide about 1200 kcal daily with aerobic exercise. Participants in each intervention group showed significant improvements in IR, varying from a reduction in the HOMA-IR score between 0.2 and 2. The control groups in each study showed little improvements or an increase in the HOMA-IR score. The

Table 2. Relevant data extracted for each dietary intervention study

References	NHMRC design	Diagnosis of NAFLD	Country of study	Sample size; male/female ratio	Age (years) and BMI (kg/m²) (mean±SD)	Intervention	Duration (weeks/months)	Result. Before/after (mean±SD)	Summary of results
Ryan et al. [35]	RCT crossover design	Biopsy	Australia	12; 6/6	Age: 55±14 BMI: 32.0±4.2 No significant differences in age and BMI between groups at baseline	All patients undertook both diets. The MedD macronutrient profile: 40% energy from fat (MUFA and omega 3 PUFA), 40% from carbohydrate, and 20% from protein. The control LF/HC diet had a macronutrient composition consisting of 30% energy from fat, 50% from carbohydrate, and 20% from protein	6 weeks of the MedD diet and 6 weeks of LF/HC with a 6-week washout period in between diets	Baseline MedD: 4.7±1.6 End of diet: 3.0±1.4* Baseline LF/HC: 4.1±2.1 End of diet: 3.9±1.4	MedD reduces steatosis and improves IR in NAFLD without weight loss
De Luis et al. [31]	RCT	Abnormal ALT liver enzymes	Spain	162; 37 male/125 female	Age: Control group with diet I: 46.9±17.3 In NAFLD group with diet I: 45.5±14.9 In control group with diet II: 45.8±14.3 In NAFLD group with diet II (age 46.8±15.9 years) BMI: Diet 1: Group 1: 35.6±6.7 Group 2: 36.3±3.7 Diet 2: Group 1: 35.6±7.2 Group 2: 38.2±5.8 No significant differences in age and BMI between groups at baseline	162 obese patients were randomly allocated to two groups: (a) diet I (low fat) and (b) diet II (low carbohydrate). Patients were classified as group 1 when serum ALT activity was normal or group II (NAFLD) when serum ALT activity was high (a) Diet I (low fat) 1500 kcal/day, 53% carbohydrates, 20% protein, 27% fat (b) Diet II low carbohydrate: 1507 kcal/day, 38% carbohydrates, 26% proteins, 36% fats	3 months	Diet 1: Group 1 (obese): Baseline 3.95±2.3 3 months 3.37±1.6* Group 2 (NAFLD): Baseline 12.1±4.6 3 months 3.1±1.8* Diet 2: Group 1 (obese): Baseline 3.46±2.1 3 months 2.71±1.33* Group 2 (NAFLD): Baseline 8.1±9.1 3 months 4.2±2.4*	Weight loss with two hypocaloric diets were associated with improvements with hypertransaminasaemia and IR
Nigam et al. [33]	RCT	Ultrasonography	India	93 males	Age: Olive oil: 37.2±6.2 Canola oil: 38.0±6.4 Control oil: 36.2±7.1 BMI: Olive oil: 27.3±2.4 Canola oil: 27.4±5.7 Control oil: 27.4±2.7 No significant differences in age and BMI between groups at baseline	Olive oil, canola oil, and soyabean/safflower oil (control) as cooking medium (not exceeding 20 g/day) A 1-month diet and exercise run-in period before the intervention The daily energy intake advised was 15–21% protein (1–1.5 g/kg of desirable body weight), 55–70% carbohydrates, and 20% fats. A 40–45 min brisk walk daily was recommended for all participants; however, it was not prescribed or mandatory All patients received advice about diet, exercise and other lifestyle factors	6 months	Preintervention: Olive oil: 2.2±2.2 Canola oil: 2.4±2.0 Control oil: 2.4±1.8 P=0.21 Postintervention: Olive oil: 0.7±1.8 Canola oil: 1.1±2.0 Control oil: 2.2±1.8 P=0.004* Pre+post olive oil: P=0.001* Pre+post canola oil: P=0.001* Pre+post control oil: P=not significant	Improvements in IR with the use of canola and olive oil compared with control oil (soyabean)

ALT, alanine aminotransferase; HC, high carbohydrate; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; LF, low fat; MedD, Mediterranean diet; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; NHMRC, National Health and Medical Research Council; PUFA, polyunsaturated fatty acid; RCT, randomized-controlled trial. *P<0.05, statistically significant.

Table 3. Relevant data extracted for each lifestyle intervention study

References	NHMRC design	Diagnosis of NAFLD	Country of study	Sample size; male/female ratio	Age (years) and BMI (kg/m²) (mean ± SD)	Intervention	Duration (weeks/ months)	Result. Before/After (mean ± SD)	Summary of results
Al-Jiffri et al. [34]	RCT	Elevated AST and/or ALT and liver biopsy	Saudi Arabia	100 males	Age: 35–55 The average age was not stated BMI: Intervention: 32.37±3.92 Control: 32.37±3.92 No significant differences in age and BMI between groups at baseline	Group A received exercise and a diet regimen Group B received no treatment The aerobic treadmill-based training programme was set to 65–75% of maximum heart rate for 30 min 3 times/week with a 5 min warm-up and 5 min recovery. Diet (low calorie) 1200 kcal 15% protein, 30–35% fat 50–55% as carbohydrates	3 months	Intervention group: Pre: 4.92±2.78 Post: 3.57±1.3 P=0.0083* Control group: Pre 4.98±2.51 Post: 5.13±2.44 P=0.161 Post-test differences between A and B intervention: 2.64±1.37 Control group: 5.13±2.44 P=0.0091*	NAFLD patients who received a diet and exercise regime resulting in weight loss showed improvements in IR
Aller et al. [32]	RCT	Elevated ALT levels	Spain	306; 86/220	Age: 49.3±16.7 BMI (overall): 36.5±5.4 Diet M: Group 1: 37.6±6.3 Group 2: 39.4±5.4 Diet P: Group 1: 38.2±6.2 Group 2: 38.9±5.3 No significant differences in age and BMI between groups at baseline	Patients classified as group I when serum ALT activity was normal or group II (NAFLD) when serum ALT activity was high Diet M (MUFA) consisted of 1342 kcal, 46.6% carbohydrates, 34.1% fat and 19.2% protein. The distribution of fat was; 21.7% sat fat, 67.5% MUFA and 10.8% PUFA Diet P (PUFA) consisted of 1459 kcal, 45.7% carbohydrates, 34.4% fat and 19.9% protein. The distribution of fat was 21.8% sat fat, 55.5% MUFA, and 22.7% PUFA. Exercise: aerobic exercise ≥ 3 times/ week (60 min each)	3 months	Diet M: Group 1 (normal ALT): Baseline 2.84±2.0 3 months 2.35±1.2* Group 2 (NAFLD): Baseline 5.21±3.5 3 months 4.40±3.3* Diet P: Group 1 (normal ALT): Baseline 3.31±2.8 3 months 2.71±1.23* Group 2 (NAFLD): Baseline 4.18±1.1 3 months 3.11±1.4*	Weight reductions secondary to two hypocaloric diets were associated with improvement in IR in NAFLD patients irrespective of quality of diet
Promrat et al. [38]	RCT	Biopsy	America	31; 22/9	Age: Lifestyle: 48.9±10.9 Control: 47.6±12.0 BMI: Lifestyle: 33.9±5.3 Control: 33.7±4.7 No significant differences in age and BMI between groups at baseline	Patients were randomized in a 2:1 ratio to lifestyle intervention or structured education (control) Control group: group sessions providing education about NAFLD, principles of healthy eating, physical activity, and weight control every 12 weeks Lifestyle group: 1000–1200 kcal/day if baseline weight <200 lb or 1200–1500 kcal/day if baseline weight > 200 lb and a daily fat gram goal designed to produce a 25% fat diet (28–33 g for 1000–1200 kcal diet or 33–42 g for the 1200–1500 kcal diet) Physical activity: 10 000/day. Bicycling, aerobic dance and strength training. Then gradually progress to 200 min/ week. Groups met weekly for the first 6 months and then biweekly for months 7 through 12	48 weeks	Lifestyle: Baseline: 7.4±4.6 End of study: 5.4±6.1 Control: Baseline: 7.3±6.2 End of study: 7.4±5.6 P=0.37 The P value compares the mean difference between the pretreatment and post-treatment changes in the variables between the two groups	The lifestyle intervention group resulting in weight loss showed improvements in IR in patients with NAFLD

Study	Design	Country	Sample	Diagnosis	Population	Intervention	Duration	Results	Conclusion
St George et al. [37]	RCT	Australia	152; 95/57	Abnormal liver enzymes (enzyme not specified)	Age: Group A: 47.5 ± 12.4; Group B: 49.3 ± 9.7; Group C: 48.4 ± 11.1; Group D: 47.3 ± 11.6. BMI: Group A: 31. ± 6; Group B: 31.5 ± 5.3; Group C: 31.8 ± 4.8; Group D: 31.6 ± 5.1. No significant differences in age and BMI between groups at baseline	Group A: low-intensity arm receiving three fortnightly consultations. Group B + C: received identical interventions of six fortnightly consultations for the first 3 months. After 3 months Group C: received a telephone-based maintenance programme through to 12 months. Group D (control group): initial consultation assessment to interpret blood results. No further support was provided. The three groups were recommended to follow a diet low in saturated fat, high in omega 3 and fibre with a reduced energy intake of 1700–2400 kcals; 150–200 min exercise	10 weeks	Baseline: Group A: 6.2 ± 5.4; Group B: 4.0 ± 2.8; Group C: 5.1 ± 3.5; Group D: 6 ± 4.2. Postintervention: Groups B and C: −0.4 ± 1.0*; Group A: −0.2 ± 2.3; Group D: 0.0 ± 1.5	Physical activity counselling as a component of a lifestyle intervention was an effective method increasing the amount of physical activity and therefore having positive effects in reducing IR in NAFLD patients
Sun et al. [36]	RCT	China	1006; 646/360	Elevated ALT and AST levels and ultrasonography	Age: Lifestyle: 38.7 ± 14.2; Control: 37.5 ± 19.2. BMI: Lifestyle: 37.3 ± 15.4; Control: 38.8 ± 17.5. No significant differences in age and BMI between groups at baseline	Randomization 2 : 1 ratio. Control group: education about NAFLD, principles of healthy eating, physical activity and weight control. Lifestyle group: a diet tailored for the individual's requirements. The diet consisted of 30% fat, 15% proteins and 55% carbohydrates, including 5% sugar. The exercise therapy consisted of walking, jogging, stair climbing and instructions in physical exercise as part of everyday life	12 months	Baseline: Lifestyle: 2.5 ± 0.6; Control: 2.4 ± 0.7. Postintervention: Lifestyle: 0.96 ± 0.5; Control: 2.87 ± 0.6. $P = 0.041$* (compares differences between the baseline and postintervention changes in the variables between lifestyle and control groups)	A lifestyle intervention was effective at improving IR and fatty liver in patients with NAFLD

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; NHMRC, National Health and Medical Research Council; PUFA, polyunsaturated fatty acid; RCT, randomized-controlled trial. *$P < 0.05$, statistically significant.

Table 4. The various dietary interventions and their effects on homeostatic model assessment of insulin resistance

References	Diet	HOMA-IR score at baseline (mean±SD)	HOMA-IR score postintervention (mean±SD)	P-value
Ryan et al. [35]	MedD: 40% energy from fat (MUFA and omega 3 PUFA), 40% from carbohydrate, and 20% from protein Control: low-fat/high-carbohydrate diet 30% energy from fat, 50% from carbohydrate, and 20% from protein	MedD: 4.7±1.6 Low-fat/high-carbohydrate diet: 4.1±2.1	End of MedD: 3.0±1.4* End of low-fat/high-carbohydrate diet: 3.9±1.4	≤0.001 ≥0.05
Al-Jiffri et al. [34]	Diet (low calorie: 1200 kcal) and exercise. 15% energy from protein, 30–35% from fat and 50–55% as carbohydrates	Diet and exercise group: 4.92±2.78	Diet and exercise group: diet and exercise group: 3.57±1.3	0.0083
Nigam et al. [33]	Olive oil, canola oil, soyabean/safflower oil (control) as cooking medium (not exceeding 20 g/day) The daily energy intake advised was 15–21% protein (1–1.5 g/kg of desirable body weight), 55–70% carbohydrates and 20% fats Exercise was recommended	Olive oil: 2.2±2.2 Canola oil: 2.4±2.0 Control oil: 2.4±1.8	Olive oil: 0.7±1.8 Canola oil: 1.1±2.0 Control oil: 2.2±1.8	Olive oil: 0.001 Canola oil: 0.001 Control oil: not significant
Promrat et al. [38]	Lifestyle group: 1000–1200 kcal/day if baseline weight <200 lb or 1200–1500/day if baseline weight > 200 lb and a daily fat gram goal designed to produce a 25% fat diet (28–33 g for 1000–1200 kcal diet or 33–42 g for the 1200–1500 kcal diet) Physical activity was also included in this lifestyle group	Lifestyle: 7.4±4.6	Lifestyle: 5.4±6.1	0.37 (this P value compares the mean difference between the pretreatment and post-treatment changes in the variables between the two groups)
Sun et al. [36]	Lifestyle group: the diet consisted of 30% fat, 15% proteins and 55% carbohydrates, including 5% sugar Physical activity was also included in this lifestyle group	Lifestyle: 2.5±0.6	Lifestyle: 0.96±0.5	0.041 (compares differences between the baseline and postintervention changes in the variables between lifestyle and control groups)
St George et al. [37]	Group A: low-intensity arm receiving three fortnightly consultations Group B+C: received identical interventions of six fortnightly consultations for the first 3 months. After 3 months. Group C: received a telephone-based maintenance programme through to 12 months Group D (control group): initial consultation assessment to interpret blood results. No further support was provided. The three groups were recommended to follow a diet low in saturated fat, high in omega 3 and fibre with a reduced energy intake of 1700–2400 kcals; 150–200 min exercise	Group A: 6.2±5.4 Group B: 4.0±2.8 Group C: 5.1±3.5 Group D: 6±4.2	Groups B and C: −0.4±1.0* Group A: −0.2±2.3 Group D: 0.0±1.5	<0.05*
Aller et al. [32]	Diet M (MUFA): consisted of 1342 kcal, 46.6% carbohydrates, 34.1% fat and 19.2% protein The distribution of fat was; 21.7% sat fat, 67.5% monounsaturated fat and 10.8% polyunsaturated fats Diet P (PUFA): consisted of 1459 kcal, 45.7% carbohydrates, 34.4% fat and 19.9% protein The distribution of fat was; 21.8% saturated fatty acid, 55.5% MUFA and 22.7% PUFA Exercise was also prescribed to both groups	Diet M: 5.21±3.5 Diet P: 4.18±1.1	Diet M: 4.40±3.3* Diet P: 3.11±1.4*	Diet M: <0.05* Diet P: <0.05*
De Luis et al. [31]	Diet 1 (low fat): 1500 kcal/day, 53% carbohydrates, 20% protein, 27% fat Diet 2 (low carbohydrate): 1507 kcal/day, 38% carbohydrates, 26% proteins, 36% fats	Diet 1: 12.1±4.6 Diet 2: 8.1±9.1	Diet 1: 3.1±1.8* Diet 2: 4.2±2.4*	Diet 1: <0.05* Diet 2: <0.05*

HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; MedD, Mediterranean diet; MUFA, monounsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; PUFA, polyunsaturated fatty acid.
*P<0.05, statistically significant.

score varied between − 1.07 and + 0.47. Although the primary goal in these studies was to improve metabolic outcomes that were associated with NAFLD, these lifestyle interventions aimed at achieving a reduction in body fat percentage by incorporating exercise as well as diet. The diet and lifestyle intervention that showed the greatest reduction in IR was a 1000–1200 kcal/day diet if baseline weight less than 200 lb or 1200–1500/day if baseline weight more than 200 lb and a daily fat gram goal of 25% total energy [38]. They incorporated an exercise regime involving either 10 000 steps/day, cycling, aerobic dance or strength training [38]. These intervention studies showed an overall positive effect in lowering the levels of IR in participants with NAFLD. In the study by Al-Jiffri *et al.* [34], there was a 15% average weight loss reduction in the intervention group, with a reduction in HOMA-IR of 1.35. The study by Aller *et al.* [32] showed a greater weight reduction in participants who consumed the diet high in monounsaturated fat (– 4.9 kg), whereas those who consumed a diet high in polyunsaturated fat lost an average 1.7 kg. However, a greater reduction in HOMA-IR was observed in the polyunsaturated fat diet group (– 1.07) compared with the monounsaturated fat group (– 0.80). The study by Promrat *et al.* [38] showed an average weight loss of 8.7 kg and a reduction in HOMA-IR of 2 U in the intervention group and a weight loss of 0.5 kg and an increase of 0.1 in HOMA-IR in the control group. In the study by St George *et al.* [37], an average weight loss of 3.8 kg was observed in the intervention groups with six fortnightly consultations and 1.9 and 0.5 kg in the low-intensity group with three fortnightly consultations and the control group with an initial consultation to interpret the patients' results, respectively. The consultations involved dietetic counselling on recommendations of healthy eating and exercise [37]. IR improved marginally in the intervention group (– 0.4), with no change in the control group. There was an average weight loss of 6.1 kg in the intervention group and an average weight gain of 1.3 kg in the control group in the study by Sun *et al.* [36] IR improved by a reduction in HOMA-IR of 1.54 U in the intervention group in this study.

The authors did not carry out a meta-analysis because of the total number of cases being small, wherein a single study would have accounted for 99% of the total weight [36]; most studies were of low quality, interventions differed in terms of diet and physical activity and/or behavioural therapy and the duration of treatment varied between 3 and 12 months.

Discussion

IR is strongly implicated in the pathogenesis and progression of NAFLD and NASH and one of the major metabolic factors associated with the metabolic syndrome [39]. In addition, it is considered to be a key cofactor associated with the progression of other liver diseases, particularly hepatitis C. Hence, there are significant implications in relation to liver disease by evaluating dietary therapy to improve IR. This systematic literature review examined the effects of diet alone or in combination with a lifestyle intervention on IR as measured by HOMA-IR in patients with diagnosed NAFLD. Interventions with

diet modifications only showed significant reductions in HOMA-IR compared with control groups. Diet and exercise interventions were also effective in reducing HOMA-IR up to two units in patients with NAFLD. Diet and lifestyle interventions that applied energy restrictions and resulted in weight reduction were the most frequently used and proved effective in reducing IR in overweight and obese NAFLD patients. It remains unclear which diet and lifestyle regime had the greatest effect in lowering IR in participants with NAFLD.

The effect of weight loss as a result of these interventions is consistent with other systematic reviews that have investigated the effect of diet and lifestyle modifications on liver specific outcome measures in NAFLD and showed an improvement with the overall NAFLD disease severity [40–42]. These studies focused on outcome measures such as histological and biochemical improvements (intrahepatic triacyglycerol concentration, and/or liver aminotransferases, glucose control and insulin sensitivity) and improvements in radiological steatosis. Although changes in liver-specific outcomes were not the focus of this review, it was evident from the studies included that the interventions used had significant favourable effects on steatosis [35,38], liver enzymes [31,32,34,36–38], liver grading [33] and disease activity of NASH [38] compared with control groups, with the majority attributable to the weight loss achieved.

In addition to the overall effect of weight loss, it is important to acknowledge that other covariates including ethnicity, age, sex distribution and baseline BMI values could play a contributory role in the link between the effect of diet and IR. The internal heterogeneity across the trials makes it difficult to objectify their role.

IR is a pathogenic factor underlying the progression of NAFLD [11]. It correlates with enhanced oxidative stress and histopathological disease severity of NAFLD correlates significantly with oxidative stress parameters [39]. Assessment of positive improvements with diet and lifestyle interventions on IR is a first step or basis for preventing further complications of NAFLD progression. In previous systematic reviews [40–42], not all studies reported on IR. They also encompassed a wide range of study interventions, such as exercise only, interventions combining diet and specific or broad physical activity/exercise advice and interventions incorporating lifestyle interventions with pharmaceuticals/supplementation such as insulin sensitizers, lipid-lowering drugs and antioxidants [40–42]. HOMA-IR is used to measure IR in many published clinical trials because of simplicity in its calculation [23]. HOMA-IR and the euglycaemic clamp have been compared and similar values for IR have been determined [22]. HOMA-IR can be measured more easily to guide clinicians in their management. Liver-specific outcomes are not always easily obtained (especially paired biopsies) and LFTs can be an unreliable outcome measure with respect to the effect of dietary change.

The majority of studies in this systematic review aimed to reduce IR through the application of diet and exercise to achieve weight loss. From this review, it was observed that body weight reductions between 4 and 15% were found to be a potential therapeutic target in lowering HOMA-IR. Elias *et al.* [43] reported that a recommended weight loss of 5% of initial body weight is an effective way to reduce

risk factors in the treatment of NAFLD. Weight loss has a significant impact in reducing IR and other related metabolic health outcomes such as an improvement of liver enzymes, weight, cholesterol levels and steatosis. The improvement in metabolic outcomes seems to be related to the amount of weight reduction [44].

There are a number of associated dietary factors that increase the development of fatty liver disease such as high intakes of refined CHOs and saturated fat [45]. There are a growing number of dietary intervention trials aiming to reverse these negative dietary habits [46]. Emerging evidence has suggested that a traditional MedD high in monounsaturated fatty acids could be an effective treatment as it has been found to reduce steatosis and IR in NAFLD and improve a cluster of metabolic risk factors [35,47,48]. In practice, when recommending a healthy dietary pattern for adults with NAFLD, adhering to a MedD is a good alternative to a western diet, wherein it is associated with an improvement in overall health status, a reduction in overall incidence mortality and mortality from cardiovascular disease [49].

It is complex to separate the beneficial effects of diet and exercise alone in clinical trials. Research papers focusing purely on exercise interventions in NAFLD were not included in this review. Currently, there is a lack of consistent and robust evidence to suggest that exercise alone improves IR, hepatic fat and inflammation [50]. Two studies reported that aerobic exercise does improve visceral lipids and serum aminotransferases, with no significant change in HOMA-IR in obese NAFLD patients [51,52].

The variety of diets and exercise patterns reported throughout this review makes it difficult to determine which interventions result in the greatest reductions in IR (Table 4). There is also conflicting evidence around whether diet and exercise independent of weight loss improves IR. The variety and lack of consistency among intervention prescription has also been noted in other studies that investigated different diet and exercise regimes on populations at risk of NAFLD such as participants with obesity, T2DM and metabolic syndrome (Table 4) [53]. Although improvements in IR were observed in NAFLD patients, the lack of consistent literature, duration and sustainability of appropriate diet and exercise lifestyle interventions limits translation into clinical practice. More robust and consistent high-quality research in this participant group is required to develop firmer dietary and lifestyle recommendations.

In this systematic review, studies used a number of different methods to diagnose NAFLD including the less invasive albeit less sensitive and precise method of measuring serum liver enzyme aminotransferases [40]. It has been shown that serum aminotransferase levels may be normal in patients with histologically proven NAFLD, wherein 10% of NASH patients have normal ALT and AST levels [54]. ALT alone is not a reliable diagnostic measure for clinical settings and interventional trials [49]. However, despite the lack of correlation with histological liver injury and liver enzymes, they can serve as an early indication of NAFLD before the definitive diagnosis of a liver biopsy and thus we believed were important to include in their assessment of response to diet and lifestyle interventions. Given the findings, it was decided by the authors to include studies that diagnosed NAFLD with liver enzymes as they also had large study populations and the effect of diet and lifestyle interventions on IR was noteworthy. We acknowledge that the use of liver enzymes to diagnose NAFLD is flawed; however, in the absence of noninvasive diagnostic tools for this population, they are easily measured and accessible and capture larger population data.

The limitations of this systematic review need to be acknowledged. Notably, among 6641 articles potentially identified for review, only eight studies were selected. The total number of cases was relatively small and one study [36] accounted for over 50% of total cases. The small number of studies included in this review is because of the inclusion criteria, which specifically screened for RCTs of diet alone or alongside lifestyle interventions. Observational studies that are well designed and carried out are useful in alluding to cause and effect relationships, however, were excluded from this review. There were a number of different interventions and the duration of these interventions varied (between 6 weeks and 12 months) across each of the articles; this inconsistency made it difficult to determine which intervention had the greatest impact on IR. Follow-up durations among the studies were also inconsistent.

The outcome measure in this systematic review was HOMA-IR, a surrogate marker of IR. The limitation of this surrogate measure needs to be acknowledged; it is not the gold standard and its clinical significance has been questioned. Using HOMA-IR as a way to monitor the disease progression of NAFLD has been debated in European guidelines; however, it is accepted in patients without diabetes. However, HOMA-IR is quick and inexpensive to carry out in a clinical setting and does not require increased labour resources. It can provide a good indication of disease progression alongside other clinical and biochemical markers. Given its flaws, it continues to be used widely in research and clinical-based studies. An improvement in HOMA-IR during weight loss may indicate metabolic improvement that is beneficial for NAFLD [55].

In terms of the quality of the studies in the review, two out of the eight articles included were assigned a neutral score on the basis of the American Dietetic Association quality-rating tool assessing the methodology of study designs because of the uncertainty as to whether or not the selection of the sample was free of bias. The other studies, although deemed positive, had some inherent biases within. Some of the full-text articles could not be retrieved from authors when contacted and it is unknown whether these findings would have altered the outcomes of this review. There was variability and no set criteria for the diagnosis of NAFLD, which is a limitation because of the inconsistencies between disease severity, diagnosis of participants and discrepancies among the interpretation of the results of the study included in this review.

Diet and lifestyle programmes are often difficult to adhere to and full-time counselling including prescriptive advice may not be obtained. Weight loss can be difficult to maintain and many patients re-establish their baseline weight. These studies did not investigate the long-term outcomes and therefore we cannot determine whether these improvements, that is, reduction in IR are

sustainable. There is a lack of robust RCTs published with a definitive histological diagnosis investigating metabolic outcomes such as IR. More extensive trials are needed to establish whether these interventions can be effective in treating NAFLD in the long term [56,57]. In addition, the mechanisms behind the benefits of hypocaloric diets and exercise on IR have not been well investigated; therefore, more physiological research is needed [58,59].

Despite these limitations, these findings are clinically important. The collective reductions in HOMA-IR observed are significant for the NAFLD population, given that IR is the underlying insult in the development and progression of the disease. Diets with and without lifestyle interventions were shown to be effective, which is essential in the absence of an effective therapy in a highly prevalent condition. IR, the underlying mechanism of NAFLD, which is related to a number of other chronic diseases, improved with the variety of interventions. However, further studies need to be carried out to determine the most effective and sustainable diet intervention.

Conclusion

The effects of diet and exercise on IR in NAFLD were evident only in overweight and obese populations with the disease. Improvements in diet and exercise can ameliorate IR in this population. It would seem that weight loss in this group is a significant driver in achieving a reduction in HOMA-IR as well as in improving liver-specific markers and the overall metabolic profile. For both normal-weight, overweight and obese patients with NAFLD, the type of intervention and specifically the composition of the diet or diet and exercise combination most effective in achieving overall metabolic benefits still needs to be elucidated. With weight loss maintenance unsupported by the literature, an intervention that can achieve better health outcomes without weight loss could potentially be superior and more sustainable in the future.

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Conflicts of interest

There are no conflicts of interest.

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