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Dietary strategies in non-alcoholic fatty liver disease patients: From evidence to daily clinical practice, a systematic review

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Abstract

Lifestyle modification comprising calorie restriction (CR) and increased physical activity enabling weight loss is the first-line of treatment for non-alcoholic fatty liver disease (NAFLD). However, CR alone is not optimal and evidence suggests that dietary pattern and composition are also critical in NAFLD management. Accordingly, high consumption of red and processed meat, saturated fat, added sugar, and sweetened beverages are associated with an increased risk of developing NAFLD and hepatocellular carcinoma, while other foods and compounds such as fish, olive oil, and polyphenols are, in contrast, beneficial for metabolic disorders. Therefore, several dietary interventions have been studied in order to determine which strategy would be the most beneficial for NAFLD. The evidence regarding the effectiveness of different dietary interventions such as low carbohydrate/low-fat diet, time-restricted eating diet, CR, and the well-studied Mediterranean diet is summarized.

KEYWORDS
dietary pattern, Mediterranean diet, NAFLD, physical activity, weight loss

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects 30% of the global population.[1–4] The rising global burden of NAFLD parallels the increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity, resulting in high healthcare resource utilization and costs.[5,6] NAFLD is a spectrum of liver diseases ranging from liver steatosis to non-alcoholic steatohepatitis (NASH), and fibrosis, which may lead to cirrhosis and hepatocellular carcinoma.[7] Furthermore, NAFLD is associated with an increased risk of incident T2DM, chronic kidney disease, extrahepatic cancers, and cardiovascular morbidity and mortality,[8–11] underscoring the multi-systemic pattern of this disease. Similarly, evidence suggests that the visceral adipose tissue (VAT), one of the hallmarks of NAFLD, is associated with increased atherosclerosis and cardiometabolic risk,[12–14], while its reduction is correlated with hepatic histologic improvements, independently of liver fat reduction.[15] Therefore, considering the aforementioned findings, NAFLD management requires a multidisciplinary care team to mitigate negative liver-related and extra-hepatic-related outcomes.

Currently, no pharmaceutical treatments are approved for NAFLD therapy. Therefore, comprehensive lifestyle modification interventions, including calorie restriction (CR) and increased energy expenditure, remain the cornerstones of NAFLD treatment.[16,17]

Although the amount of weight loss is the most important determinant of liver histological feature outcomes[18,19] and the most well-validated treatment, healthy eating patterns and dietary composition can also have a beneficial impact on the risk of new-onset NAFLD,[20] and can provide additional benefits such as the reduction of cardiovascular disease risk,[21,22] improvements in metabolic outcomes,[23,24] and reductions in mortality.[25] However, only a few patients reach the significant and sustained weight loss needed for a positive effect on liver damage, and maintaining long-term adherence to lifestyle modification remains a challenge.

The evidence in the literature is growing with regard to the specific dietary patterns associated with greater cardiovascular and metabolic benefits, but is scarce regarding strategies to adjust the pattern to individual patients based on socio-economic, cultural background, and personal preferences for promoting long-term adherence. Recent research has demonstrated that the Mediterranean diet (MD) is beneficial for the prevention of cardiovascular disease,[26] and the management of NAFLD.[27,28] However, various other dietary strategies exist that are less well studied in the area of NAFLD. This systematic review aims to summarize the effects of different dietary strategies and exercise interventions on liver function in patients with NAFLD.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29]

Data sources and search strategy

We searched four databases, MEDLINE, EMBASE, Web of SCIENCE, and Cochrane Central Register of Controlled Trials (CENTRAL), from 2010 to September 2022. The formulation of search terms was designed and conducted jointly by a medical librarian with study investigators. The list of search terms is provided in Supporting Information S1. Reference lists of previously published systematic reviews and meta-analyses were examined to find additional relevant studies. Only articles published in English were considered.

Eligibility criteria

We included only randomized controlled trials (RCTs) and clinical controlled trials in this systematic review. The inclusion criteria were as follows: (a) adult patients (>18 years old); (b) dietary and exercise interventions on surrogate markers of NAFLD; (c) interventions: MD intervention and/or CR intervention and/or time-restricted eating and/or low-fat diet (LFD) and/or low-carbohydrate diet (LCD) and/or physical activity (PA); (e) surrogate markers of NAFLD: histology (NAFLD activity score [NAS], individual scoring of ballooning, lobular inflammation, and steatosis) and/or liver function tests (LFTs) (including alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and/or non-invasive markers of liver fibrosis (NAFLD fibrosis score, fibrosis 4 index [FIB-4], elastography, FibroScan-AST [FAST] score), and/or non-invasive markers of liver steatosis evaluated either by imaging: controlled attenuation parameter (CAP), magnetic resonance imaging or spectroscopy (MRI/MRS) proton density fat fraction (PDFF), ultrasonography, or serologically: fatty liver index (FLI), hepatic steatosis index (HIS); (f) minimal sample size of 30 patients (total); (g) human studies.

The following were exclusion criteria: (a) lab-based feeding trials; (b) animal studies; (c) in vitro studies; and (d) other study designs.

Primary outcomes included surrogate markers of NAFLD (histological features and/or LFTs, and/or non-invasive assessment of liver fibrosis and steatosis) and secondary outcomes included total body weight loss (TBWL), waist circumference, quality of life, cardiometabolic parameters (blood pressure, lipid profile, cardiovascular risk) and glycated hemoglobin (HbA1C).

Two reviewers (AH, MA) independently assessed relevant studies for eligibility. The final study selection was reached by a mutual agreement between the two reviewers.

RESULTS

A total of 4374 studies were identified, 20 of which were duplicates. After title and abstract review, 241 studies were scanned for full-text review. The full-text review resulted in 61 studies, of which 10 were systematic reviews and meta-analyses used for checking reference lists. Finally, 51 studies were included in this narrative systematic review (Figure 1).

Table 1 outlines the characteristics and efficacy outcomes of different lifestyle interventions in NAFLD.

Table 2 depicts the characteristics and efficacy outcomes of different lifestyle interventions on liver histology in NAFLD patients.

Mediterranean diet (with or without calorie-restriction)

MD is characterized by a high intake of olive oil, vegetables, fruits, nuts, legumes, whole grains, fish, and seafood, while reducing the intake of red meat (mainly processed meat), added sugars, and refined carbohydrates characterized by a high glycemic index, all of which lower nutrients and fiber content resulting in low nutritional values.[81]

MD is designed to have a low intake of saturated fat versus a high intake of mono-unsaturated fat and omega-3 poly-unsaturated fat[28] (Figure 2a).

Due to the fact that weight loss achieved by a CR LFD (Figure 2A) along with exercise has been shown to provide resolution of NASH and even regression of fibrosis when TBWL is >10%,[18] several RCTs[30,43] have been conducted to compare the effects of the

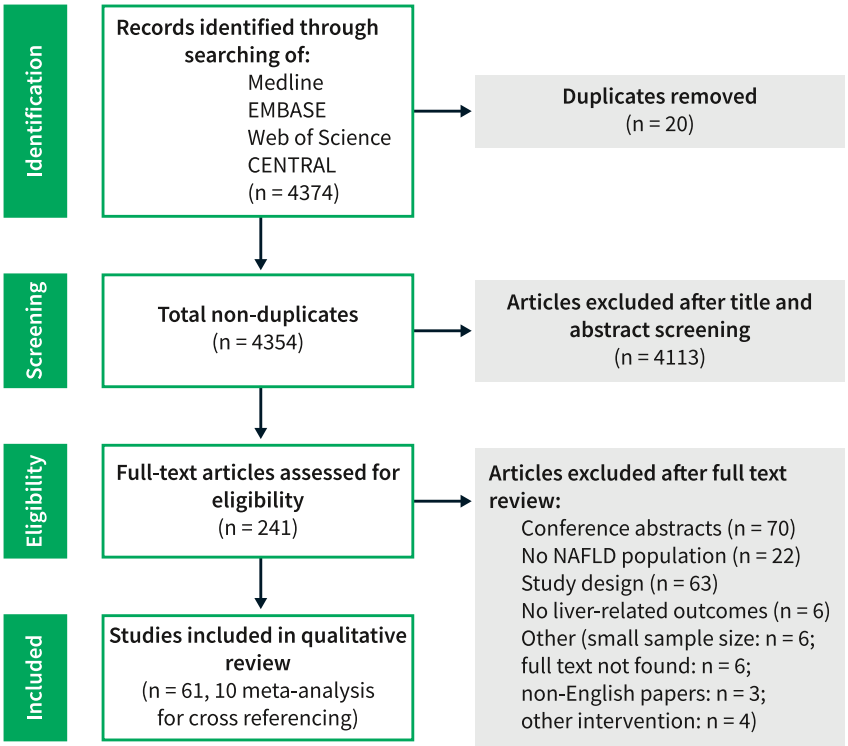

FIGURE 1 Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram.

two aforementioned diets in NAFLD patients. In two short-term RCTs[30,43] of 12-week dietary interventions (MD vs. LFD), no significant differences in terms of liver steatosis and metabolic outcomes between the two strategies were demonstrated. Hepatic steatosis (evaluated by MRS), was significantly reduced only in the LFD group in the MEDINA trial.[43] However, the Framingham risk score (a validated tool for evaluating 10-year cardiovascular risk[82]) was only significantly improved in the MD intervention, and there was a greater adherence to the MD compared with the LFD.[30]

In order to determine the long-term effect of these two interventions, an 18-month RCT[37] was performed among patients with central obesity ($N = 278$, 53% had NAFLD) assessing the effects on liver fat content and visceral adiposity of four different lifestyle modification strategies: (i) isocaloric LFD with/without moderate PA, and (ii) isocaloric MD-low carbohydrate (LC) diet with/without moderate PA. This study showed that, independent of weight loss, PA (with either diet) had a significantly greater effect on VAT, whereas the MD-LC diet was superior to LFD in terms of liver fat improvement. Similarly, studies[34,39,42] comparing the isocaloric MD diet to standard of care (healthy lifestyle advice) have also observed significant decreases in liver fat content, non-invasive markers of liver fibrosis, and LFTs.

Since CR plays a role in weight loss, personalizing the dietary pattern of an MD diet to ensure greater adherence and weight loss could be advantageous. In this regard, two RCTs[33,35] have recently assessed the influence of increasing meal frequency (7 meals/day) of a MD-LC calorie-restricted dietary intervention along with PA on liver surrogate outcomes in NAFLD patients. Although this intervention induced significant improvements in liver steatosis and LFTs, no significant difference was found between the higher meal frequency MD diet, the classic MD intervention (5 meals/day), and the control group who was advised to follow a healthy lifestyle diet. Several other studies[31,32,40,41] assessed CR MD diet strategies in the setting of NAFLD, and showed that this strategy was associated with improvements in non-invasive markers of liver fibrosis, steatosis, and LFTs.

On the other hand, it has been recently shown that polyphenol intake (abundant in food such as berries, nuts, coffee, tea, and whole grains) improves not only glucose and lipid metabolism[83,84] but also may have a protective effect on NAFLD.[85] The DIRECT plus RCT trial[36] assessed the effect of a green MD diet enriched with polyphenols (28 g/day of walnuts, 3–4 cups per day of green tea, 100 g per day of Mankai strain and a green shake) combined with PA on liver steatosis and liver function tests as compared to either a classic MD diet (with PA) or a control group following the standard of care. Both MD groups were restricted in processed and red meat. Two hundred and ninety-four patients (of which 62% had NAFLD) were included and followed for 18 months. The modified green MD diet led to greater hepatic fat loss (−38.9%) as compared to MD (−19.6%, $p = 0.035$) and the control group (−12.2%, $p < 0.001$), adjusted for weight loss. Interestingly, the following factors were independently associated with greater hepatic fat loss: high intake of Mankai and walnuts, reduction of red and

TABLE 1 Characteristics and main results of clinical trials testing the effects of different lifestyle interventions on liver outcomes.

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Mediterranean diet (MD)									
Properzi 2018, Australia[30]	RCT	48 11 (44%)	NAFLD	53	30.9	**Intervention:** MD, traditional Cretan diet (40% CHO, 20% PRO, 35%–40% FAT and <10% SFA). **Control:** Low fat/high CHO (LFD). Based on National Health and Medical Research Council and American Heart Association guidelines (50% CHO, 20% PRO, 30% FAT and <10% SFA).	**MD:** 750 g nuts and 750 mL olive oil. **LFD:** 1 kg natural muesli, 200 g low fat snack bars, every 4 weeks.	12 weeks	↓ HS (MRS-PDFF) ↓ ALT HS RR: −32.4% ± 25.5% versus −25% ± 25.3% (intervention vs. comparator) ns
Katsagoni 2018, Greece[31]	RCT	63 13 (61.9%)	NAFLD	44 (median)	31.7 (median)	**Intervention:** MD, based on MD pyramid and Greek guidelines (45% CHO, 20% PRO and 35% FAT). Counseling program, 7 × 60 min every 2 weeks for the first 2 months and every month for the next 4 months. **Comparator:** MLG: MD + optimal sleep (≥7 and ≤9 h/d) and moderate physical activity (30 min/day). Same counseling program as the intervention group. **Control:** Standard care (healthy lifestyle).	**Calorie restriction:** 1500 kcal/d (women); 1800 kcal/d (men). **Physical activity:** Moderate-vigorous intensity: Fast or very fast walking, slow or fast running, dancing, tennis.	6 months	↓ LSM (intervention/comparator vs. control) ↓ ALT (comparator vs. control)
Misciagna 2017, Italy[32]	RCT	98 34 (47.2%)	NAFLD	-	-	**Intervention:** MD based on traditional Cretan diet and low glycaemic index foods (≤10% SFA). Brochure was provided. **Control:** Standard care (healthy lifestyle). Based on INRAN guidelines.		6 months	NAFLD score: Negative interaction between time/intervention ↓ FLI and ALT

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Marin-Alejandre 2019, Spain[33]	RCT	98 23 (46%)	NAFLD	49.2	33.3	**Intervention:** FLIO-MD diet, higher meal frequency (7 meals/d) (40%–45% CHO, 25% PRO [mainly vegetable sources] and 30%–35% FAT). **Control:** Standard care (healthy diet lifestyle). Based on American Heart Association guidelines, 3–5 meals/d (50%–55% CHO, 15% PRO and 30% FAT).	**Calorie restriction:** 30% calorie less (both). **Dietary pattern,** FAT: Extra virgin olive oil and omega-3 fatty acids to the detriment of saturated and trans fats. **Physical activity:** 10,000 steps/d (both).	6 months	↓ HS, FLI, and ALT (both) ↓ AST (control) HS: −4.2% versus −3.6% (intervention vs. control) ns
Nourian 2020, Iran[34]	RCT	82 9 (27.3%)	NAFLD	49.4	32.3	**Intervention:** MD. Based on the health belief model (HBM). **Control:** Standard care.	**Physical activity:** General (MD). **Behavior change:** HBM (MD).	2 months	↓HS (intervention vs. control) ↓ ALT (intervention), AST (both) ↓ ALT and AST (intervention vs. control)
Abbate, 2021, Spain[35]	RCT	128 27 (60.8%)	NAFLD	52.3	34.3	**Intervention:** MD. Higher meal frequency (7 meals/d) (40%–45% CHO [low glycaemic index] 25% PRO [mainly veg PRO] and 30%–35% FAT [mainly MUFA and PUFA]). **Comparator:** MD physical activity group, meal frequency (4–5 meals/d) 35%–40% FAT (8%–10% SFA, >20% MUFA, >10% PUFA and >300 mg/day of cholesterol), 20% PRO, 40%–45% CHO low glycaemic index). **Control:** Standard care (healthy diet lifestyle). Based on AASLD guidelines (45%–65% CHO, 10%–35% PRO and 30%–35% FAT).	**Calorie restriction:** 25%–30% deficit (both). **Physical activity:** 10,000 steps/d (both).	6 months	↓ HS (intervention vs. control) ↓ ALT (both) ↓ AST (control) HS: (intervention: −6.6% vs. control: −4.9%)

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Yaskolka Meir 2021, Israel[36]	RCT	294 87 (88.8%)	Central obesity/ dyslipidaemia NAFLD (62%)	50.5	31.3	**Intervention:** Green MD (<40 g/d CHO then 80 g/day, ~40% FAT [PUFA and MUFA]) and polyphenol-rich products. Restriction on processed and red meat. Physical activity. **Comparator:** MD diet rich in vegetables, with poultry and fish replacing beef and lamb. **Control:** Standard care in addition to physical activity.	**Diet food:** 28 g/d walnuts (MD + MD green groups); 3–4 cups/d green tea and 100 g/d wolffia globosa (mankai strain) as green shake replacing dinner (MD green); lunch. **Calorie restriction:** 1200–1400 kcal/d (women); 1500–1800 kcal/d (men) (MD and Green MD groups). **Physical activity:** Aerobic/ resistance 45–60 min/3–4 d/week (all).	18 months	↓ HS (intervention vs. comparator/control) ↓ ALT (intervention/ comparator vs. control) ↓ AST (intervention/ comparator) Median HS: (intervention: −2% vs. comparator: −1.1% and control: −0.7%)
Gepner 2018, Israel[37]	RCT	278 12,589.9%	Central obesity/ dyslipidaemia NAFLD (53%)	47.4	30.9	**Intervention:** MD/low carbohydrate diet. <40 g/d CHO (2 months) then gradual increase ≤70 g/day with 1 polyphenol-rich product (from 3 m). **Comparator:** Low-fat/high CHO 30% FAT, ≤10% SFA and ≤300 mg/d cholesterol.	**Diet food:** 28 g/d walnuts (MD). **Physical activity:** 60 min/ month educational workshop. Aerobic/resistance 30–60 min/ 3 d/week (for those randomized after 6 months) (both).	18 months	↓ HS (intervention vs. comparator)
Mazzotti 2018, Italy[38]	CCT	716 186 (66.9%)	NAFLD	46	33.7	**Intervention:** MD Web-based intervention reproduces group sessions with interactive games, tests and mail contacts. **Comparator:** MD Group-based multi-disciplinary intervention. (5 × 120 min/ week sessions).	**Calorie restriction**: General (both). Physical activity (both). **Behavior change**: Motivational interviewing; stimulus control; and weight loss maintenance strategies (both).	24 months	↓ FLI, FIB-4 and ALT (both) ↓ FLI (intervention vs. comparator)
Dorosti 2020, Iran[39]	RCT	47 21 (44.7%)	NAFLD	43.1	32.5	**Intervention:** MD component Increased whole grain intake (≥1/2 of cereal servings/d). **Control:** Standard care (healthy diet lifestyle).	No advice on calorie allowances, physical activity or behavior changes (both).	12 weeks	↓ HS, ALT, and AST (intervention vs. control)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Shidfar 2018, Iran[40]	RCT	53 13 (61.9%)	NAFLD	46.1	29.6	**Intervention:** MD component Increased olive oil intake (20% of total fat). **Control:** Standard care (healthy diet lifestyle) All: 50% CHO, 20% PRO and 30% FAT.	**Calorie restriction**: Personalized calorie deficit (both). Olive oil dosage supplied (MD component).	12 weeks	↓ HS and AST (intervention) ↓ ALT (both) ↓ ALT and AST (intervention vs. control)
Rezaei 2019, Iran[41]	RCT	66 12 (37.5%)	NAFLD	46.3	30.6	**Intervention:** MD component Increased olive oil intake (20 g/d). **Comparator:** Increased sunflower oil intake (20 g/d). All: 50–55% CHO, 10%–15% PRO and 30%–35% FAT.	**Diet food:** Olive oil and sunflower oil dosages provided (both). **Calorie restriction:** 500 kcal/day deficit. **Physical activity:** Moderate intensity 30–40 min/day (both).	12 weeks	↓ HS and AST (both) ↓ ALT (comparator) ↓ HS (intervention vs. comparator)
Naimimohasses 2022, Iran[42]	CCT	50 7 (46.7%)	NAFLD	58	33.9	**Intervention:** MD, weekly group meetings. **Comparator:** Exercise, 3–5 aerobic exercise/week, increasing in number over time. Session's duration of 21–42 min. Supervised (2) and unsupervised sessions. **Control:** Standard of care.	**MD:** High fiber content, low glycaemic load CHO, and replacement of saturated fat with MUFA and PUFA. Increasing whole foods, fish, nuts/seeds, legumes, vegetables, and complex CHO, and reducing meat and processed foods. **AE:** Intensity of exercise 40%–75% HRR. Exercises on treadmills, cycle ergometers, and elliptical trainers.	12 weeks	↓ CAP (intervention and comparator) ↓ LS, FAST score and FIB-4 (all) ↓ ALT (all) ↓ AST (control and intervention)
George 2022, Australia[43]	RCT	42 8 (42%)	NAFLD	52.6	31.6	**Intervention:** Based on traditional Cretan diet. FAT 44% (>50% MUFA), 33% CHO, 15%–20% PRO and up to 5% from alcohol (<20 g/day). Three face to face visits (baseline, week 6 and 12) + 3 phone calls. **Comparator:** LFD based on the recommendations of Australian Dietary	**MD:** Hampers including extra virgin olive oil and nuts for the intervention duration, as well as canned fish and legumes, to model the diet and showcase examples of appropriate staple foods and a Mediterranean diet cookbook. **LFD:** Received $20 AUD Coles supermarket vouchers at each face-to-face	12 weeks	↓ IHL and LSM (ns between intervention and comparator)

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						Guidelines and the Heart foundation. FAT 30%, CHO 50%, PRO 20%. Three face to face visits (baseline, week 6 and 12) + 3 phone calls.	appointment to be spent on key staple foods outlined in the dietary recommendations.		
Ghetti 2019, Brazil[44]	RCT	40 12 (60%)	NASH	48.3	30.1	**Intervention:** Cal restricted dietary intervention. Based on American Dietetic Association guidelines and nutritional orientation (food guide Brazil) nutritional orientation + individualized diet. CHO: 47%, FAT: 28%, PRO: 25%. **Control:** Only nutritional orientation.	**Calorie restriction:** 500–750 kcal/d deficit	3 months	↓ ALT and AST (intervention) ↓ AST (intervention vs. control)
Marin-Alejandre 2021, Spain[45]	RCT	98 27 (54%)	NAFLD	49.2	33.3	**Intervention:** FLIO diet: CR of 30% of the total energy requirements, higher meal frequency (7 meals/d) 40%–45% CHO (low glycaemic index), 25% PRO (mostly from vegetable sources), 30%–35% FAT (extra virgin olive oil, omega-3 PUFA, low saturated and trans-fat). **Control:** 55% CHO, 15% PRO, 30% FAT (healthy fatty acid profile) based on the AHA guidelines.		6 months	↓ BW in intervention and control Secondary (↓ ALT, FLI, LSM in intervention)
Calorie restriction diet (CR)									
Wong, 2013, Hong Kong[46]	RCT	154 41 (52%)	NAFLD	51	25.5	**Intervention:** Calorie-restricted dietary intervention. Based on American Dietetic association guidelines.	**Calorie restriction:** General. **Physical activity:** Moderate intensity/resistance training 30 min/3–5 days/week.	12 months	↓ HS, LSM and ALT (intervention vs. control) HS: −6.7% ± 6.1% versus −2.1% ± 6.4% (intervention vs. control)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						Control: Standard care (healthy diet lifestyle).	**Behavior change:** Coping with risky situations.		
Dong 2016, China[47]	RCT	280 141 (100%)	NAFLD	56.7	26	**Intervention:** Calorie-restricted dietary 50%–60% CHO, 15%–20% PRO, 23%–30% FAT. Physical activity. Counseling by phone calls every 3 months. **Control:** Standard care (habitual diet). Physical activity. Counseling once/year.	**Calorie restriction:** BMI-dependent calorie balance (overweight, obese, 25–35 calories/kg/day; normal BMI 30–35 calories/kg/day) (calorie restricted). **Physical activity:** Moderate (60–80% of target HR)-vigorous (>80% of target HR) 30–60 min/3–4 days/week (calorie restricted).	2 years	↓ HS, ALT and FLI (intervention) (intervention vs. control) ↓ NFS, both
Promrat 2010, USA[48]	RCT	31 14 (66.7%)	NASH	48.9	33.9	**Intervention:** Cal-restricted dietary intervention. Based on American Heart Association; American Diabetic Association; American College of sports medicine, and fluid guide pyramid. Sessions every week for the first 6 months, then biweekly for months 7–12. **Control:** Standard care (healthy diet lifestyle) sessions every 12 weeks.	**Diet food:** Commercial portion-controlled foods (calorie restricted). **Calorie restriction:** 1000–1200 kcal/d <91 kg BW 1200–1500 kcal/d >91 kg BW (cal restricted). **Physical activity:** Moderate intensity 200 min/week. Unsupervised. **Behavior change:** Stimulus control, problem solving and relapse prevention (cal restricted).	48 weeks	↓ HS, NAS, and ALT (intervention vs. control) ↓ Ballooning injury and AST (both) HS: −1.1 ± 0.8% versus −0.3% ± 0.8% (intervention vs. control)
Cheng 2017, China[49]	RCT	115 7 (24.1%)	NAFLD	60	26.4	**Intervention:** Cal restricted dietary intervention. Fiber enriched diet + aerobic exercise (AED group). **Comparator:** AE group and diet groups. **Control:** Standard care (habitual diet).	**Diet food:** Lunch as 30%–40% of total energy intake/d (37%–40% CHO, 9–13 g fiber, 5 g soluble fiber, 25%–27% PRO, 35%–37% FAT) meals prepared at the canteen of Shangai University. **AE:** 2–3 times/week, supervised. (Nordic brisk walking + stretching) 30–60 min/session.	8.6 months	↓ HS (intervention) HS RR: −47.9% (AED), −24.4% (AE), −23.2% (diet group) and 20.9% (control)

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Johari 2019, Malaysia[50]	RCT	43 24 (72.7%)	NAFLD	45.3	31.6	**Intervention:** Modified alternate-day calorie restriction (MACR group). **Control:** Standard care (habitual diet).	**Calorie restriction:** Restrict 70% of their calorie requirements between 2 and 8 p.m. (on fast days) and ad libitum (on non-fast days).	8 weeks	↓ HS, LSM, ALT and AST (intervention) ↓ HS, LSM and ALT (intervention vs. control)
Shojasaadat 2019, Iran[51]	RCT	114 19 (45.7%)	NAFLD	41	31.7	**Intervention:** Low energy diet intervention. 52% CHO, 18% PRO, and 30% FAT. **Comparator:** N-3 PUFA, 2500 mg/d fish oil. **Control:** Standard care (habitual diet).	**Calorie restriction:** 350–700 kcal/d deficit.	12 weeks	↓ AST (intervention)
Atefi 2022, Iran[52]	RCT	60 0	NAFLD	38.9	30.9	**Intervention:** CR (500 kcal less) and sesame oil. CHO: 50%–55%, PRO: 14%–18%, FAT: 27%–32%. **Control:** CHO: 50%–55%, PRO: 14%–18%, FAT: 27%–32%, hypocaloric diet and sunflower oil.	**Dietary pattern:** 30 g of oil/day.	12 weeks	↓ Fatty liver grade (both) (intervention vs. control)
Asghari 2022, Iran[53]	RCT	60 20 (67%)	NAFLD	40.1	31.3	**Intervention:** CR, 500–1000 kcal based on BW. CHO: 53%, PRO: 17%, FAT: 30%. **Control:** Healthy eating, according to the food guide pyramid and the Obesity Education Initiative Expert Panel.		12 weeks	↓ ALT and AST only in intervention
Arefhosseini 2011, Iran[54]	RCT	44 12 (54.5%)	NAFLD	38	28.9	**Intervention:** 500 kcal deficit, CHO: 55%, FAT: 25%, PRO: 25%. **Comparator:** 500 kcal deficit, CHO: 40, FAT: 40, PRO: 20.			↓ Of grade of hepatic steatosis (both)
Garousi 2021, Iran[55]	RCT	80 15 (40.5%)	NAFLD	43.5	32	**Intervention:** 500 kcal deficit, lacto-ovo-vegetarian diet (LOV-D).	**LOV-D:** Restraining in the consumption of meat and meat products, poultry, fish	3 months	↓ ALT, AST (both) (intervention vs. control)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						CHO: 50%–55%, PRO: 15%–20%, FAT: 25%–30%. **Control:** CHO: 50%–55%, PRO: 15%–20%, FAT: 25%–30%. Based on the food pyramid.	and seafood, and flesh of any other animal. Included protein sources from egg (24%), dairy (19%), gluten (26%), soy (16%), nuts (8%), vegetables, and fruits (7%). **Control:** 18% of protein sources from meat and meat products, poultry, fish and seafood, and flesh of any other animal.		
Wong 2018, Hong Kong[56]	RCT	77 BMI <25: 23 (59%) BMI >25: 16 (42%)	NAFLD	BMI <25: 50.8 BMI >25: 51.7	-	**Intervention:** Reducing calorie intake and increasing energy expenditure. Individual education at 2 community centers, 1 session/week during the first 4 months then monthly. Exercise instructor designed a suitable exercise regime. **Control:** Routine care. Advises to reduce fat and CHO intake, and to exercise 3 times/week (30 min of session).		12 months	Remission of NAFLD (IHTG, H-MRS) Non obese (67% vs. 18%) Obese (61% vs. 21%) (intervention vs. control)
Time-restricted eating (TRE)									
Cai 2019, China[57]	RCT	271 29 (69.5%)	NAFLD	33.6	26.8	**Intervention:** Alternate-day fasting (ADF), fast day (24 H): 25% of the baseline energy needs, based on the American Heart Association guidelines (30% kcal from FAT, 15% kcal from PRO, 55% kcal from CHO). **Comparator:** TRE, 16 h of fasting (food and beverages that included energy).	No physical activity or behavioral advice provided.	12 weeks	No change in LSM (both)

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						Control: 80% of their energy need without any advice or restrictions on their usual lifestyle patterns.			
Varkaneh HK 2022, Iran[58]	RCT	52 12 (57.1%)	NAFLD	46.4	30.4	**Intervention:** 5:2 diet, 5 days normal food, 2 consecutive days fasting. On fasting days, 25% of recommended calorie intake from 12–2 p.m. (30% FAT, 15% PRO, 55% CHO). **Control:** 30% FAT, 15% PRO, 55% CHO.		12 weeks	↓ ALT (both, intervention vs. control) ↓ AST GGT (intervention) ↓ CAP (both) (intervention vs. control) ↓ Fibrosis score (intervention) (intervention vs. control)
Mari 2021, Israel[59]	CCT	155 39 (52.7%)	NAFLD	51.8	36.7	**Intervention:** Ramadan fasting. **Control:** No fasting.		4 weeks	↓ NFS
Low carbohydrate (LCH)—Low fat diet (LFD)									
Jang 2018, South Korea[60]	RCT	106 LCH: - LFD: -	NAFLD	LCH: 43.6 LFD: 42.4	LCH: 27.3 LFD: 27.1	**Intervention:** LCH: 25 kcal/kg of ideal BW, 50%–60% CHO, 20%–25% PRO, 20%–25% FAT. **Comparator:** LFD: 25 kcal/kg of ideal BW, 60%–70% CHO, 15%–20% PRO, 15%–20% FAT.	Booklet with informations regarding calorie intake, macronutrient composition and specific food consumption patterns was proposed.	8 weeks	↓ ALT (both, significant greater reduction with LCH) ↓ Liver/spleen ratio (greater reduction with LCH)
Kani AH 2014, Iran[61]	RCT	45 7 (46.7%)	NAFLD	48.5	31.3	**Intervention:** CR-LCH + soy, 30 g of soy nut instead of 30 g of red meat. **Comparator:** CR-LCH, 45% CHO, 35% FAT, 20% PRO. **Control:** Low calorie diet, CR, 300–500 kcal deficit according to the BMI. 55% CHO, 15% PRO, 30% FAT.	Moderate daily physical activity of 30 min	8 weeks	↓ ALT (all)
Eckard 2013, USA[62]	RCT	56 6 (50%)	NAFLD (biopsy-proven)	44	32.7	**Intervention:** LFD with moderate exercise (FAT 20%, 60% CHO, 20% PRO). **Comparators:**	Supplemental materials were provided to patients with healthy cooking, grocery shopping, and dining out.	6 months	↓ NAS score (ns for control)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						a) Moderate fat low processed carbohydrate diet (30% FAT, 50% CHO, 20% PRO) b) Moderate exercise only. **Control:** Standard care.	Received a set of measuring cups and spoons and were also instructed on estimating portion sizes using the MyPyramid serving size guidelines. Physical activity (intervention, a) and b)): Exercise program, based on FITT (frequency, intensity, time and type) principles. 20–60 min, 4–7 days/week in a supervised environment.		
Razavi 2016, Iran[63]	RCT	60 15 (50%)	NAFLD	39.7	28.5	**Intervention:** CR-DASH diet, 350–700 kcal less based on the BMI, 52%–55% CHO, 16%–18% PRO, 30% FAT. **Control:** Calorie restricted, 52%–55% CHO, 16%–18% PRO, 30% FAT.	**Dietary pattern:** DASH diet rich in fruits, vegetables, whole grains, and low-fat dairy products and low saturated fats, cholesterol, refined grains and sweets. Sodium <2400 mg/d.	8 weeks	↓ Grade of fatty liver (control and intervention) ↓ ALT (intervention) (intervention vs. control)
Sun 2012, China[64]	RCT	1087 464 (64.1%)	NAFLD	39.9	37.7	**Intervention:** Low fat diet: CHO: 55%, 30% FAT, 15% PRO. No calorie restriction. Physical activity. **Control:** Basic education about NAFLD and principles of healthy eating, physical activity and weight control.	**Physical activity:** Walking, jogging, stair climbing.	12 months	↓ ALT
Sun 2022, China[65]	RCT	63 19 (65.5%)	NAFLD	39.8	28.6	**Intervention:** HPLG: PRO 40%–45%, CHO 20%–25%, FAT 30%–35% with restricted energy content. **Control:** 10%–20% PRO, CHO 50%–65%, FAT 20%–30%, same energy restriction.		12 weeks	↓ CAP (both) (intervention vs. control)
Rodriguez-Hernandez 2011, Spain[66]	RCT (not controlled)	59 0	NAFLD	46.3	38.7	**Intervention:** LCD, PRO 27%, FAT 28%, CHO 45%		6 months	↓ ALT (both)

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						Comparator: LFD 21% FAT, <10% saturated fat, 25% PRO, 54% CHO			
Internet-based approaches									
Vilar-Gomez 2019, USA[67]	CCT	349 87 (33.2%)	NAFLD	53.8	40.4	**Intervention:** Comprehensive continuous care intervention (CCI), encouraging nutritional ketosis. **Control:** Usual care based on the American Diabetes Association recommendations.	**CCI:** Remote personal health coach and medical providers, either on site or via web-based educational content.	12 months	↓ N-LFS (intervention) ↓ NFS (intervention vs. group)
Physical activity approaches									
Zelber-Sagi 2014, Israel[68]	RCT	82 16 (48.5%)	NAFLD	46.3	30.8	**Intervention:** Resistance training (3 times weekly) based on the ACSM 2009 position paper on "progression models in resistance training for healthy adults" in a community setting. Load was gradually increased by 2%–10% in the following training sessions according to the patient's ability. Patients received a comprehensive booklet. They were advised no to perform aerobic training. **Control:** Home stretching. Patients received a comprehensive booklet.	**Resistance training:** Leg press, leg extension, leg curl, seated chest press, seated rowing, latissimus pull down, biceps curl and shoulder press with 8–12 repetitions, three sets for each exercise with 1–2 min rest between sets, for a total duration of about 40 min. Phone call every 2 weeks. **Control:** The program included eight stretching exercises for the major muscle/tendon groups using the static stretching technique. The participants performed four repetitions of these static stretches each lasting 20 s. Each session was performed on three non-consecutive days a week.	3 months	↓ Liver steatosis (intervention vs. control)
Abdelbasset 2019, Saudi Arabia[69]	RCT	32 10 (62.5%)	NAFLD	54.4	36.3	**Intervention:** High-intensity interval (HII). High intensity aerobic exercise,	**HII:** Performed on a cycle Ergometer. Five minutes warm-up followed by three sets of 4-min cycling	8 weeks	↓ IHTG (MRI)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						3 times/week. Session of 40 min. **Control:** No exercise program.	sessions at 80%–85% of the VO_2 max with 2-min interval at 50% of the $VO_{2\ max}$ between sets.		
Bacchi 2013, Italy[70]	RCT	40 12 (70.6%)	NAFLD	56	28.8	**Intervention:** Resistance training (RT): Three series of 10 repetitions at 70%–80% 1-RM, with 1 min of recovery between series. Performed at the university setting. **Comparator:** Aerobic exercise training (AE): Sessions of 60 min at 60%–65% of heart rate. **All:** Nutritional follow-up. Maintenance of baseline calorie intake.	**RT:** Chest press, shoulder press, vertical traction, leg press, leg extension, leg curl, abdominal crunch. Performed at the university setting. **AE:** Activities such as treadmill, cycle, or elliptical machines.	4 months	↓ hepatic fat (both)
Rezende 2016, Brazil[71]	RCT	40 0	NAFLD	56.2	31.1	**Intervention:** Exercise training. Supervised aerobic exercise training twice/week. Sessions of 30–50 min with increase in exercise duration every 8 weeks. **Control:** No exercise. All: Standardized diet, calorie deficit of 500 kcal/d, 35% PRO, 25% FAT and 40% CHO.	**Exercise training:** Treadmill aerobic exercise.	24 weeks	No significant decrease of liver fat
Zhang 2016, China[72]	RCT	220 21 (28.8%)	NAFLD	53.2	27.9	**Intervention:** Vigorous (5 sessions/week)-moderate exercise. Six months vigorous exercise program and 6 months moderate exercise program (5 sessions/week). Supervised. **Comparator:** Moderate exercise. Supervised.	**Vigorous-exercise:** Treadmill and gradually increased intensity to 35%–80% of their maximum predicted HR. Session of 30 min. **Moderate-exercise:** Walking 120 steps/min of 45%–55% of their maximum predicted HR. Session of 30 min.	12 months	↓ IHTG (intervention, comparator vs. control) No significant difference between intervention and comparator

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						Control: No exercise. Attendance to group health education sessions.	**Intervention and comparator:** Behavioral component on adherence to exercise programs. **All:** Group health education sessions (general health knowledge of NAFLD, smoking cessation, and elements of a healthy lifestyle).		
Abd El-Kader 2016, Saudi Arabia[73]	RCT	100 34 (68%)	NAFLD	50.8	32.4	**Intervention:** Aerobic exercise (AE) training program and diet regimen. Three sessions (30 min)/week. Based on the recommendations of Aerobic College of Sports medicine. Low calorie diet: PRO 15%, 30%–35% FAT, 50%–55% CHO, ~1200 kcal/d **Control:** Ordinary current lifestyle.	**AE:** Treadmill-based training program at 65%–75% of the maximum heart rate.	3 months	↓ ALT, AST (only intervention)
Cuthbertson 2016, UK[74]	RCT	69 23 (76.7%)	NAFLD	50	30.6	**Intervention:** Supervised exercised. Three times/week 30 min moderate (30% HRR) aerobic exercise (AE). **Control:** Counseling.	**AE:** Treadmill, cross-trainer, bike ergometer, rower.	16 weeks	↓ IHTG (intervention vs. control)
Shamsoddini 2015, Iran[75]	RCT	30 10 (100%)	NAFLD	45.9	30.6	**Intervention:** Resistance training (RT), 3 times/week of 45 min session. Supervised. **Comparator:** Aerobic program (AE), 3 times/week of 45 min session. **Control:** No exercise training.	**RT:** Triceps press, biceps curl, calf raise, leg press, leg extension, lat pull down and sit-ups. **AE:** Stretching movements + slowly running on treadmill (warm up). Training phase: 2 × 15 min running on treadmill at 60% of maximal heart rate, increased to 75% MHR the following weeks.	8 weeks	↓ hepatic fat in intervention and comparator

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
Takahashi 2015, Japan[76]	CCT	53 9 (29%)	NAFLD	55.5	28.5	**Intervention:** Resistance training (RT). Session of 20–30 min 3 times/week. **Control:** Education about dietary restrictions and encourage to participate in regular physical activities according to the American gastroenterological association for NAFLD and the physical activity of health promotion guidelines recommended by the ministry of health, labor and welfare of Japan.	**RT:** Push-ups (3 sets of 10) + squats (3 sets of 10).	12 weeks	↓ ALT, hepatic steatosis (only intervention)
Oh 2021, Japan[77]	CCT	45 24 (100%)	NAFLD	49.7	28.1	**Intervention:** Aerobic exercise (AE) program. Sessions of 90 min, 3 days/week. Supervised. **Comparator:** Restriction calorie intake to 1680 kcal/day. Sessions of 90 min once/week by registered dietician. Advises regarding daily physical activity.	**AE:** Incremental increase over the time. Fast walking and/or light jogging.	3 months	↓ Liver steatosis, liver stiffness, FAST score
Nath 2020, India[78]	CCT	37 18 (100%)	NAFLD	37.3	26.9	**Intervention:** Moderate intensity exercise group (AE). Session of 50–60 min, 5–6 sessions/week. MET between 3 and 5.9. **Comparator:** Low intensity exercise group (AE). MET <3.	**AE:** Walking, jogging, marching drill, "lathi drill," and yoga.	6 months	↓ ALT, AST (only significant in the intervention group)
OH 2017, Japan[79]	RCT	61 19 (100%)	NAFLD	51.2	27.2	**Intervention:** Resistance training (RT), based on the ACSM 2009 position paper on "progressive models in	**RT:** Sit-ups, leg presses, leg extensions, leg curls, chest presses, seated rows and pull downs.	12 weeks	↓ Liver fat in intervention and comparators. ↓ Liver stiffness but only in HIAT exercise regimen.

(Continues)

TABLE 1 (Continued)

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/control groups	Intervention characteristics	Intervention duration	Primary outcome
						resistance training for healthy adults." **Comparator:** a) HIAT, high-intensity interval aerobic training, b) MICT, moderate-intensity continuous aerobic training.	**HIAT:** Three sets of 3-min cycling sessions at 80%–85% VO_2 max with a 2 min active rest at 50% VO_2 max between sets. **MICT:** 40 min of cycling at 60%–65% VO_2 max (40 min, 360 kcal).		
Babu 2022, Finland[80]	RCT	46 7 (53.8%)	NAFLD	59.9	29.7	**Intervention:** HIIT, high-intensity interval training. Twice/week. Session of 40 min with incremental increase to 50 min. Supervised sessions. Individualized exercise training program was prescribed for home (low to moderate intensity aerobic exercise). **Control:** Sedentary lifestyle. **All:** Diet habits unchanged.	**HIIT**: Five bouts of 2–4 min work intervals (at 85% of max W4) interspersed by 3 min of active recovery.	12 weeks	No change regarding liver outcomes.

Note: Number of males, mean age and BMI are data related to the intervention group.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, australian dollars; BW, body weight; CAP, controlled attenuated parameter; CCT, clinical controlled trial; CHO, carbohydrate; FAST score, Fibroscan-AST score; FIB-4, fibrosis-4 index; FLI, fatty liver index; HS, hepatic steatosis; IHL, intrahepatic lipid content; IHTG, intrahepatic triglyceride; LS, liver stiffness; LSM, liver stiffness measurement; MLG, Mediterranean lifestyle group; MRS-PDFF, magnetic resonance-spectroscopy-measured proton density fat fraction; MUFA, monounsaturated fat; NAFLD, non-alcoholic fatty liver disease; NAS, non-alcoholic fatty liver disease activity score; NFS, NAFLD fibrosis score; N-LFS, NAFLD liver fat score; ns, non-significant; PRO, protein; PUFA, polyunsaturated fat; RCT, randomized controlled trial; RR, relative reduction; SFA, saturated fat.

TABLE 2 Characteristics of the studies and effects of different lifestyle interventions on liver histology in NAFLD patients.

Author	Design	Sample size Male *n* (%)	Group	Mean age (years)	Mean BMI (kg/m^2)	Intervention and comparator/ control groups	Intervention characteristics	Intervention duration	Primary outcome
Calorie restriction diet (CR)									
Promrat 2010, USA[48]	RCT	31 14 (66.7%)	NASH	48.9	33.9	**Intervention:** Cal-restricted dietary intervention Based on American Heart Association; American Diabetic Association; American College of sports medicine, and fluid guide pyramid. Sessions every week for the first 6 months, then biweekly for months 7–12. **Control:** Standard care (healthy diet lifestyle) sessions every 12 weeks	**Diet food:** commercial portion-controlled foods (calorie restricted) **Calorie restriction:** 1000–1200 kcal/d < 91 kg BW 1200–1500 kcal/d > 91 kg BW (cal restricted) **Physical activity:** Moderate intensity 200 min/week. Unsupervised **Behavior change:** Stimulus control, problem solving and relapse prevention (cal restricted)	48 weeks	↓ HS, NAS, and ALT (intervention vs. control) ↓ ballooning injury and AST (both) HS: −1.1 ± 0.8% versus −0.3% ± 0.8% (intervention vs. control)
Low carbohydrate (LCH)—Low fat diet (LFD)									
Eckard 2013, USA[62]	RCT	56 6 (50%)	NAFLD (biopsy-proven)	44	32.7	**Intervention:** LFD with moderate exercise (FAT 20%, 60% CHO, 20% PRO) **Comparators:** a) Moderate fat low processed carbohydrate diet (30% FAT, 50% CHO, 20% PRO) b) Moderate exercise only. **Control:** Standard care	Supplemental materials were provided to patients with healthy cooking, grocery shopping, and dining out. Received a set of measuring cups and spoons and were also instructed on estimating portion sizes using the MyPyramid serving size guidelines Physical activity (intervention, a) and b)): Exercise program, based on FITT (frequency, intensity, time and type) principles. 20–60 min, 4–7 days/week in a supervised environment.	6 months	↓ NAS score (ns for control)

Note: Number of males, mean age and BMI are data related to the intervention group.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; CCT, clinical controlled trial; CHO, carbohydrate; HS, hepatic steatosis; NAFLD, non-alcoholic fatty liver disease; NAS, non-alcoholic fatty liver disease activity score; PRO, protein; RCT, randomized controlled trial.

(a)

Dietary strategies in NAFLD				
Low fat diet	**Low carbohydrate diet**	**Ketogenic diet**	**Time restricted eating**	**Mediterranean diet**
Carbohydrate, % **60%**	Carbohydrate, % **25%**	Carbohydrate, % **10%**	Carbohydrate, % **40%**	Carbohydrate, % **40%**
Fat, % **20%**	Fat, % **35%**	Fat, % **55%**	Fat, % **40%**	Fat, % **40%**
Protein, % **20%**	Protein, % **40%**	Protein, % **35%**	Protein, % **20%**	Protein, % **20%**

(b)

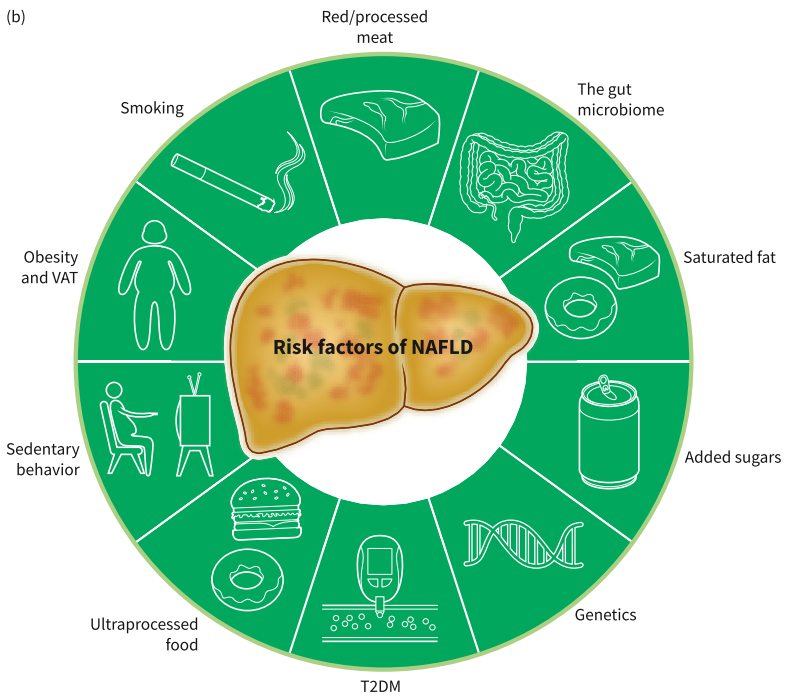

FIGURE 2 Macronutrient distribution of different dietary interventions and modifiable and non-modifiable risk factors of NAFLD onset and progression. Macronutrients are presented as percentages of total energy intake. We recommend that the macronutrient distribution of the time-restricted eating be in accordance with the Mediterranean diet, but this can vary. The modifiable and non-modifiable risk factors of NAFLD onset and progression should be taken into consideration in any dietary strategy chosen. (A) Dietary strategies in NAFLD. (B) Risk factors of NAFLD. NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue. *Source*: Figures created with BioRender.com.

processed meat consumption, improved serum folate and adipokine/lipid biomarkers, changes in the microbiome composition (beta-diversity), and specific bacteria ($p < 0.05$ for all).

Lastly, a comprehensive CR MD web-based structured motivational program[38] implemented for 24 months did not seem to be inferior to a group-based MD intervention (5 weekly meetings) in terms of reduction of liver fibrosis (FIB-4) and steatosis (FLI). This strategy is likely more suited and tailor-made for younger patients.

Calorie restriction

Numerous studies[44–56] have evaluated the effect of a CR diet with or without PA on NAFLD. In most of these studies, the CR consisted of a 500–1000 kcal deficit of total energy requirements and was usually adjusted to body weight. Although the studies were heterogeneous regarding intervention and outcome assessment modalities, there was compelling evidence supporting a dose-response relationship

between the degree of CR and improvements in liver histological features and weight loss.

Time-restricted eating

Intermittent fasting (IF) is deemed to be associated with several positive metabolic benefits by depleting the body's glycogen stores and activating lipolysis within adipocytes. Consequently, several signaling pathways are activated (such as peroxisome proliferator activated receptor alpha [PPAR-α] and activating transcription factor 4 [ATF4]), resulting in improvement in insulin resistance and inhibition of hepatic lipogenesis.[86–89] Different modalities of IF exist daily time-restricted feeding regimen (TRF) (18-h fasting period and 6-h eating period), alternate-day fasting (ADF) (24-h of fasting at 25% of baseline energy), and the 5:2 intermittent regimen, which consists of fasting 2 days a week (intake of 500 calories). The effect of an ADF regimen in NAFLD patients has been compared to TRF (16 h of fasting) and a control group where patients consumed 80% of their daily energy requirement.[57] After 12 weeks, both ADF and TRF were associated with a reduction in weight, fat mass, and serum triglycerides. However, there was no change in terms of liver stiffness, albeit, regression of liver fibrosis usually occurs at later stages. Conversely, the 5:2 intermittent regimen also administered for a short-term (12 weeks)[58] induced reductions in liver stiffness and steatosis as compared to a control group (standard of care), but similar to a LCD following an equal weight reduction of about 7 kg. Similar findings were found in a retrospective comparative study comparing NAFLD patients who had fasted during Ramadan to a control group.[59] These discrepancies regarding liver fibrosis could be explained by the fact that these studies used surrogate endpoints of liver fibrosis (liver stiffness or NAFLD fibrosis score) and, therefore, a reduction does not particularly correlate with histological fibrosis stage reduction if the value is still within the same cut-off range.

Low carbohydrate diet-Low fat diet

Several studies[60–66] sought to compare the effectiveness of LCD and LFD (Figure 2A) on surrogate liver outcomes for NAFLD. Similar to time-restricted eating studies, most of these studies were of short-term course and LCD seemed to be superior to LFD in terms of liver fat reduction and LFTs, adjusted for equal weight loss. Nevertheless, these studies presented several drawbacks such as small sample size, various LCD dietary type compositions, and different modalities for assessing liver fat content, making it difficult to draw any convincing conclusions. Results from a long-term study[66] comparing LCD to LFD diets showed a decrease in ALT in both interventions. This was also confirmed by a recent meta-analysis showing that there was no significant difference between the LCD and LFD diets on liver fat reduction and LFTs in NAFLD patients.[90]

Very low carbohydrate ketogenic diet

Very low carbohydrate ketogenic diet (Figure 2A) (VLCKD) is characterized by a low intake of carbohydrates (<10% of total daily energy, <20–50 g/day), 1.2–1.5 g of protein/kg of ideal body weight (hence preserving lean body mass), and a high fat macronutrient composition (70%–80% of total daily energy).[91] A few short and small studies[92,93] have evaluated the effect of VLCKD on NAFLD compared with a standard CR diet and found significant reductions in liver fat content. Despite the substantial weight loss induced in a short-term course by this type of dietary approach, its long-term maintenance is not sustainable or recommended due to the lack of long-term data on efficacy and safety.

DISCUSSION

NAFLD is likely a result of the interplay between genetic predisposition, and environmental, behavioral, and health factors including diet, T2DM, and obesity (Figure 2B).[94,95] Compelling evidence suggests that overconsumption of added sugars (especially fructose containing sugars),[96,97] and saturated fat,[98,99] or specific foods such as processed/red meat,[100] ultra-processed food,[101] and sugar sweetened beverages is associated with an increased risk of developing NAFLD. In addition, sugar-sweetened beverage consumption is strongly linked to the risk of hepatocellular carcinoma.[102,103]

Since dietary pattern and composition drive NAFLD development, different dietary strategies, highlighted in this review, have been studied in order to determine which approach could be more beneficial in NAFLD patients. To date, the most studied dietary intervention is the MD diet, which combines moderately reduced intake of carbohydrates and minimal consumption of added sugars, and has been found to be achievable and acceptable by patients.[104] However, despite the convincing results of MD diet effectiveness on surrogate markers of NAFLD, the impact of this dietary strategy on liver histological features as well as clinical outcomes of NAFLD still needs to be addressed. Furthermore, economical, geographical, and cultural barriers[105] could jeopardize adherence to this dietary intervention, which emphasizes the importance of personalizing our approach to not only the patient's needs but also their socioeconomic status. Ultimately, as previously mentioned, CR and increased energy expenditure remain the cornerstones of NAFLD treatment. Therefore, the approach of lifestyle modification should be holistic (Figure 3A), encompassing recommendations regarding dietary pattern and composition but also promoting PA[106] and behavioral strategies to ensure greater adherence and benefits in terms of mortality. In this regard, comprehensive structured web-based programs maintaining NAFLD awareness[38,67] (Figure 3B) could not only be an asset for managing attrition, and hence, adherence, but also a way to reduce cost and health care resource utilization. Some patients will find web-based interventions convenient and some patients will need the in-person interventions or a

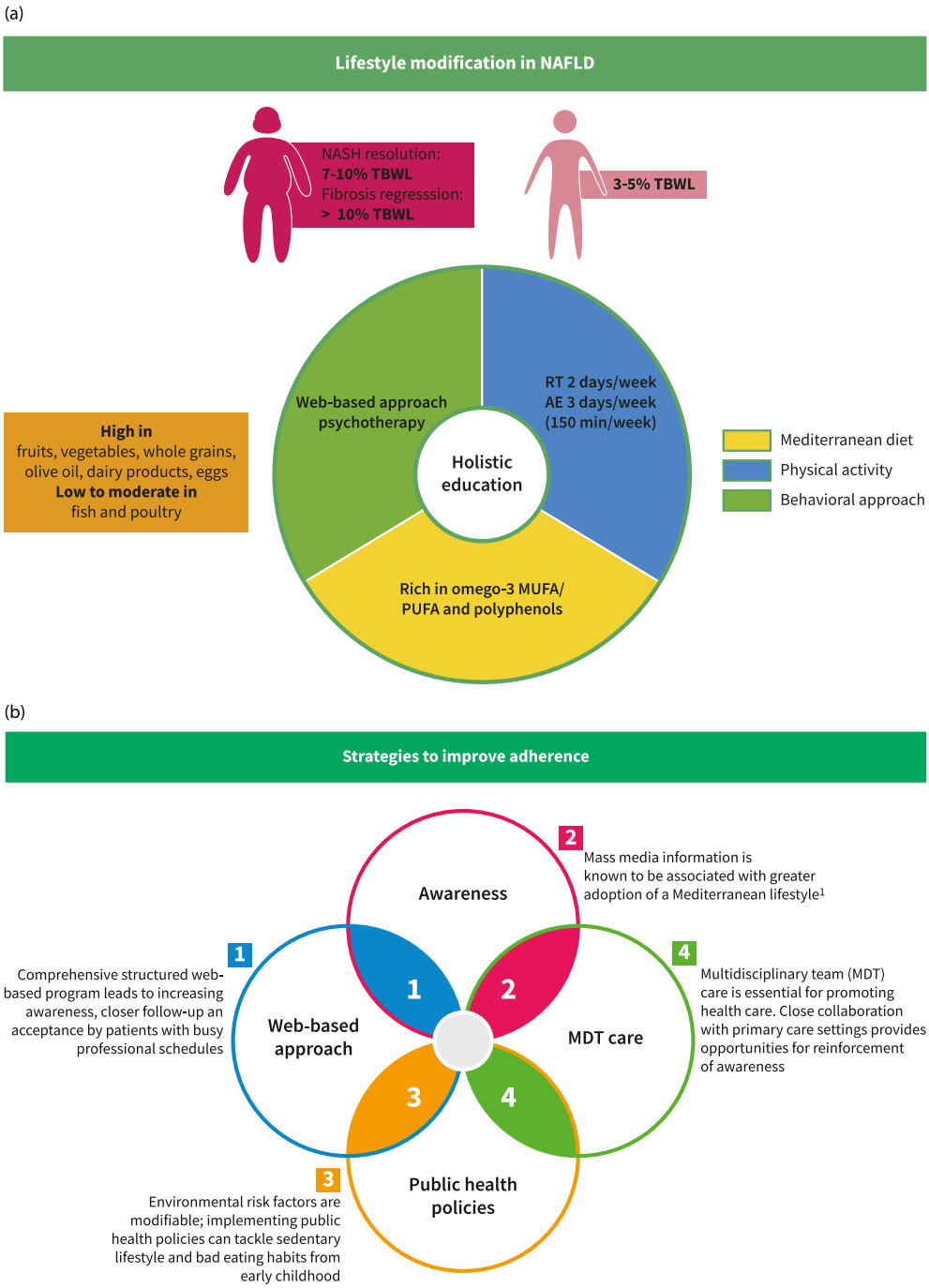

FIGURE 3 Holistic education in NAFLD and strategies to improve adherence. (A) Holistic education in NAFLD and strategies to improve adherence. (B) Strategies to improve adherence. AE, aerobic exercise; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PUFA, polyunsaturated fatty acid; RT, resistance training; TBWL, total body weight loss.

combination of both. Other actions for increasing compliance to lifestyle modification are summarized in Figure 3B.

PERSPECTIVES AND CONCLUSION

Since NAFLD is a chronic disease requiring life-long therapy, there are several unmet needs to address in order to better characterize an effective diet and lifestyle intervention in NAFLD patients. Considering that NAFLD is a heterogeneous disease, patient stratification is crucial for establishing a personalized and tailored dietary approach. Nutrigenomics and nutrigenetics could be a promising tool to decipher the effect of different dietary strategies on the modulation of different NAFLD variants.[107] Additionally, more robust data are needed in the assessment of dietary intake and in the characterization of the interventions associated with greater adherence. Long-term longitudinal studies will likely help to fill these knowledge gaps.

In conclusion, lifestyle modification comprising CR, increased PA, and changes in dietary composition remain the cornerstones of NAFLD management. Since most dietary and sedentary lifestyle environmental risk factors are modifiable, health policies are essential to tackle obesity, unhealthy eating, and sedentary lifestyle. Finally, multidisciplinary care teams led by primary care healthcare providers should be implemented in order to provide to best structured care to NAFLD patients.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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