Received: 23 April 2021 | Revised: 6 July 2021 | Accepted: 10 July 2021

DOI: 10.1111/liv.15024

REVIEW

Liver INTERNATIONAL WILEY

Diet and exercise in NAFLD/NASH: Beyond the obvious

Georg Semmler[1] | Christian Datz[2] | Thomas Reiberger[1] | Michael Trauner[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[2]Department of Internal Medicine, General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Salzburg, Austria

Correspondence
Michael Trauner, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.
Email: michael.trauner@meduniwien.ac.at

Editor: Luca Valenti

Abstract

Lifestyle represents the most relevant factor for non-alcoholic fatty liver disease (NAFLD) as the hepatic manifestation of the metabolic syndrome. Although a tremendous body of clinical and preclinical data on the effectiveness of dietary and lifestyle interventions exist, the complexity of this topic makes firm and evidence-based clinical recommendations for nutrition and exercise in NAFLD difficult. The aim of this review is to guide readers through the labyrinth of recent scientific findings on diet and exercise in NAFLD and non-alcoholic steatohepatitis (NASH), summarizing "obvious" findings in a holistic manner and simultaneously highlighting stimulating aspects of clinical and translational research "beyond the obvious". Specifically, the importance of calorie restriction regardless of dietary composition and evidence from low-carbohydrate diets to target the incidence and severity of NAFLD are discussed. The aspect of ketogenesis—potentially achieved via intermittent calorie restriction—seems to be a central aspect of these diets warranting further investigation. Interactions of diet and exercise with the gut microbiota and the individual genetic background need to be comprehensively understood in order to develop personalized dietary concepts and exercise strategies for patients with NAFLD/NASH.

KEYWORDS

diet, lifestyle, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, nutrition, physical activity

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) may present as "simple" steatosis or with a potentially progressive inflammatory phenotype of non-alcoholic steatohepatitis (NASH) that can progress to cirrhosis and/or hepatocellular cancer, thus being expected to become the leading cause of liver-related morbidity and mortality.[1] Since no drug has yet been approved specifically for the treatment of NASH and/or associated cirrhosis,[2] dietary interventions and physical activity (PA) and exercise are generally regarded the cornerstones of NAFLD/NASH treatment. These interventions might be specifically effective to target the "triple hit" of modern-day lifestyle

Abbreviations: β-OHB, β-hydroxybutyrate; AcAc, acetoacetate; ADF, alternate day fasting; BW, body weight; DNL, de-novo lipogenesis; FA, fatty acid; FGF-21, fibroblast growth factor 21; HCC, hepatocellular carcinoma; HCD, high-carbohydrate diet; HFCS, high-fructose corn syrup; HFD, high-fat diet; ICR, intermittent calorie restriction; IHLC, intrahepatic lipid content; IR, insulin resistance; KD, ketogenic diet; LCD, low-carbohydrate diet; LFD, low-fat diet; LSM, liver stiffness measurement; MED, Mediterranean diet; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NEFA, non-esterified fatty acids; PA, physical activity; PPARα, peroxisome proliferator-activated receptor α; PUFA, polyunsaturated fatty acid; RCT, randomized controlled diet; SSB, sugar-sweetened beverages; TCA, tricarboxylic-acid-cycle; VLCD, very-low carbohydrate diet; WD, Western diet; WL, weight loss.

(ie sedentary behaviour, low PA and poor diet) that contributes to the "multiple-hit" pathogenesis of NAFLD.[3,4] The aim of this review is to provide an overview of recent research findings covering diet and PA "beyond the obvious", thereby presenting stimulating aspects of this topic complimentary to state-of-the-art reviews (eg Refs. [5-7]).

2 | THE OBVIOUS – GUIDELINE RECOMMENDATIONS

Although being regarded as the key component to tackle the NAFLD epidemic, guidelines[8-11] are rather unspecific and vague regarding recommendations for diet and exercise in NAFLD patients (Table 1, reviewed in[12]). Several scientific associations (EASL-EASD–EASO 2016,[8] AASLD 2018,[9] ESPEN 2019[10] and APASL 2020[11]) highlight the importance of weight loss (WL)—targeting a 7%-10% reduction in body weight (BW)—achieved by a hypocaloric diet (energy deficit of 500-1000 kcal/d) and/or PA (in order to promote a caloric deficit). However, specific recommendations are divergent. While the EASL-EASD–EASO and APASL recommend the exclusion of processed food and any beverages/food high in added fructose, AASLD and ESPEN do not provide such recommendations. Although all highlight the low evidence supporting any dietary composition (eg low-carbohydrate/low-fat diets), EASL-EASD–EASO, ESPEN and APASL specifically mention the Mediterranean diet (MED) as beneficial in patients with NAFLD. While EASL-EASD–EASO and AASLD discussed beneficial effects of light (<1 drink/d)[9] or moderate alcohol consumption (<20 g/d for ♀ and <30 g/d for ♂),[8] more recent ESPEN and APASL guidelines recommend complete abstinence. No recommendations are given for coffee consumption or other macronutrients. Finally, an increase in PA is generally recommended in all guidelines, but no recommendations exist for a specific type or amount of PA and/or duration. Importantly, recommendations on diet and PA are similar in NAFLD patients with type-2 diabetes mellitus emphasizing an individual approach aiming at calorie-restriction and MED diet.[13] However, dietary recommendations for cirrhotic patients avoiding malnutrition, sarcopenia and a low-protein diet need specific attention, and are not covered in this review.[14]

3 | TYPES OF DIET

Apart from a MED, several types of diet have been proposed to tackle NAFLD (interventional studies are summarized in Table 2).

3.1 | Mediterranean diet

In contrast to the Western diet (WD) rich in animal products including red and processed meat, refined grains, potatoes and sugar sweetened beverages (SSB),[15] the MED containing vegetables, fruits, whole grains, nuts and legumes, olive oil, and fish,[16] and has been promoted for WL and improvement of metabolic parameters.[17] Also, the MED has been reported to prevent cardiovascular disease.[18] Since most of its components have either been (inversely) associated with the prevalence, severity or regression of NAFLD (see chapter 4), it is not surprising that the MED is recommended over the WD for individuals with NAFLD.[19] Generally speaking, studies have shown that adherence to a MED is inversely associated with NAFLD prevalence and severity,[20-22] and reduces hepatic steatosis[23-28] and liver stiffness measurement (LSM).[26,29] In addition, MED might even be associated with a reduced risk of HCC or liver-related death.[30,31] However, high-quality randomized controlled trials (RCTs) are still scarce,[24-29] and dietary and caloric composition of MED was divergent across different studies, thus, complicating direct comparison and firm conclusions. As one of these studies, the DIRECT-PLUS randomized clinical trial recently showed that a calorie-restricted MED successfully induces WL and reduction in intrahepatic lipid content (IHLC) while the addition of dietary polyphenols via green-tea and Mankai additionally decreased IHLC.[28]

3.2 | High-protein diet

Studies investigating an increase in dietary protein content are less common given the data on the potentially negative effects of red meat on NAFLD (see chapter 4.1). A RCT by Markova et al (2017)[32] showed that two isocaloric diets rich in animal or plant protein (30% protein, 40% carbohydrates and 30% fat) were both able to reduce IHLC by 36%-48% in individuals with type-2-diabetes-mellitus. Another study by Xu et al[33] found different decreases in IHLC among three hypocaloric diets: Subjects consuming a high-protein diet (~40% carbohydrates, ~30% protein, ~30% fat) had a 43% decrease in IHLC, subjects with a normal-protein diet (~20% protein) had a 37% decrease while those with a low-protein/high-carbohydrate diet (HCD; ~10% protein, ~60% carbohydrates,~30% fat) had no reduction despite similar WL. Nevertheless, these differences might also be attributed to the differences in carbohydrates (see chapter 3.4 and 3.5).

3.3 | Hypocaloric diet

Another more general approach to achieve caloric deficit and consecutive WL is a hypocaloric diet regardless of its dietary composition.[34] Several studies have shown that a total energy deficiency leads to a decrease in BW, transaminase levels, total body fat, visceral fat and IHLC, regardless of how it is achieved.[35-37] This is supported by similar long-term outcomes after 7% WL following a low-carbohydrate-diet (LCD) vs a HCD despite short-term effects in favour of a LCD.[38]

With this regard, an important study was done by Vilar-Gomez et al[39] who reported a strong correlation of the degree of WL following a hypocaloric diet with the degree of histological NAFLD improvement including NASH resolution and fibrosis regression in NASH patients. This correlation was recently confirmed by a meta-analysis

TABLE 1 Comparison of guideline recommendations of the EASL-EASD–EASO guideline 2016, AASLD guidance 2018, ESPEN guideline 2019 and APASL guideline 2020. Modified after Miller (2020)[1]

	EASL-EASD–EASO 2016[8]	AASLD 2018[9]	ESPEN 2019[10]	APASL 2020[11]
Recommendations	• In overweight/obese NAFLD, a 7%-10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology (**B1**). • Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose). The macronutrient composition should be adjusted according to the Mediterranean diet (**B1**). • Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients' preferences to be maintained in the long-term (**B2**).	• Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. A combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time. • Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis. • Exercise alone in adults with NAFLD may prevent or reduce hepatic steatosis, but its ability to improve other aspects of liver histology remains unknown. • Patients with NAFLD should not consume heavy amounts of alcohol. • There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD.	• In overweight/obese NAFL/NASH patients a 7%-10% weight loss shall be aimed for to improve steatosis and liver biochemistry; a weight loss of >10% shall be aimed for in order to improve fibrosis. (**A**) • In overweight/obese NASH patients, intensive lifestyle intervention leading to weight loss in conjunction with increased physical activity shall be used as first-line treatment. (**A**). • In normal weight NAFL/NASH patients, increased physical activity to improve insulin resistance and steatosis can be recommended (**GPP**). • Overweight and obese NAFL/NASH patients shall follow a weight reducing diet to reduce the risk of comorbidity and to improve liver enzymes and histology (necroinflammation) (**A**) • In order to achieve weight loss, a hypocaloric diet shall be followed according to current obesity guidelines irrespective of the macronutrient composition (**A**) • A Mediterranean diet should be advised to improve steatosis and insulin sensitivity. (**B**) • NAFL/NASH patients shall be advised to exercise in order to reduce hepatic fat content, but there are no data regarding the efficacy of exercise in improving necroinflammation. (**A**) • NAFL/NASH patients shall be encouraged to abstain from alcohol in order reduce risk for comorbidity and to improve liver biochemistry and histology. (**A**)	• Lifestyle change towards a healthy diet and physical activity norms via structured programs are recommended for MAFLD (**C2**). • Patients without steatohepatitis or fibrosis should receive counselling for a healthy diet and physical activity and no pharmacotherapy for their liver disease (**B2**). • Both overweight/obese and nonobese MAFLD can benefit from weight loss. In the former, a 7%-10% weight loss is the target of most lifestyle interventions and results in improvement of liver enzymes and histology (**B1**). • Dietary recommendations should consider energy restriction and exclusion of MAFLD-mediating components (processed food, food and beverages high in added fructose). A Mediterranean type diet is advisable (**B1**). • Combined diet/exercise strategies are more effective in normalization of liver enzymes levels and reducing liver fat and improving histology (**B1**). • Both aerobic exercise and resistance training effectively reduce liver fat and should be tailored based on patient preferences to ensure long-term adherence. Resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor fitness (**B2**).

(Continues)

TABLE 1 (Continued)

	EASL-EASD–EASO 2016[8]	AASLD 2018[9]	ESPEN 2019[10]	APASL 2020[11]
Energy restriction	500-1000 kcal energy deficit/day to induce a weight loss of 500-1000 g/week	Decrease caloric intake by at least 30% or by approximately 750-1000 kcal/day	Hypocaloric diet	Hypocaloric diet (500-1000 kcal deficit/day).
Weight loss	7%-10% total weight loss target	≥5% for steatosis improvement, ≥7% for histological improvement	7%-10% in overweight/obese patients >10% to improve fibrosis	7%-10% weight loss, gradual weight loss (up to 1 kg/week)
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein	NS	• Irrespective of macronutrient composition • Mediterranean diet to improve steatosis and insulin sensitivity	• No strong evidence to support a particular dietary approach. • Plans should encourage low-carbohydrate, low-fat and Mediterranean-type diets
Fructose	Avoid fructose-containing beverages and foods	NS	NS	Exclusion of beverages high in added fructose
Alcohol	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women) • Moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis	• Should not consume heavy amounts of alcohol. • Insufficient data on nonheavy consumption of alcohol	Abstain	• The "cut-off" values of alcohol intake in MAFLD should be set lower than the apparent "threshold levels". • Patients with MAFLD should be advised to avoid alcohol and if that is not possible, to consume the lowest amount possible.
Coffee	No liver-related limitations.	NS	More likely to benefit health than harm	NS
Physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise	• Physical activity more than 150 minutes/week • Moderate intensity exercise	Increase physical activity	• Aerobic exercise and resistance training effectively should be tailored based on patient preferences to ensure long-term adherence. • Resistance exercise may be more feasible than aerobic exercise for patients with poor fitness.

Note: Bold-letters indicate the grade of evidence according to the respective guidelines.

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; NS, not specified.

TABLE 2 Overview and characterization of individual studies on dietary interventions discussed in this manuscript

Study	Type of study	Duration of intervention	Types of diet (± calorie intake)	Macronutrient composition	Individuals analysed*	Patients	Outcome measure (liver-related)	Outcome (liver-related)
Mediterranean diet (MED)								
Ryan (2013)[24]	RCT	6w	MED vs LFD/HCD (both diets after one another)	MED: 40% C, 20% P, 40% F LFD/HCD: 50% C, 20% P, 30% F	6 vs 6	Biopsy-proven NAFLD	^{1}H-MRS	-39% vs -7% reduction in IHLC after MED compared to LFD/HCD
Trovato (2015)[23]	Single-arm	6m	Increase the adherence to Mediterranean Diet Score and reduce sedentary habits	NS	90	Non-diabetic NAFLD	Bright Liver Score (BLS)	Adherence to MED independently explain considerable variance of BLS
Misciagna (2017)[25]	RCT	6m	Low Glycemic Index MED vs CD	NS	44 vs 46	Moderate or severe NAFLD (US)	US (semi-quantitatively)	Negative interaction between time and MED on NAFLD (semi-quantitatively)
Abenavoli (2017)[26]	RCT	6m	Hypocaloric MED± antioxidant supplementation (1400-1600 kcal/d) vs CD	MED: 50%-60% C, 15%-20% P, <30% F	20 vs 20 vs 10	Overweight NAFLD	US (semi-quantitatively), FLI, LSM (FibroScan)	Decrease in FLI and LSM following both diets
Katsagoni (2018)[29]	RCT	6m	Hypocaloric diets (1500 kcal/d ♀, 1800 kcal/d ♂) MED vs MED +lifestyle intervention vs CD	45% C, 20% P, 35% F	21 vs 21 vs 21	Overweight/ obese NAFLD	LSM (Aixplorer)	Decrease in LSM following both diets, improvement in ALT only in MED +lifestyle intervention-group
Marin-Alejandre (2019)[27]	RCT	6m	Personalized hypocaloric diets (−30%): FLiO-diet vs CD (AHA-recommendations)	FLiO: 40%-45% C, 25% P, 30%-35% F CD: 50%-55% C, 15% P, 30% F	37 vs 39	Overweight/ obese NAFLD	MRI, LSM (ARFI)	Reduction in IHLC +FLI following both diets
Yaskolka Meir (2020)[28]	RCT	18m	Hypocaloric MED +28g/d walnuts ± green tea/Mankai (1500-1800 kcal/d ♂, 1200-1400 kcal/d ♀) vs healthy diet	MED: <35% F	89 vs 84 vs 91	Abdominal obesity/ dyslipidemia	^{1}H-MRS	IHLC reduced following all diets, greater following green-MED compared to MED
Diets focussing on proteins								
Markova (2017)[32]	RCT	6w	Isocaloric animal-protein vs plant-protein diet	40% C, 30% P, 30% F	18 vs 19	T2DM + NAFLD	^{1}H-MRS	-48.0% vs −35.7% reduction in IHLC
Xu (2020)[33]	RCT	3w	Hypocaloric LPD vs HPD vs reference-protein diet	LPD: 55%-65% C, 10% P, 25%-35% F HPD: 35%-45% C, 30% P, 25%-30% F Ref.-prot: 20%-22% P	10 vs 9 vs 10	Morbid obesity	^{1}H-MRS	-36.7% vs −42.6% reduction in IHLC vs no changes in IHLC
Hypocaloric diet								
De Luis (2008)[37]	Single-arm	3m	Hypocaloric diet (1520 kcal/d)	52% C, 23% P, 25% F	142	Non-diabetic and obese	Serum biomarkers	Improved ALT/AST

(Continues)

TABLE 2 (Continued)

Study	Type of study	Duration of intervention	Types of diet (± calorie intake)	Macronutrient composition	Individuals analysed*	Patients	Outcome measure (liver-related)	Outcome (liver-related)
Krik (2009)[38]	RCT	48h	Hypocaloric LCD vs HCD (~1100 kcal/d)	LCD: ~10% C (≤50g), 15% P, 75% F HCD: ~65% C (≥180g), 15% P, 20% F	11 vs 11	Non-diabetic and obese	^{1}H-MRS	-29.6% vs −8.9% reduction in IHLC
Haufe (2011)[35]	RCT	6m	Hypocaloric LCD vs LFD (−30%)	LCD: ≤90g C, 0.8g/kg BW P, ≥30% F LFD: 0.8g/kg BW P, ≤20% F	52 vs 50	Overweight/obese and otherwise healthy (non-diabetic)	^{1}H-MRS	-42% vs −47% reduction in IHLC
Vilar-Gomez (2015)[39]	Single-arm	52w	Hypocaloric LFD (−750 kcal/d) + PA	64% C, 14% P, 22% F	261	Histological NASH w/o cirrhosis	Liver biopsy	Correlations between weight loss and histological improvement
Low-carbohydrate diet (LCD)/ Very-low-carbohydrate diet (VLCD)								
Browning (2011)[51]	Non-randomized controlled trial	2w	VLCD vs hypocaloric (1200 kcal/d ♀, 1500 kcal/d ♂) diet	LCD: 8% C, 33% P, 59% F Cal-restr.: 50% C, 16% P, 34% F	9 vs 9	NAFLD w/o cirrhosis	^{1}H-MRS	-55% vs −28% reduction in IHLC
Mardinoglu (2018)[54]	Single-arm	2w	Isocaloric VLCD (~3115 kcal/d)	4% C (23-30g), 24% P, 72% F	10	Obese NAFLD	^{1}H-MRS	-43.8% reduction in IHLC
Gepner (2019)[53]	RCT	18m	LFD w/o PA vs LFD with PA vs MED/LCD w/o PA vs MED/LCD with PA (MED +28g walnuts/d); all diets hypocaloric	LFD: <30% F; LCD/MED: <35% F(<40g C in first 2m, then up to 70g/d)	76 vs 63 vs 73 vs 66	Abdominal obesity/dyslipidaemia	MRI	-7.3% (MED/LCD) vs −5.8% (LFD) reduction in IHLC after 6 months; −4.2% vs −3.8% after 18 months
Luukkonen (2020)[57]	Single-arm	6d	Hypocaloric VLCD (~1440 kcal/d)	~6% C (≤25 g), 28% P, ~64% F	10	Overweight/obese NAFLD	^{1}H-MRS	-31% reduction in IHLC
Goss (2020)[58]	RCT	8w	LCD vs LFD	LCD: ≤25% C, 25% P, ≥50% F LFD: 55% C, 25% P, 20% F	14 vs 11	Obese NAFLD (9-17 years)	MRI	LCD: −6.2% absolute decrease in IHLC, LFD: −1.0% absolute decrease in IHLC; no significant difference
Intermittent calorie restriction (ICR)								
Johari (2019)[69]	RCT	8w	Modified alternate-day calorie restriction (MACR) vs CD; MACR: 70% calorie-restriction on fasting day, ad libitum on non-fasting day; CD: no changes	NS	30 vs 9	NAFLD +elevated ALT/AST	Serum biomarkers, US (semiquantitatively), LSM (Aixplorer)	ALT reduced; reduction in steatosis and LSM scores

(Continues)

TABLE 2 (Continued)

Study	Type of study	Duration of intervention	Types of diet (± calorie intake)	Macronutrient composition	Individuals analysed*	Patients	Outcome measure (liver-related)	Outcome (liver-related)
Cai (2019)[70]	RCT	12w	ADF vs TRF vs. CD ADF: −75% calorie-restriction on fasting day, ad libitum on non-fasting day TRF: 8h ad libitum eating CD: −20% calorie-restriction	ADF: 55 C, 15% P, 30% F; TRF: NS	90 vs 95 vs 79	Overweight/obese NAFLD (BMI >24kg/m^2), ≥9.6kPa, 18-65y	LSM (FibroScan)	LSM not different
Holmer (2021)[71]	RCT	12w	LCD vs 5:2 diet vs CD; LCD: 1600 kcal/d ♀, 1900 kcal/d ♂; 5:2 diet: 500 kcal/d ♀ and 600 kcal/d ♂ on 2 non-consecutive days; 2000 kcal/d ♀ and 2400 kcal/d ♂ on other days CD: healthy diet	LCD: 5%-10% C, 15%-40% P, 50%-80% F; 5:2 diet: 45%-60% C, 10%-20% P, 25% F	20 vs 24 vs 20	NAFLD	^{1}H-MRS; LSM (FibroScan) with CAP	-53.1% vs −50.9% vs −16.8% reduction in IHLC; −61.9% vs −63.8% vs −20.2% reduction in CAP; change in IHLC 3.9% greater in LCD compared to CD and 2.6% in 5:2 diet compared to CD; reduction in LSM in 5:2 diet and CD compared to LCD
Fructose-restriction								
Geidl-Flück (2021)[90]	RCT	7w	SSB with 80g/day of fructose vs sucrose vs glucose vs no SSB	45%-56% C, 15%-19% P, 30%-37% F	32 vs 31 vs 32 vs 31	Healthy men	Fatty acid-synthesis	2-fold increase in basal hepatic fractional fatty acid-secretion rates compared to controls in fructose/sucrose group; no diff in glucose group
Simons (2021)[91]	RCT	6w	Dietary fructose-restriction; control-group: supplemented with fructose powder; intervention group: supplemented with glucose powder	35%-40% C, 15%-20% P, 35%-40% F	21 vs 16	Overweight +FLI ≥ 60	^{1}H-MRS	IHLC reduction greater by −0.7% absolute difference in the intervention group; IHLC reduction in both groups

*per protocol; ADF, alternate date fasting; BLS, bright liver score; BW, body weight; C, carbohydrates; CAP, controlled attenuation parameter; CD, control diet; F, fat; FLI, fatty liver index; ^{1}H-MRS, proton magnetic resonance spectroscopy; HFF, hepatic fat fraction; HPD, high-protein diet; ICR, intermittent calorie restriction; IHLC, intrahepatic lipid content; LCD, low-carbohydrate diet; LFD, low-fat diet; LPD, low-protein diet; LSM, liver stiffness measurement; m, months; MED, Mediterranean diet; MRI, magnetic resonance imaging (Dixon techniques); NS, not specified; P, protein; PA, physical activity; RCT, randomized controlled trial; SSB, sugar-sweetened beverages; TRF, time-restricted feeding; US, ultrasonography; w, weeks; w/o, without; WL, weight loss.

promoting WL-interventions including calorie restriction over specific dietary compositions in NAFD/NASH.[40] Nevertheless, further adherence to a MED might enhance the decrease in BW, total fat mass and hepatic fat.[27]

3.4 | High-carbohydrate/low-fat diet

For years, high dietary fat has been considered the cause of obesity and the metabolic syndrome because of its high energy density leading to an increase in total energy intake. Thus, scientists called for a low-fat diet (LFD) with compensatory increase in dietary carbohydrates. Although early studies suggested that dietary fat might inhibit hepatic glucose disposal and increase storage of glucose,[41] increasing concerns regarding the harmful effect of HCD are arising[42] and the number of studies promoting HCD over LCD are a minority. However, if a caloric deficit is achieved, HCD/LFD may still improve liver histology in the mid-term.[39] With this regard, the type of fat consumed in these studies needs to be taken into account, with saturated fatty acids (FA) and trans-FA increasing and poly-unsaturated FA decreasing BW despite their high energy content.[43,44]

3.5 | Low-carbohydrate/high-fat diets

According to the "Carbohydrate-Insulin-Model" of obesity, an increase in the consumption of processed carbohydrates produces hormonal changes (especially by inducing insulin secretion) that promote "energy storage" in adipose tissue, exacerbate hunger and lower energy expenditure.[45] By stimulating glucose uptake, suppressing release of FAs from adipose tissue, and promoting fat and glycogen production, hyperinsulinemia following carbohydrate intake again induces hunger and predisposes to weight gain.[46] Animal models have previously confirmed several advantages of LCD (especially those with a low glycemic-index) over HCDs.[47,48] In these studies, energy restriction while on a high glycemic-index-diet did neither prevent weight gain nor increases in blood lipids and glucose,[47] while a LCD indeed increased energy expenditure and decreased BW.[48]

Thus, several types of LCD or "very-low carbohydrate diet" (VLCD) have been studied for their effect on NAFLD.[49,50] Important differences exist for their respective carbohydrate-content and associated ketogenic potential, with ketogenesis occurring if <20-50 g/d carbohydrate are consumed corresponding to carbohydrate constituting 5%-10% of daily energy intake (ie VLCD, see chapter 7.1).[49]

Early studies comparing hypocaloric diets low or high in carbohydrates (LCD vs HCD) showed a significant stronger short-term reduction of IHLC after VLCD,[51] but similar levels in the long-term (ie after 7% WL)[38] while insulin sensitivity was durably improved also in the long-term.[38] An important study by Gepner et al[52,53] demonstrated that a hypocaloric LCD in combination with a MED (±PA) achieved the greatest reduction in visceral adipose tissue and IHLC compared to an hypocaloric LFD. Interestingly, this effect was achieved despite only moderate WL, which might inadequately reflect the beneficial effects of a LCD.[52] Also, the reduction in IHLC was similar between patients performing different amounts of PA, highlighting the essential role of diet for this outcome parameter.[53]

Similarly, Mardinoglu et al[54] observed significant short-term changes in IHLC following an isocaloric VLCD, linking it to increased ketogenesis and changes in gut microbiota (see chapters 7.1 and 7.2). Ebbeling et al[55] used heavy water to assess energy expenditure following HCD, moderate or LCDs. Interestingly, energy expenditure followed a linear trend of +52 kcal/d for every 10% decrease in the contribution of carbohydrates to total energy intake. Also, ghrelin and leptin levels were significantly lower contributing to decreased hunger, fat deposition and increased leptin sensitivity. Again, these effects were independent of BMI and were greatest in patients with high post-prandial insulin levels suggesting pronounced benefits in patients with pre-existing hyperinsulinemia.[55] These data go in line with a previous meta-analysis showing reduced appetite and increased satiety following VLCD.[56]

Finally, a recent study by Luukkonen et al (2020)[57] assessed IHLC using proton magnetic resonance spectroscopy (^{1}H-MRS) in 10 overweight individuals with NAFLD on VLCD/ketogenic diet and showed a marked decrease in IHLC by 31% accompanied by a decrease in insulin resistance (IR, −57%). Also in adolescents, LCD seems to outperform HCD regarding WL and reduction in IHLC and IR.[58]

Despite these data on LCDs seem promising, meta-analyses directly comparing several dietary interventions in NAFLD are still lacking. Also, improvements of BMI, HDL-cholesterol and triglyceride profiles must be balanced with potential consequences of raised LDL- and total-cholesterol levels in the long-term.[59,60] On a long-term perspective, carbohydrate intake and overall mortality might still follow a U-shaped curve.[61]

Last but not least, a recent Mendelian randomization analysis aimed at validating the aforementioned Carbohydate-Insulin-Model.[62] In this study, 30 genetic polymorphisms being linked with glucose-stimulated insulin secretion were tested in ~500.000 subjects and found to be significantly associated with BMI. In contrast, SNPs linked with BMI were not associated with glucose-stimulated insulin secretion. The authors thus hypothesize that post-prandial hyperinsulinemia centrally influences BMI and associated comorbidities while vice-versa, BMI itself might be less important for hyperinsulinemia.

3.6 | Intermittent calorie restriction

Intermittent calorie restriction (ICR) is another way to reduce calorie intake. Following this approach, individuals consume significantly reduced calories or no calories over a certain period ("fast days") followed by intervals with ad-libitum food consumption ("feast days"). A common variant is the intermittent fasting (or alternate day fasting, ADF) which consists of fasting periods over 36-hours and periods of ad-libitum food consumption over 12 hours, among other

forms (reviewed in Ref. [63]). This periodic calorie restriction seems to provoke several physiological changes contributing to health benefits (reviewed in Refs. [64-66])—among others, it might counteract the disruption of circadian rhythm being associated with development of NAFLD and metabolic syndrome.[67]

Among the first, Stekovic et al[68] investigated the effects of ADF for 4 weeks and >6 months on BW and markers of ageing. Compared with the control group continuing their usual diet, ADF led to a significant reduction in BMI, central fat, Framingham Risk Score, LDL, total cholesterol, triglyceride and triiodothyronine levels after 4 weeks and 6 months. Also, serum β-hydroxybutyrate (β-OHB) levels significantly increased after 4 weeks indicating an induction of ketogenesis (see chapter 7.1). The authors conclude that the periodic stimulus to the organism seems to exert several beneficial effects on human health that cannot be solely attributed to calorie restriction.[68]

So far, three studies have been performed focussing on NAFLD patients. Johari et al[69] applied a modified alternate-day calorie restriction (ie 70% calorie-restriction on fasting day, ad-libitum eating on non-fasting day) to demonstrate an improvement in ALT levels as well as LSM and sonographically assessed steatosis.[69] Another study showed a decrease in BMI and triglyceride levels following 12 weeks of ADF or time-restricted feeding (energy intake only during an 8h-window each day) despite no changes in LSM.[70] Finally, Holmer et al[71] compared ICR on two non-consecutive days/week (ie 5:2 diet, <500/600 kcal/d) vs a LCD/HFD in patients with NAFLD. This diet was associated with a significant reduction of IHLC on MRI and was assessed via controlled attenuation parameter, as well as improvement of BMI and IR was compared to a "healthy diet", among others. Interestingly, ICR was similarly effective as LCD/HFD. In general, previous studies have largely demonstrated effective WL following ICR in overweight/obese individuals without serious adverse events.[72] However, it remains to be answered whether ICR is equally or more effective than continuous calorie restriction,[73,74] and whether it is effective if no calorie-restriction/dietary counselling is applied.[75] Also, although ICR has also been shown to be effective and safe in overweight/obese patients with type-2 diabetes mellitus,[76] close monitoring of diabetes medication and blood glucose is needed because of concerns about hypoglycemia.[77]

4 | DIETARY COMPOSITION AND SELECTED FOOD GROUPS

4.1 | Red and processed meat

An increasing number of recent studies showed a striking inverse association between red and processed meat and NAFLD.[21,78-80] Importantly, this association seems to be driven by animal protein since vegetable protein did not show a similar association.[78,80] A compelling explanation for this phenomenon was reported by Alferink et al[81] proposing that the diet-dependent acid-load is the driving component of this association. Specifically, animal protein might cause low-grade metabolic acidosis by supplementation of acid precursors,[82] which lead to a disturbance in acid-base-balance.[83] Other studies reporting on the U-shaped association between carbohydrate-consumption and mortality hypothesized that the substitution with animal-protein might cause the rise in mortality following a LCD, which was not evident when plant-based protein was substituted.[61]

4.2 | Sugar-sweetened beverages and high-fructose consumption

By searching for explanations between the parallel increase of fructose-consumption through high-fructose corn syrup (HFCS) and the increase in NAFLD/metabolic syndrome,[84] fructose has been associated with IR, intrahepatic lipid accumulation and hypertriglyceridemia, which contribute to the development of type 2 diabetes and cardiovascular diseases.[84] This is because the first-pass hepatic extraction of fructose is nearly 100% after ingestion, and metabolization occurs solely in the liver.[85,86] In contrast to glucose, it might provide a more direct substrate for de-novo lipogenesis (DNL) and increase IHLC on a larger scale.[86] Unlike glucose metabolism, gluconeogenesis from fructose occurs independent of insulin and the energy status of the cell,[85,86] leading to a depletion in ATP and subsequent generation of uric acid, in terms promoting oxidative stress and IR.[87,88]

Thus, fructose- but not glucose-sweetened beverages have been associated with increased DNL, dyslipidemia, visceral adiposity and impaired insulin sensitivity.[89] This was recently confirmed by a RCT showing an increased basal secretion rate of FA in both fructose and sucrose (ie glucose and fructose) groups raising the hypothesis of an adaptive response to regular fructose exposure by SSB consumption.[90] Also, restricting fructose-intake led to a reduction in IHLC[91]

In line, SSB have been associated with higher NAFLD prevalence,[92-95] NASH presence[96] and even a higher degree of fibrosis.[97] However, the differences in study design need to be considered since less significant alterations seem to occur in otherwise healthy subjects.[98] Interestingly, this might provide an explanation why young and metabolically healthy subjects could compensate for increased fructose intake while these mechanisms tilt in the presence of metabolic dysregulation.

Aiming at investigating physiological differences in mice fed with either glucose- or fructose-supplemented water, Softic et al[99] found that fructose supplementation was associated with an increased expression of Srebp1c and Chrebp-β, increased FA synthesis and hepatic IR, while glucose supplementation was associated with increased total Chrebp and Chrebp-β and liver triglyceride accumulation, but not with IR.[99] The increased expression of Chrebp-β further upregulating FGF-21 could be one mechanism of action by which fructose contributes to fibrogenesis and hepatic stellate cell activation[100]

4.3 | Alcohol

In the context of NALFD, the controversy on the potential beneficial effects of moderate alcohol consumption (<20 g/d for ♀ and <30 g/d for ♂) on the prevalence and severity of NAFLD is still ongoing. Although data on the protective effect of moderate alcohol consumption on the prevalence of NAFLD[101-104] and NASH[102,104,105] exist, several concerns have been raised questioning the rationale behind this phenomenon and adequate addressing of confounders.[106-108] Within the last two years, evidence is accumulating that supports a rather harmful effect, and recent guidelines recommend complete abstinence.[10,11] Ajmera et al (2018)[109] showed that modest alcohol use was associated with less improvement in steatosis and level of aspartate transaminase, as well as lower odds of non-alcoholic steatohepatitis resolution compared to non-drinkers. Another study reported faster worsening of non-invasive fibrosis scores in patients with moderate alcohol consumption compared to abstainers,[110] recent analyses also support a linear positive association with NAFLD and advanced liver disease.[111,112]

4.4 | Coffee

Any coffee consumption was associated with a 29% lower risk of NAFLD, a 30%-39% lower risk of liver fibrosis and a 39% lower risk of cirrhosis in two meta-analyses.[113,114] Also, a dose-dependent inverse relationship was evident in two different meta-analyses for cirrhosis and liver-related death[115] as well as chronic liver disease and HCC.[116] However, another meta-analysis describes a non-linear relationship with a reduced risk of NAFLD only starting at >3 cups/d.[117] In line, the proportion of patients with LSM ≥8.0k Pa decreases among higher coffee consumption.[118] On a mechanistic basis, these beneficial effects might be explained by a reduction in hepatic fat accumulation by increased β-oxidation, and a reduction of systemic and liver inflammation and oxidative stress.[119] Specifically, coffee enhances the expression of chaperones and antioxidant proteins such as glutathione ensuring correct protein folding and degradation in the liver.[120] Also, chlorogenic acid, caffeine and kahweol exhibit antifibrotic properties by inhibition of hepatic stellate cell activation[121] via down-regulation of the transforming-growth-factor-β (TGF-β) pathway and inhibiting connective tissue growth factor.[122,123] Possible influences on the gut microbiome could contribute to these observed associations including an increase in *Bifidobacterium* spp.[124,125] and a decrease in *Escherichia coli* and *Clostridium* spp.[125] With this regard, coffee consumption seems to be associated with microbial richness even in patients with cirrhosis.[126,127]

4.5 | Nuts and seeds

Nuts and sees contain several bioactive compounds that have been regarded beneficial for human's health including monounsaturated FAs and polyunsaturated FAs (PUFA), vegetable protein, fiber, minerals, vitamins, tocopherols, phytosterols and polyphenols.[128] Recently, several studies investigated their influence on NAFLD: a Chinese study reported a significantly lower prevalence of NAFLD in patients consuming nuts ≥4 times/wk[129] while another Chinese study confirmed this inverse association of NAFLD and nut consumption only in men when consuming ≥8.86 g/d.[130] These findings have been validated in a Caucasian cohort being again more pronounced in males,[131] and another cross-sectional study.[132] Interestingly, daily nut consumption might even be negatively associated with advanced fibrosis in NALFD patients with further research needed to confirm these associations.[131] Despite their high energy content, nut consumption has not been associated with weight gain.[133,134] In contrast, anti-inflammatory components (eg ω-3 PUFAs) might contribute to their beneficial effects on NAFLD,[135,136] and they have recently been added to a MED showing a significant WL and decrease in IHLC in NAFLD paients.[28,53]

5 | MICRONUTRIENT COMPOSITION

Although the pathogenic role of specific food-types and macronutrients is well-established in NAFLD, the impact of micronutrients (including minerals, fat and water-soluble vitamins, and carotenoids) on disease pathogenesis has garnered less attention (reviewed in Ref. [137]). While the relevance of dysmetabolic iron overload in NAFLD has been largely studied,[138,139] both zinc[140] and copper[141] deficiencies have also been observed in NAFLD. Interestingly, zinc supplementation has shown favorable effects on glycemic parameters and plasma lipids.[142,143] The link between high fructose-consumption and copper deficiency[144] potentially contributing to NAFLD pathogenesis also deserves further research.[145] Building upon the negative influence of red meat consumption on NAFLD (see chapter 4.1), an increased amount of iron intake—independent of red meat as a source—may also contribute to NAFLD pathogenesis.[146]

Apart from minerals, deficiencies in vitamins A, B3, B12, C, D and E—although mostly of mild severity—have been reported in NAFLD.[137,147] While systematic supplementation of these vitamins has not been studied, vitamin E supplementation has been addressed several beneficial properties in NAFLD.[148,149] Just recently, vitamin E supplementation has been reported to improve transplant-free survival and hepatic decompensation in patients with NASH and advanced fibrosis,[150] and published guidelines recommend vitamin E supplementation to non-diabetic patients with NASH.[8-11] Finally, the beneficial effects of nuts and seeds in NAFLD might partially be explained by their high content of micronutrients and antioxidative compounds.[128]

6 | PHYSICAL ACTIVITY AND EXERCISE

While the EASL and AASLD both recommend ≥150 min of moderate-intensity PA per week, novel ESPEN and APASL guidelines only recommend an increase of PA tailored based on patient preferences.

This might be the case since meta-analyses proved that PA reduces IHLC and markers of hepatocellular injury (especially in patients with increased BMI[151]), but fail to clearly recommend one type of exercise over another.[151-154] Also, there does not seem to be a significant difference between dose or intensity of aerobic exercise.[155-157]

Despite aerobic exercise cannot be recommended over resistance training, overall energy consumption seems to be lower during resistance training compared to aerobic exercise while leading to a similar improvement of steatosis.[158] Thus, resistance exercise might be better tolerated by NAFLD patients with poor cardiorespiratory fitness and musculoskeletal issues because of overweight.[11,158]

Several aspects need to be highlighted which go beyond WL and explain benefits from PA and exercise: Exercise improves peripheral insulin sensitivity with only little effect on hepatic insulin sensitivity, leading to a net improvement in insulin metabolism.[159] Also, exercise increases very-low-density-lipoprotein clearance enabling the liver to export triglycerides,[160] improves appetite-control[161] and counteracts sarcopenia, which has been identified as independent risk factor for NAFLD and fibrosis.[162,163] Thus, exercise is also recommended and is safe in patients with NASH cirrhosis and portal hypertension improving physical function, sarcopenia and even portal hypertension.[164]

6.1 | Sedentary behaviour

Sedentary behaviour is not only associated with obesity, but also >30 health outcomes[165] and NAFLD.[166] Specifically, television-viewing-time was independently associated with higher fatty-liver-index in Finnish adults[167] and computer/mobile-devices-usage-time with Odds of NAFLD in Chinese adults.[168] Nevertheless, PA in-between sitting time/sedentary time still attenuates post-prandial glucose and insulin, with greater glycaemic attenuation in people with higher BMI.[169]

Interesting data about a protective effect on carcinogenesis can be derived from mice-models comparing mice with access to a running wheel to those without.[170-173] All studies showed a striking reduction of HCC cases in the exercise groups compared to the sedentary groups, which might even be independent of weight gain[171] and diet.[172] Similar results were obtained from epidemiological studies reporting a lower incidence of liver cancer and especially HCC between the groups with the least and most-frequent PA.[174]

6.2 | Combination of physical activity and dietary interventions

Noteworthy, evidence exists that the combination of exercise and dietary interventions lead to a greater improvement of metabolic parameters and IHLC.[154,175,176]

The combination of a low-glycemic-index-MED with either aerobic exercise or both aerobic exercise and resistance training led to the greatest reduction in controlled attenuation parameter as a measure of hepatic steatosis in NAFLD patients after three months.[177] However, further research is needed regarding potentially counteracting effects of antioxidants (vitamin C and E) and exercise-induced mitohormesis.[178-180]

7 | NOVEL MOLECULAR AND TRANSLATIONAL ASPECTS

7.1 | PPARα-signalling and ketogenesis

An important aspect contributing to the success of (V)LCD is ketogenesis, leading to the alternative term "ketogenic diet" (KD).[54] Ketogenesis is the production of ketone bodies acetoacetate (AcAc), β-hydroxybutyrate (β-OHB) or acetone from FAs which serve as an alternative energy supply from the liver to peripheral tissues when the supply of glucose is too low for the body's energetic needs.[181] From a historical perspective, mild ketosis was the normal metabolic state in most cultures before the agricultural revolution leading to a shift from hunter-gathered diets to rather monotonous carbohydrate-based diets.[182,183] However, when carbohydrate stores are available, the main source of energy is glycogenolysis and gluconeogenesis in case of a catabolic state while ketogenesis is suppressed by the presence of insulin.[184]

The nuclear receptor peroxisome proliferator-activated receptor α (PPARα) is a central transcriptional factor regulating FA metabolism (ie FA oxidation, FA transport and ketogenesis), which is upregulated during fasting or ketogenic states.[184] One mechanism of action is the induction of fibroblast growth factor 21 (FGF-21) while PPARα-independent activation of FGF-21 also exists.[185,186] Fasting significantly induces hepatic expression and circulating levels of FGF-21, which is then rapidly suppressed by refeeding.[185,186] As a proof-of-concept, PPARα-deficient mice or FGF-21 knockout mice developed severe metabolic abnormalities including fatty liver during feeding-period and hypoglycemia/hypoketonemia during starvation, highlighting the regulatory role of the PPARα-FGF-21-pathway for ketogenesis in response to fasting or (V)LCD/KD.[185-187] Another regulator of PPARα function is the mechanistic target of rapamycin complex 1 (mTORC1) kinase, the inhibition of which is necessary for ketogenesis.[188]

Based on knowledge of the impaired PPAR-signalling in NAFLD and NASH,[189] the induction of this pathway may serve as an additional explanation of the beneficial effects of KD or ICR. Specifically, PPARα exerts several anti-inflammatory activities and protection from intrahepatic lipid accumulation, inflammation and fibrosis.[189] For example, while PPARα gene expression in the liver negatively correlates with NASH severity, histological improvement is associated with an increase in expression of PPARα.[190] Thus, while waiting for selective or pan-PPAR-agonists to be proven effective for NAFLD/NASH therapy,[191] KD or ICR might be the alternatives to induce the PPARα-pathway. However, in human studies it has been shown that FGF-21 serum levels largely vary as dietary response,[33,54,192] and might therefore not be the target-substrate to

measure. Nevertheless, regarding other PPARα targets in the liver, an upregulation has been shown in a mice model only following KD without any carbohydrate intake, but not following a non-ketogenic LCD/HFD,[193] highlighting the importantance of carbohydrate restriction for ketogenesis.

Moreover, ketone bodies β-OHB and AcAc have several direct and indirect signalling-properties that contribute to the success of KD or ICR. Apart from their function as an energy substrate, β-OHB and AcAc themselves have several anti-inflammatory functions (reviewed in Refs. 194,195). For example, both protect against oxidative stress by decreasing the production of mitochondrial reactive oxygen species, by increasing expression or protein content of antioxidant enzymes through inhibition of histone deacetylases,[196] and by directly scavenging hydroxyl radicals (•OH).[197] The inhibition of the NLRP3 inflammasome—which controls the activation of caspase-1 and the release of the pro-inflammatory cytokines IL-1β and IL-18 in macrophages—and activation of the hydroxycarboxylic acid receptor 2 (HCA_2) seem to be other mechanisms.[198,199]

Following a 6-day KD (~6% carbohydrate, ~64% fat, ~28% protein), Luukoonen et al (2020)[57] demonstrated a 10-fold and six-fold increase in β-OHB and AcAc serum concentrations while endogenous β-OHB assessed by stable isotope infusions of [$^{13}C_4$]β-OHB increased three-fold. However, this increase seems to depend on the presence and severity of NAFLD as shown by Fletcher et al (2019).[200] They measured non-esterified FAs (NEFAs) from peripheral lipolysis and AcAc+β-OHB serum concentrations in NAFLD patients after 24h of fasting, and showed ~30% lower levels compared to controls. Interestingly, patients with higher IHLC had lower β-OHB serum levels after 24h indicating an inverse relationship between the severity of HS and ketogenesis after fasting. Contrarily, oxidation of acetyl-CoA in the tricarboxylic-acid-cycle (TCA, ie the alternative pathway for acetyl-CoA metabolism) increased ~60% in NAFLD patients Fletcher et al (2019).[200] Most interestingly, these differences were independent of BMI indicating that NAFLD itself seems to influence ketogenesis. Another recent study confirmed ~15% lower β-OHB serum concentration correlating weakly with liver fat.[201]

These studies go in line with previous ones showing that ketogenesis is significantly impaired in NAFLD ('ketogenic insufficiency') independent of fasting.[202-205] Simultaneously, the high "energy-processing burden" is mismatched to the mitochondrial capability of the liver leading to an increase in anaplerotic and oxidative TCA flux and consecutive oxidative stress and inflammation.[202-205] Most interestingly, a study in obese NAFLD/NASH patients showed that this compensatory upregulation of mitochondrial activity (ie "hepatic metabolic flexibility") seems to fail following excessive hepatic oxidative stress, leading to a decrease in mitochondrial functionality and progression to NASH and IR.[206] Evidence that impaired ketogenesis contributes to this phenomenon comes from mice models.[207] After blocking the ketogenic pathway by knocking-out the 3-hydroxymethylglutaryl-CoA synthase 2 (ie a key enzyme during ketogenesis), LFD induced hyperglycaemia, increased hepatic gluconeogenesis and increased DNL because of excess acetyl-CoA and increased TCA flux.

7.2 | Gut microbiota and exercise

An emerging research topic is the relationship between exercise and the gut microbiota (reviewed in).[208,209] Despite methodological difficulties and inhomogeneities in the studied cohorts, cardiorespiratory fitness and activeness is usually associated with higher microbial diversity.[208,210] Two prominent studies on professional rugby players earlier reported this higher diversity, which translates into differences in faecal metabolites (eg short-chain FA).[211,212]

Although differences have been reported for numerous taxa, specific consideration might be drawn to the taxus Akkermansia, which seems to be more present in athletes than in non-athletes.[211,213] Akkermansia muciniphilia has previously been associated with a healthy metabolic status[214] and lower BW[215] while supplementation reversed metabolic dysfunction in mice.[215]

Regarding the effects of PA on gut microbiota, PA could lead to a assimilation of microbiota to healthy individuals already after 12 weeks of training.[216] However, these changes might be small,[217] and it is unclear whether these changes are only transient returning to a baseline profile after termination of the PA-intervention.[218,219] Also, the effect of ones microbiota on the efficacy of PA is similarly interesting. Liu et al (2020)[217] identified the intestinal microbiota as a potential driver of exercise-induced alterations in fasting glucose and insulin. If these microbiota were transplanted to obese mice, it induced similar changes as in the respective humans. Again, abundance of Akkermansia muciniphilia was significantly higher in subjects with metabolic changes following exercise intervention, and a machine-learning algorithm could successfully predict glycemic response to exercise based on gut microbiota.[217] Similarly, another study reported different exercise gains following cardiorespiratory exercise or resistance training.[218] Finally, an increase in Veillonella abundance in marathon runners metabolizing lactate led to the hypothesis that this genus might increase athletic performance.[220]

7.3 | Gut microbiota and nutrition

In recent years, promising data have evolved characterizing the interactions between diet and intestinal microbiota (reviewed in Refs. [221,222]). Specifically, differences in gut microbiota have been reported in the short-term following a LCD[54] as well as a KD.[223] Specifically, significant differences among Actinobacteria, Bacteroidetes, Firmicutes and Bifidobacterium were observed between KD vs LFD vs HFD with Bifidobacterium showing the greatest decline following KD.[223] Interestingly, Bifidobacterium negatively correlated with β-OHB concentration in the intestinal lumen indicating that β-OHB inhibits Bifidobacterium growth, which was also confirmed in vitro.[223] What is more, the KD-associated microbiota-signature reduced the level of intestinal pro-inflammatory Th17 cells.[223]

Also, different formulations of high-fructose diets induce distinct alterations of gut microbiota: HFCS reduced butyrate-producing bacteria and the Firmicutes/Bacteroidetes ratio, while a high-fructose-diet from fruits created an opposite shift.[224] This is relevant

since a higher Firmicutes/Bacteroidetes ratio has been linked to the pathogenesis of the metabolic syndrome.[225,226]

Finally, individuals with higher abundance of Akkermansia muciniphilia displayed greater improvement in insulin sensitivity markers and other clinical parameters after calorie restriction.[214] Also, a LCD/KD increased Akkermansia muciniphilia abundance.[227] Oral supplementation of Akkermansia muciniphilia even improved insulin sensitivity and cholesterol levels in overweight/obese insulin-resistant volunteers.[228]

7.4 | Personalized approaches

Future nutritional and lifestyle interventions will largely benefit from personalized treatment strategies tailored to individual subjects (ie "precision nutrition"). A landmark study from Zeevi et al (2015)[229] demonstrated that large interpersonal variability exists in the postprandial glycemic response to identical meals. Most surprisingly, a machine-learning algorithm including blood-derived metabolic parameters, dietary habits, PA and data on microbiota could predict the individual postprandial glycemic response. Similarly, the PREDICT1 study assessed postprandial glucose, insulin and triglycerides in 1002 twins and unrelated healthy adults.[230] Notably, microbiota had a greater influence than macronutrients on postprandial triglycerides, and the influence on postprandial glucose was considerable. Also, machine-learning algorithm considering genetic variants allowed for prediction of triglyceride and glucose responses to food intake.[230]

As the first of its kind, the PNPLA3 polymorphism has been studied as a modifier for dietary response. Specifically, the improvement in IHLC and insulin sensitivity following a LCD was influenced by PNPLA3-genotype with (homozygous) carriers of the G-allele achieving a higher reduction in IHLC than individuals harbouring only PNPLA3 C/C alleles.[231,232] The DNA methylation profile may also provide prognostic information on successful WL during dietary/lifestyle interventions.[233] Recently, Vilar-Gomez et al[234] confirmed a modulatory effect of PNPLA3 on the relationship between reported carbohydrate-/PUFA-/flavonoid-intake and significant fibrosis. From these data, one might hypothesize that the genetic predisposition centrally influences ones response to a specific diet, and implications on liver disease severity.

Finally, web-based applications might increase adherence to lifestyle interventions as they have been discussed as alternatives to group-based interventions for maintaining individuals' adherence to lifestyle interventions[235] or exercise programs[236] despite concerns about lower attrition rates.[235]

8 | STRENGTHS AND LIMITATIONS OF LIFESTYLE INTERVENTIONS

From a holistic point of view, lifestyle interventions have certain unique advantages, but also limitations that need to be considered. Given promising data on NASH regression when WL is achieved,[39,237] the cost-effectiveness of lifestyle interventions is favorable. Noteworthy, the annual healthcare expenditure for unhealthy diets are estimated to range from 3 to 148€ per capita and from 3-181€ per capita for low PA,[238] and unhealthy lifestyle can be attributed to ~6 years of life-expectancy lost.[239,240] Targeting both aspects by lifestyle interventions does therefore indeed make sense although specific data on the cost-effectiveness in NAFLD are missing. Moreover, diet and lifestyle interventions improve metabolism and health in a versatile way as outlined above, triggering beneficial health effects presumably more efficient than NASH drugs targeting only a certain mechanism of NASH-development.

Nevertheless, several caveats need to be kept in mind that limit these promising aspects. As a result of the heterogeneity of dietary interventions and study cohorts (see also Table 2), results of individual studies can hardly be directly compared, making strong guideline-recommendations significantly more difficult. Next, outcome measures differ across studies, and it remains to be answered whether changes in IHLC/ transaminase levels are a valid endpoint for dietary interventions with questionable influence on long-term prognosis. Also, the adherence to lifestyle interventions declines in parallel with the duration of the intervention, resulting in a rebound-phenomenon that has largely been shown for BW.[241] In terms of adherence, underestimated factors such as gender, intrinsic and extrinsic motivation (including monitoring of the intervention), socioeconomic status, among others, are also known to influence adherence to lifestyle interventions, and thus complicate interpretation of the outcome.[242]

9 | CONCLUSION

In conclusion, diet and exercise will likely remain the key therapeutic elements to fight the burden of fatty liver disease. Recent studies have highlighted the importance of calorie restriction regardless of dietary composition and while low-carbohydrate diets were most promising for reducing metabolic dysregulation and severity of NAFLD. Promotion of ketogenesis—potentially achieved via intermittent calorie restriction—seems to be the central mechanistic aspect of beneficial diets in NAFLD/NASH. Interactions of diet and exercise with the gut microbiota and the individual genetic background will need to be comprehensively understood to develop personalized life-style intervention strategies for patients with NAFLD/NASH.

CONFLICTS OF INTEREST

The authors have nothing to disclose regarding the work under consideration for publication. The following authors disclose conflicts of interests outside the submitted work: CD is part of the scientific advisory board of SPAR Oesterreich AG. TR received grant support from AbbVie, Boehringer-Ingelheim, Gilead, MSD, Philips Healthcare, Gore; speaking honoraria from AbbVie, Gilead, Gore, Intercept, Roche, MSD; consulting/advisory board fee from AbbVie,

Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; and travel support from Boehringer-Ingelheim, Gilead and Roche. MT received grant support from Albireo, Cymabay, Falk, Gilead, Intercept, MSD and Takeda, honoraria for consulting from Albireo, Boehringer Ingelheim, BiomX, Falk, Genfit, Gilead, Intercept, MSD, Novartis, Phenex, Regulus and Shire, speaker fees from Bristol-Myers Squibb, Falk, Gilead, Intercept and MSD, as well as travel support from AbbVie, Falk, Gilead and Intercept. He is also the coninventor on patents for the medical use of norUDCA filed by the Medical Universities of Graz and Vienna.

ORCID

Georg Semmler https://orcid.org/0000-0002-0411-166X
Christian Datz https://orcid.org/0000-0001-7838-4532
Thomas Reiberger https://orcid.org/0000-0002-4590-3583
Michael Trauner https://orcid.org/0000-0002-1275-6425

REFERENCES

1. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2018;15(1):11-20.
2. Neuschwander-Tetri BA. Therapeutic landscape for NAFLD in 2020. *Gastroenterology*. 2020;158(7):1984-1998.e1983.
3. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016;65(8):1038-1048.
4. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology (Baltimore, MD)*. 2010;52(5):1836-1846.
5. Berná G, Romero-Gomez M. The role of nutrition in non-alcoholic fatty liver disease: pathophysiology and management. *Liver Int*. 2020;40(S1):102-108.
6. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol*. 2017;67(4):829-846.
7. Hallsworth K, Adams LA. Lifestyle modification in NAFLD/NASH: facts and figures. *JHEP Rep*. 2019;1(6):468-479.
8. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;64(6):1388-1402.
9. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Clin Liv Dis*. 2018;11(4):81.
10. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr (Edinburgh, Scotland)*. 2019;38(2):485-521.
11. Eslam M, Sarin SK, Wong VW-S, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hep Intl*. 2020;14(6):889-919.
12. Miller EF. Nutrition management strategies for nonalcoholic fatty liver disease: treatment and prevention. *Clin Liv Dis*. 2020;15(4):144-148.
13. Lifestyle Management: Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019;42(Supplement 1):S46-S60.
14. Merli M, Berzigotti A, Zelber-Sagi S, et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70(1):172-193.
15. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81(2):341-354.
16. Plaz Torres MC, Aghemo A, Lleo A, et al. Mediterranean diet and NAFLD: what we know and questions that still need to be answered. *Nutrients*. 2019;11(12):2971.
17. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;57(11):1299-1313.
18. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a mediterranean diet. *N Engl J Med*. 2013;368(14):1279-1290.
19. Zelber-Sagi S, Salomone F, Mlynarsky L. The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: evidence and plausible mechanisms. *Liver Int*. 2017;37(7):936-949.
20. Kontogianni MD, Tileli N, Margariti A, et al. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. *Clin Nutr (Edinburgh, Scotland)*. 2014;33(4):678-683.
21. Baratta F, Pastori D, Polimeni L, et al. Adherence to mediterranean diet and non-alcoholic fatty liver disease: effect on insulin resistance. *Am J Gastroenterol*. 2017;112(12):1832-1839.
22. Khalatbari-Soltani S, Imamura F, Brage S, et al. The association between adherence to the Mediterranean diet and hepatic steatosis: cross-sectional analysis of two independent studies, the UK Fenland Study and the Swiss CoLaus Study. *BMC Med*. 2019;17(1):19.
23. Trovato FM, Catalano D, Martines GF, Pace P, Trovato GM. Mediterranean diet and non-alcoholic fatty liver disease: the need of extended and comprehensive interventions. *Clin Nutr*. 2015;34(1):86-88.
24. Ryan MC, Itsiopoulos C, Thodis T, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol*. 2013;59(1):138-143.
25. Misciagna G, del Pilar DM, Caramia DV, et al. Effect of a low glycemic index Mediterranean diet on non-alcoholic fatty liver disease. A randomized controlled clinici trial. *J Nutr Health Aging*. 2017;21(4):404-412.
26. Abenavoli L, Greco M, Milic N, et al. Effect of mediterranean diet and antioxidant formulation in non-alcoholic fatty liver disease: a randomized study. *Nutrients*. 2017;9(8):870.
27. Marin-Alejandre BA, Abete I, Cantero I, et al. The metabolic and hepatic impact of two personalized dietary strategies in subjects with obesity and nonalcoholic fatty liver disease: the fatty liver in obesity (FLiO) randomized controlled trial. *Nutrients*. 2019;11(10):2543.
28. Yaskolka Meir A, Rinott E, Tsaban G, et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. *Gut*. 2021.
29. Katsagoni CN, Papatheodoridis GV, Ioannidou P, et al. Improvements in clinical characteristics of patients with non-alcoholic fatty liver disease, after an intervention based on the Mediterranean lifestyle: a randomised controlled clinical trial. *Br J Nutr*. 2018;120(2):164-175.
30. Bogumil D, Park SY, Le Marchand L, et al. High-quality diets are associated with reduced risk of hepatocellular carcinoma and chronic liver disease: the multiethnic cohort. *Hepatol Commun*. 2019;3(3):437-447.
31. Li WQ, Park Y, McGlynn KA, et al. Index-based dietary patterns and risk of incident hepatocellular carcinoma and mortality from chronic liver disease in a prospective study. *Hepatology (Baltimore, MD)*. 2014;60(2):588-597.
32. Markova M, Pivovarova O, Hornemann S, et al. Isocaloric diets high in animal or plant protein reduce liver fat and inflammation in individuals with type 2 diabetes. *Gastroenterology*. 2017;152(3):571-585.e578.
33. Xu C, Markova M, Seebeck N, et al. High-protein diet more effectively reduces hepatic fat than low-protein diet despite lower autophagy and FGF21 levels. *Liver Int*. 2020;40(12):2982-2997.
34. Garcêz LS, Avelar CR, Fonseca NSS, et al. Effect of dietary carbohydrate and lipid modification on clinical and anthropometric parameters in nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Nutr Rev*. 2021.
35. Haufe S, Engeli S, Kast P, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat

in overweight and obese human subjects. *Hepatology (Baltimore, MD)*. 2011;53(5):1504-1514.
36. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab*. 2016;23(4):591-601.
37. de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Conde R, Gonzalez JM. Effect of a hypocaloric diet in transaminases in nonalcoholic fatty liver disease and obese patients, relation with insulin resistance. *Diabetes Res Clin Pract*. 2008;79(1):74-78.
38. Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology*. 2009;136(5):1552-1560.
39. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-378.e5; quiz e314–365.
40. Koutoukidis DA, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179(9):1262-1271.
41. Bisschop PH, de Metz J, Ackermans MT, et al. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am J Clin Nutr*. 2001;73(3):554-559.
42. Pompili S, Vetuschi A, Gaudio E, et al. Long-term abuse of a high-carbohydrate diet is as harmful as a high-fat diet for development and progression of liver injury in a mouse model of NAFLD/NASH. *Nutrition (Burbank, Los Angeles County, Calif)*. 2020;75–76:110782.
43. Beulen Y, Martínez-González MA, van de Rest O, et al. Quality of dietary fat intake and body weight and obesity in a mediterranean population: secondary analyses within the PREDIMED trial. *Nutrients*. 2018;10(12).
44. Liu X, Li Y, Tobias DK, et al. Changes in types of dietary fats influence long-term weight change in US women and men. *J Nutr*. 2018;148(11):1821-1829.
45. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "Calories In, Calories Out". *JAMA Intern Med*. 2018;178(8):1098-1103.
46. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287(18):2414-2423.
47. Pawlak DB, Kushner JA, Ludwig DS. Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *Lancet (London, England)*. 2004;364(9436):778-785.
48. Kennedy AR, Pissios P, Otu H, et al. A high-fat, ketogenic diet induces a unique metabolic state in mice. *Am J Physiol Endocrinol Metab*. 2007;292(6):E1724-E1739.
49. Watanabe M, Tozzi R, Risi R, et al. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature. *Obesity Rev*. 2020;21(8):e13024.
50. Ahn J, Jun DW, Lee HY, Moon JH. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: review and meta-analyses. *Clin Nutr (Edinburgh, Scotland)*. 2019;38(5):2023-2030.
51. Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr*. 2011;93(5):1048-1052.
52. Gepner Y, Shelef I, Schwarzfuchs D, et al. Effect of distinct lifestyle interventions on mobilization of fat storage pools: CENTRAL magnetic resonance imaging randomized controlled trial. *Circulation*. 2018;137(11):1143-1157.
53. Gepner Y, Shelef I, Komy O, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. *J Hepatol*. 2019;71(2):379-388.
54. Mardinoglu A, Wu H, Bjornson E, et al. An Integrated understanding of the rapid metabolic benefits of a carbohydrate-restricted diet on hepatic steatosis in humans. *Cell Metab*. 2018;27(3):559-571.e555.
55. Ebbeling CB, Feldman HA, Klein GL, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. *BMJ (Clin Res ed)*. 2018;363:k4583.
56. Gibson AA, Seimon RV, Lee CM, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obesity Rev*. 2015;16(1):64-76.
57. Luukkonen PK, Dufour S, Lyu K, et al. Effect of a ketogenic diet on hepatic steatosis and hepatic mitochondrial metabolism in nonalcoholic fatty liver disease. *Proc Natl Acad Sci USA*. 2020;117(13):7347-7354.
58. Goss AM, Dowla S, Pendergrass M, et al. Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with nonalcoholic fatty liver disease: a pilot, randomized trial. *Pediatr Obes*. 2020;15(7):e12630.
59. Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D. The effect of low-fat and low-carbohydrate diets on weight loss and lipid levels: a systematic review and meta-analysis. *Nutrients*. 2020;12(12):3774.
60. Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2016;115(3):466-479.
61. Seidelmann SB, Claggett B, Cheng S, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health*. 2018;3(9):e419-e428.
62. Astley CM, Todd JN, Salem RM, et al. Genetic evidence that carbohydrate-stimulated insulin secretion leads to obesity. *Clin Chem*. 2018;64(1):192-200.
63. Duregon E, Pomatto-Watson LCDD, Bernier M, Price NL, de Cabo R. Intermittent fasting: from calories to time restriction. *GeroScience*. 2021;43(3):1083-1092.
64. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. *Science (New York, NY)*. 2018;362(6416):770-775.
65. Duregon E, Pomatto-Watson LCDD, Bernier M, Price NL, de Cabo R. Intermittent fasting: from calories to time restriction. *GeroScience*. 2021;43(3):1083-1092.
66. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med*. 2019;381(26):2541-2551.
67. Saran AR, Dave S, Zarrinpar A. Circadian rhythms in the pathogenesis and treatment of fatty liver disease. *Gastroenterology*. 2020;158(7):1948-1966.e1941.
68. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metabol*. 2019;30(3):462-476.e466.
69. Johari MI, Yusoff K, Haron J, et al. A Randomised controlled trial on the effectiveness and adherence of modified alternate-day calorie restriction in improving activity of non-alcoholic fatty liver disease. *Sci Rep*. 2019;9(1):11232.
70. Cai H, Qin Y-L, Shi Z-Y, et al. Effects of alternate-day fasting on body weight and dyslipidaemia in patients with non-alcoholic fatty liver disease: a randomised controlled trial. *BMC Gastroenterol*. 2019;19(1):219.
71. Holmer M, Lindqvist C, Petersson S, et al. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet: a randomized controlled trial. *JHEP Rep*. 2021;3(3):100256. https://doi.org/10.1016/j.jhepr.2021.100256
72. Welton S, Minty R, O'Driscoll T, et al. Intermittent fasting and weight loss: systematic review. *Can Fam Physician*. 2020;66(2):117-125.
73. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med*. 2017;177(7):930-938.

74. Alhamdan BA, Garcia-Alvarez A, Alzahrnai AH, et al. Alternate-day versus daily energy restriction diets: which is more effective for weight loss? A systematic review and meta-analysis. *Obes Sci Pract*. 2016;2(3):293-302.
75. Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: The TREAT randomized clinical trial. *JAMA Intern Med*. 2020;180(11):1491-1499.
76. Carter S, Clifton PM, Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. *JAMA Network Open*. 2018;1(3):e180756.
77. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabet Med*. 2018;35(5):588-594.
78. Rietman A, Sluik D, Feskens EJM, Kok FJ, Mensink M. Associations between dietary factors and markers of NAFLD in a general Dutch adult population. *Eur J Clin Nutr*. 2018;72(1):117-123.
79. Zelber-Sagi S, Ivancovsky-Wajcman D, Fliss Isakov N, et al. High red and processed meat consumption is associated with non-alcoholic fatty liver disease and insulin resistance. *J Hepatol*. 2018;68(6):1239-1246.
80. Alferink LJ, Kiefte-de Jong JC, Erler NS, et al. Association of dietary macronutrient composition and non-alcoholic fatty liver disease in an ageing population: the Rotterdam Study. *Gut*. 2019;68(6):1088-1098.
81. Alferink LJM, Kiefte-de Jong JC, Erler NS, et al. Diet-dependent acid load - the missing link between an animal protein-rich diet and non-alcoholic fatty liver disease? *J Clin Endocrinol Metab*. 2019;104(12):6325-6337.
82. Ströhle A, Hahn A, Sebastian A. Estimation of the diet-dependent net acid load in 229 worldwide historically studied hunter-gatherer societies. *Am J Clin Nutr*. 2010;91(2):406-412.
83. Remer T. Influence of diet on acid-base balance. *Semin Dial*. 2000;13(4):221-226.
84. Taskinen MR, Packard CJ, Borén J. Dietary fructose and the metabolic syndrome. *Nutrients*. 2019;11(9):1987.
85. Tounian P, Schneiter P, Henry S, Jéquier E, Tappy L. Effects of infused fructose on endogenous glucose production, gluconeogenesis, and glycogen metabolism. *Am J Physiol*. 1994;267(5 Pt 1):E710-E717.
86. Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev*. 2010;90(1):23-46.
87. Softic S, Stanhope KL, Boucher J, et al. Fructose and hepatic insulin resistance. *Crit Rev Clin Lab Sci*. 2020;57(5):308-322.
88. Abdelmalek MF, Lazo M, Horska A, et al. Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. *Hepatology (Baltimore, MD)*. 2012;56(3):952-960.
89. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119(5):1322-1334.
90. Geidl-Flueck B, Hochuli M, Németh Á, et al. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: a randomized controlled trial. *J Hepatol*. 2021.75(1):46–54.
91. Simons N, Veeraiah P, Simons P, et al. Effects of fructose restriction on liver steatosis (FRUITLESS); a double-blind randomized controlled trial. *Am J Clin Nutr*. 2021;113(2):391-400.
92. Ma J, Fox CS, Jacques PF, et al. Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts. *J Hepatol*. 2015;63(2):462-469.
93. Chen H, Wang J, Li Z, et al. Consumption of sugar-sweetened beverages has a dose-dependent effect on the risk of non-alcoholic fatty liver disease: an updated systematic review and dose-response meta-analysis. *Int J Environ Res Public Health*. 2019;16(12):2192.
94. Asgari-Taee F, Zerafati-Shoae N, Dehghani M, Sadeghi M, Baradaran HR, Jazayeri S. Association of sugar sweetened beverages consumption with non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Nutr*. 2019;58(5):1759-1769.
95. Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. *J Hepatol*. 2009;51(5):918-924.
96. Mosca A, Nobili V, De Vito R, et al. Serum uric acid concentrations and fructose consumption are independently associated with NASH in children and adolescents. *J Hepatol*. 2017;66(5):1031-1036.
97. Abdelmalek MF, Suzuki A, Guy C, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology (Baltimore, MD)*. 2010;51(6):1961-1971.
98. Smajis S, Gajdošík M, Pfleger L, et al. Metabolic effects of a prolonged, very-high-dose dietary fructose challenge in healthy subjects. *Am J Clin Nutr*. 2020;111(2):369-377.
99. Softic S, Gupta MK, Wang GX, et al. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. *J Clin Invest*. 2017;127(11):4059-4074.
100. Fisher FM, Kim M, Doridot L, et al. A critical role for ChREBP-mediated FGF21 secretion in hepatic fructose metabolism. *Mol Metab*. 2017;6(1):14-21.
101. Moriya A, Iwasaki Y, Ohguchi S, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. *J Hepatol*. 2015;62(4):921-927.
102. Dunn W, Sanyal AJ, Brunt EM, et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). *J Hepatol*. 2012;57(2):384-391.
103. Hashimoto Y, Hamaguchi M, Kojima T, et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. *J Gastroenterol Hepatol*. 2015;30(3):546-552.
104. Kwon I, Jun DW, Moon JH. Effects of moderate alcohol drinking in patients with nonalcoholic fatty liver disease. *Gut and liver*. 2019;13(3):308-314.
105. Kwon HK, Greenson JK, Conjeevaram HS. Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease. *Liver Int*. 2014;34(1):129-135.
106. Lee HW, Wong VW. Is modest drinking good for the liver? *Clin Gastroenterol Hepatol*. 2018;16(9):1404-1406.
107. Idalsoaga F, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic fatty liver disease and alcohol-related liver disease: two intertwined entities. *Front Med*. 2020;7:448.
108. Cainelli F, Thao T, Pung C, Vento S. Alcohol? Not for non-alcoholic fatty liver disease patients. *Front Med*. 2020;7:14.
109. Ajmera V, Belt P, Wilson LA, et al. Among patients with nonalcoholic fatty liver disease, modest alcohol use is associated with less improvement in histologic steatosis and steatohepatitis. *Clin Gastroenterol Hepatol*. 2018;16(9):1511-1520.e1515.
110. Chang Y, Cho YK, Kim Y, et al. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: a cohort study. *Hepatology (Baltimore, MD)*. 2019;69(1):64-75.
111. Long MT, Massaro JM, Hoffmann U, Benjamin EJ, Naimi TS. Alcohol use is associated with hepatic steatosis among persons with presumed nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2020;18(8):1831-1841.e1835.
112. Åberg F, Puukka P, Salomaa V, et al. Risks of light and moderate alcohol use in fatty liver disease: follow-up of population cohorts. *Hepatology (Baltimore, MD)*. 2020;71(3):835-848.
113. Wijarnpreecha K, Thongprayoon C, Ungprasert P. Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastro Hepatol*. 2017;29(2):e8-e12.

114. Liu F, Wang X, Wu G, et al. Coffee consumption decreases risks for hepatic fibrosis and cirrhosis: a meta-analysis. *PLoS ONE*. 2015;10(11):e0142457.
115. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment Pharmacol Ther*. 2016;43(5):562-574.
116. Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur J Cancer Prev*. 2017;26(5):368-377.
117. Chen YP, Lu FB, Hu YB, Xu LM, Zheng MH, Hu ED. A systematic review and a dose–response meta-analysis of coffee dose and nonalcoholic fatty liver disease. *Clin Nutr*. 2019;38(6):2552-2557.
118. Alferink LJM, Fittipaldi J, Kiefte-de Jong JC, et al. Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: The Rotterdam study. *J Hepatol*. 2017;67(2):339-348.
119. Vitaglione P, Morisco F, Mazzone G, et al. Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. *Hepatology (Baltimore, MD)*. 2010;52(5):1652-1661.
120. Salomone F, Li Volti G, Vitaglione P, et al. Coffee enhances the expression of chaperones and antioxidant proteins in rats with nonalcoholic fatty liver disease. *Transl Res*. 2014;163(6):593-602.
121. Shi H, Dong L, Dang X, et al. Effect of chlorogenic acid on LPS-induced proinflammatory signaling in hepatic stellate cells. *Inflamm Res*. 2013;62(6):581-587.
122. Seo HY, Jung YA, Lee SH, et al. Kahweol decreases hepatic fibrosis by inhibiting the expression of connective tissue growth factor via the transforming growth factor-beta signaling pathway. *Oncotarget*. 2017;8(50):87086-87094.
123. Alferink LJM, Kiefte-de Jong JC, Darwish MS. Potential mechanisms underlying the role of coffee in liver health. *Semin Liver Dis*. 2018;38(3):193-214.
124. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol*. 2009;130(2):117-121.
125. Nakayama T, Oishi K. Influence of coffee (Coffea arabica) and galacto-oligosaccharide consumption on intestinal microbiota and the host responses. *FEMS Microbiol Lett*. 2013;343(2):161-168.
126. Hussain SK, Dong TS, Agopian V, et al. Dietary protein, fiber and coffee are associated with small intestine microbiome composition and diversity in patients with liver cirrhosis. *Nutrients*. 2020;12(5):1395.
127. Bajaj JS, Idilman R, Mabudian L, et al. Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort. *Hepatology (Baltimore, MD)*. 2018;68(1):234-247.
128. Ros E. Health benefits of nut consumption. *Nutrients*. 2010;2(7):652-682.
129. Zhang S, Fu J, Zhang Q, et al. Association between nut consumption and non-alcoholic fatty liver disease in adults. *Liver Int*. 2019;39(9):1732-1741.
130. Bb C, Han Y, Pan X, et al. Association between nut intake and non-alcoholic fatty liver disease risk: a retrospective case-control study in a sample of Chinese Han adults. *BMJ Open*. 2019;9(9):e028961.
131. Semmler G, Bachmayer S, Wernly S, et al. Nut consumption and the prevalence and severity of non-alcoholic fatty liver disease. *PLoS ONE*. 2020;15(12):e0244514.
132. Bullón-Vela V, Abete I, Tur JA, et al. Influence of lifestyle factors and staple foods from the Mediterranean diet on non-alcoholic fatty liver disease among older individuals with metabolic syndrome features. *Nutrition (Burbank, Los Angeles County, Calif)*. 2020;71:110620.
133. de Souza RGM, Schincaglia RM, Pimentel GD, Mota JF. Nuts and human health outcomes: a systematic review. *Nutrients*. 2017;9(12):1311.
134. Ruisinger JF, Gibson CA, Backes JM, et al. Statins and almonds to lower lipoproteins (the STALL Study). *J Clin Lipidol*. 2015;9(1):58-64.
135. Yan JH, Guan BJ, Gao HY, Peng XE. Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Medicine*. 2018;97(37):e12271.
136. Musa-Veloso K, Venditti C, Lee HY, et al. Systematic review and meta-analysis of controlled intervention studies on the effectiveness of long-chain omega-3 fatty acids in patients with nonalcoholic fatty liver disease. *Nutr Rev*. 2018;76(8):581-602.
137. Pickett-Blakely O, Young K, Carr RM. Micronutrients in nonalcoholic fatty liver disease pathogenesis. *Cell Mol Gastroenterol Hepatol*. 2018;6(4):451-462.
138. Dongiovanni P, Fracanzani AL, Fargion S, Valenti L. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. *J Hepatol*. 2011;55(4):920-932.
139. Datz C, Müller E, Aigner E. Iron overload and non-alcoholic fatty liver disease. *Minerva Endocrinol*. 2017;42(2):173-183.
140. Zolfaghari H, Askari G, Siassi F, Feizi A, Sotoudeh G. Intake of nutrients, fiber, and sugar in patients with nonalcoholic fatty liver disease in comparison to healthy individuals. *Int J Prev Med*. 2016;7:98.
141. Aigner E, Theurl I, Haufe H, et al. Copper availability contributes to iron perturbations in human nonalcoholic fatty liver disease. *Gastroenterology*. 2008;135(2):680-688.
142. Jafarnejad S, Mahboobi S, McFarland LV, Taghizadeh M, Rahimi F. Meta-analysis: effects of zinc supplementation alone or with multi-nutrients, on glucose control and lipid levels in patients with type 2 diabetes. *Prev Nutr Food Sci*. 2019;24(1):8-23.
143. Wang X, Wu W, Zheng W, et al. Zinc supplementation improves glycemic control for diabetes prevention and management: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2019;110(1):76-90.
144. Harder NHO, Hieronimus B, Stanhope KL, et al. Effects of dietary glucose and fructose on copper, iron, and zinc metabolism parameters in humans. *Nutrients*. 2020;12(9):2581.
145. Song M, Li X, Zhang X, et al. Dietary copper-fructose interactions alter gut microbial activity in male rats. *Am J Physiol Gastrointest Liver Physiol*. 2018;314(1):G119-g130.
146. Fleming DJ, Tucker KL, Jacques PF, Dallal GE, Wilson PW, Wood RJ. Dietary factors associated with the risk of high iron stores in the elderly Framingham Heart Study cohort. *Am J Clin Nutr*. 2002;76(6):1375-1384.
147. Nelson JE, Roth CL, Wilson LA, et al. Vitamin D deficiency is associated with increased risk of non-alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease: possible role for MAPK and NF-κB? *Am J Gastroenterol*. 2016;111(6):852-863.
148. Sato K, Gosho M, Yamamoto T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition (Burbank, Los Angeles County, Calif)*. 2015;31(7–8):923-930.
149. Hariri M, Zohdi S. Effect of vitamin d on non-alcoholic fatty liver disease: a systematic review of randomized controlled clinical trials. *Int J Prev Med*. 2019;10:14.
150. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. *Hepatology (Baltimore, MD)*. 2020;71(2):495-509.
151. Orci LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol*. 2016;14(10):1398-1411.
152. Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: a meta-analysis. *Metab, Clin Exp*. 2017;68:119-132.
153. Wang ST, Zheng J, Peng HW, et al. Physical activity intervention for non-diabetic patients with non-alcoholic fatty liver disease: a

meta-analysis of randomized controlled trials. *BMC Gastroenterol*. 2020;20(1):66.
154. Golabi P, Locklear CT, Austin P, et al. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: systematic review. *World J Gastroenterol*. 2016;22(27):6318-6327.
155. Keating SE, Hackett DA, Parker HM, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. *J Hepatol*. 2015;63(1):174-182.
156. Zhang H-J, He J, Pan L-L, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial. *JAMA Intern Med*. 2016;176(8):1074-1082.
157. Zhang H-J, Pan L-L, Ma Z-M, et al. Long-term effect of exercise on improving fatty liver and cardiovascular risk factors in obese adults: a 1-year follow-up study. *Diabetes Obes Metab*. 2017;19(2):284-289.
158. Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. *J Hepatol*. 2017;66(1):142-152.
159. Cuthbertson Daniel J, Shojaee-Moradie F, Sprung Victoria S, et al. Dissociation between exercise-induced reduction in liver fat and changes in hepatic and peripheral glucose homoeostasis in obese patients with non-alcoholic fatty liver disease. *Clin Sci*. 2015;130(2):93-104.
160. Shojaee-Moradie F, Cuthbertson DJ, Barrett M, et al. Exercise training reduces liver fat and increases rates of VLDL clearance but not VLDL production in NAFLD. *J Clin Endocrinol Metab*. 2016;101(11):4219-4228.
161. Martins C, Morgan L, Truby H. A review of the effects of exercise on appetite regulation: an obesity perspective. *Int J Obes (2005)*. 2008;32(9):1337-1347.
162. Lee YH, Jung KS, Kim SU, et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008–2011). *J Hepatol*. 2015;63(2):486-493.
163. Koo BK, Kim D, Joo SK, et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. *J Hepatol*. 2017;66(1):123-131.
164. Tapper EB, Martinez-Macias R, Duarte-Rojo A. Is exercise beneficial and safe in patients with cirrhosis and portal hypertension? *Current Hepatol Rep*. 2018;17(3):175-183.
165. Thyfault JP, Du M, Kraus WE, Levine JA, Booth FW. Physiology of sedentary behavior and its relationship to health outcomes. *Med Sci Sports Exerc*. 2015;47(6):1301-1305.
166. Ryu S, Chang Y, Jung H-S, et al. Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *J Hepatol*. 2015;63(5):1229-1237.
167. Helajärvi H, Pahkala K, Heinonen OJ, et al. Television viewing and fatty liver in early midlife. The cardiovascular risk in young finns study. *Ann Med*. 2015;47(6):519-526.
168. Meng G, Liu F, Fang L, et al. The overall computer/mobile devices usage time is related to newly diagnosed non-alcoholic fatty liver disease: a population-based study. *Ann Med*. 2016;48(7):568-576.
169. Loh R, Stamatakis E, Folkerts D, Allgrove JE, Moir HJ. Effects of interrupting prolonged sitting with physical activity breaks on blood glucose, insulin and triacylglycerol measures: a systematic review and meta-analysis. *Sport Med (Auckland, NZ)*. 2020;50(2):295-330.
170. Piguet AC, Saran U, Simillion C, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. *J Hepatol*. 2015;62(6):1296-1303.
171. Arfianti A, Pok S, Barn V, et al. Exercise retards hepatocarcinogenesis in obese mice independently of weight control. *J Hepatol*. 2020;73(1):140-148.
172. Guarino M, Kumar P, Felser A, et al. Exercise attenuates the transition from fatty liver to steatohepatitis and reduces tumor formation in mice. *Cancers*. 2020;12(6):1407.
173. Saran U, Guarino M, Rodríguez S, et al. Anti-tumoral effects of exercise on hepatocellular carcinoma growth. *Hepatol Commun*. 2018;2(5):607-620.
174. Behrens G, Matthews CE, Moore SC, et al. The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study. *Eur J Epidemiol*. 2013;28(1):55-66.
175. Cheng S, Ge J, Zhao C, et al. Effect of aerobic exercise and diet on liver fat in pre-diabetic patients with non-alcoholic-fatty-liver-disease: a randomized controlled trial. *Sci Rep*. 2017;7(1):15952.
176. Kenneally S, Sier JH, Moore JB. Efficacy of dietary and physical activity intervention in non-alcoholic fatty liver disease: a systematic review. *BMJ Open Gastroenterol*. 2017;4(1):e000139.
177. Franco I, Bianco A, Mirizzi A, et al. Physical activity and low glycemic index mediterranean diet: main and modification effects on NAFLD score. Results from a randomized clinical trial. *Nutrients*. 2020;13(1).
178. Ristow M, Zarse K, Oberbach A, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci USA*. 2009;106(21):8665-8670.
179. Paulsen G, Cumming KT, Holden G, et al. Vitamin C and E supplementation hampers cellular adaptation to endurance training in humans: a double-blind, randomised, controlled trial. *J Physiol*. 2014;592(8):1887-1901.
180. Morrison D, Hughes J, Della Gatta PA, et al. Vitamin C and E supplementation prevents some of the cellular adaptations to endurance-training in humans. *Free Radic Biol Med*. 2015;89:852-862.
181. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab*. 2017;25(2):262-284.
182. Ludwig DS, Willett WC, Volek JS, Neuhouser ML. Dietary fat: from foe to friend? *Science (New York, NY)*. 2018;362(6416):764-770.
183. Green H. Dietary carbohydrates: a food processing perspective. *Nutr Bull*. 2015;40(2):77-82.
184. Grabacka M, Pierzchalska M, Dean M, Reiss K. Regulation of ketone body metabolism and the role of PPARα. *Int J Mol Sci*. 2016;17(12):2093.
185. Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab*. 2007;5(6):415-425.
186. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab*. 2007;5(6):426-437.
187. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J Clin Invest*. 1999;103(11):1489-1498.
188. Sengupta S, Peterson TR, Laplante M, Oh S, Sabatini DM. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature*. 2010;468(7327):1100-1104.
189. Francque S, Szabo G, Abdelmalek MF, et al. Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors. *Nat Rev Gastroenterol Hepatol*. 2021;18(1):24-39.
190. Francque S, Verrijken A, Caron S, et al. PPARα gene expression correlates with severity and histological treatment response in patients with non-alcoholic steatohepatitis. *J Hepatol*. 2015;63(1):164-173.
191. Sven MF, Pierre B, Manal FA, et al. A randomised, double-blind, placebo-controlled, multi-centre, dose-range, proof-of-concept, 24-week treatment study of lanifibranor in adult subjects with non-alcoholic steatohepatitis: design of the NATIVE study. *Contemp Clin Trials*. 2020;98:106170.
192. Gälman C, Lundåsen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARα activation in man. *Cell Metab*. 2008;8(2):169-174.
193. Newman JC, Covarrubias AJ, Zhao M, et al. Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell Metab*. 2017;26(3):547-557.e548.
194. Miller VJ, Villamena FA, Volek JS. Nutritional ketosis and mitohormesis: potential implications for mitochondrial function and human health. *J Nutr Metab*. 2018;2018:5157645.

195. Newman JC, Verdin E. β-hydroxybutyrate: a signaling metabolite. *Annu Rev Nutr*. 2017;37:51-76.
196. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science (New York, NY)*. 2013;339(6116):211-214.
197. Haces ML, Hernández-Fonseca K, Medina-Campos ON, Montiel T, Pedraza-Chaverri J, Massieu L. Antioxidant capacity contributes to protection of ketone bodies against oxidative damage induced during hypoglycemic conditions. *Exp Neurol*. 2008;211(1):85-96.
198. Youm Y-H, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med*. 2015;21(3):263-269.
199. Graff EC, Fang H, Wanders D, Judd RL. Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. *Metab, Clin Exp*. 2016;65(2):102-113.
200. Fletcher JA, Deja S, Satapati S, Fu X, Burgess SC, Browning JD. Impaired ketogenesis and increased acetyl-CoA oxidation promote hyperglycemia in human fatty liver. *JCI Insight*. 2019;5(11).
201. Mey JT, Erickson ML, Axelrod CL, et al. β-Hydroxybutyrate is reduced in humans with obesity-related NAFLD and displays a dose-dependent effect on skeletal muscle mitochondrial respiration in vitro. *Am J Physiol Endocrinol Metab*. 2020;319(1):E187-E195.
202. Satapati S, Kucejova B, Duarte JAG, et al. Mitochondrial metabolism mediates oxidative stress and inflammation in fatty liver. *J Clin Invest*. 2015;125(12):4447-4462.
203. Satapati S, Sunny NE, Kucejova B, et al. Elevated TCA cycle function in the pathology of diet-induced hepatic insulin resistance and fatty liver [S]. *J Lipid Res*. 2012;53(6):1080-1092.
204. Sunny Nishanth E, Parks Elizabeth J, Browning Jeffrey D, Burgess SC. Excessive hepatic mitochondrial TCA cycle and gluconeogenesis in humans with nonalcoholic fatty liver disease. *Cell Metab*. 2011;14(6):804-810.
205. d'Avignon DA, Puchalska P, Ercal B, et al. Hepatic ketogenic insufficiency reprograms hepatic glycogen metabolism and the lipidome. *JCI insight*. 2018;3(12).
206. Koliaki C, Szendroedi J, Kaul K, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. *Cell Metab*. 2015;21(5):739-746.
207. Cotter DG, Ercal B, Huang X, et al. Ketogenesis prevents diet-induced fatty liver injury and hyperglycemia. *J Clin Invest*. 2014;124(12):5175-5190.
208. Mohr AE, Jäger R, Carpenter KC, et al. The athletic gut microbiota. *J Int Soc Sports Nutr*. 2020;17(1):24.
209. Aya V, Flórez A, Perez L, Ramírez JD. Association between physical activity and changes in intestinal microbiota composition: a systematic review. *PLoS One*. 2021;16(2):e0247039.
210. Estaki M, Pither J, Baumeister P, et al. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome*. 2016;4(1):42.
211. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*. 2014;63(12):1913-1920.
212. Barton W, Penney NC, Cronin O, et al. The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. *Gut*. 2018;67(4):625-633.
213. Petersen LM, Bautista EJ, Nguyen H, et al. Community characteristics of the gut microbiomes of competitive cyclists. *Microbiome*. 2017;5(1):98.
214. Dao MC, Everard A, Aron-Wisnewsky J, et al. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut*. 2016;65(3):426-436.
215. Everard A, Belzer C, Geurts L, et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci*. 2013;110(22):9066-9071.
216. Quiroga R, Nistal E, Estébanez B, et al. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. *Exp Mol Med*. 2020;52(7):1048-1061.
217. Liu Y, Wang Y, Ni Y, et al. Gut Microbiome fermentation determines the efficacy of exercise for diabetes prevention. *Cell Metab*. 2020;31(1):77-91.e75.
218. Bycura D, Santos AC, Shiffer A, et al. Impact of different exercise modalities on the human gut microbiome. *Sports (Basel, Switzerland)*. 2021;9(2).
219. Allen JM, Mailing LJ, Niemiro GM, et al. Exercise alters gut microbiota composition and function in lean and obese humans. *Med Sci Sports Exerc*. 2018;50(4):747-757.
220. Scheiman J, Luber JM, Chavkin TA, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. *Nat Med*. 2019;25(7):1104-1109.
221. Shortt C, Hasselwander O, Meynier A, et al. Systematic review of the effects of the intestinal microbiota on selected nutrients and non-nutrients. *Eur J Nutr*. 2018;57(1):25-49.
222. Mokkala K, Houttu N, Cansev T, Laitinen K. Interactions of dietary fat with the gut microbiota: evaluation of mechanisms and metabolic consequences. *Clin Nutr (Edinburgh, Scotland)*. 2020;39(4):994-1018.
223. Ang QY, Alexander M, Newman JC, et al. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. *Cell*. 2020;181(6):1263-1275.e1216.
224. Beisner J, Gonzalez-Granda A, Basrai M, Damms-Machado A, Bischoff SC. Fructose-induced intestinal microbiota shift following two types of short-term high-fructose dietary phases. *Nutrients*. 2020;12(11):3444.
225. Horne RG, Yu Y, Zhang R, et al. High fat-high fructose diet-induced changes in the gut microbiota associated with dyslipidemia in syrian hamsters. *Nutrients*. 2020;12(11):3557.
226. Magne F, Gotteland M, Gauthier L, et al. The firmicutes/bacteroidetes ratio: a relevant marker of gut dysbiosis in obese patients? *Nutrients*. 2020;12(5):1474.
227. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell*. 2018;173(7):1728-1741.e1713.
228. Depommier C, Everard A, Druart C, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat Med*. 2019;25(7):1096-1103.
229. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. *Cell*. 2015;163(5):1079-1094.
230. Berry SE, Valdes AM, Drew DA, et al. Human postprandial responses to food and potential for precision nutrition. *Nat Med*. 2020;26(6):964-973.
231. Sevastianova K, Kotronen A, Gastaldelli A, et al. Genetic variation in PNPLA3 (adiponutrin) confers sensitivity to weight loss-induced decrease in liver fat in humans. *Am J Clin Nutr*. 2011;94(1):104-111.
232. Shen J, Wong GL, Chan HL, et al. PNPLA3 gene polymorphism and response to lifestyle modification in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2015;30(1):139-146.
233. Keller M, Yaskolka Meir A, Bernhart SH, et al. DNA methylation signature in blood mirrors successful weight-loss during lifestyle interventions: the CENTRAL trial. *Genome Med*. 2020;12(1):97.
234. Vilar-Gomez E, Pirola CJ, Sookoian S, et al. Impact of the association between pnpla3 genetic variation and dietary intake on the risk of significant fibrosis in patients with NAFLD. *Am J Gastroenterol*. 2021;116(5):994-1006.
235. Mazzotti A, Caletti MT, Brodosi L, et al. An internet-based approach for lifestyle changes in patients with NAFLD: two-year effects on weight loss and surrogate markers. *J Hepatol*. 2018;69(5):1155-1163.
236. Huber Y, Pfirrmann D, Gebhardt I, et al. Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. *Aliment Pharmacol Ther*. 2019;50(8):930-939.

237. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology (Baltimore, MD)*. 2010;51(1):121-129.
238. Candari C, Cylus J, Nolte E. *Assessing the economic costs of unhealthy diets and low physical activity: An evidence review and proposed framework* [Internet]. European Observatory on Health Systems and Policies; 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK447219/. Health Policy Series, No 47. 2017
239. Chudasama YV, Khunti K, Gillies CL, et al. Healthy lifestyle and life expectancy in people with multimorbidity in the UK Biobank: a longitudinal cohort study. *PLoS Med*. 2020;17(9):e1003332.
240. Manuel DG, Perez R, Sanmartin C, et al. Measuring burden of unhealthy behaviours using a multivariable predictive approach: life expectancy lost in Canada attributable to smoking, alcohol, physical inactivity, and diet. *PLoS Med*. 2016;13(8):e1002082.
241. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr*. 2001;74(5):579-584.
242. Leung AWY, Chan RSM, Sea MMM, Woo J. An overview of factors associated with adherence to lifestyle modification programs for weight management in adults. *Int J Environ Res Public Health*. 2017;14(8):922.

How to cite this article: Semmler G, Datz C, Reiberger T, Trauner M. Diet and exercise in NAFLD/NASH: Beyond the obvious. *Liver Int*. 2021;41:2249–2268. https://doi.org/10.1111/liv.15024