

Oily fish, coffee and walnuts: Dietary treatment for nonalcoholic fatty liver disease

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Abstract

Rates of non-alcoholic fatty liver disease (NAFLD) are increasing worldwide in tandem with the metabolic syndrome, with the progressive form of disease, non-alcoholic steatohepatitis (NASH) likely to become the most common cause of end stage liver disease in the not too distant future. Lifestyle modification and weight loss remain the main focus of management in NAFLD and NASH, however, there has been growing interest in the benefit of specific foods and dietary components on disease progression, with some foods showing protective properties. This article provides an overview of the foods that show the most promise and their potential benefits in NAFLD/NASH, specifically; oily fish/fish oil, coffee, nuts, tea, red wine, avocado and olive oil. Furthermore, it summarises results from animal and human trials and highlights potential areas for future research.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Diet; Coffee; Tea; Olive oil; Nuts; Walnuts; Fish; Fish oils; Red wine

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Core tip: Over and above a low calorie diet to assist with weight loss, specific foods may modify the course of Non-alcoholic fatty liver disease. Two or more serves of oily fish per week has a beneficial effect on lipids and may reduce hepatic steatosis, regular filtered unsweetened coffee is associated with reduced fibrosis severity in non-alcoholic steatohepatitis and a handful of nuts per day improves liver function tests. Addition of avocado and olive oil to the diet is associated with weight loss and improved liver tests while moderate consumption of tea and red wine appears safe.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is increasing worldwide in tandem with the epidemics of obesity and type 2 diabetes mellitus (T2DM). In population-based studies from industrialised nations, the prevalence of NAFLD is upwards of 40%, 20% of whom have non-alcoholic steatohepatitis (NASH), the progressive inflammatory form of disease with sequelae of cirrhosis and end stage liver failure^[1]. The pathogenesis of NASH is complex, but invariably begins with the trifecta of a sedentary lifestyle, "western" diet and genetic predisposition. Insulin resistance is intrinsic to the disease and is considered to be the initiating event that causes increased hepatic triglyceride synthesis and steatosis. Subsequent insults to the liver including oxidative stress, cytokine and adipokine dysregulation, immune mediated events and the ongoing pro-inflammatory effects of insulin lead to liver damage and fibrosis^[2].

Lifestyle modification to achieve weight loss and promote fitness has traditionally been the cornerstone of management in NASH, with dietary advice frequently concentrated on the need for low fat and restricted calorie content. Recent data suggests that reduction in body weight of 7% or greater is associated with reduction in hepatic inflammation and steatosis^[3]. Furthermore, a growing body of evidence supports the concept that a diet high in macronutrients such as monounsaturated fatty acids (MUFAs) and omega-3 (n-3), and low in carbohydrates such as fructose, can improve NAFLD independent of weight loss^[3].

Correlation studies with diet are difficult and rely on self-reporting, which introduces recall bias. Subjects who are overweight often underreport energy intake and thus, isolating the effects of specific nutrients is challenging^[4]. Nonetheless, delineating the benefits of specific dietary macronutrients and foods is important in order to give patients a sense of control over their disease and an ability to maintain a healthy and interesting diet that may also improve hepatic and metabolic outcomes. In this review we examine the potential benefits and mechanisms of seven specific dietary components that have shown the most promise for NAFLD/NASH and metabolic disease, specifically; oily fish, coffee, nuts, tea, red wine, avocado and olive oil (Table 1).

OILY FISH AND FISH OIL

Much of the interest on fish oil and its health effects comes from studies by Bang and Dyerberg in the early 1970s who observed that Greenland Eskimos had lower rates of coronary events as well as lower serum cholesterol, phospholipids and triglyceride levels, compared to people living in Denmark. Further analyses of the serum fatty acids found that Greenland Eskimos had lower levels of linolenic acid and arachidonic acids (AA) with higher concentrations of docosahexaenoic acids (DHA), likely due to their high consumption of poly-unsaturated fatty acids (PUFAs) from whale and seal meats. Hence, they speculated that PUFAs were somehow involved in the lower serum lipid levels found in Greenland Eskimos^[5].

Long chain PUFAs consist of omega-3 and omega-6 (n-6) fatty acids. Omega-3 fatty acids include the precursor α -linoleic acid (ALA) and its metabolites eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It is important to recognize that the human body does not produce its own omega-3 fatty acids due to a lack of certain enzymes. Instead, they are obtained through diet (*e.g.*, fatty fish, flaxseed), supplements or omega-3 enriched foods^[6]. Fish synthesize omega-3 fatty acids from ingestion of marine plants. Fish rich in omega-3 fatty acids are those that store lipids in their flesh, such as mackerel, tuna, salmon, sturgeon, mullet, bluefish, anchovy, sardines, herring, trout and menhaden. Leaner fish such as cod and haddock contain less omega-3 as they store lipids in their liver^[7]. Omega-6 fatty acids are commonly found in Western diets and are abundant in plant oils such as corn, soybean and sunflower oil. Omega-6 PUFA metabolism involves its precursor linoleic acid and its metabolite, AA, which has pro-inflammatory and pro-thrombotic properties^[6,8].

Early trials showed compelling evidence that omega-3 PUFAs have beneficial effects on cardiovascular disease, stroke and diabetes^[9]. For people with coronary artery disease, the American Heart Association (AHA) recommends an average of 1 g/d of combined EPA and DHA intake or 2-4 g/d for those with hypertriglyceridemia. For those without coronary artery disease, they recommend at least two servings (3.5 oz/serve) of fatty fish per week. Most people across the globe, however, are not meeting these dietary recommendations, with the average weekly intake of fatty fish somewhere between 10-20 times less than this^[10-12].

Given its positive effects in cardiovascular disease, fish oil has been of significant interest as a potential treatment for NAFLD. Through various mechanisms, omega-3 PUFAs in fish oil have been shown to reduce lipid accumulation and liver enzyme levels, improve insulin sensitivity, and have anti-inflammatory effects^[8,13,14]. Conversely, depletion of omega-3 or

Table 1 Mechanisms of action and potential health benefits of foods

Food	Active components	Metabolic benefits	Hepatic benefits
Oily fish/fish oil	Omega-3 PUFAs (EPA, DHA)	↑ Insulin sensitivity ↑ Adiponectin/PPAR γ ↓ Inflammation ↓ Serum lipids ↓ Blood pressure	↓ LFTs ↑ Fatty acid oxidation ↓ Hepatic steatosis
Coffee	Caffeine Diterpenes Polyphenols (chlorogenic acid)	↓ BMI ↑ Insulin sensitivity ↓ Development of T2DM ↓ Development of CVD ↓ Serum lipids ↓ Blood pressure	↓ LFTs ↓ Development of NAFLD ↓ Development of HCC ↓ Severity of NASH ↓ LFTs
Nuts	MUFAs and PUFAs Vitamin E Phytochemicals (phenolic acid)	↓ Blood pressure ↓ Development of T2DM ↓ Cardiovascular mortality ↓ All cause mortality ↓ BMI	↓ Development of NAFLD ↓ Oxidative stress
Tea	Polyphenols (catechins such as ECGC), Caffeine Flavonol glycosides	↑ Insulin sensitivity	↓ LFTs ↓ Hepatic steatosis
Red wine	Phenols (resveratrol)	↓ Serum lipids ↑ Insulin sensitivity ↓ Cardiovascular mortality	↓ Oxidative stress
Avocado	MUFAs and PUFAs Phytosterols (β -sitosterol) Phytochemicals (carotene, lutein, phenolics) Fiber	↑ Satiety and ↓ Body weight ↓ Inflammation ↓ Blood glucose ↓ Serum lipids ↓ BMI	↓ LFTs ↓ Oxidative stress ↓ Hepatic steatosis
Olive oil	MUFAs (oleic acid)	↑ Insulin sensitivity ↓ Serum lipids	↓ LFTs ↓ Oxidative stress ↓ Hepatic steatosis

BMI: Body mass index; CVD: Cardiovascular disease; DHA: Docosahexaenoic acids; ECGC: Epigallocatechin-3-gallate; EPA: Eicosapentaenoic acid; HCC: Hepatocellular carcinoma; LFT: Liver function test; MUFA: Monounsaturated fatty acid; n-3: Omega-3; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PPAR γ : Peroxisome proliferator-activated receptor gamma; PUFA: Polyunsaturated fatty acid; T2DM: Type 2 diabetes mellitus.

increased omega-6:omega-3 (pro-inflammatory: anti-inflammatory) ratios are implicated in the development of hepatic steatosis and subsequently NAFLD/NASH^[8]. A systematic review and meta-analysis of the efficacy of omega-3 supplementation in NAFLD including 9 eligible trials (4 randomized placebo-controlled) analyzed 355 individuals with NAFLD/NASH, given either omega-3 PUFA supplementation or placebo treatment, for a median duration of 6 mo (see Table 2). Median dose of PUFA treatment was 4 g/d. Despite marked heterogeneity between studies, omega-3 PUFA supplementation reduced liver fat as measured by ultrasound, MRI or biopsy and improved liver enzymes (AST and ALT), with the reduction in liver fat remaining significant even when randomized controlled trials (RCTs) only were considered^[14]. In 2008, a pilot study involving 23 subjects with biopsy proven NASH showed promising results of improved liver enzymes, steatosis and fibrosis with ethyl EPA (E-EPA)^[15]. In NASH, a number of RCTs with histological end points have been unsuccessful in replicating these initial positive results. The largest study involving 243 biopsy-proven NASH subjects given placebo, low-dose E-EPA (1.8 g/d) or high-dose E-EPA (2.7 g/d) for 12 mo did not show any significant effects on liver steatosis, inflammation or fibrosis across treatment groups^[16]. There was also no significant improvement in metabolic parameters

including HbA1c, total cholesterol and BMI. The exception was serum triglycerides, which was lower in the high-dose E-EPA group compared to placebo. It is worthwhile noting, however, that almost 25% of subjects did not complete the trial. Three further RCTs in patients with NASH have shown similar results^[17-19], with reductions in liver fat, but no significant improvement in other histological parameters. Interestingly, Dasarathy *et al.*^[17], who only investigated patients with NASH and diabetes, found omega-3 PUFAs to be inferior to placebo in its effects on hepatic steatosis, NAFLD activity score and insulin resistance. Moreover, glycemic control and insulin resistance worsened with treatment. To date, these results have not been replicated.

A limited number of studies have examined omega-3 PUFA supplementation in patients with pediatric NAFLD with results largely mirroring those seen in adult populations^[20]. Nobili *et al.*^[21] prospectively followed 60 children with biopsy confirmed NAFLD and showed that both short (6 mo) and longer term (24 mo)^[22] DHA supplementation, reduced liver steatosis as measured by ultrasound in addition to improving ALT and triglycerides, irrespective of DHA dose (250 mg/d vs 500 mg/d). In a follow up study the same authors showed that supplementation of 250 mg DHA for 18 mo improved hepatic steatosis

Table 2 Important human studies assessing effect of foods on non-alcoholic fatty liver disease

Food	Ref.	Sample (n)	Study type	Intervention	Duration	Outcomes
Oily Fish/ Fish oil (n-3 PUFAs)	Parker <i>et al</i> ^[14]	355	Meta-analysis	4 g/d (median); range 0.83-13.7 g/d	6 mo (median); range 8 wk-12 mo	Improvement in liver fat ($P < 0.001$); AST ($P = 0.02$) Sub-analyses of RCTs only: Significant reduction in liver fat ($P < 0.001$); No significant improvement in ALT ($P = 0.74$) or AST ($P = 0.28$)
Coffee	Molloy <i>et al</i> ^[50]	306	Cross-sectional	Validated questionnaire for coffee caffeine and total caffeine consumption NAFLD cases - liver biopsy	Recall	Coffee caffeine intake (but not total caffeine intake) demonstrated negative correlation with fibrosis stage ($r = -0.215$, $P = 0.035$) and associated with reduced incidence advanced NASH (F2-4).
Nuts	Barrera <i>et al</i> ^[3]	106 17	Longitudinal	Walnut and other nut intake assessed	6 mo	Walnut intake correlated with reduced GGT ($r = -0.26$), ALT ($r = -0.31$) and AST ($r = -0.21$, $P < 0.05$ for all) at 3 months. At 6 months intake of other nuts was associated with reduced GGT ($r = -0.23$, $P = 0.03$), while both walnuts and other nut intake correlated to reduced AST ($r = -0.22$, $P < 0.05$)
Tea	Sakata <i>et al</i> ^[85]		Pilot RCT	Green tea; High catechin (1080 mg) <i>vs</i> standard catechin (200 mg) <i>vs</i> placebo	12 wk	Significant reductions in ALT, body fat percentage and hepatic fat based on CT in high catechin green tea group alone
Avocado	Pahua-Ramos <i>et al</i> ^[120]	35		Group 1: Control Group 2: ↑ cholesterol diet + 60% Fructose (HHF) Group 3: HHF + Avocado Group 4: HHF + reduced-calorie avocado paste (P) Group 5: HHF + P + fiber	7 wk	Addition of avocado paste to high cholesterol/fructose diet (HHF) was associated with decreased total cholesterol, LDL, TG, ALT and AST (43.1%, 45.4%, 32.8%, 39.8% and 35.1% respectively; $P \leq 0.05$) and improved insulin sensitivity compared to HHF diet alone HHF + avocado paste and fiber <i>vs</i> HHF associated with reduced hepatic steatosis and inflammation, reduced total cholesterol, AST, ALT, LDL and glucose levels ($P \leq 0.05$ for all)
Olive oil	Nigam <i>et al</i> ^[133]	93	Randomised controlled parallel study	Olive oil <i>vs</i> canola oil <i>vs</i> control (< 20 g/d) with normal diet and 40-45 min morning walk advised for all groups	6 mo	Weight loss: -6% (olive oil, $P < 0.05$) 2% (control, NS) Histology: significant reduction in steatosis grading ($P < 0.05$) Other: significant reduction in BMI ($P < 0.05$) and insulin resistance ($P < 0.05$)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CT: Computed tomography; GGT: Gamma-glutamyl transferase; LFT: Liver function test; MUFA: Monounsaturated fatty acid; n-3: Omega-3; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PUFA: Polyunsaturated fatty acid; RCT: Randomised control trial; TG: Triglycerides.

and ballooning as measured on paired biopsies, but did not affect fibrosis^[23]. Importantly however, a marked anti-inflammatory effect was noted in these biopsies, characterized by reductions in hepatic progenitor cell activation, reduced numbers of inflammatory macrophages and G-protein receptor changes associated with inhibition of TNF and toll like receptor pathways^[20]. In pediatric patients with obesity or metabolic syndrome the addition of omega-3 has also variably been associated with reductions in hypertension, improvement in lipid profile and reductions in insulin resistance^[20] suggesting it is likely to be of benefit in NAFLD.

FISH OIL CAPSULES OR FISH

According to data from the USDA Nutrient Data Laboratory, Atlantic salmon and herring provide the most EPA + DHA content, leaner fish such as cod and haddock have 6-8 times less. Standard fish oil capsules also have variable ratio and total EPA and DHA dose, ranging from 300 to 750 mg per capsule, thus requiring 2-4 capsules per day

to achieve the AHA recommendation of > 1 g/d. Harris *et al*^[24] measured omega-3 in red blood cells and phospholipids in 24 participants after a 16 wk period of equivalent doses of combined EPA and DHA consumed either as fish oil capsules taken daily or servings of either salmon or albacore tuna taken twice weekly. The study found that there was no significant difference in efficacy between the two. Subsequently, a 12 mo double-blind, RCT involving 80 participants demonstrated that supplementation of fish oil capsules daily provided greater cellular incorporation of EPA and DHA as compared to those in patients given an equivalent weekly dose of fish oil twice per week^[9]. Results of this study may have implications on the current AHA recommendations of 2 oily fish servings per week. For young children, the situation is somewhat altered with regulatory agencies recommending less than 60 g of fish per week, due to the potential risk of environmental contaminants, but also the avoidance of fish oil supplements without a doctor's prescription^[25]. Nonetheless the World Health Organization recommends consumption of at least 400 mg per 10 kg bodyweight omega-3 each day,

while the International Society for the Study of Fatty Acids and Lipids suggests 350–750 mg per 10 kg of body weight^[25]. Thus far, data for recommendations for cardiovascular and pro-inflammatory disease such as NAFLD have been extrapolated from studies, which have primarily involved daily fish oil supplementation.

While there appears to be ample evidence that regular consumption of oily fish has metabolic benefit, the effect of additional oily fish or fish oil supplementation in NAFLD is uncertain and the current optimal dose is not known. Despite studies showing consistent improvement in liver fat content as semi-quantitatively measured by ultrasound or other imaging, recent RCTs have not shown a significant benefit in the harder endpoints of liver histology or fibrosis. Importantly, there have not been any detrimental effects apart from one study suggesting that glycemic control worsened in NASH patients with diabetes. Further RCTs with histological end-points, larger sample size, and with better quantification of compliance will need to be evaluated.

COFFEE

From the apocryphal legend of how coffee was discovered by Kaldi and his jumping goats, to the use of ground coffee beans mixed with animal fat by Abyssinian tribes as an energy food, coffee has long captured the imagination of mankind. Writings on coffee by the famed Arabian physician Rhazes professed its beneficial health effects, and since its arrival in Europe in the 17th century, it has played an even greater role in shaping human history^[26]. Today it is undoubtedly a cultural phenomenon with hundreds of billions of cups consumed every year, and is the second most traded commodity on world markets, second only to oil^[27].

The exact milieu and concentration of biologically active compounds in coffee can vary according to the species, farming practices and the method of preparation, be it the roast, blend or brew^[27]. Coffee contains caffeine, phenols, chlorogenic acids, sugars, organic acids, polysaccharides and aromatics, among over a thousand compounds. Lipids found in coffee include triacylglycerols, tocopherols, diterphenolic alcohols and fatty acids (e.g., cafestol and kahweol)^[27-29].

Coffee drinking was first reported to have a protective effect against the development of cirrhosis close to two decades ago^[30], with a recent study pointing towards an inverse relationship with total and non-cancer related mortality^[31]. This latter data however was limited by self reporting of coffee consumption at a single time point, uncertainty over caffeine content and a lack of information on the method of coffee preparation^[31]. Initially the association between coffee drinking and lower risk of liver disease was found in the context of alcoholic liver disease alone^[30,32], but later in all patients with cirrhosis independent of alcohol or disease

aetiology^[33]. A subsequent large epidemiological study based on NHANES-I clinical outcome data associated prospectively collected coffee consumption with a decreased risk of liver enzyme derangement and reduced mortality and hospitalisations in all cirrhotics^[34]. The limitations of this study were noteworthy, with a significant proportion of subjects excluded from the analysis due to a lack of data on coffee or tea consumption, ascertainment of liver disease based on hospital discharge records and death certificates as opposed to verifiable clinical records, and a lack of detail regarding the amount and type of beverage consumed^[34]. Furthermore, the inverse association between coffee consumption and BMI meant healthier dietary practices and reduced incidence of metabolic syndrome (and hence NAFLD) could not be excluded.

Coffee consumption appears to reduce the risk of fibrosis progression in HCV^[35] and improves the response to interferon based anti-HCV therapy^[36]. It also protects against the development of hepatocellular carcinoma (HCC) irrespective of the aetiology of liver disease^[37], with a dose dependant decrease in the incidence of HCC seen with consumption of up to 6 cups of coffee per day^[38,39]. This relationship may well be driven by the inverse relationship between coffee and liver cirrhosis^[30,33,40], given the strong relationship between cirrhosis and the incidence of HCC^[41,42].

An increasing body of evidence suggests that coffee may be beneficial in NAFLD through a direct effect on the liver as well as beneficial systemic metabolic effects. Recent reports have elegantly demonstrated a significantly reduced risk of T2DM and cardiovascular disease in coffee drinkers^[43,44]. These studies are particularly relevant in the context of advanced liver fibrosis where morbidity and mortality primarily relates to metabolic and cardiovascular disease, in addition to liver endpoints^[45,46].

Epidemiological data suggests that coffee may have a protective effect against the development of NAFLD. Data published in 2012, based on four continuous cycles of the United States National Health and Nutrition Examination Survey (NHANES 2001-2008) showed caffeine consumption and plain water intake to be independently associated with a lower risk of NAFLD, even when patient demographics (e.g., race and gender), clinical parameters such as metabolic syndrome components and other dietary constituents were considered^[47]. In those who already have NAFLD/NASH, coffee appears to reduce the risk of hepatic fibrosis. Anty *et al.*^[48] studied 161 morbidly obese European women and 34 men referred for bariatric surgery. All patients filled out a specific questionnaire and also underwent hepatic wedge resection alongside bariatric surgery. Consumption of regular filtered coffee but not espresso was independently associated with a lower level of fibrosis in these individuals. It was postulated that espresso drinkers more frequently added sugar, explaining the beneficial effect of filtered,

but not espresso coffee^[48].

Caffeine is perhaps the most well-known biochemical compound in coffee. Previous studies have shown associations between caffeine consumption, lower risk of elevated aminotransferases^[49] and an apparent hepatoprotective effect of coffee against liver disease^[34]. A limitation in studies in establishing a direct link has been the close correlation of caffeine and coffee consumption, thus not allowing the demonstration of a relationship independent of non-caffeine ingredients. The anti-fibrotic effects of coffee is thought partly to be mediated by reduced transforming growth factor (TGF) and connective tissue growth factor (CTGF) expression^[29] while many substances such as tocopherols and chlorogenic acid demonstrate antioxidant activity. Cafestol and kahweol raise serum cholesterol but may also exert an anti-carcinogenic effect. Filtered coffee can reduce levels of cafestol and kahweol but maintain chlorogenic acid and caffeine content, providing the maximum benefit^[28]. Coffee may protect the liver through increased PPAR- α mediated fatty acid oxidation, decreased collagen deposition, and a general increase in protective antioxidants^[4].

Coffee caffeine consumption has been associated with reduced risk of hepatic fibrosis in patients with NASH. Extending their work on a previously published NAFLD prevalence study, Molloy *et al.*^[50] enrolled 400 patients at a United States Army clinic with 306 respondents to a validated coffee questionnaire segregated based on ultrasound. Those with no steatosis formed controls and those with steatosis underwent liver biopsies. Patients were categorised as having bland steatosis, mild NASH (F 0-1) or advanced NASH (F 2-4). This study provided histopathologic evidence that greater coffee consumption resulted in a significantly decreased risk of advanced fibrosis, although the exact level of coffee consumption that conferred the greatest risk reduction was not clear. The same study showed that controls and those with bland steatosis drank less coffee than those with NASH stage 0-1 fibrosis suggesting that a protective effect may only be seen in those predisposed to hepatic fibrosis, namely patients with NASH. Non-coffee sources of caffeine and overall caffeine consumption were also evaluated with no significant correlation with the risk of NASH versus not-NASH^[50]. A further study of 782 adults with NAFLD was also able to demonstrate a reduced risk for advanced NASH in patients who regularly consumed coffee, but interestingly this effect was only noted in patients with low but not high levels of insulin resistance (HOMA-IR < 4.3)^[51]. Furthermore, a recent meta-analysis, including three animal studies and eleven epidemiological and clinical studies, supported the concept that coffee intake protects against the development of metabolic syndrome and NAFLD in experimental models and clinical settings^[27].

Based on recent literature, a growing and pervasive argument is mounting that coffee may protect ag-

ainst the development of NAFLD and reduce NASH severity. It would appear that the effects of coffee on the aetiology of liver disease are multifactorial, and whilst more detailed mechanistic studies are required to elucidate this further, the addition of filtered unsweetened coffee may be a reasonable adjunct to diet and exercise in patients on the fatty liver spectrum^[27-29].

NUTS

The belief that tree nuts are beneficial for health was first documented in the *Corpus Hippocraticum*, a compendium of medical works pioneered by Hippocrates in the 5th century, B.C.^[52]. At that time, they were widely believed to remedy various ailments - such as headaches, insomnia and colic. Almost 1500 years later - during the Islamic renaissance - nuts were even considered medicinal, prescribed for treating liver disease and expectorating phlegm^[52]. At present, there is emerging evidence to support their therapeutic value, particularly in modifying metabolic disease and cardiovascular outcomes.

Nuts are nutritionally dense fruits, consisting of a unique blend of fatty acids, bioactive compounds, and essential nutrients^[53]. Most nuts (with the exception of chestnuts) have a high total fat content, of which almost half comes from MUFAs and PUFAs. MUFAs are the predominant form in almonds, cashews, hazelnuts, macadamia nuts, pecans and pistachios, while PUFAs are the predominant form in walnuts and pine nuts^[54]. Nuts are exceptionally rich in the antioxidant vitamin E^[55], with a single 1 ounce serve providing over one third of our daily requirements, are high in fibre^[56], and have high levels of phytosterols and polyphenols (such as phenolic acids, ellagic acid, and flavonoids) - effective phytochemicals capable of lowering serum low-density lipoprotein concentrations and free radicals, respectively^[57-59].

The first epidemiologic study demonstrating the health benefits of nuts came from the early nineties^[60]. In this study, individuals who consumed nuts more than four times per week had lower rates of fatal and non-fatal cardiac events, signifying an inverse relationship between nut consumption and cardiovascular mortality. Since then, this observation has been consistently replicated - irrespective of gender, BMI or type of nut consumed^[61-64]. Paralleling such findings, regular weekly consumption of nuts is associated with improvements in lipid profile^[65-68] and decreased incidence of obesity^[69,70], T2DM^[70-72], hypertension^[73] and the metabolic syndrome^[70,74]. In the largest epidemiological study to date that followed over 118000 patients for up to 30 years, overall nut consumption correlated with reduced all-cause mortality for both men and women and with reduced deaths due to cancer, heart disease and respiratory disease, effects most pronounced in those who consumed higher quantities of nuts^[75]. No conclusions could be drawn as to the influence of

preparation methods (roasted, salted, spiced or raw) on mortality, as this data was not collected^[75]. But not all nuts are equal. Compared with other tree nuts, walnuts have substantially higher omega-3 and omega-6 PUFA content (47%) and the highest level of antioxidant polyphenols, whether consumed raw or roasted^[54]. Indeed, data from the long running Nurses' health study showed a protective effect of walnut consumption on the development of T2DM independent of BMI, an effect not seen with the consumption of other tree nuts or total nut consumption^[72].

In recent work from our group at the Storr Liver Unit, walnuts in particular, but also other tree nuts improved liver function tests (LFTs) in patients with NAFLD. 106 patients were enrolled into a longitudinal dietary composition study for six months. At three months follow-up, walnut intake was negatively correlated with changes to GGT ($r = -0.26$, $P = 0.008$), ALT ($r = -0.31$, $P = 0.001$) and AST ($r = -0.21$, $P = 0.034$). At six months follow-up, intake of other nuts ($r = -0.23$, $P = 0.03$) and non-white fish (salmon, tuna, sardines and mackerel) ($r = -0.25$, $P = 0.02$) correlated negatively with changes to GGT, whilst AST was negatively correlated to both walnuts ($r = -0.22$, $P = 0.04$) and other nuts ($r = -0.219$, $P = 0.04$)^[76]. An additional epidemiological study from Korea has shown that a low intake of nuts and seeds (OR = 3.66) was associated with a significantly higher risk for developing NAFLD in male subjects^[77], but more direct data or interventional trials in NAFLD are lacking. There are, however, numerous trials testing the therapeutic value of vitamin E, including the landmark PIVENS trial where vitamin E was seen to significantly improve LFTs, increase adiponectin and reduce hepatic steatosis and lobular inflammation, demonstrating superiority to placebo for the treatment of NASH in adults without diabetes^[78]. It should be noted that these trial results were seen with ingestion of 800 IU of vitamin E, daily, while in comparison, almonds (which have the highest amounts of vitamin E amongst the tree nuts)^[55] contain only 17 IU of vitamin E in a 100 g serving^[79]. Although this value is comparatively deficient, it is likely that bioactive compounds may work synergistically *in vivo* - producing effects far greater than the sum of their individual components. There has been conflicting evidence on whether various nuts are capable of attenuating insulin resistance, the *sine qua non* of NAFLD and NASH in particular. In one small RCT of 50 patients, incorporation of mixed raw nuts (walnuts, almonds and hazelnuts) into a healthy diet significantly reduced fasting insulin levels from baseline, decreased insulin resistance and improved serum LDL compared to controls^[80]. These results were not replicated in another study of 60 patients with the metabolic syndrome however, where the addition of a handful of almonds to a low calorie diet resulted in reductions in insulin resistance and lipids that were no different to control, albeit with more substantial improvements in

BMI and waist circumference seen^[81]. No benefit was observed in T2DM patients fed almonds daily as part of a low-fat or high-fat diet (HFD), perhaps due to the lack of statistical power in the latter study (only 20 patients)^[65].

In summary, nuts show much therapeutic potential in treating patients with NAFLD through improvements to lipid profile, hepatic steatosis and inflammation. As no RCTs have been conducted in humans testing improvements to histological parameters, further studies are warranted.

TEA

Tea (*Camellia sinensis*) has been consumed for its medicinal properties at least since the Han dynasty, although Chinese tradition traces its origin, even as a medicine, to the legendary emperor Shennong many millennia before. Whilst historically infusions have been claimed to increase longevity and cure ailments from infections to malignancies, the scientific evidence for tea's health benefits is more circumspect. First cultivated in China, tea rapidly spread around the world from the 15th century onward. Green, black and oolong tea originate from the bud and leaf of *Camellia sinensis*. Post harvest processing determines the polyphenol content with black tea fermented, oolong partially fermented and green tea not fermented. Tea is rich in catechins (flavan-3-ols), the predominant tea polyphenols, antioxidants thought to modulate inflammation and have beneficial metabolic effects^[82]. Other compounds include caffeine and flavonol glycosides. Green tea, the most studied tea, appears to have health benefits in epidemiological studies when 5-10 cups/d are consumed, in keeping with low bioavailability and rapid elimination of green tea catechins^[83]. Indeed, previous studies have show antioxidant, anti-neoplastic, hypolipidemic, and hypoglycaemic effects of tea^[84].

These potential therapeutic effects in the context of NAFLD were first demonstrated almost two decades ago in a Japanese study of 1371 men that showed green tea consumption to be associated with lower aminotransferase levels and improved lipid profile, evident at relatively high green tea intake of 5-10 cups/d^[83]. More recent epidemiological data from the Ohsaki study suggests lower cardiovascular and all-cause, but not cancer mortality with green tea consumption^[84]. A recent randomised pilot study has investigated the potential benefits of catechin-enhanced green tea in 17 adult patients with NAFLD. Patients were supplemented with green tea for 12 wk with high catechin content (1080 mg/700 mL, $n = 7$), standard catechin content (200 mg/700 mL, $n = 5$) or placebo with no catechin ($n = 5$). At the end of the study those in the high, but not standard dose catechin group showed significant reductions in ALT, body fat percentage and improvement in

liver to spleen attenuation on CT suggesting possible reduction in hepatic steatosis. Those with high catechin supplementation also had significantly reduced urinary 8-isoprostane excretion, suggesting a reduction in oxidative stress, although the relevance of this marker in NAFLD is questionable. No adverse effects were noted in this short study^[85].

Studies in murine models have also demonstrated beneficial effects of green tea consumption, portending a possible role in patients with risk factors for the metabolic syndrome. Epigallocatechin-3-gallate (EGCG) is thought to play a major role in improving metabolic outcomes. Experimental data in mice suggest that green tea and green tea extract (GTE) may reduce insulin resistance, body weight, visceral fat, hepatic lipid accumulation and increase energy expenditure through beta-oxidation and thermogenesis^[86]. Mouse models suggest that reducing oxidative stress and inflammation ameliorates progression to NASH. Multiple antifibrotic, antioxidant and anti-inflammatory pathways including TGF/SMAD, FoxO1 and NF- κ B have been implicated^[87].

Black tea extract (BTE) has also shown capacity for a hepatoprotective effect. Wistar rats with HFD induced NASH with higher levels of aminotransferases, serum glucose, cholesterol, triglycerides, LDL, VLDL, bilirubin and decreased HDL compared to control rats were supplemented with BTE. The chemoprotective effects of BTE were evident with reversal of the increased pro-oxidant and decreased anti-oxidant milieu seen in the livers of rats with NASH. BTE exposed rats had suppression of liver apoptotic markers (DNA fragmentation and caspase-3 activity). In rats with HFD induced biochemical changes, adding BTE also resulted in a significant improvement in lipid profile, glucose, ALT, AST and bilirubin. Furthermore, histological changes seen in the livers of HFD rats, namely steatosis, presence of inflammatory cells, hepatocyte ballooning, were ameliorated with the addition of BTE to the rats' diets^[88].

Although a potential protective effect of tea holds promise for patients with NAFLD, caution should be advised with tea extracts given previous reports of hepatotoxicity in individuals taking weight loss products that included GTE^[89]. Despite the recent interest in antioxidant and other properties of catechins that may have potential benefit, a definite protective effect against chronic liver disease remains to be determined in human subjects^[90]. Whilst there is an increasing epidemiological data and experimental evidence base in animal models, that tea could likely mitigate the development or progression of NAFLD, the lack, particularly of high quality interventional data in human cohorts, means currently tea or tea extracts cannot be specifically recommended for NAFLD patients.

RED WINE

Wine has held prominent cultural and religious significance since antiquity. Perhaps for its sanguine colour, red wine in particular has long been believed to have healing properties and is one of the oldest recorded man-made medicines. Hippocrates used wine as an analgesic, a disinfectant for wounds and a remedy for digestive ailments including indigestion and diarrhoea^[91].

Wine is composed of numerous organic compounds and phytochemicals dissolved in alcohol. The predominant phytochemicals in wine are phenols, of which red wine contains a significantly higher concentration than white wine. Much of the research on red wine has focused on these phenol components, in particular resveratrol. It is widely believed that phenols are the active component in red wine with beneficial effects to health^[92-94]. With the rise in alcohol consumption and increased awareness of the adverse health effects of alcohol, there is a scientific consensus on the importance of moderate consumption. Current guidelines from the United Kingdom, United States and Australia each determine moderate consumption to be 1-2 drinks (100-200 mL of wine) per day.

Epidemiological studies suggest that moderate consumption of red wine reduces all-cause mortality, in particular cardiovascular mortality^[95,96]. Very little published data exists regarding the effects of red wine in NASH or NAFLD specifically. Most research has investigated the effects of red wine in the context of cardiovascular and metabolic disease, and assessed biological markers such as plasma lipid profile, fasting glucose levels and insulin sensitivity, all of which are relevant to the pathogenesis of NAFLD^[97].

The relative importance of alcohol to the health benefits conferred by red wine is not entirely clear-cut. In obese rodent models, phenol extract decreases plasma triglyceride and cholesterol levels while phenol with alcohol does not^[98,99]. Human studies investigating the effects of phenols on plasma lipid profile suggest that alcohol containing red wine increases HDL, ApolipoproteinA (ApoA) and total plasma cholesterol but decreases LDL, while dealcoholised red wine decreases HDL, without altering LDL or total cholesterol^[100-102]. Both red wine and alcohol-free red wine increase HMG-CoA reductase expression and increased LDL receptor binding activity, thereby increasing the propensity of cholesterol to be catabolised, and reducing plasma LDL levels^[103].

Studies investigating the effects of red wine in T2DM suggest it may play a role in the attenuation of insulin resistance. Napoli *et al.*^[104] demonstrated improved insulin-mediated glucose disposal with the addition of 360 mL of red wine per day (compared to abstinence) in 17 diabetic adults treated for 2 wk, however, this

study was not placebo controlled. In a subsequent randomised crossover trial, 66 men at high risk of cardiovascular disease were supplemented with 30 g/d of red wine, 30 g/d of gin or an equivalent amount of dealcoholised red wine. The authors found that supplementation with red wine or dealcoholised red wine (both rich in polyphenols), but not gin, which does not contain polyphenols, led to significant reductions in plasma insulin and insulin resistance (measured by HOMA-IR) while glucose levels remained constant. Furthermore, red wine intervention increased HDL and reduced Lipoprotein(a)^[105]. Likewise, diabetic or obese animals supplemented with resveratrol or dealcoholised red wine have improved insulin sensitivity and glucose metabolism^[106-108]. Red wine has also been widely investigated for its purported antioxidant effects, with animal models suggesting that red wine (or its phenol component) increase antioxidant activity and decrease lipid peroxidation^[98,108]. Kasdallah-Grissa *et al.*^[109] demonstrated the inhibition of lipid peroxidation with the supplementation of resveratrol to the diets of rats, however this effect was not seen with supplementation of resveratrol and alcohol combined (as in red wine), and alcohol alone lead to hepatotoxicity and fatty change.

Based on available data, particularly in the context of reduced cardiovascular mortality, a modest consumption of red wine appears to be safe. In patients with NAFLD it may improve insulin resistance and lipid profile. Further study is required to determine the safety and efficacy of red wine in NASH and optimal levels of consumption.

AVOCADO

The Avocado (scientifically known as *Persea Americana*) is a fruit belonging to the berry family, with more than 400 varieties. It is thought to have originated from and around Central America and Mexico and has long been considered to have special medical properties. Over time its leaves have been used to treat neuralgia, diarrhoea, and sore throat, while the extracted oil has been used topically as an anti-microbial and analgesic to relieve toothache, skin sores and arthralgia^[110-112]. In modern medicine, avocados have been implicated to have cardiovascular benefits, protective effects against UV damage in skin and eyes, anti-inflammatory, analgesic, anti-microbial and also anti-carcinogenic properties^[113-116].

Avocados are a low to medium energy dense fruit with a high content of water (about 75%) and fibre (6%), but a low content of sugar and sodium. They contain essential vitamins (B, C, E), minerals, lipids and phytochemicals such as carotene and lutein. Avocados are a rich source of oil, producing 15-30 g/100 g of fruit^[117], mostly composed of MUFAs with a relatively low composition of saturated fatty acids^[114,118,119].

A study analysing the 2001-2008 NHANES data incorporating the dietary habits of 17567 adults,

suggested that avocado consumption was associated with improved weight, waist circumference and BMI, higher HDL and decreased risk of metabolic syndrome^[118]. The energy density and fibre content of avocado may play a role in enhancing early satiety and maintaining weight control^[114,120,121]. Avocado has the highest fibre content amongst fruit, with approximately 70% being insoluble and 30% soluble^[114]. Dietary fibre may aid in maintaining insulin sensitivity as well as reducing fat absorption, factors which are important in preventing the metabolic syndrome and development of NAFLD. In a small animal study, rats fed a cholesterol containing diet supplemented with varying quantities of avocado pulp or cellulose gained less weight when fed avocado pulp and consumed less food overall. Furthermore, a strong negative correlation was seen between hepatic fat deposition and increasing intake of avocado pulp^[121]. In another study, rats fed a hypercholesterolemic/fructose diet were compared to rats supplemented with defatted avocado pulp. This resulted in a significant ($P \leq 0.05$) decrease in plasma total cholesterol (43.1%), LDL (45.4%) and triglycerides (32.8%), and a significant decrease in LFTs. Subsequent histological analysis also demonstrated reduced liver damage and steatosis in the rats fed avocado^[112,120]. Data from other animal studies suggest avocados may possess systemic anti-inflammatory properties^[117], can protect against chemically induced liver damage and have antioxidant effects^[122].

To date, there have been only a few small preliminary studies in humans looking at the metabolic benefits of avocados, concentrating mainly on the effects on lipid profiles. These showed that avocado enriched diets were associated with a reduction in serum total cholesterol, LDLs and triglycerides, with varying results on HDLs^[114]. The exact mechanism of lipid lowering effects of avocados are unknown, but may relate to alterations in PPAR- γ expression, upregulation of adiponectin activity and regulation of glucose and lipid transporting genes^[123,124]. These changes are driven by MUFAs, phytochemicals such as carotenoids, chlorophylls and polyphenols, vitamin E and beta-carotene^[125,126].

Clinical trials directly evaluating the effect of avocado consumption on NAFLD are lacking, however, given their high MUFA content, lipid lowering, antioxidant, anti-inflammatory and weight maintenance properties, they are a reasonable addition to a low fat diet. Further studies are required to determine if supplementation has specific benefits for patients with NAFLD.

OLIVE OIL

Olive oil, derived from the olive fruit (*Olea europea*), has long been considered one of the great natural assets of the ancient world, offering humanity health and wealth. According to legend, the olive tree was

a gift from the warrior god Athena to the people of ancient Greece. Hippocrates used olive oil to treat a wide variety of diseases and even believed it could cure mental illness^[127]. Today olive oil continues to be revered for its health benefits as the main source of dietary fat in the Mediterranean diet. Olive oil is predominantly comprised of MUFAs (73 g/100 g olive oil) such as oleic acid, and is a good source of vitamin E and phenolic compounds, all of which are known to have anti-inflammatory, hypolipidemic and anti-oxidant properties^[128,129]. Higher grades of olive oil (extra-virgin and virgin olive oil) are believed to have higher nutritional value as they contain antioxidants and phytochemicals that are lost when olive oil is refined or heated.

Regular consumption of olive oil can decrease the risk of certain cancers, particularly breast cancer^[130], reduce cardiovascular disease including hypertension and atherosclerosis, and as part of the Mediterranean diet is associated with reductions in plasma cholesterol and LDL^[131]. In healthy Mediterranean populations, olive oil also reduces mortality, especially from cardiovascular disease^[128,129]. Buckland *et al.*^[129] showed that this occurs in a dose dependent fashion with those in the highest quartile of olive oil consumption having the greatest reduction in overall mortality (26%) and CVD mortality (44%) irrespective of the type of olive oil (virgin or ordinary) used^[129]. A recent study furthered these observations, showing that a Mediterranean diet supplemented with virgin olive oil or nuts substantially reduced the risk of serious cardiac events or death by up to 30% in the primary prevention setting of patients at high risk for cardiovascular disease^[62].

A number of small, but promising trials exist suggesting a benefit of olive oil supplementation in NAFLD. In a yearlong study of 11 patients with NAFLD from 2010, 6 subjects received 6.5 mL/d of olive oil (rich in n-3 PUFA), while 5 were selected as controls. At the end of treatment, patients given olive oil supplementation had significantly reduced liver enzymes and triglycerides, increased adiponectin levels compared to controls. There was also a reduction in liver steatosis based on ultrasound and increased Doppler perfusion index suggesting haemodynamic improvement^[132]. A subsequent study from 2014 enrolled 93 age and BMI matched Asian Indian males with NAFLD and randomly allocated them olive oil, canola oil or soybean/safflower oil as cooking medium in addition to lifestyle counselling. At the end of the 6-mo trial, those in the olive oil intervention group had significantly decreased BMI compared to control, reduced fasting insulin and HOMA-IR, increased HDL levels and decreased triglycerides. Olive and canola oil treated patients also had a reduced liver span and a reduction in hepatic steatosis by ultrasound at the end of therapy^[133]. Similarly, an 8 wk randomised study of 45 overweight diabetics demonstrated that a MUFA enriched diet with olive oil led to substantial reductions in magnetic resonance spectroscopy (¹H

MRS) measured liver fat (-29%) when compared to isocaloric high carbohydrate diet (-4%). These changes were independent of physical activity^[134]. A number of studies have now evaluated the effects of the Mediterranean diet (where olive oil is the main source of dietary fat) on patients with NAFLD, with largely positive outcomes^[135]. Compared to diets with similar calorie restriction and low fat content, adherence to the Mediterranean diet is associated with improvements in lipid profile and insulin sensitivity, reductions in ALT and significant improvements in hepatic steatosis as measured by ultrasound. In a number of studies weight loss was also more substantial in those individuals adhering to a Mediterranean diet^[135].

Most rodent studies have demonstrated a decrease in total hepatic lipid and phospholipid levels in animals whose diet has been supplemented with olive oil compared to saturated and/or PUFAs^[136,137]. In contrast, Ronis *et al.*^[138] found an increase in hepatic steatosis in rats overfed with olive oil, compared to corn oil or echium oil. Importantly however, the olive oil group had no evidence of oxidative stress or necrosis as seen in the liver biopsies from the other groups. Affymetrix gene analysis demonstrated an increase in antioxidant pathways and a reduction in genes linked to inflammation and fibrosis^[138]. Even when rats were overfed olive oil for prolonged periods there was no progression of liver disease beyond simple steatosis. Animal studies investigating the role of olive oil as an antioxidant have shown a significant decrease in hepatic lipid peroxidation and increased glutathione peroxidase^[139-142]. Park *et al.*^[137] demonstrated a downregulation of genes associated with hepatic lipogenesis and decreased expression of proinflammatory cytokines, providing insight into the mechanism by which olive oil reduces oxidative stress in the liver.

Olive oil can be recommended for patients with NAFLD when used as part of a low fat Mediterranean diet. The role of direct olive oil supplementation in addition to its use in food or cooking needs further investigation, particularly to clarify the dose and formulation that is most effective.

CONCLUSION

Evidence continues to emerge from population-based analysis derived from epidemiological data, animal experimental models and more recently human clinical studies that in addition to caloric restriction, energy expenditure and macronutrient composition of diet, specific foods may have a benefit. Although causality is yet to be established, these data, reviewed here, suggest that consumption of specific foods may modulate the risk of NAFLD, the progression of NASH and the risk of other entities comprising the metabolic syndrome. Based on the available data we have made an assessment of the likely benefit of specific dietary components to NAFLD and to metabolic disease (Table

Table 3 Recommendations

Food	Evidence level (good, moderate, poor)	Dose
Oily fish/fish oil (Omega-3 PUFAs)	Moderate (NAFLD) Good (Metabolic disease)	≥ 0.83 g/d n-3 or 2 servings of oily fish/wk (3.5 oz/serve) ¹ Coronary artery disease (CAD): 1 g/d Hypertriglyceridemia: 2-4 g/d ≥ 3 cups per day ¹
Coffee	Moderate (NAFLD) Moderate (Metabolic disease)	≥ 3 cups per day ¹
Nuts	Moderate (NAFLD) Good (Metabolic disease)	100 g (handful)/d ¹
Tea	Poor (NAFLD) Poor (Metabolic disease)	≥ 5-10 cups per day ¹
Red wine	Poor (NAFLD) Moderate (Metabolic disease)	100-200 mL/d ¹
Avocado	Poor (NAFLD) Moderate (Metabolic disease)	1/2 avocado (68 g)/per day ¹
Olive oil	Poor (NAFLD) Moderate (Metabolic disease)	Consumption as part of Mediterranean diet < 20 g/d ¹

¹Optimal dose not yet defined. NAFLD: Non-alcoholic fatty liver disease; PUFA: Polyunsaturated fatty acid.

3). At the present time oily fish, coffee and nuts have the most current and compelling evidence (Table 2) from human trials to suggest these foods may be suitable adjuncts in addition to recommendations of physical activity and caloric restriction in patients with fatty liver disease. Moderate consumption of tea, red wine, avocado and olive oil appear to be safe, however studies particularly examining their therapeutic role in patients with NAFLD/NASH are lacking. While specific recommendations regarding their benefit and dosing cannot be made, patients should be allowed to consume these foods as part of an overall diet and exercise plan.

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