

Lifestyle Interventions Beyond Diet and Exercise for Patients With Nonalcoholic Fatty Liver Disease

James Philip Esteban, MD, and Amreen Dinani, MD, FRCPC

Dr Esteban is an assistant professor in the Division of Gastroenterology and Hepatology at the Medical College of Wisconsin in Milwaukee, Wisconsin. Dr Dinani is an assistant professor in the Division of Liver Diseases at the Icahn School of Medicine at Mount Sinai in New York, New York.

Address correspondence to:

Dr Amreen Dinani

Division of Liver Diseases

Icahn School of Medicine

at Mount Sinai

1425 Madison Ave, Box 1123

New York, NY 10029

Tel: 212-659-9501

Fax: 212-849-2574

E-mail: amreen.dinani@mssm.edu

Abstract: Nonalcoholic fatty liver disease (NAFLD) is a growing worldwide concern, affecting approximately 30% of the US adult population. Developing pharmacologic therapies for NAFLD is crucial, especially as there are currently no treatments approved by the US Food and Drug Administration. However, weight loss remains the cornerstone of treatment and has been shown in controlled trials to improve hepatic steatosis, hepatic inflammation, and fibrosis. Healthy diet and exercise are the most well-known and frequently recommended lifestyle modifications for patients with NAFLD. This article presents the data on other aspects of healthy lifestyle modifications for patients with this condition, focusing on light alcohol consumption, coffee, circadian misalignments, and sleep.

Nonalcoholic fatty liver disease (NAFLD) is a growing global public health concern and is highly prevalent in Western countries, affecting approximately 90 million adults in the United States.¹ Nonalcoholic steatohepatitis (NASH), considered a more aggressive form of NAFLD, is the fastest growing indication for liver transplantation² and cause of hepatocellular carcinoma (HCC) among transplant candidates.³ While the development of efficacious pharmacologic therapies for NAFLD is critical, lifestyle modification remains the backbone of therapy for this condition.⁴ A weight loss of 3% is sufficient to reduce liver steatosis, while a weight loss of 7% to 10% can ameliorate steatohepatitis and even improve hepatic fibrosis.^{5,6} Healthy diet (eg, avoidance of excessive dietary fat and carbohydrates) and exercise are the most frequently recommended lifestyle modifications for patients with NAFLD that are backed by data from randomized trials.^{5,7,8} This article discusses other aspects of healthy lifestyle modifications for patients with NAFLD, focusing on light alcohol consumption, coffee, circadian misalignments, and sleep (Table 1).

Light Alcohol Consumption

Although the definition of NAFLD excludes significant alcohol consumption (ie, ≥ 21 standard drinks/week for men, ≥ 14 standard drinks/week for women), approximately 60% of patients with NAFLD will consume some alcohol in their lifetime.^{4,9} According to

Keywords

Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, lifestyle intervention

Table 1. Summary of Lifestyle Interventions Other Than Diet and Exercise for Patients With NAFLD

Lifestyle Intervention	Recommendation(s)	Evidence and Rationale
Light Alcohol Consumption	<ul style="list-style-type: none"> • There are insufficient data whether lifetime abstainers should begin light alcohol consumption for potential cardiovascular and/or liver benefits. • Cirrhotic patients with NASH should be advised to abstain from all alcohol use. • There are insufficient data to recommend continued alcohol use or complete abstinence in current moderate to high alcohol users with NAFLD or NASH without cirrhosis. 	<ul style="list-style-type: none"> • Light alcohol use has no impact on markers of cardiovascular disease.⁹ • Any alcohol use increases the risk of HCC in cirrhotic NASH patients (HR, 3.8; 95% CI, 1.6-8.9; $P < .01$).²⁷ • ≥ 1 binge drink/month significantly increases the risk of fibrosis progression (OR, 42.1; 95% CI, 5.39-328.57; $P < .01$).²⁵ • Persistent modest drinkers are 70% less likely to achieve NASH resolution than either lifetime abstainers or former modest drinkers (OR, 0.32; 95% CI, 0.11-0.92; $P = .04$).²⁶
Coffee	<ul style="list-style-type: none"> • Consider recommending 2-3 8-oz servings of regular brewed coffee per day. • Counsel on limiting daily caffeine intake to < 400 mg (< 200 mg in pregnant and lactating women or if there are symptoms of caffeine toxicity). 	<ul style="list-style-type: none"> • Coffee is associated with a 40%-80% reduction in cirrhosis-related hospitalizations and death and 35%-45% lower odds of HCC.³⁴⁻³⁷ • Each additional cup of coffee consumed per day decreases the odds of advanced fibrosis by 36% (OR, 0.64; 95% CI, 0.46-0.88; $P < .01$) in insulin-sensitive NASH patients.³²
Shift Work	<ul style="list-style-type: none"> • Shift workers may be advised to eat at the beginning or toward the end of their shift. 	<ul style="list-style-type: none"> • Restricting meals to the normal active period reduces hepatic steatosis by 50% in mice⁵⁶ and reduces insulin resistance and weight gain in humans.^{71,72}
Social Jet Lag	<ul style="list-style-type: none"> • Improve sleep hygiene to match sleep and wake times during workdays and weekends. 	<ul style="list-style-type: none"> • Social jet lag is associated with increased body fat content, body mass index, and central obesity.⁸⁰⁻⁸²
Meal Timing	<ul style="list-style-type: none"> • Consider recommending habitual daytime food consumption with avoidance of calorie-dense nighttime meals. 	<ul style="list-style-type: none"> • Skipping morning and midday meals increases the odds of sonographic steatosis by 20% and 73%, respectively.⁸⁶ • Calorically heavier dinners are associated with 40% less weight loss, 50% lower reduction in waist circumference, 42% lower reduction on HOMA-IR, and 15% increase in triglycerides.⁹²
Sleep	<ul style="list-style-type: none"> • Consider recommending 7-9 hours of sleep nightly. • Suggest techniques to improve sleep hygiene, such as using blackout curtains, turning off lights at bedtime, and limiting nighttime use of electronic devices and stimulants (eg, caffeine, alcohol, cigarettes). 	<ul style="list-style-type: none"> • Short sleep duration increases the odds of hepatic steatosis (OR, men: 1.28; $P < .01$; OR, women: 1.71; $P < .01$).¹¹⁹ • Individuals who sleep 7-9 hours nightly have a 75% lower likelihood of having $\geq F2$ fibrosis on transient elastography.¹²⁰ • Meta-analyses show an increased risk of obesity, metabolic syndrome, and type 2 diabetes mellitus in individuals with an abnormally short or long sleep duration.¹²³⁻¹²⁵

HCC, hepatocellular carcinoma; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

the US Department of Agriculture, a standard drink contains 14 g of pure alcohol, which is equivalent to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirit.¹⁰

Heavy alcohol use is detrimental in patients with NAFLD. Observational studies demonstrate an increased risk of hepatic inflammation, cirrhosis, and HCC in obese and diabetic individuals who consume alcohol in excess of

2 drinks per day.¹¹⁻¹³ Interest in a potentially beneficial role for light alcohol use in NAFLD comes from several studies that indicate a protective effect of light alcohol use in cardiovascular (CV) health.^{14,15} In a meta-analysis of 84 prospective studies, light alcohol consumption decreased the risk of CV-related mortality and incident coronary artery disease by 25% to 30% compared with lifetime

abstainers.¹⁴ CV disease is the second most common cause of death among patients with NAFLD and is believed to be a stronger determinant of outcomes than liver disease.¹⁶

Several cross-sectional studies suggest that light alcohol drinkers are 30% to 65% less likely than nondrinkers to have NASH and 75% less likely to have advanced fibrosis on biopsy, which some authors suggest may be due to alcohol-induced improvement in insulin sensitivity (Table 2).¹⁷⁻²⁰ Indeed, light alcohol consumption has been shown in randomized crossover trials of healthy adults to improve insulin sensitivity, decrease serum triglycerides (TGs), increase high-density lipoprotein, and increase serum adiponectin levels.^{21,22} A cross-sectional study from Brazil does not show an association between alcohol consumption and hepatic steatosis, inflammation, or fibrosis.²³ Epidemiologic studies are limited by use of cross-sectional designs and failure to account for lifetime drinking histories. The challenge with defining alcohol use as current consumption alone is that it potentially classifies former heavy drinkers or individuals who decreased their alcohol consumption for health reasons as abstainers, which may overestimate the risk of CV and liver disease in this group.²⁴

There are no randomized trials to date on the relationship between alcohol use and NAFLD, partly due to ethical considerations. However, 2 well-designed prospective observational studies on patients with biopsy-proven NASH show that light alcohol use increases the risk of progression of hepatic fibrosis in a dose-dependent manner (odds ratio [OR], 1.01/g ethanol/week; 95% CI, 1.00-1.03; $P=0.06$), and that NASH resolution occurs significantly less frequently in consistent light drinkers than in consistent abstainers (11% vs 22%; OR, 0.32; 95% CI, 0.11-0.92; $P=0.04$).^{25,26} Moreover, heavy episodic drinking (ie, binges) in habitually light drinkers increases the odds of fibrosis progression up to 40-fold.²⁵ A prospective study⁹ showed that light alcohol use does not affect subclinical markers of CV disease, such as coronary artery calcium and myocardial tissue strain, although the impact of light alcohol use on clinical CV morbidity and mortality among the NAFLD population is largely unexplored. Finally, HCC risk is increased (hazard ratio, 3.8; 95% CI, 1.6-8.9; $P<0.01$) in cirrhotic patients with NASH who consume any amount of alcohol, and the risk is not modified by the volume of alcohol use or former drinking.²⁷

Thus, heavy alcohol use should be avoided by patients with NAFLD or NASH, and cirrhotic NASH patients should avoid all alcohol consumption due to risk of HCC and, likely, hepatic decompensation. Owing to conflicting evidence on benefit and harm, it is not possible to make a firm recommendation regarding light alcohol consumption in NAFLD at this time, which is echoed in the American Association for the Study of Liver Diseases guidelines.⁴

Specifically, it is not clear whether NAFLD patients who are lifetime abstainers should consider light alcohol use for its CV benefits, or whether noncirrhotic NAFLD or NASH patients who are currently light drinkers should be advised to continue or abstain from alcohol. In favor of complete abstinence are the arguments that (1) alcohol hepatotoxicity is modulated by individual genetic, physiologic, and behavioral factors that are virtually impossible to ascertain; (2) alcohol dosage and serving size limits may be interpreted in different ways; and (3) CV benefits are attainable through more well-established means, such as diet and exercise.²⁸ Patients who choose to continue drinking should be advised to account for alcohol-derived calories when setting their daily caloric limits.¹⁰

Coffee

Given coffee's global appeal, any health effect attributable to the beverage significantly impacts public health. Coffee has been linked to a lower risk of death, CV disease, Parkinson disease, and several cancers.²⁹ Epidemiologic studies demonstrate potentially hepatoprotective effects of coffee (Table 2).³⁰⁻³⁷ Cross-sectional studies show that drinking more than 2 cups of coffee daily decreases the odds of elevated levels of alanine transaminase by 43%, elevated levels of γ -glutamyltransferase by 71%, and advanced fibrosis by 71%.³⁰⁻³² A meta-analysis involving more than 400,000 patients demonstrated that drinking 2 cups of coffee per day, compared to no consumption, decreases the risk of cirrhosis by 43%, and that risk reduction is dose-dependent (23% for 1 cup daily vs 65% for 4 cups daily).³³ Importantly, 2 large prospective studies showed that drinking 4 or more cups of regular coffee daily reduces the risk of cirrhosis-related hospitalizations and death by 40% and 80%, respectively.^{34,35} In a meta-analysis of more than 2 million patients, drinking 2 cups of coffee daily decreases HCC risk by 35%.³⁶ The protective effect of coffee on cirrhosis and HCC is more pronounced in individuals with preexisting liver disease or risk factors for liver disease, such as alcohol use, obesity, and viral hepatitis.^{36,37}

The relationship between coffee and NAFLD is less clear. Coffee decreased the odds of sonographic steatosis in an observational Italian study, but not in another.^{38,39} Mice that were fed a high-fat diet and coffee-derived polyphenols and melanoidins were less likely to have steatosis, steatohepatitis, and fibrosis compared to mice fed a high-fat diet alone.⁴⁰ Polyphenols and melanoidins potentially increase antioxidant activity, lower proinflammatory and profibrotic cytokines (eg, tumor necrosis factor α , transforming growth factor β , interleukin [IL] 1), increase anti-inflammatory cytokines (eg, IL-4, IL-10), and increase expression of adiponectin and peroxisome proliferator-activated receptor (PPAR) α in the liver.⁴⁰

Table 2. Select Studies of Lifestyle Modifications and NAFLD

Authors	Study Design; Patient Population (N)	Outcome	Intervention or Exposure	Finding(s)
Light Alcohol Consumption				
Kwon et al ¹⁷	Cross-sectional; adults with presumed NAFLD (77)	NAFLD by biopsy	Lifetime alcohol use	Light alcohol users have lower total body fat and cholesterol and lower odds of advanced fibrosis (OR, 0.26; $P=.05$).
Hagström et al ¹⁸	Cross-sectional; adults with presumed NAFLD (101)	NAFLD by biopsy	Lifetime alcohol use	An additional unit of alcohol/week decreases the odds of higher fibrosis stage (OR, 0.86; $P=.02$). Light alcohol users have lower serum TNF and C-reactive protein.
Dunn et al ¹⁹	Cross-sectional; adults with presumed NAFLD (582)	NAFLD by biopsy	Lifetime alcohol use	Light alcohol users have lower odds of NASH (OR, 0.56; $P<.01$).
Ekstedt et al ²⁵	Prospective cohort; adults with biopsy-proven NAFLD and paired biopsies (71)	NAFLD by biopsy	Change in alcohol use between biopsies	Alcohol users, particularly those who binge, are more likely to have progression of fibrosis.
Ajmera et al ²⁶	Prospective cohort; adults with biopsy-proven NAFLD and paired biopsies (285)	NAFLD by biopsy	Change in alcohol use between biopsies	Consistent alcohol users are less likely to have NASH resolution (OR, 0.32; $P=.04$) compared to consistent nondrinkers and recent abstainers.
Ascha et al ²⁷	Prospective cohort; adults with NASH or HCV (510)	HCC	Lifetime alcohol use	Any alcohol use increases HCC risk in cirrhotic NASH patients (HR, 3.8; $P<.01$). HCC risk is the same in mild, heavy, and former drinkers.
Coffee				
Ruhl and Everhart ³⁰	Cross-sectional; adults at risk for chronic liver disease (5944)	Elevated ALT levels, any liver disease	Coffee and caffeine from all sources	Drinking >2 cups of coffee daily decreases odds of elevated ALT levels (OR, 0.56). Individuals at the highest quintile of caffeine intake have lower odds of elevated ALT levels (OR, 0.31).
Nakanishi et al ³¹	Cross-sectional; adult male office workers (1176)	Elevated GGT levels, any liver disease	Coffee intake	Drinking >2 cups of coffee daily decreases the odds of elevated GGT levels (OR, 0.29).
Modi et al ³²	Cross-sectional; adults with HCV and cirrhosis (177)	Liver biopsy	Caffeinated and decaffeinated coffee	Drinking >2 cups of coffee daily decreases the odds of advanced fibrosis (OR, 0.29; $P=.05$). Individuals at >75th percentile of caffeine consumption have lower odds of advanced fibrosis (OR, 0.25; $P=.01$). Caffeine is protective only if it is derived from coffee.
Kennedy et al ³³	Meta-analysis of observational studies; adults (432,133)	Clinical cirrhosis	Coffee intake	Drinking 2 cups of coffee daily decreases the risk of cirrhosis (RR, 0.56; 95% CI, 0.44-0.68). Cirrhosis risk reduction is dose-dependent.
Setiawan et al ³⁵	Prospective cohort; adults (162,022)	Incident HCC, liver-related death	Coffee intake	Drinking ≥ 4 cups of coffee daily decreases the risk of HCC (RR, 0.59; 95% CI, 0.35-0.99; $P<.01$) and liver-related death (RR, 0.71; 95% CI, 0.17-0.50; $P<.01$).
Catalano et al ³⁸	Prospective cohort; adults (310)	NAFLD by ultrasound	Coffee intake	Each cup of coffee decreases the risk of severe steatosis.
Vitaglione et al ⁴⁰	Animal study; male rats (unspecified)	NAFLD by biopsy	Decaffeinated coffee with polyphenol and melanoidin extracts	Coffee, polyphenols, and melanoidins reduce steatosis, necroinflammation, and fibrosis; increase antioxidant activity; decrease proinflammatory cytokines in the liver; and promote lipid breakdown in the liver.
Molloy et al ⁴¹	Cross-sectional; adults (302)	NAFLD by biopsy	Coffee intake	Coffee-derived caffeine intake is not associated with NASH but has an inverse association with fibrosis stage.

(Table continues on following page)

Table 2. (Continued) Select Studies of Lifestyle Modifications and NAFLD

Authors	Study Design; Patient Population (N)	Outcome	Intervention or Exposure	Finding(s)
Coffee (continued)				
Anty et al ⁴³	Cross-sectional; obese adults undergoing bariatric surgery (197)	NAFLD by biopsy	Coffee intake	Coffee and caffeine consumption are not associated with NASH and NASH severity, but coffee-derived caffeine decreases the odds of advanced fibrosis (OR, 0.7; 95% CI, 0.58-0.98; $P=.03$).
Shift Work				
Balakrishnan et al ⁷¹	Cross-sectional; adults (8159)	NAFLD by ALT levels	Regular night or rotating shift work	Shift work increases the odds of NAFLD in a lean population (OR, 1.66).
Lin and Chen ⁷²	Prospective cohort; adults (758)	NAFLD by ALT levels and ultrasound	Rotating shift work	Shift work increases the risk of elevated levels of ALT if there is baseline hepatic steatosis (OR, men: 3.2; $P<.01$; OR, women: 8.5; $P=.04$).
Wang et al ⁷³	Meta-analysis of observational studies; adults (15,594)	MetS	Night shift work	Night shift work increases the risk of MetS (pooled RR, 1.57) in a dose-dependent manner.
Gan et al ⁷⁴	Meta-analysis of observational studies; adults (226,652)	T2DM	Regular night or rotating shift work	Shift work increases the odds of T2DM (pooled OR, 1.09; $P=.01$), particularly in men.
Social Jet Lag				
Islam et al ⁸⁰	Cross-sectional; adults, nonshift workers (1164)	MetS	Social jet lag	Social jet lag >2 hrs increases the likelihood of MetS (OR, 1.92) and central obesity (OR, 2.26).
Koopman et al ⁸¹	Cross-sectional; adults (1585)	MetS, T2DM	Social jet lag	Social jet lag >2 hrs increases the likelihood of MetS (OR, 1.64). Social jet lag affects MetS risk in a dose-dependent manner.
Anothaisintawee et al ⁸²	Cross-sectional; adults (2133)	BMI, waist-to-hip ratio	Social jet lag	Each additional hour of social jet lag is associated with a 3% increase in body fat, 0.9 kg/m ² increase in BMI, and 0.13 increase in waist-to-hip ratio.
Meal Timing				
Esteban et al ⁸⁶	Cross-sectional; adults (9015)	NAFLD by ultrasound	Meal timing	Skipping morning and midday meals increases the odds of NAFLD.
Miyake et al ⁹³	Cross-sectional; adults (6370)	NAFLD by ultrasound	Snacking	NAFLD is more common in individuals who snack ≥ 2 times per day.
Ma et al ⁸⁷	Prospective cohort; adults (499)	Obesity	Breakfast skipping	Skipping breakfast increases the odds of obesity (OR, 4.5), controlling for caloric intake and physical activity.
Bi et al ⁸⁸	Meta-analysis of observational studies; adults (106,935)	T2DM	Breakfast skipping	Skipping breakfast increases the odds of T2DM (pooled OR, 1.15; $P=.05$).
Jakubowicz et al ⁹²	RCT; adult overweight women (93)	Obesity, glucose tolerance, insulin sensitivity	Heavy breakfast vs heavy dinner	Relatively heavier breakfasts lead to greater weight loss, waist circumference reduction, lower triglycerides, improvement in insulin sensitivity and glucose tolerance, and less hunger throughout the day.
OSA				
Türkay et al ¹⁰³	Cross-sectional; adults diagnosed with OSA (106)	NAFLD by ultrasound	OSA	OSA is more common in patients with NAFLD (71% vs 36%; $P<.001$). The severity of NAFLD runs parallel to the severity of OSA.
Campos et al ¹⁰⁴	Cross-sectional; obese adults undergoing bariatric surgery (200)	NAFLD by biopsy	OSA	OSA independently predicts NASH (OR, 4.0; 95% CI, 1.3-12.2).

(Table continues on following page)

Table 2. (Continued) Select Studies of Lifestyle Modifications and NAFLD

Authors	Study Design; Patient Population (N)	Outcome	Intervention or Exposure	Finding(s)
OSA (continued)				
Mishra et al ¹⁰⁵	Cross-sectional; obese adults undergoing bariatric surgery (101)	NAFLD by biopsy	OSA	Individuals with more severe OSA and nocturnal hypoxia are more likely to have NASH.
Aron-Wisniewsky et al ¹⁰⁶	Prospective cohort; obese adults undergoing bariatric surgery (101)	NAFLD by biopsy	OSA, CIH	Nocturnal hypoxia is associated with more severe NASH lesions and more advanced fibrosis in a dose-dependent manner.
Jullian-Desayes et al ¹¹²	RCT; adults diagnosed with OSA (103)	NAFLD by FibroMax (BioPredictive)	CPAP	6-12 weeks of effective CPAP does not reduce steatosis, NASH, or fibrosis.
Sleep Duration				
Kim et al ¹¹⁸	Cross-sectional; adults (17,425)	Sleep duration, sleep quality	NAFLD by ALT levels and Fatty Liver Index	Short sleep duration, but not sleep quality, increases the odds of elevated levels of ALT (OR, 1.35; $P < .01$) and positive Fatty Liver Index (OR, 1.45; $P < .01$ for trend).
Kim et al ¹¹⁹	Cross-sectional; adults (45,293)	Sleep duration, sleep quality	NAFLD by ultrasound	Short sleep duration increases the odds of NAFLD in men (OR, 1.28; $P < .01$) and women (OR, 1.71; $P < .01$) by promoting obesity. Poor sleep quality also increases the odds of NAFLD in men (OR, 1.1) and women (OR, 1.4).
Katsagoni et al ¹²⁰	Case-control; adults (155)	Sleep duration	NAFLD by elastography	Elevated liver stiffness is less common in individuals who sleep 7-9 hrs/night (55% vs 77%; $P = .04$).
Liu et al ¹²¹	Prospective cohort; older adults (8965)	Sleep duration	NAFLD by ultrasound	Long sleep duration (>9 hrs) increases the risk of NAFLD (RR, 1.31; $P < .01$).
Bernsmeier et al ¹²²	Prospective cohort; adults (46)	Sleep quality	NAFLD by biopsy	Individuals with NAFLD have longer sleep latency and shorter sleep duration. Individuals with NASH have longer sleep latency than individuals with simple steatosis alone (31 vs 19 mins; $P < .05$).
Wu et al ¹²³	Meta-analysis of prospective studies; adults (197,906)	Sleep duration	Obesity	Short sleep duration increases the risk of obesity (pooled OR, 1.45).
Xi et al ¹²⁴	Meta-analysis of observational studies; adults (89,553)	Sleep duration	MetS	Short sleep duration increases the risk of MetS (pooled OR, 1.27).
Shan et al ¹²⁵	Meta-analysis of prospective studies; adults (482,505)	Sleep duration	T2DM	Short and long sleep duration increase the risk of T2DM (pooled OR, 1.09/hr shorter; OR, 1.14/hr longer).
Rao et al ¹³¹	RCT; adults (14)	Restricted vs normal sleep	Insulin sensitivity	Sleep restriction decreases whole body, peripheral, and hepatic insulin sensitivity.
Broussard et al ¹³²	RCT; adults (7)	Restricted vs normal sleep	Insulin sensitivity	Sleep restriction reduces adipocyte and total body insulin sensitivity.

ALT, alanine aminotransferase; BMI, body mass index; CIH, chronic intermittent hypoxia; CPAP, continuous positive airway pressure; GGT, γ -glutamyl-transferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; OSA, obstructive sleep apnea; RCT, randomized, controlled trial; RR, relative risk; T2DM, type 2 diabetes mellitus; TNE, tumor necrosis factor.

In cross-sectional studies of humans, coffee consumption was not associated with biopsy-proven NASH⁴¹ but is associated with a 25% to 35% reduction in the odds of advanced fibrosis in insulin-resistant patients.^{42,43}

It remains to be elucidated which of the more than 1000 bioactive compounds in coffee is responsible for its hepatoprotective and antifibrotic properties. Coffee is the richest source of caffeine in a person's diet, and caffeine has been shown to inhibit hepatic stellate cell activation, suppress collagen synthesis and deposition, and reduce hepatic steatosis by stimulating β -oxidation and lipid clearance.^{44,46} The antifibrotic and antineoplastic effects appear to be confined to caffeinated brewed coffee vs caffeine from noncoffee beverages such as tea, suggesting that compounds other than caffeine may be responsible for coffee's benefits.^{31,34,47} Chlorogenic acid and the diterpenes cafestol and kahweol are potent antioxidants found in coffee that have antifibrotic, antisteatogenic, anti-inflammatory, anticarcinogenic, and insulin-sensitizing properties.⁴⁸ Cafestol and kahweol are also farnesoid X receptor (FXR) and fibroblast growth factor 15 receptor ligands that inhibit bile acid synthesis⁴⁹; both receptors are molecular targets for drugs under development for NAFLD.

Thus, patients with NAFLD may be advised to drink the equivalent of 2 to 3 8-oz cups of regular brewed coffee daily. This is well within the recommended 400-mg daily limit for caffeine.⁵⁰ Pregnant and lactating women should consume no more than 200 mg of caffeine daily due to a possibly increased risk of adverse fetal outcomes.²⁹ Patients should decrease consumption if there are symptoms of caffeine overdose such as tremors, palpitations, insomnia, or headaches. Coffee additives such as sugar, creamer, and milk should be avoided because their high fat and carbohydrate content potentially negates the protective effects of coffee in NAFLD.⁵¹

Circadian Misalignments

Human physiology and behavior exhibit rhythmic patterns organized around the 24-hour day-night cycle. These circadian rhythms facilitate organismal adaptation to predictable environmental changes brought about by light and darkness. A master clock residing in the suprachiasmatic nucleus in the hypothalamus generates circadian rhythms and synchronizes peripheral tissues and organs through neural and hormonal signals.⁵² Light is the principal environmental cue that entrains the master clock to the 24-hour day.⁵³ At the molecular level, the circadian clock is composed of genes and proteins (specifically *CLOCK*, *BMAL1*, *Cry*, and *Per*) that are locked in a self-sustaining transcription feedback loop with a roughly 24-hour period.⁵⁴ Clock genes are directly coupled to glucose and fatty acid (FA) metabolism and control expression of downstream genes.^{55,56}

Electric light and air travel have allowed modern society to disregard the impositions of day and night, but have led to human behaviors that are misaligned with the circadian clock. Shift work, social jet lag, and wrong-time feeding are common causes of circadian misalignment, which has been associated with functional gastrointestinal disorders, peptic ulcer disease, CV disease, obesity, type 2 diabetes mellitus (T2DM), and cancer.^{57,58}

The circadian clock plays important roles in regulating hepatic lipid metabolism, inflammation, oxidative stress, mitochondrial function, and gut microbiota.⁵⁹ Nearly 20% of lipids, as well as key enzymes in glucose, lipid, and bile acid metabolism (including patatin-like phospholipase domain-containing protein 3), oscillate in a circadian manner in the mouse liver.^{60,61} The circadian clock regulates key enzymes involved in hepatic TG biosynthesis (eg, glycerol 3-phosphate pathway) and FA biosynthesis (eg, FA synthase, *ELOVL3*, *ELOVL6*) as well as in important regulatory transcription factors in lipid metabolism (eg, PPAR- α , - γ , and - δ).⁵⁹ Bile acid synthesis, important for signaling molecules in glucose, lipid, and energy homeostasis via FXR, follows a diurnal pattern due to circadian control of cholesterol 7 α -hydroxylase expression and activity.^{62,63} The gut microbiome exhibits circadian rhythmicity that is determined by the host circadian clock and influenced by circadian timing of meals.^{64,65}

Therefore, circadian disruptions can plausibly promote NAFLD. Indeed, knockout of clock genes induces insulin resistance and leads to increased serum levels of free FAs and TGs and, ultimately, to hepatic steatosis and obesity.⁶⁶ Mice exposed to simulated shift work develop hepatic steatosis and experience upregulation of hepatic genes associated with FA and TG synthesis and downregulation of genes involved in β -oxidation.^{67,68} Induced jet lag in mice causes obesity, insulin resistance, hepatic steatosis, accelerated hepatic necroinflammation and fibrosis, and early-onset HCC, presumably due to a shift toward hepatic lipid synthesis, increased oxidative stress, deregulation of hepatocarcinogenic genes such as FXR and constitutive androstane receptor, and intestinal dysbiosis.^{65,69} Conversely, restricting food intake during the circadian day in mice decreases hepatic TGs through transcriptional and enzymatic regulation of FA synthesis, lipolysis, and β -oxidation by the clock genes *Rev-ErbA α* , *Per2*, and *PPAR- γ* .^{60,70} Time-restricted feeding is also associated with reduced amounts of proinflammatory long-chain FAs in the liver and increased synthesis of the antioxidant glutathione, offering a potential protective mechanism against steatohepatitis.⁷⁰

Epidemiologic studies and several controlled trials provide evidence that circadian misalignment may also promote NAFLD in humans, as discussed in the following sections.

Shift Work

Night shift work is an example of severe circadian misalignment because workers are active and feeding during the normal rest phase, and sleeping and fasting during the normal active phase. According to a National Health and Nutrition Examination Survey (NHANES), shift work increases the likelihood of NAFLD by 66% in lean, but not in obese, individuals (Table 2).⁷¹ A 5-year prospective observational study revealed that shift workers have elevated levels of alanine transaminases, particularly individuals who have hepatic steatosis at baseline, suggesting that shift work may compound and/or exacerbate hepatocellular injury.⁷² Two meta-analyses of large observational studies associate shift work with an increased risk of metabolic syndrome (MetS) and T2DM,^{73,74} and, although NAFLD was not the outcome of interest in these studies, it is reasonable to extrapolate these findings to NAFLD, as the condition commonly coexists with, and is widely viewed as, the hepatic manifestation of MetS.¹ Shift work may cause NAFLD and MetS by inducing insulin resistance, reducing body energy expenditure, decreasing leptin levels, and promoting consumption of unhealthy diets, as shown in controlled human trials.⁷⁵⁻⁷⁷ Less than a week of circadian misalignment is enough to decrease glucose tolerance in otherwise healthy individuals to levels typically seen in patients with diabetes.⁷⁵

Social Jet Lag

Under typical work schedules, late chronotype individuals wake up early (ie, social clock) despite going to sleeping late (ie, biologic clock), leading to a sleep debt that is repaid during weekends and free days by sleeping in. The term social jet lag is used for these shifts in sleeping hours between work days and weekends, as it resembles travel between time zones.⁷⁸ Social jet lag can be quantified by obtaining the absolute difference between the midpoints of sleep during work and free days.⁷⁸ Up to 70% of the European population experiences at least 1 hour of social jet lag, and 30% experiences at least 2 hours.⁷⁹ To date, no human studies have investigated a direct relationship between social jet lag and NAFLD. However, in Japanese and Dutch cross-sectional studies that excluded shift workers, social jet lag of more than 2 hours increased the likelihood of MetS 2-fold (Table 2).^{80,81} Among prediabetic adults in Thailand, each additional hour of social jet lag increased relative body fat by 3%, mean body mass index by 0.9 kg/m², and mean waist-to-hip ratio by 0.13.⁸²

Wrong-Time Feeding

Feeding behavior and macronutrient metabolism are under circadian control.⁸³ Conversely, the liver circadian clock is entrained by the timing and composition of meals in a process that is independent of the suprachiasmatic nucleus.⁸⁴ Hence, feeding at inappropriate times can be

considered a form of circadian misalignment. Over the last 4 decades, daytime meal skipping, eating at later clock times, and frequent snacking have become more prevalent in the general population.⁸⁵ Results from observational studies and small human trials demonstrate that particular meal-timing habits may predispose individuals to NAFLD (Table 2).⁸⁶⁻⁹⁴ Data from NHANES III show that skipping morning (ie, 4:00 am–10:00 am) and midday (ie, 10:00 am–4:00 pm) meals increases the odds of more severe sonographic steatosis by 20% and 73%, respectively, while consuming a greater share of the day's calories in the morning decreases the odds of steatosis by 14% to 21%.⁸⁶ Consistent with these observations, results of a prospective observational study show that skipping breakfast increases the risk of obesity 4.5-fold after adjusting for energy intake and physical activity,⁸⁷ and a meta-analysis shows that skipping breakfast increases the likelihood of T2DM by 15%.⁸⁸ Randomized trials found that skipping breakfast induces insulin resistance, increases expression of the proinflammatory cytokines IL-1 β and IL-6,⁸⁹ and increases total energy intake through compensatory overeating later in the day.⁹⁰ Breakfast skippers may also have less healthy lifestyles that include a higher prevalence of smoking, alcohol use, sedentariness, and poor-quality diets.⁹¹ In a randomized trial comparing an isoenergetic heavy breakfast with a heavy dinner, participants in the heavy breakfast arm lost more weight and waist circumference, had better insulin sensitivity, and reported lower hunger scores.⁹² Having more frequent meals, particularly grazing or snacking outside of conventional meal times, is associated with an increased likelihood of NAFLD and obesity.^{93,94}

Thus, although there are data to suggest that circadian misalignments promote NAFLD, the evidence is weak and based on cross-sectional and small prospective observational studies and indirect, nonhistologic definitions of NAFLD. However, it may be reasonable to ask patients with NAFLD about their work schedules (ie, shift work, social jet lag), sleep habits, and general feeding schedule through a 24-hour dietary recall. In addition to the standard recommendation of caloric restriction and healthy diet, patients may be encouraged to avoid skipping breakfast or lunch and consuming calorie-dense dinners. It is not possible to completely avoid rotating shift work in some patients' work schedules; in these situations, shift workers may be advised to eat at the beginning or toward the end of the night shift and avoid eating during the biologic night (eg, midnight–6:00 am), and to avoid large meals just before their scheduled daytime sleep.⁹⁵ Animal studies and small human trials suggest that restricting meals to the normal active period, which is daytime in diurnal organisms such as humans, may reduce hepatic lipid content, improve insulin sensitivity, and prevent excessive weight gain.^{60,96,97}

Sleep

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a breathing disorder characterized by narrowing and collapse of the upper airway during sleep, leading to episodic reduction or cessation of ventilation, intermittent hypoxia and hypercapnia, and fragmented sleep.⁹⁸ OSA is estimated to affect 14% of men and 5% of women in the general population, and up to 70% of morbidly obese patients.^{99,100} OSA is a well-known risk factor for CV disease, atherosclerosis, and MetS by promoting insulin resistance, inducing dyslipidemia, increasing sympathetic nervous activity, and inducing endothelial dysfunction.^{101,102} There is also evidence that OSA predisposes individuals to NAFLD (Table 2).¹⁰³⁻¹⁰⁶ Polysomnographically diagnosed OSA is significantly more common in patients with NAFLD on ultrasound than in patients without steatosis (71% vs 36%; $P < .001$), and steatosis severity increases in parallel with OSA severity.¹⁰³ OSA is an independent risk factor of biopsy-proven NASH (OR, 4.0; 95% CI, 1.3-12.2) in obese patients undergoing bariatric surgery,¹⁰⁴ and, moreover, biopsy-proven steatohepatitis is significantly more common in patients with severe OSA.¹⁰⁵ Chronic intermittent hypoxia (CIH), one of the fundamental physiologic derangements in OSA, leads to higher NAFLD activity scores and more advanced fibrosis in a dose-dependent manner.¹⁰⁶ CIH can trigger NAFLD and NASH by aggravating insulin resistance and dyslipidemia, inducing expression of lipogenic genes (eg, *SREBP1*, acetyl coenzyme A carboxylase, FA synthase), increasing hepatic lipid peroxidation and oxidative stress, promoting mitochondrial dysfunction, activating intrahepatic macrophages and increasing tumor necrosis factor α expression in the liver, and increasing intestinal permeability and endotoxemia.¹⁰⁷ CIH also promotes expression of lysyl oxidase, the enzyme responsible for collagen crosslinking, providing a possible mechanism in which CIH induces hepatic fibrosis.¹⁰⁸

Continuous positive airway pressure (CPAP) is considered first-line treatment for symptomatic or moderate to severe OSA.¹⁰⁹ While CPAP has been shown to improve blood pressure,¹¹⁰ randomized, controlled trials show that up to 12 weeks of CPAP does not improve insulin sensitivity and presumed NAFLD, NASH, and fibrosis.^{111,112} NAFLD was not defined histologically but through noninvasive biomarkers in one trial.¹¹² Longer duration of CPAP may be necessary to demonstrate disease improvement; however, expert opinion is that CPAP may at least stabilize the disease and limit NASH progression.¹⁰⁷

Sleep Duration

Experts recommend 7 to 9 hours of sleep nightly to maintain optimal health in adults.¹¹³ However, only

60% to 70% of US adults sleep within this range, and the proportion of the population that sleeps fewer than 6 hours nightly increased by 30% in the last 3 decades due to changing occupational and social activities.¹¹⁴ Epidemiologic studies link short and long sleep duration with increased risk of death, CV disease, and cancer.^{115,116}

Short sleep duration is associated with NAFLD in several population-based studies (Table 2).¹¹⁷⁻¹²² Large cross-sectional studies in the United States and Korea showed that sleeping fewer than 5 hours nightly may increase the risk of NAFLD, defined as elevated levels of alanine transaminases and positive Fatty Liver Index and sonographic steatosis, by 35% to 70%.¹¹⁷⁻¹¹⁹ Similarly, sleeping within the recommended duration of 7 to 9 hours reduces the likelihood of significant fibrosis (eg, $\geq F2$) measured by transient elastography by 75%.¹²⁰ Conversely, in a Chinese prospective cohort study, long sleep duration increases NAFLD risk by 30%.¹²¹ Poor sleep quality may also predispose individuals to NAFLD and NASH. Patients with biopsy-proven NASH are found to have longer sleep latency (31 min) than patients with simple steatosis (19 min) or healthy controls (10 min).¹²² Because patients were not screened for OSA in this study, it is unclear if the association between poor sleep quality and NAFLD is due to sleep quality itself or from comorbid OSA.

Short sleep duration may promote NAFLD by increasing the risk of obesity and MetS because body mass index attenuates the effect of sleep duration, according to some studies. Indeed, meta-analyses demonstrated an increased risk of obesity, MetS, and T2DM in individuals with an abnormally short or long sleep duration and poor sleep quality.¹²³⁻¹²⁵ Moreover, sleep restriction appears to induce a state of positive energy balance, which when chronic can predispose individuals to obesity and, by extension, NAFLD. Controlled trials that intentionally curtail sleep in patients demonstrate that patients who slept less consumed more calories and had less healthy diets, without a proportionate increase in their physical activity and energy expenditure.¹²⁶⁻¹²⁸ Sleep restriction also enhances hunger and appetite, presumably through an imbalance of satiety (eg, leptin) and orexigenic (eg, ghrelin) hormones and abnormal responses in neural reward pathways to food-related stimuli.^{129,130} Additionally, sleep restriction induces adipose and hepatic insulin resistance, which are fundamental in the etiopathogenesis of NAFLD.^{131,132}

Thus, due to the moderately strong association between OSA, CIH, and NAFLD, NAFLD patients who are at risk for OSA (eg, owing to unrefreshing sleep, obesity, loud snoring) should undergo polysomnography. NAFLD patients with symptomatic or moderate to severe OSA should be treated with CPAP in keeping with standard practice,⁹⁸ although current data do not support a

direct benefit of CPAP on NAFLD. It is also reasonable to recommend 7 to 9 hours of sleep nightly to patients with NAFLD as part of healthy lifestyle modifications. Practical interventions to promote optimal nighttime sleep duration and quality include using blackout curtains, turning off lights at bedtime, limiting the use of electronic devices, and minimizing the use of stimulants such as caffeine, alcohol, and cigarettes in the evening.

Conclusion

Even with the prospect of effective pharmacotherapies, the mainstay of treatment for NAFLD remains weight loss through healthy lifestyle modifications. Patients with NAFLD should be counseled to reduce their consumption of unhealthy calories and to incorporate exercise in their daily routines. Clinicians may consider inquiring about patients' alcohol use, coffee consumption, timing of meals, and sleep patterns, as there are data to suggest that these are potentially modifiable risk factors for NAFLD. However, more data from prospective controlled trials are required before practice-changing recommendations can be made.

The authors have no relevant conflicts of interest to disclose.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84.
2. Cholaneril G, Wong RJ, Hu M, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. *Dig Dis Sci*. 2017;62(10):2915-2922.
3. Younossi Z, Stepanova M, Ong JP, et al; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol*. 2019;17(4):748-755.e3.
4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357.
5. 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.
6. Hannah WN Jr, Harrison SA. Effect of weight loss, diet, exercise, and bariatric surgery on nonalcoholic fatty liver disease. *Clin Liver Dis*. 2016;20(2):339-350.
7. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad libitum Mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial. *Hepatology*. 2018;68(5):1741-1754.
8. Zhang HJ, He J, Pan LL, 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.
9. VanWagner LB, Ning H, Allen NB, et al. Alcohol use and cardiovascular disease risk in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2017;153(5):1260-1272.e3.
10. Office of Disease Prevention and Health Promotion. Appendix 9. Alcohol. <https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/appendix-9/>. Accessed March 2, 2020.
11. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*. 2002;36(5):1206-1213.
12. Ruhl CE, Everhart JE. Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. *Clin Gastroenterol Hepatol*. 2005;3(12):1260-1268.
13. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology*. 1997;25(1):108-111.
14. Ronskley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342:d671.
15. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N Engl J Med*. 1997;337(24):1705-1714.
16. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;363(14):1341-1350.
17. Kwon HK, Greenon 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.
18. Hagström H, Nasr P, Ekstedt M, et al. Low to moderate lifetime alcohol consumption is associated with less advanced stages of fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol*. 2017;52(2):159-165.
19. 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.
20. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology*. 2001;121(1):91-100.
21. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. *JAMA*. 2002;287(19):2559-2562.
22. Brien SE, Ronskley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ*. 2011;342:d636.
23. Cotrim HP, Freitas LA, Alves E, Almeida A, May DS, Caldwell S. Effects of light-to-moderate alcohol consumption on steatosis and steatohepatitis in severely obese patients. *Eur J Gastroenterol Hepatol*. 2009;21(9):969-972.
24. Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet*. 1988;2(8623):1267-1273.
25. Ekstedt M, Franzén LE, Holmqvist M, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol*. 2009;44(3):366-374.
26. Ajmera V, Belt P, Wilson LA, et al; Nonalcoholic Steatohepatitis Clinical Research Network. 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.e5.
27. Ascha MS, Hanounch IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology*. 2010;51(6):1972-1978.
28. Stockwell T, Room R. Constructing and responding to low-risk drinking guidelines: conceptualisation, evidence and reception. *Drug Alcohol Rev*. 2012;31(2):121-125.
29. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.
30. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2005;128(1):24-32.
31. Nakanishi N, Nakamura K, Suzuki K, Tataru K. Lifestyle and serum gamma-glutamyltransferase: a study of middle-aged Japanese men. *Occup Med (Lond)*. 2000;50(2):115-120.
32. Modi AA, Feld JJ, Park Y, et al. Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology*. 2010;51(1):201-209.
33. 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.
34. Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, and transaminase enzymes. *Arch Intern Med*. 2006;166(11):1190-1195.
35. Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. *Gastroenterology*. 2015;148(1):118-125.
36. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open*.

- 2017;7(5):e013739.
37. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology*. 2007;132(5):1740-1745.
 38. Catalano D, Martínez GF, Tonzuso A, Pirri C, Trovato FM, Trovato GM. Protective role of coffee in non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci*. 2010;55(11):3200-3206.
 39. Veronese N, Notarnicola M, Cisternino AM, et al; MICOL Group. Coffee intake and liver steatosis: a population study in a Mediterranean area. *Nutrients*. 2018;10(1):89-97.
 40. 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*. 2010;52(5):1652-1661.
 41. Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology*. 2012;55(2):429-436.
 42. Bambha K, Wilson LA, Unalp A, et al; Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). Coffee consumption in NAFLD patients with lower insulin resistance is associated with lower risk of severe fibrosis. *Liver Int*. 2014;34(8):1250-1258.
 43. Anty R, Marjoux S, Iannelli A, et al. Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery. *J Hepatol*. 2012;57(5):1090-1096.
 44. Yamaguchi M, Saito SY, Nishiyama R, et al. Caffeine suppresses the activation of hepatic stellate cells cAMP-independently by antagonizing adenosine receptors. *Biol Pharm Bull*. 2017;40(5):658-664.
 45. Wang H, Guan W, Yang W, et al. Caffeine inhibits the activation of hepatic stellate cells induced by acetaldehyde via adenosine A2A receptor mediated by the cAMP/PKA/SRC/ERK1/2/P38 MAPK signal pathway. *PLoS One*. 2014;9(3):e92482.
 46. Sinha RA, Farah BL, Singh BK, et al. Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. *Hepatology*. 2014;59(4):1366-1380.
 47. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A; Collaborative SIDER Group. Coffee, caffeine, and the risk of liver cirrhosis. *Ann Epidemiol*. 2001;11(7):458-465.
 48. Salomone F, Galvano F, Li Volti G. Molecular bases underlying the hepatoprotective effects of coffee. *Nutrients*. 2017;9(1):85-97.
 49. Ricketts ML, Boekschoten MV, Kreeft AJ, et al. The cholesterol-raising factor from coffee beans, cafestol, as an agonist ligand for the farnesoid and pregnane X receptors. *Mol Endocrinol*. 2007;21(7):1603-1616.
 50. European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies. Scientific opinion on the safety of caffeine. *EFSA J*. 2015;13(5):4102.
 51. Kim HJ, Cho S, Jacobs DR Jr, Park K. Instant coffee consumption may be associated with higher risk of metabolic syndrome in Korean adults. *Diabetes Res Clin Pract*. 2014;106(1):145-153.
 52. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002;418(6901):935-941.
 53. Challet E, Caldelas I, Graff C, Pévet P. Synchronization of the molecular clockwork by light- and food-related cues in mammals. *Biol Chem*. 2003;384(5):711-719.
 54. King DP, Takahashi JS. Molecular genetics of circadian rhythms in mammals. *Annu Rev Neurosci*. 2000;23:713-742.
 55. Marcheva B, Ramsey KM, Buhr ED, et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*. 2010;466(7306):627-631.
 56. Oishi K, Miyazaki K, Kadota K, et al. Genome-wide expression analysis of mouse liver reveals CLOCK-regulated circadian output genes. *J Biol Chem*. 2003;278(42):41519-41527.
 57. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)*. 2003;53(2):103-108.
 58. Straif K, Baan R, Grosse Y, et al; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12):1065-1066.
 59. Reinke H, Asher G. Circadian clock control of liver metabolic functions. *Gastroenterology*. 2016;150(3):574-580.
 60. Adamovich Y, Rousoo-Noori L, Zwighaft Z, et al. Circadian clocks and feeding time regulate the oscillations and levels of hepatic triglycerides. *Cell Metab*. 2014;19(2):319-330.
 61. Panda S, Antoch MP, Miller BH, et al. Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell*. 2002;109(3):307-320.
 62. Arab JP, Karpen SJ, Dawson PA, Arrese M, Trauner M. Bile acids and nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. *Hepatology*. 2017;65(1):350-362.
 63. Le Martelot G, Claudel T, Gatfield D, et al. REV-ERB α participates in circadian SREBP signaling and bile acid homeostasis. *PLoS Biol*. 2009;7(9):e1000181.
 64. Liang X, Bushman FD, FitzGerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *Proc Natl Acad Sci U S A*. 2015;112(33):10479-10484.
 65. Thaiss CA, Zeevi D, Levy M, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*. 2014;159(3):514-529.
 66. Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science*. 2005;308(5724):1043-1045.
 67. Salgado-Delgado R, Angeles-Castellanos M, Saderi N, Buijs RM, Escobar C. Food intake during the normal activity phase prevents obesity and circadian desynchrony in a rat model of night work. *Endocrinology*. 2010;151(3):1019-1029.
 68. Marri AR, Meerlo P, Grønli J, et al. Shift in food intake and changes in metabolic regulation and gene expression during simulated night-shift work: a rat model. *Nutrients*. 2016;8(11):E712.
 69. Kettner NM, Voicu H, Finegold MJ, et al. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. *Cancer Cell*. 2016;30(6):909-924.
 70. Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab*. 2012;15(6):848-860.
 71. Balakrishnan M, El-Serag HB, Kanwal F, Thrift AP. Shiftwork is not associated with increased risk of NAFLD: findings from the National Health and Nutrition Examination Survey. *Dig Dis Sci*. 2017;62(2):526-533.
 72. Lin YC, Chen PC. Persistent rotating shift work exposure is a tough second hit contributing to abnormal liver function among on-site workers having sonographic fatty liver. *Asia Pac J Public Health*. 2015;27(2):NP1765-NP1774.
 73. Wang F, Zhang L, Zhang Y, et al. Meta-analysis on night shift work and risk of metabolic syndrome. *Obes Rev*. 2014;15(9):709-720.
 74. Gan Y, Yang C, Tong X, et al. Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occup Environ Med*. 2015;72(1):72-78.
 75. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A*. 2009;106(11):4453-4458.
 76. McHill AW, Melanson EL, Higgins J, et al. Impact of circadian misalignment on energy metabolism during simulated nightshift work. *Proc Natl Acad Sci U S A*. 2014;111(48):17302-17307.
 77. Hemiö K, Puttonen S, Viitasalo K, Härmä M, Peltonen M, Lindström J. Food and nutrient intake among workers with different shift systems. *Occup Environ Med*. 2015;72(7):513-520.
 78. Wittmann M, Dinich J, Mewro M, Roenneberg T. Social jet lag: misalignment of biological and social time. *Chronobiol Int*. 2006;23(1-2):497-509.
 79. Roenneberg T, Allebrandt KV, Mewro M, Vetter C. Social jet lag and obesity. *Curr Biol*. 2012;22(10):939-943.
 80. Islam Z, Akter S, Kochi T, et al. Association of social jet lag with metabolic syndrome among Japanese working population: the Furukawa nutrition and health study. *Sleep Med*. 2018;51:53-58.
 81. Koopman ADM, Rauh SP, van 't Riet E, et al. The association between social jet lag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the New Hoorn study. *J Biol Rhythms*. 2017;32(4):359-368.
 82. Anothaisintawee T, Lettrattananon D, Thamakaision S, Thakkinian A, Reutrakul S. The relationship among morningness-eveningness, sleep duration, social jet lag, and body mass index in Asian patients with prediabetes. *Front Endocrinol (Lausanne)*. 2018;9:435.
 83. Mendoza J. Circadian clocks: setting time by food. *J Neuroendocrinol*. 2007;19(2):127-137.
 84. Stokkan K-A, Yamazaki S, Tei H, Sakaki Y, Menaker M. Entrainment of the circadian clock in the liver by feeding. *Science*. 2001;291(5503):490-493.
 85. Kant AK, Graubard BI. 40-year trends in meal and snack eating behaviors of American adults. *J Acad Nutr Diet*. 2015;115(1):50-63.
 86. Esteban JPG, Rein LE, Szabo A, et al. Not just what, but also when you eat: analyzing the impact of meal timing patterns on non-alcoholic fatty liver disease. *Hepatology*. 2016;64(suppl 1):S17A.
 87. Ma Y, Bertone ER, Stanek EJ III, et al. Association between eating patterns and obesity in a free-living US adult population. *Am J Epidemiol*. 2003;158(1):85-92.
 88. Bi H, Gan Y, Yang C, Chen Y, Tong X, Lu Z. Breakfast skipping and the risk of type 2 diabetes: a meta-analysis of observational studies. *Public Health Nutr*. 2015;18(16):3013-3019.
 89. Nas A, Mirza N, Hägele F, et al. Impact of breakfast skipping compared with dinner skipping on regulation of energy balance and metabolic risk. *Am J Clin*

- Nutr.* 2017;105(6):1351-1361.
90. Farshchi HR, Taylor MA, Macdonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. *Am J Clin Nutr.* 2005;81(2):388-396.
 91. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. *Am J Clin Nutr.* 2012;95(5):1182-1189.
 92. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring).* 2013;21(12):2504-2512.
 93. Miyake T, Kumagi T, Hirooka M, et al. Significance of exercise in nonalcoholic fatty liver disease in men: a community-based large cross-sectional study. *J Gastroenterol.* 2015;50(2):230-237.
 94. Leech RM, Timperio A, Livingstone KM, Worsley A, McNaughton SA. Temporal eating patterns: associations with nutrient intakes, diet quality, and measures of adiposity. *Am J Clin Nutr.* 2017;106(4):1121-1130.
 95. Lowden A, Moreno C, Holmbäck U, Lennernäs M, Tucker P. Eating and shift work—effects on habits, metabolism and performance. *Scand J Work Environ Health.* 2010;36(2):150-162.
 96. Grant CL, Coates AM, Dorrian J, et al. Timing of food intake during simulated night shift impacts glucose metabolism: a controlled study. *Chronobiol Int.* 2017;34(8):1003-1013.
 97. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring).* 2009;17(11):2100-2102.
 98. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med.* 2019;380(15):1442-1449.
 99. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9):1006-1014.
 100. Ravesloot MJL, van Maanen JB, Hilgevoord AAJ, van Wagenveld BA, de Vries N. Obstructive sleep apnea is underrecognized and underdiagnosed in patients undergoing bariatric surgery. *Eur Arch Otorhinolaryngol.* 2012;269(7):1865-1871.
 101. Marin JM, Carrizo SJ, Vicente E, Agustí AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005;365(9464):1046-1053.
 102. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol.* 2013;62(7):569-576.
 103. Türkay C, Ozol D, Kasapoğlu B, Kirbas I, Yıldırım Z, Yiğitoğlu R. Influence of obstructive sleep apnea on fatty liver disease: role of chronic intermittent hypoxia. *Respir Care.* 2012;57(2):244-249.
 104. Campos GM, Bamba K, Vittinghoff E, et al. A clinical scoring system for predicting nonalcoholic steatohepatitis in morbidly obese patients. *Hepatology.* 2008;47(6):1916-1923.
 105. Mishra P, Nugent C, Afendy A, et al. Apnoeic-hypopnoeic episodes during obstructive sleep apnoea are associated with histological nonalcoholic steatohepatitis. *Liver Int.* 2008;28(8):1080-1086.
 106. Aron-Wisniewsky J, Minville C, Tordjman J, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. *J Hepatol.* 2012;56(1):225-233.
 107. Aron-Wisniewsky J, Clement K, Pépin JL. Nonalcoholic fatty liver disease and obstructive sleep apnea. *Metabolism.* 2016;65(8):1124-1135.
 108. Mesarwi OA, Shin MK, Drager LF, et al. Lysyl oxidase as a serum biomarker of liver fibrosis in patients with severe obesity and obstructive sleep apnea. *Sleep.* 2015;38(10):1583-1591.
 109. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2019;15(2):301-334.
 110. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM. Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J.* 2007;29(4):720-727.
 111. Hecht L, Möhler R, Meyer G. Effects of CPAP-respiration on markers of glucose metabolism in patients with obstructive sleep apnoea syndrome: a systematic review and meta-analysis. *Ger Med Sci.* 2011;9:Doc20.
 112. Jullian-Desayes I, Tamisier R, Zarski JP, et al. Impact of effective versus sham continuous positive airway pressure on liver injury in obstructive sleep apnoea: data from randomized trials. *Respirology.* 2016;21(2):378-385.
 113. Watson NF, Badr MS, Belenky G, et al; Consensus Conference Panel. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep.* 2015;38(8):1161-1183.
 114. Ford ES, Cunningham TJ, Croft JB. Trends in self-reported sleep duration among US adults from 1985 to 2012. *Sleep.* 2015;38(5):829-832.
 115. Yin J, Jin X, Shan Z, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2017;6(9):e005947.
 116. Jiao L, Duan Z, Sangi-Haghpeykar H, Hale L, White DL, El-Serag HB. Sleep duration and incidence of colorectal cancer in postmenopausal women. *Br J Cancer.* 2013;108(1):213-221.
 117. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther.* 2015;41(1):65-76.
 118. Kim D, Kim HJ, Kushida CA, Heo NY, Ahmed A, Kim WR. Short sleep duration is associated with abnormal serum aminotransferase activities and nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2018;16(4):588-590.
 119. Kim C-W, Yun KE, Jung H-S, et al. Sleep duration and quality in relation to non-alcoholic fatty liver disease in middle-aged workers and their spouses. *J Hepatol.* 2013;59(2):351-357.
 120. Katsagoni CN, Georgoulis M, Papatheodoridis GV, et al. Associations between lifestyle characteristics and the presence of nonalcoholic fatty liver disease: a case-control study. *Metab Syndr Relat Disord.* 2017;15(2):72-79.
 121. Liu C, Zhong R, Lou J, et al. Nighttime sleep duration and risk of non-alcoholic fatty liver disease: the Dongfeng-Tongji prospective study. *Ann Med.* 2016;48(6):468-476.
 122. Bernsmeier C, Weisskopf DM, Pflueger MO, et al. Sleep disruption and daytime sleepiness correlating with disease severity and insulin resistance in non-alcoholic fatty liver disease: a comparison with healthy controls. *PLoS One.* 2015;10(11):e0143293.
 123. Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med.* 2014;15(12):1456-1462.
 124. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: a systematic review and meta-analysis. *Sleep Med Rev.* 2014;18(4):293-297.
 125. Shan Z, Ma H, Xie M, et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care.* 2015;38(3):529-537.
 126. Beebe DW, Simon S, Summer S, Hemmer S, Strotman D, Dolan LM. Dietary intake following experimentally restricted sleep in adolescents. *Sleep.* 2013;36(6):827-834.
 127. Calvin AD, Carter RE, Adachi T, et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest.* 2013;144(1):79-86.
 128. St-Onge MP, Roberts AL, Chen J, et al. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am J Clin Nutr.* 2011;94(2):410-416.
 129. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141(11):846-850.
 130. St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. *Am J Clin Nutr.* 2012;95(4):818-824.
 131. Rao MN, Neylan TC, Grunfeld C, Mulligan K, Schambelan M, Schwarz JM. Subchronic sleep restriction causes tissue-specific insulin resistance. *J Clin Endocrinol Metab.* 2015;100(4):1664-1671.
 132. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med.* 2012;157(8):549-557.