Boyle M, Masson S, Anstee QM.

The bidirectional impacts of alcohol consumption and the metabolic syndrome: Cofactors for progressive fatty liver disease.

***Journal of Hepatology* 2017**

DOI: https://doi.org/10.1016/j.jhep.2017.11.006

THE BIDIRECTIONAL IMPACTS OF ALCOHOL CONSUMPTION AND THE METABOLIC SYNDROME: COFACTORS FOR PROGRESSIVE FATTY LIVER DISEASE

Marie Boyle[1, 2], Steven Masson[1, 2] & Quentin M. Anstee[1,2]

[1] Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, United Kingdom.
[2] Liver Unit, Newcastle Upon Tyne Hospitals NHS Trust, Freeman Hospital, Newcastle upon Tyne, United Kingdom.

Corresponding Author/Reprint Requests:

Professor Quentin M. Anstee BSc (Hons), MB BS, PhD, MRCP(UK), FRCP
Professor of Experimental Hepatology & Honorary Consultant Hepatologist,
Institute of Cellular Medicine,
The Medical School,
Newcastle University,
4th Floor, William Leech Building,
Framlington Place,
Newcastle-upon-Tyne, NE2 4HH, Great Britain.

Telephone: + 44 (0) 191 208 7012
Fax: + 44 (0) 191 208 0723
Email: quentin.anstee@newcastle.ac.uk

Keywords: NAFLD, ALD, Pathogenesis, Liver, Alcohol

Short Title: Alcohol & Metabolic Syndrome in Fatty Liver Disease

Acknowledgements
QMA is a member of the EPoS (Elucidating Pathways of Steatohepatitis) consortium funded by the Horizon 2020 Framework Program of the European Union under Grant Agreement 634413.

Abstract

Current medical practice artificially dichotomises a diagnosis of fatty liver disease into one of two common forms: Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD). Together, these make up the majority of chronic liver disease worldwide. In recent years, there has been a dramatic increase in the prevalence of obesity and metabolic syndrome risk-factors within the general population and so these factors now coexist with alcohol consumption in a substantial proportion of the population. Each exposure sensitises the liver to the injurious effects of the other; an interaction that drives and potentially accelerates the genesis of liver disease. We review the epidemiological evidence and scientific literature that considers how alcohol consumption interacts with components of the metabolic syndrome to exert additive and synergistic effects on the development and progression of liver disease and discuss how these interactions may be addressed in clinical practice.

1. Introduction

Current medical practice tends to dichotomise a diagnosis of fatty liver disease into one of two common forms, Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD), based on a widely-adopted threshold for alcohol consumption set at 20g/day for women and 30g/day for men [1, 2]. Together, ALD and NAFLD make up the vast majority of chronic liver disease worldwide and are consuming an increasing proportion of healthcare resources. Both conditions share many pathophysiological processes and have similar histological features: steatosis (hepatic triglyceride content [HTGC] > 5%), steatohepatitis, fibrosis and cirrhosis [3].

In terms of aetiology, the relationship between sustained high alcohol consumption and progressive liver disease is well established. The risk of liver disease increases as alcohol consumption rises beyond ~30g/day: 7.1-fold relative risk at 50g/day, rising to a 26-fold relative risk at 100g/day [4, 5]. Similarly, NAFLD is driven by the presence of sustained dietary calorific excess, being most commonly found in patients that exhibit multiple features of the metabolic syndrome (central obesity, type 2 diabetes mellitus [T2DM], dyslipidaemia and hypertension) [6].

Both ALD and NAFLD are characterized by substantial interpatient variation in disease severity, risk of progression to cirrhosis and long-term outcomes such as hepatic decompensation or hepatocellular carcinoma (HCC). Over the last 50-years, lifestyles have become increasingly sedentary and dietary patterns have changed, dramatically increasing the prevalence of obesity and metabolic syndrome risk-factors within the general population. Given that approximately 70% of the adults in the WHO European Region drink alcohol [7], with a mean consumption of 10.7 litres of pure ethanol per year [8], metabolic risk factors and some level of alcohol consumption now coexist in a substantial proportion of the population with each exposure potentially sensitizing the liver to the injurious effects of the other. Much emphasis has been placed on exploring how genetic factors modify disease progression in NAFLD and ALD [3] but it is also important to consider how the combined environmental challenges of alcohol consumption and calorific excess/metabolic risk may interact to modify progression of liver disease. Such interactions are clearly relevant at excessive levels of alcohol consumption but perhaps even more so in patients where alcohol consumption is less extreme. For the purpose of this article, a search of the PubMed MEDLINE database was conducted, and the reference lists in review articles and original research were examined.

2. Epidemiology: Frequency of Obesity and Alcohol as cofactors for Liver Disease

The burden of ALD is hard to accurately quantify with wide international variations and trends in the reported prevalence and impact of ALD. The prevalence of ALD in the US population is currently estimated to be 2.0%–2.5% [9]. The National Health and Nutrition Examination Survey (NHANES) reports that ALD prevalence increased from 1.38% during the period from 1988 to 1994 to 2.21% during the period from 1999 to 2004, but then remained stable, at 2.05%, during the period from 2005 to 2008 [10]. In Europe, some countries have reported a decline in the burden of ALD, while others have reported a recent increase in mortality from ALD cirrhosis [11]. However, it is clear that excessive alcohol consumption is a significant public health challenge, with an attributable burden of premature mortality and ill-health which is highest in Europe and North America and disproportionately affects younger people [12].

Obesity rates have been increasing in all territories worldwide but particularly in middle- and high-income countries. The 2014 WHO *Report on Non-Communicable Diseases* found that 39% of adults (38% of males and 40% of females) worldwide were overweight with a near 2-fold increase in the prevalence of obesity between 1980 and 2014 [13]. The highest prevalence of overweight and obesity was seen in the Americas where 61% were overweight or obese (27% obese) and lowest in South-East Asia (22% overweight, 5% obese). In Europe, over half the adult population is overweight and 20-25% of the population is obese. Similarly, 8-10% of the adult population have T2DM [13]. In light of this it is perhaps unsurprising that there is also a high prevalence of NAFLD worldwide, with approximately 25% of the adult population affected by NAFLD [14, 15]. Even if one adopts a conservative approach and assumes that up to 1 in 10 cases may be undetected excessive drinkers that have been being misclassified as NAFLD, it is apparent that a substantial burden of NAFLD exists within the general population [16].

The association between alcohol consumption and obesity is complex. Numerous studies have linked moderate to heavy alcohol use with weight gain and obesity [17-20]. In a recent review of alcohol consumption and obesity, it was concluded that alcohol intake may confer an increased risk of obesity in some individuals. Available studies reviewed were however conflicting, variously finding either no association, a positive, or a negative association with binge/heavy drinking, frequency and intensity [21]. Worryingly, in a recent study in young adults, regular heavy alcohol consumption was associated with weight gain [22]. Data from the

German Study of Health in Pomerania (SHIP) established the prevalence of people meeting the criteria for both NAFLD and ALD [23]. In the adult male population of Northeast Germany 17.5% of subjects exhibit risk criteria for both NAFLD and ALD (i.e. obese and consuming >30 g alcohol/day) [23]. Similar findings have been reported in Finnish adults [24], where patients with ALD were as likely to be obese as patients identified as having "non-alcoholic" fatty liver disease. Indeed, the same study reported that the metabolic syndrome was more frequently present in ALD than NAFLD patients. These data highlight the degree of overlap that exists and that coexisting high alcohol consumption and overweight/obesity are frequently encountered in day-to-day clinical practice.

Further emphasising the relationship between alcohol and obesity as co-factors for liver disease, it has been shown that patients often develop obesity after drinking cessation. In a Danish cohort of 6,514 individuals, a variant in *FGF21* was associated with increased consumption of candy and increased alcohol intake, suggesting that the FGF21 hormone secreted by the liver may influence nutrient choices [25]

3. Pathogenesis of ALD and NAFLD

A full discussion of the pathogenesis of NAFLD and ALD is outside the scope of the current article. Both ALD and NAFLD unarguably exhibit disease specific components [26, 27]**.** However, given their striking histological similarities, it is not surprising that there are many mechanisms common to the development and progression of both (**Figure 1**) [26, 28]. Numerous studies demonstrate that the transition from steatosis to steatohepatitis in both NAFLD and ALD is characterised by both mitochondrial dysfunction and increasing hepatocellular oxidative stress [29-31]. Other well validated contributory factors include endotoxaemia derived from gram-negative bacteria amongst the gut flora that enter the portal circulation due to increased gut permeability and subsequently provoke inflammatory processes in both NAFLD and ALD [26, 32, 33]. In addition, there is also some evidence to suggest that the bacterial flora within the gut may contribute to the pathogenesis of NAFLD through endogenous alcohol production. Murine studies have demonstrated alcohol may be produced by the gut flora, with greater amounts being produced in obese vs. lean animals[34]. Supporting this contributory hypothesis, hepatocytes from young patients with NASH have been found to express genes encoding alcohol degradation pathways despite patients abstaining from alcohol [35]. Furthermore, in a recent animal study [36], researchers attempted to demonstrate that NAFLD is, at least in part,

the product of endogenous alcohol production [37-39] and that potentially hepatotoxic levels of alcohol could be produced and upregulation of genes in relevant metabolic pathways [40-43]. It is unlikely that endogenous alcohol production alone is sufficient to cause NAFLD and further validation of these findings in humans is clearly needed but the endogenous alcohol hypothesis could open new avenues for the treatment and prevention of NAFLD.

3.1. Genetics in NAFLD and ALD

Further evidence for a shared pathophysiology and the central role of lipid metabolism in both conditions may be derived from genetic studies, which have demonstrated that the severity and progression of both NAFLD and ALD are influenced by a number of the same genetic variants, recently reviewed [3]. These include a common non-synonymous variant (rs738409 c.444 C>G p.I148M) in the *patatin-like phospholipase domain-containing 3* (*PNPLA3*) gene that encodes adiponutrin, a protein involved in lipid metabolism [44], which has been shown to influence severity of steatosis, steatohepatitis and fibrosis and HCC risk in NAFLD [45-47] and ALD [48-51]. Similarly, a variant in the *transmembrane 6 superfamily member 2* (*TM6SF2*) gene (rs5854296 c.449 C>T, p.E167K) is associated with increased severity of liver disease in NAFLD [52, 53] and ALD [48] but is protective against dyslipidaemia and cardiovascular disease [54-56]. Most recently, a variant (rs641738) in the *membrane bound O-acyltransferase domain containing 7- transmembrane channel-like 4 (MBOAT7)* gene has also been shown to influence disease progression in both conditions [3, 48].

3.2. Environmental Factors influencing the development and progression of NAFLD and ALD

A diagnosis of NAFLD implies that an individual has evidence of hepatic steatosis (biopsy/radiology) and that other causes of fatty liver disease have been excluded, in particular excessive alcohol consumption. However, what precise threshold defines significant alcohol consumption for discriminating NAFLD and ALD remains unclear. Furthermore, it has also been observed that in addition to quantity; alcoholic beverage type, drinking patterns, lifestyle patterns and types of dietary fats are significant in metabolic liver disease, adding further complexity to study interpretation.

3.2.1 ***Quantity and Pattern of Alcohol Consumption & Disease Risk***

The alcohol consumption threshold for hepatotoxicity is complicated and dependent on a variety of modifiers (for example, gender, genetic factors and ethnicity) [57]. It is generally

accepted that daily alcohol consumption below two drinks in men and one drink in women is unlikely to cause hepatic steatosis [58, 59]. The safe levels of alcohol consumption proposed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD) are 30g/day and 20g/day of alcohol in men and women respectively [57, 60] whilst the Asian Pacific for the Study of the Liver (APASL) adopts a more conservative threshold of <20g/day in men and 10g/day in women [61]. It is also apparent that the marked differences between a linear relationship and a "J-shaped" curve with regard to risk/benefit of alcohol consumption may harbour problems when disseminating clear public health messages. Indeed, it has been advised that the public should focus on the nadir of the J-shaped curve for making decisions about drinking. Instead, many moderate drinkers are inclined to view the point on the curve where the risk of adverse health outcomes exceeds that of abstainers and these data do not consider the synergistic effects of alcohol and obesity. [62].

In addition to the quantity, the pattern of alcohol use may be relevant in assessing the level of harm. The number of days per week on which alcohol is consumed, the typical number of drinks per day, and evaluation for the presence of episodic heavy drinking should be performed to characterize the moderate alcohol user. For example, in a recent Danish study, the amount of alcohol consumed per session has been proposed to be more important in relation to risk of developing T2DM than drinking frequency [63]. However, previous studies have reported that binge drinking increases the risk of T2DM in men, but not women [63-66]. Regarding drinking patterns, the CAS study found the "five/four" measure of binge drinking to be associated with a substantially greater risk of alcohol-related health and social problems [67]. However, an additional study examining liver disease in heavy drinkers that did/did not exhibit features of alcohol withdrawal demonstrated a negative association of alcohol withdrawal and liver cirrhosis, an effect that persisted even after adjustment for gender, duration and pattern of alcohol consumption [68]

3.2.2. Dietary Constituents & Disease Risk

Epidemiological and experimental studies indicate that both quantity and the type of dietary fat can influences pathogenesis of ALD [69, 70] and NAFLD [71, 72]. Saturated FFA causes more apoptosis than unsaturated fats in vitro. Quality of carbohydrates also affects hepatic steatosis, inflammation and fibrosis in animal models [73, 74].

A cross-sectional Danish study reported that people who buy wine tended to also buy more "healthy" food items than those that purchased beer (i.e. wine buyers favoured fruit/vegetables, olives and low-fat products; beer buyers favoured ready meals, sugar, chips, butter, sausages and soft drinks) [75]. These findings are supported by other studies from the United States and Europe link purchase of wine with fruit, vegetables, fish and consumption of less saturated fat [76-78]. Some reports also suggest that proportionately greater red wine consumption may reduce the relative risk of cirrhosis [79]. This requires independent validation however is perhaps related to resveratrol, a polyphenol found in grapes [80, 81]. Several studies have suggested that hop ingredients, related to beer making may contain substances that protect from liver damage [82] and may also positively impact components of the metabolic syndrome such as IR and body weight [83]. However, a study by Pelletier et al reported that wine consumption is not associated with a decrease in alcoholic cirrhosis in heavy drinkers [84]. Extending this to T2DM, regarding beverage type, a recent Danish analysis suggests a lower risk of diabetes associated with a moderate to high intake of wine and, among women, a higher risk of diabetes associated with a high intake of spirits [85].

3.3. Experimental (animal) Models analysing the pathological effect of alcohol on Hepatic Steatosis development and fibrosis progression

Animal studies have been invaluable; increasing our understanding of the combined effects of alcohol and obesity on hepatic steatosis and fibrosis progression. A consistent observation during the development of rodent models of ethanol induced liver injury in animals was that isolcaloric substitution of ethanol for dietary fat did not produce hepatic steatosis. Furthermore, rats fed an ethanol containing diet exhibited less overall weight gain than controls. Therefore, a 35% fat, alcohol-containing diet comparable to the original "Lieber-DeCarli formula" (1965) has been widely adopted. This in effect means that many rodent studies into ALD models are in fact already dietary models of combined ALD and NAFLD. [86-89] *In vivo* studies have shown that consumption of such a high fat (HFD)/high alcohol diet, promotes an accelerated progression of hepatic steatosis, inflammation and fibrosis. The available data suggests that moderate alcohol intake augments inflammation and apoptosis in murine models with underlying NASH. Overall, from animal studies we can conclude that the effect of ethanol consumption on NAFLD, and its association with obesity are complex, difficult

to measure and largely deleterious. Selected animal experiments that investigate the interaction between alcohol and obesity in liver injury are summarised in **Table 1.**

An interesting recent study by Duly et al attempted to recapitulate the frequently encountered human pattern of background high fat diet (HFD) consumption combined with intermittent alcohol 'binge' drinking in mice [90]. This produced more severe histological liver injury than either HFD or alcohol consumption did alone [90]. They showed that alcohol and HFD synergistically increased histological steatosis, inflammation and promoted a molecular profile consistent with active fibrogenesis. Beyond the effects of HFD alone, alcohol altered the pattern of histological steatosis: increasing micro- and macro-vesicular lipid deposits, as well as a greater Kupffer cell inflammatory infiltrate and more fibrogenic HSCs. These changes being accompanied by upregulation of SREBP-1 and TGF-β [90]. However, not all in vivo studies have supported these findings. Leptin deficient *ob*/*ob* mice develop obesity, insulin resistance and NAFLD [91]. Kanuri at al reported that moderate alcohol intake ameliorated NAFLD in *ob*/*ob* mice and attributed this apparent protective effect to the induction of SIRT1-/adiponectin-signalling in visceral adipose tissue that in turn modulated hepatic adiponectin/AKT/PAI-1 signalling [92, 93]. However of note, the lack of leptin in this model is not consistent with human NAFLD phenotype and leads to a number of other physiological changes that do not well recapitulate human NAFLD [91].

To translate the results into clinical decision making, there is a need to establish the potential cumulative effects of ethanol on the modulation of factors involved in the pathogenesis of NAFLD; these include the inflammasome, gut microbiota and intestinal permeability, and obesity-related carcinogenesis [94].

4. Natural History/Progression of Liver Disease in the setting of alcohol and obesity

Both ALD and NAFLD are characterized by substantial interpatient variation in disease severity and risk of progression to cirrhosis [5, 95]. We reviewed the published literature relating to the combined effects of alcohol and increased adiposity/obesity in liver disease. It is noteworthy that the epidemiological literature falls into two seemingly diametrically opposed groups: the first reports patients that are primarily diagnosed with NAFLD but who also consume moderate levels of alcohol are at increased risk of developing more severe liver disease; the second suggests that there may be a beneficial effect derived from light/moderate drinking.

Unfortunately, to date, the highest quality data on the relationship between alcohol consumption and clinical outcomes in patients with NAFLD are derived only from observational studies.

4.2. Bidirectional Impact of Alcohol and Metabolic Syndrome as co-factors for Liver Disease

4.2.2. The effects of Alcohol on Metabolic Syndrome related liver disease

Several epidemiological studies support the view that there is a strong causal relationship between consumption of a diet high in fat (and/or presence of T2DM), the consumption of alcohol and progressive liver disease. A summary of these studies is provided in **Table 2**. The Dionysos study in Northern Italy was one of the first epidemiological studies to show that hepatic steatosis prevalence was increased to 46% in subjects with an alcohol intake >60g/day, and to 76% in the obese whereas steatosis was only found in 16% of lean controls [96]. Similar additive/synergistic effects are observed in the case of hepatocellular injury and inflammation, hepatic fibrosis and the development of cirrhosis [97-102]. In addition, the presence of NAFLD potentially makes the liver more sensitive to other injurious processes such as alcohol consumption. In the UK prospective Million Women Cohort study (1,230,662 women; mean age 56; 6.2-years of follow-up), the relative risk of cirrhosis in individuals with BMI >30 and >150 g/week alcohol use was 6.53, and in individuals with normal BMI and >150 g/week alcohol use the relative risk was 3.44 compared with individuals with normal BMI and <70g/week alcohol use [103]. In a prospective evaluation in 9,559 men in Scotland, there was a supra-additive between alcohol consumption and BMI on liver disease morbidity and mortality. Obese men who consumed more than 120g of alcohol per week had a relative rate of liver disease mortality that was 19 times greater than normal or underweight individuals who did not consume alcohol [104]. This equated to a 5.58-fold relative excess risk due to the interaction between BMI and alcohol consumption [104]. In a Finnish population-based health study, out of 6,000 individuals, 84 patients developed advanced liver disease, weekly binge drinking, in combination with MetS, produced a super-additive increase in the risk of decompensated liver disease [105]

In contrast, other epidemiologic studies from Europe, USA and Japan have suggested that moderate alcohol consumption may ameliorate hepatic steatosis consequent to an improvement in peripheral insulin resistance [106]. The epidemiological studies discussed below demonstrate a “J-shaped’ relationship between degree of alcohol consumption and total

mortality, with reduced risk (largely attributable to less cardiovascular disease) for light drinkers and increased risk for those taking more than 3-drinks/day. Infrequent drinkers have risk similar to that of lifelong abstainers, while former drinkers are at increased risk [107]. Quantitative evidence from nine cross-sectional studies on NAFLD implied beneficial effects of moderate alcohol consumption (MAC) defined as less than 40g/day on degree of hepatic steatosis. MAC reduced the risk of having NAFLD by 31% in a pooled sample of 43,175 individuals (30,791 non-drinkers and 12,384 modest drinkers) [108]. MAC showed a protective effect of 50% on the risk of developing NASH in data from 822 patients (550 non-drinkers and 272 modest drinkers)[108]. Further evidence was obtained from a longitudinal study from Japan (5437 individuals with 10 years' follow-up). The calculated adjusted hazard risk of MAC for the development of NAFLD was 0.69 when compared with non-drinkers [109]. **Table 3** shows the studies supporting the beneficial effects of moderate alcohol consumption on hepatic steatosis development in the setting of metabolic syndrome.

In addition to these widely cited epidemiological studies, a number of smaller studies have examined the effect of alcohol drinking on the underlying hepatic histopathology in subjects with a firm diagnosis of NAFLD. **Table 4** provides a summary of these studies. Examining the effect of alcohol as a co-factor for fibrosis is solely a histological diagnosis and thus we are limited in the amount of studies available for review and the size of the cohorts studied. The study by Ekstedt et al reported a more rapid rate of fibrosis progression in patients with NAFLD that drank moderate amounts of alcohol. Among 71 patients with paired-liver biopsies, binge drinking and insulin resistance were independent factors associated with fibrosis progression over a mean 13.8-year interval [102]. Similarly, in a cohort of 112 patients with liver biopsies, Peterson et al found that there was a correlation between increasing weight and degree of fatty liver only in patients who were overweight and had a moderate alcohol consumption [110].

Not all histological studies have found this association. Studying a group of 132 morbidly obese individuals undergoing bariatric surgery Cotrim et al identified no relationship between alcohol consumption and histological liver injury. An effect possibly explained, at least in part, by their observation that there was as inverse relationship between insulin resistance and light to moderate alcohol consumption [111]. Similarly, Dixon et al reported a lower prevalence of steatohepatitis amongst morbidly obese patients reporting moderate alcohol consumption, although this finding was not sustained in a multivariate analysis controlling for insulin

'life-time' exposure in patients with fatty liver was associated with less severe disease [113]. A publication from the *NIH NASH Clinical Research Network* suggested that modest alcohol consumption was associated with favourable hepatic histology in NAFLD patients. However the study was limited to individuals drinking <20 grams/day and excluded binge drinkers or those with any history of previous higher alcohol consumption [114]. In a recent study, Hagstrom et al examined the impact of lifetime alcohol consumption on fibrosis severity in NAFLD in a prospective study involving 120 subjects with biopsy proven NAFLD. They concluded lifetime alcohol consumption with up to 13 units/week was associated with lower fibrosis stage in NAFLD. However, the same study did find that an elevated level of phosphatidyl ethanol (PEth), serving as a biomarker for recent alcohol consumption, was associated with higher stages of fibrosis and so these data require further clarification[115].

From these studies, it would appear that alcohol consumption may have mixed effects. These data should be interpreted with caution however. The vast majority of studies have been cross-sectional, limiting the ability to assess temporal associations, and have often failed to consider potential sources of bias and error. It is important to appreciate that moderate alcohol use is not randomly distributed among patients with NAFLD. Various lifestyle factors (socioeconomic status, education, co-morbid conditions, sex, race, previous history of alcohol excess) affect the pattern of alcohol use and the severity of underlying liver disease [16, 116-118]. Not adjusting for these factors could lead to confounding and an overestimation of benefits from low to moderate alcohol consumption. Indeed, a recent critical review of the effect of moderate alcohol consumption on cardiovascular and liver disease in patients with NAFLD (seven observational studies) concluded that no strong recommendation to support the benefit of moderate alcohol use could be made due to significant methodological limitations in the source data [119]. Furthermore, it is doubtful that there is a protective effect of MAC in patients with pre-existing underlying liver disease. Indeed, a retrospective cohort study provided evidence that subjects consuming moderate to heavy amounts of alcohol with severe liver fibrosis have an increased risk of developing hepatocellular carcinoma (HCC) [120].

Crucially, the level at which any potentially beneficial effect derived from the consumption of alcohol shifts to become clearly harmful is neither consistent nor clearly defined with sufficient accuracy in patients that have co-existent features of the metabolic syndrome.

The available evidence supports the view that obesity confers a predisposition to development of both ALD [100] and NAFLD [121]. Whilst obesity *per se* is not directly associated with more advanced hepatic fibrosis stage in patients with NAFLD [122], a higher BMI has been found to associated with more advanced hepatic fibrosis in ALD [100, 101]. Insulin resistance (IR) and T2DM are generally considered key components of the metabolic syndrome [123] that are strongly associated with NAFLD development [24, 112, 121]. There is also mounting evidence of a close relationship with ALD [124] and that the metabolic syndrome and/or T2DM may promote the development of ALD [24]. A large cohort study found that IR/T2DM was an independent predictor of overall and liver-related mortality in ALD and NAFLD patients [125]. A recent study reported no significant difference in post-transplant survival or CVD mortality amongst patients with NASH-related or ALD cirrhosis [126].

Amongst patients with high alcohol consumption, obesity is an independent risk factor for acute alcoholic hepatitis and cirrhosis [100, 101]. It has been demonstrated that alcohol and obesity/T2DM confer quantitative and qualitative changes to the intestinal microbiome and impair the intestinal barrier thus promoting steatohepatitis and fibrosis [127, 128]. Obesity and alcohol also reduces adipokine production in visceral adipose tissue. Adiponectin (anti-fibrotic) is reduced in individuals with obesity or sustained high alcohol consumption [69, 129, 130].

In a recent study of 107,735 middle-aged Korean men who participated in a postal survey in 2004 and then followed for 6 years, each 5-drink higher alcohol use increment was associated with increased risk of non-neoplastic liver disease mortality. In this population, low BMI was generally associated with higher mortality. However, amongst those with a BMI ≥25 kg/m^2, each 5 kg/m^2 increment was also associated with an elevated mortality from non-neoplastic liver diseases [131]. In a large French study, 1,604 alcoholics were evaluated to determine whether obesity was a risk factor for the development of ALD. They reported that being obese or overweight were independent risk factors for fatty liver (402 cases) and cirrhosis (608 cases) among various stages of ALD. Specifically, being overweight for more than 10 years increased the likelihood of steatosis, alcoholic hepatitis and cirrhosis by 2.5-, 3- and 2.15-fold compared to a patient who was not overweight after adjustment for other variables [100].

4.2.4. The effects of Alcohol and on Metabolic Syndrome on HCC Development

One of the first studies to observe the effects of varying levels of alcohol consumption on the development of HCC in patients with radiologically confirmed hepatic steatosis was conducted in Japan. [132]. The incidence of HCC after long-term follow-up in these patients was 0.28%, with an annual incidence of 0.05%. The incidence of HCC related with high-intermediate ethanol intake and FLD was 0.63% with an annual rate of 0.16%. The risk of hepatocarcinogenesis was increased significantly by a daily ethanol consumption >40 g, with the risk of hepatocarcinogenesis associated with a high-intermediate to excessive level of ethanol consumption being almost 2–12 times higher than that observed in patients with a daily ethanol consumption of <40 g. These findings are supported by a recent Japanese study where researchers reported a synergistic effect of obesity and alcohol consumption on hepatocarcinogenesis in patients positive for the hepatitis B virus antigen [133]. The group identified serum GGT as a risk factor for the development of HCC, leading to speculation that ethanol consumption may be a major factor in the cause of this malignancy.

Studies have shown that alcohol use and obesity demonstrate a synergistic association. The risk of incident HCC in a large study from Taiwan (N= 23,712) among alcohol drinkers showed that the cumulative risk of HCC in non-obese subjects was 2.7% compared to 8.7% in obese participants [94]. The subjects were followed up for 11.6 years. On analysis investigators determined that obesity increased the risk of incident HCC by 3.82-fold [94]. It is proposed that visceral obesity increases lipid peroxidation and production of inflammatory cytokines, which may contribute to the progression of NAFLD and ALD to cirrhosis and its complications, including HCC [134]. In addition to lipid peroxidation and pro-inflammatory cytokines, variants in *PNPLA3* also have been associated with increased risk of HCC in NAFLD and ALD [135-137]. In a case-controlled study by Lok et al, the authors reported an approximate 6-fold increased risk of HCC with alcohol consumption (compared to a 5-fold risk with tobacco and 4-fold risk for obesity) among Americans with cirrhosis [138]. **Table 5** provides a summary of the epidemiological and experimental evidence of the combined effects of alcohol and adiposity/obesity on HCC risk.

4.3. Influence of Metabolic Syndrome and Alcohol Consumption on Extra-Hepatic Disease

It is well accepted that NAFLD and the wider metabolic syndrome are associated with a range of extra-hepatic disease manifestations, in particular T2DM and cardiovascular disease (reviewed

[139]). It is, at least in part, due to a putative cardio-protective effect that modest alcohol consumption has been supported by some clinicians.

Epidemiological studies have suggested that consumers of moderate levels of alcohol have a lower risk of T2DM compared with non-drinkers [140-142]. In a recent Danish cohort study, the lowest risks of diabetes were reported in men who consumed 14 drinks/week and women who consumed 9 drinks/week [85]. Furthermore, findings from a meta-analysis based on 13 prospective studies showed that wine consumption was associated with a significantly lower risk of T2DM: 20% risk reduction at 20–30 g pure alcohol/day [143].

A cross-sectional study of patients with NAFLD by Sinn et al reported moderate alcohol use (<20 g/day) was associated with decreased odds of carotid plaque (OR 0.74; 95% CI 0.60-0.92) and carotid stenosis (OR 0.62; 95% CI 0.43-0.90) compared to non-drinkers [144]. Results were adjusted for smoking, metabolic syndrome and age however socioeconomic status and physical activity were not considered. [144]. Several other studies also report decreased mortality with MAC [145-147]. However, a meta-analysis by Carrao et al that reviewed data from case control and cohort studies concluded that the protective effects of moderate alcohol intake lacked a sufficiently clear definition of the dose of alcohol consumed or an accurate estimate of the size of the derived protective effect. Publication bias was recognised as responsible for a potential overestimation of the reported effects and it was noted that studies displayed substantial heterogeneity with gender significantly modifying the shape of the dose response function[148].

5. Practical issues for clinicians

In clinical practice, in a patient with a fatty liver, it can be difficult to determine the relative contributions of alcohol consumption and the metabolic syndrome when both risk factors are present. Indeed, it is well recognised that even amongst patients referred to a liver clinic with a diagnosis of NAFLD, their alcohol consumption is often significantly higher than initially recognised [149]. Therefore, the possibility of the combined effects of alcohol and the metabolic syndrome should be considered in all patients with suspected NAFLD. In particular, consideration should be given to the role of biomarkers and universal screening for identification of risky, often under-reported, alcohol consumption.

5.1. Detecting alcohol excess: biomarkers

Some patients may exhibit physical signs that might suggest harmful alcohol use or complications of the metabolic syndrome. Routine laboratory tests, including Mean Corpuscular Volume (MCV), gamma glutamyl transpeptidase (GGT) and the aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio can indicate excessive alcohol consumption, though their specificity is limited [150]. Whilst GGT remains a commonly adopted surrogate for the detection of alcohol excess, it is actually a poor indicator of excessive alcohol consumption as levels may be increased by other factors such as obesity [151] and can be elevated in patients with advanced fibrosis, regardless of aetiology [152]. Likewise, whilst an increased AST/ALT ratio was historically thought to be indicative of excess alcohol [153], more recently this has been realised as a marker of advanced fibrosis [154, 155]. Conversely, the effect of alcohol consumption on the AST/ALT ratio confounds simple non-invasive fibrosis scores that have been validated for the non-invasive assessment of NAFLD [156]. Therefore, such scores, including the FIB-4 and NAFLD fibrosis scores cannot meaningfully be applied to heavy alcohol drinkers [157, 158]. The ratio may also be influenced by age [159].

The detection of alcohol in blood (or breath) is the most direct method of alcohol detection but is valid only for recent consumption, given its rapid clearance[160]. In an effort to extend this narrow detection window, indirect markers of alcohol markers are increasingly used. Amongst these, Carbohydrate deficient transferrin (CDT) is reported to have the best sensitivity and specificity for regular long-term excessive alcohol consumption and can be used to differentiate between heavy drinking and abstinence, often amongst populations who are required to prove abstinence [150, 161]. However, CDT results can be confounded by obesity, with lower CDT levels being found in obese compared to non-obese subjects that consume similar amounts of alcohol [162]. Alcohol metabolites, notably ethyl-glucuronide (EtG) and ethyl-sulfate can be measured in the urine for several days after alcohol consumption [163]. However, these are not widely available and have primarily been used to help prove or disprove self-reported abstinence in targeted alcohol assessments [164]. Little is known about their application or validation amongst patients with fatty liver, more generally. Therefore, no single laboratory marker can definitively establish the relative contribution from alcohol consumption or metabolic risk factors.

5.2. Screening for risky alcohol consumption

Indeed, in detecting risky alcohol consumption, there is considerable evidence that screening tools are more effective than biochemical markers of alcohol use [165]. Several screening tools have been developed to identify adults with risky alcohol drinking and alcohol dependence. Amongst these, the best validated is the Alcohol Use Disorders Identification Test (AUDIT), developed by the World Health Organisation [166]. These screening tools can be used effectively to identify and intervene with risky alcohol consumption [167]. However, they have variable sensitivity depending on the population being screened and the validity of alcohol screening tools amongst patients with combined alcohol and metabolic risk factors has not specifically been studied.

5.3. Weight loss surgery

A specific clinical scenario in which effective alcohol screening is even more topical, is amongst patients undergoing weight loss surgery for the management of their NAFLD/NASH. Soon after the advent of bariatric surgery, concerns emerged that some patients may have an increased tendency to develop post-operative alcohol use disorders (AUD). This may relate to pharamacokinetic changes, with accelerated alcohol absorption after bariatric surgery compared to controls or pre-operatively [168, 169]. Additionally, this has been conceptualised as 'addiction transfer', behavioural subsitution of drinking alcohol rather than eating [170]. Initial reports provided conflicting assessments of the risk of post-operative AUD but were limited by small sample sizes in retrospective analyses [171-173]

More recently, robust prospective data has been provided by the large US multi-center longitudinal assessment of bariatric surgery cohort study. A significantly higher prevalence of AUD was identified after the second post-operative year, compared with the year immediately before and after surgery [174]. Subsequent extension, with follow-up to 7 years, confirmed a high prevalence of AUD post-operatively. In particular, one-fifth of those undergoing Roux-en-Y gastric bypass developed AUD within 5 years of surgery, which was twice the rate of those undergoing laparasopic adjustable gastric banding [175]. Similar results have been reported from a large retrospective population-based cohort study including all patients who underwent weight loss surgery in Sweden [176] and in some smaller prospective studies [177, 178]. Therefore, patients in whom weight loss surgery is being considered, or has been performed, require careful evaluation with respect to screening for risky alcohol consumption

5.4. Nutritional support in the setting of Alcohol or Nicotine Use Disorders

Overlap exists between obesity and alcohol and/or nicotine use, where weight gain has been observed in patients with ALD that stop drinking or among ex-smokers [179-182]. Potential benefits may therefore be derived by providing combined nutritional and substance abuse counselling in patients with fatty liver disease. Chemically, there are similarities between alcohol abuse and obesity centred around dopamine activity [183]. A reduced numbers of dopamine (D2) receptors in the brain of obese individuals and those with chronic alcohol abuse have been observed [184, 185]. This receptor deficiency is thought to drive a compulsive engagement in pleasurable behaviours, such as alcohol use and eating i.e. a "Reward Deficiency Syndrome" [186, 187]. Another prominent neurotransmitter is leptin. During alcohol withdrawal, leptin, although primarily associated with food intake regulation, has demonstrated increased levels correlating with the increased intensity of alcohol cravings during this period. A concept has emerged that leptin interacts with the brain reward system in producing its effects on both food and alcohol intake [188]. However, despite the level of evidence that would suggest the potential value of combined nutrition and alcohol counselling in primary care practices this is something that is not routinely offered. Indeed, it is still uncommon for substance disorder treatment facilities to offer nutrition or lifestyle education. In a study, where nutrition education was provided to men in a residential treatment program the outcome was reduced weight gain during recovery [189]. Regarding nicotine addiction, data has shown that levels of overweight and obesity peak in middle age (45–64 years) which overlaps with the period when smoking cessation is more likely to occur [190]. In a population study of middle aged men, 44% of overweight men and 48% of obese men were former smokers [190]. The corollary, therefore, is that weight gain may partially counteract the accrued health benefits of quitting smoking by contributing to an increased risk of metabolic syndrome development, which demonstrates a strong association with CVD and NAFLD. [191, 192]

In clinical practice, the evaluation of all patients with suspected NAFLD, including those being considered for weight loss surgery, should include careful screening for at-risk alcohol consumption, with defined clinical pathways to intervene, refer and treat when AUD is detected. In order to optimise the health benefits of both excessive alcohol cessation and smoking cessation in the setting of fatty liver disease, a better understanding of the behavioral relationships between smoking, alcohol consumption and dietary habits is needed in order to

6. **Conclusions**

ALD and NAFLD are the two most frequent liver diseases worldwide. It is also clear that both conditions may co-exist to varying degrees in a significant number of patients. There is strong epidemiological and experimental evidence that alcohol and components of the metabolic syndrome exert synergistic effects promoting liver injury and progression towards cirrhosis. When considering the impact of alcohol as a cofactor for steatosis and fibrosis in patients with metabolic syndrome, it is astute to critically assess the degree of overlap that exists between NAFLD and ALD. At present, clinicians may find it necessary to assign both aetiologies to a patient in their medical records to ensure appropriate long-term consideration of the complications relating to both alcohol consumption and the metabolic syndrome. However, in light of the rising prevalence of metabolic syndrome, NAFLD and ALD, the plausible concept of "dual-aetiology fatty liver disease" may serve as a more tractable diagnostic category that reflects the co-existence of these diverse processes in patients with fatty liver disease and higher-than-recommended alcohol consumption that however falls short of a clear ALD diagnosis. This construct opens up multiple questions of clinical relevance that we have alluded to in this review. For example, the need to critically examine the hepatotoxic dose thresholds for alcohol and the guideline recommendations for 'safe' alcohol consumption, which in addition to gender should also take into account the presence of overweight/obesity. The future research agenda remains open, looking for answers from prospective cohort studies, elucidating the exact role and interaction of ethanol consumption and features of the metabolic syndrome on liver injury.

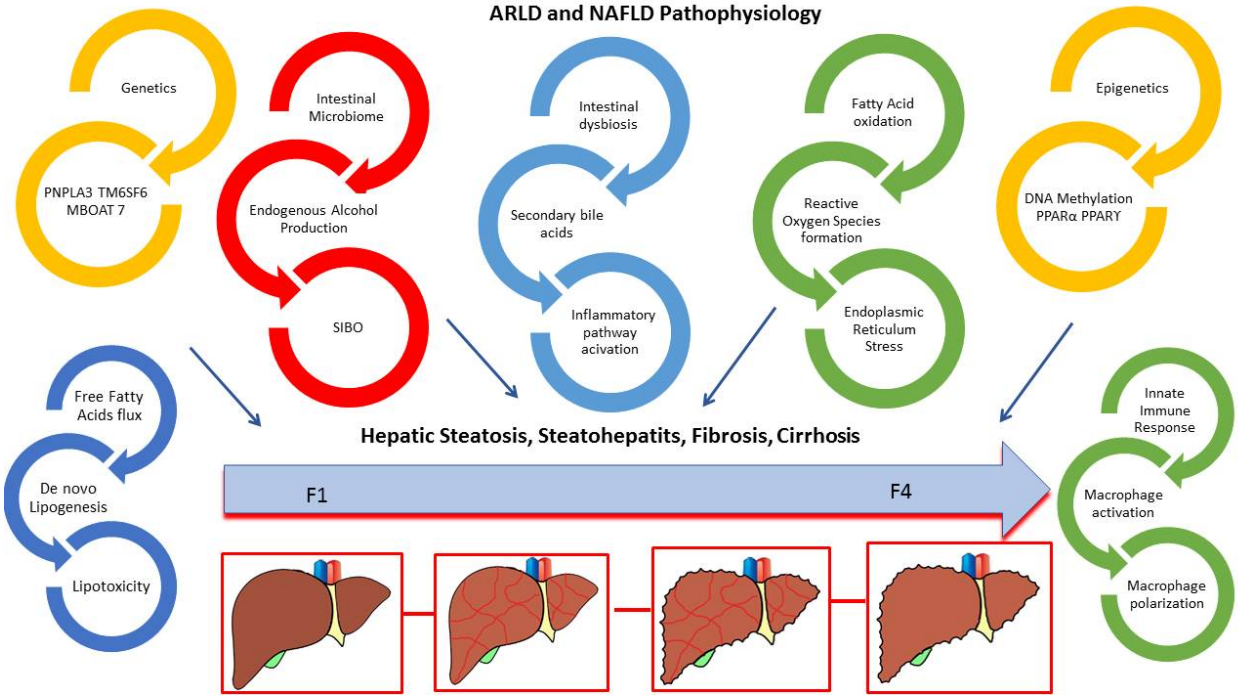

Figure 1: **Shared Pathogenic Mechanisms in NAFLD and ALD**

The pathogenesis of NAFLD and ALD share many common factors that combine in varying degrees to drive disease progression. These include the role of Free Fatty Acids, FFA oxidation, reactive oxygen species, endoplasmic reticulum stress, genetics/epigenetics, the innate immune system, gut derived endotoxins, endogenous alcohol, intestinal dysbiosis and small intestinal bacterial overgrowth (SIBO).

Table 1: Studies using in vivo and ex vivo models to explore the interaction of NAFLD and ALD

Study	Key reported findings
Karsenty et al, 1985 [193]	Hepatic lipogenesis and fatty degeneration reduced in obese (fa/fa) rats given an ethanol diet showing a paradoxical effect of ethanol on liver lipogenesis in the genetically-obese Zucker rat
Carmiel-Haggai et al, 2003 [194]	Binge ethanol exposure increases liver injury in obese rats
Olleros et al, 2008 [195]	Moderately FAT diet and low-dose EtOH generate steatohepatitis and TNF liver expression. Changes in regulation of TNF associated with increased IL-6, IFN-gamma and iNOS expression.
Wang et al. 2009 [196]	Ethanol-induced cytochrome P4502E1 causes carcinogenic etheno-DNA lesions in alcoholic liver disease.
Wang et al, 2010 [197]	Moderate alcohol consumption aggravates high-fat diet induced steatohepatitis in rats.
Gabele at al, 2011 [198]	In combination with High fat diet, alcohol significantly enhanced proinflammatory and pro-fibrotic gene expression, stellate cell activation, ECM deposition compared to the HF diet alone.
Xu et al, 2011 [199]	Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK.
Everitt et al, 2013 [200]	Ethanol administration to obese mice exacerbates fatty liver via impairment of the hepatic lipid metabolism pathways. This effect is mediated via SIRT1-AMPK signalling.
Nascimento et al, 2013 [201]	Aggravation of NASH by moderate alcohol consumption is associated with lower SIRT1 activity in rats.
Duryee et al, 2014 [202]	Precision-cut liver slices from diet-induced obese rats exposed to ethanol are susceptible to oxidative stress and increased fatty acid synthesis.
Minato et al, 2014 [203]	Binge alcohol consumption aggravates oxidative stress and promotes pathogenesis of NASH from obesity-induced simple steatosis.
Alwahsh et al, 2014 [204]	Combination of alcohol and fructose exacerbates metabolic imbalance in terms of hepatic damage, dyslipidaemia, and insulin resistance in rats.
Chang et al, 2015 [205]	Short- or long-term high-fat diet consumption combined with an acute ethanol binge synergistically induces liver injury in mice. CXCL1 plays an important role.
Duly et al, 2015 [90]	Alcohol and high fat diet produced maximum hepatic steatosis, increased micro- and macro-vesicular lipid droplets, increased de novo lipogenesis and decreased fatty acid β-oxidation; with increased inflammation and fibrogenesis in mice livers.
Song et al, 2016 [206]	Chronic alcohol consumption promotes liver damage in high-fructose diet fed mice due to an increased inflammatory response.

Table 2: Epidemiological studies Showing a Negative Effect of light/moderate alcohol consumption on Liver Disease

Study	Study Number	Type of Study	Country	Diagnosis of fatty liver	Alcohol consumption categories	Key reported findings
Petersen, 1977 [110]	112	Retrospective	Denmark	Biopsy	Moderate alcohol > five drinks per day for more than two years	Higher frequency of fatty liver was found to occur in cases of moderate alcohol consumption alone, or when combined overweight and obesity
Bellentani et al, 2000 [96]	257	Cross-sectional	Italy	Ultrasound	No alcohol Heavy alcohol >40g/week	The risk of steatosis by abdominal US was increased by 2.8-fold in heavy drinkers, 4.6-fold in individuals with obesity, and by 5.8-fold in those with both obesity and heavy alcohol use
Ruhl et al, 2005 [97]	13,580	Cross-sectional	USA	Elevated ALT/AST	Moderate alcohol consumption >2 drinks	Raised ALT amongst obese consumers of 1-2 drinks/day.
Alatalo et al, 2008 [98]	2164	Cross-sectional	Finland	Elevated ALT/AST	Moderate alcohol <40 g per day	The effect of moderate alcohol consumption on liver enzymes increases with increasing BMI
Loomba et al, 2009 [99]	2364	Cross-sectional	USA	Elevated ALT/AST	Moderate alcohol >3 drinks/day	8.9-fold increased risk of raised ALT 21-fold risk of raised AST in obese consuming >3 alcoholic drinks/day
Lau et al, 2015 [207]	4009	Cross-sectional	Germany	Ultrasound	Low-risk drinking (women: 1-20 g, men: 1-40 g), medium-risk (women: 21-40 g, men: 41-60 g) and high-risk (women: >40 g, men: >60 g)	Steatosis risk increased with increasing levels of average daily alcohol consumption/binge drinking in combination with adiposity.

OR: Odds Ratio; 95%CI: 95% Confidence interval; MAC: moderate alcohol consumption

Table 3: Epidemiological studies Showing a Beneficial Effect of light/moderate alcohol consumption on Liver Disease

Study	Study Participants	Type of Study	Country	Diagnosis of fatty liver	Alcohol consumption categories	Key reported findings
Suzuki et al, 2007 [208]	1177	Cross-sectional	USA	ALT/AST	None or minimal <70 g/wk, light ≥ 70 g and <140 g/wk, moderate ≥ 140 g and <280 g/wk, excessive ≥ 280 g/wk	MAC associated with decreased incidence of hyper-transaminasemia (adjusted hazard ratio 0.4 [0.1-0.9], P= 0.02]
Dunn et al, 2008 [209]	8156	Cross-sectional	USA	Elevated ALT	Moderate alcohol consumption ≥ 10g/day	NAFLD in 3.2% of non-drinkers and 0.4% of modest wine drinkers. OR 0.15 (0.05-0.49).
Gunji et al, 2009 [210]	7431	Cross-sectional	Japan	Ultrasound	Light (40-140 g/week) and moderate (140-280 g/week) alcohol consumption	Light and moderate alcohol consumption independently reduced likelihood of fatty liver (OR=0.824 and 0.754, (0.683-0.994) and 0.612-0.928, P=0.044 and 0.008, respectively
Yamada et al, 2010 [211]	63447	Cross-sectional	Japan	Ultrasound	Moderate drinkers >23 g/day, heavy drinkers >46 g/day	Daily moderate/heavy alcohol consumption protective in men
Shen et al, 2010 [212]	500	Retrospective cohort	China	Abnormal liver enzymes	Moderate alcohol <40 g/day	No significant dose-response relationship between daily alcohol intake/duration of drinking and raised ALT or AST.
Hiramine et al, 2011 [213]	9886	Cross-sectional	Japan	Ultrasound	Non-, light-, moderate-, and heavy-drinkers (0, <20, 20-59 and ≥60 g/day)	The prevalence of FL was associated positively with body mass index and inversely with alcohol consumption (light, OR 0.71 [95%CI 0.59-0.86]; moderate, OR 0.55 [CI 0.45-0.67]; heavy, OR 0.44 [CI 0.32-0.62])
Moriya et al, 2011 [214]	7112	Cross-sectional	Japan	Ultrasound	None: 0.1–69.9 g/week, 70.0–139.9 g/week, 140.0–279.9 g/week, and ⩾280.0 g/week	Alcohol consumption inversely associated with steatosis (OR 0.54 [95%CI 0.46-0.63]).
Hamaguchi et al, 2012 [215]	18571	Cross-sectional	Japan	Ultrasound	Minimal alcohol consumption, < 40 g/wk; light,40-140 g/wk; moderate, 140-280 g/wk; and excess, > 280 g/wk	OR for fatty liver < 1.0 in men with any level of alcohol consumption and in women with light/moderate consumption.
Wong et al,2012 [216]	922	Cross-sectional	Japan	Proton-Magnetic resonance spectroscopy; fibroscan	Modest drinkers (<10 g per day)	Modest alcohol consumption does not increase the risk of fatty liver or hepatic fibrosis
Taniai et al, 2012 [217]	266	Cross-sectional	Japan	Cirrhosis Biopsy/Imagi	Diagnosis of ALD based on alcohol intake (>70g/day for >5-years)	The prevalence of obesity and T2DM similar in non-cirrhotic and cirrhotic female ALD patients

				ng		
Sookoian at al, 2014 [108]	43175	Meta-analysis	Argentina	Biopsy	Non-drinkers: 0 g/day; modest drinkers <40 g/day	MAC confers a ~31% protective effect on the risk of NAFLD.
Moriya et al, 2015 [218]	5297	Longitudinal study	Japan	Ultrasound	None: 0.1-69.9 g/week, 70.0-139.9 g/week, 140.0-279.9 g/week, and ≥280.0 g/week.	Light/moderate alcohol consumption likely to protect against fatty liver
Takahashi et al, 2015 [219]	8029	Cross-sectional	Japan	Ultrasound	Non-drinkers (<20 g daily), moderate drinkers (20–50 g daily), or heavy drinkers (>50 g daily).	MAC a negative risk factor for fatty liver in subjects with BMI ≥25 (OR, 0.74 for non-obese; 0.39 for obese). Heavy alcohol intake a negative risk factor in obese males (OR 0.62) but a positive risk factor in non-obese males (OR 1.29) and in all females (OR 2.22 for non-obese and 6.6 for obese).

OR: Odds Ratio; 95%CI: 95% Confidence interval; MAC: moderate alcohol consumption

Table 4: Studies Examining the Histological effects of Alcohol Consumption on Subjects with Confirmed NAFLD

Study	Number of participants	Diagnosis of NAFLD	Alcohol consumption categories	Key reported findings	Histology End-point
Dixon et al, 2001 [112]	105	Biopsies at obesity surgery	Minimal consumption (20 g/week), moderate > 20 g/week and excessive < 100 g/week > 100 g/week	IR (OR 9.3 [95%CI 3.4-26]), hypertension (OR 5.2 [95%CI 2.0-13.5]), raised ALT (OR 8.6 [95%CI 3.1-23.5]) independent predictors of NASH.	NASH
Ekstedt et al, 2009 [102]	71	Biopsy based on elevated LFTS	Low-risk drinking (women: 1–20 g, men: 1–40 g), medium-risk drinking (women: 21–40 g, men: 41–60 g) and high-risk drinking (women: >40 g, men: >60 g	Mean follow-up 13.8 years. 17 patients (24%) fulfilled the criteria for significant fibrosis progression. More patients reporting heavy episodic drinking with fibrosis progression and trend towards higher weekly alcohol consumption.	Fibrosis
Cotrim et al, 2009 [111]	132	Obese patients undergoing liver biopsy at bariatric surgery	G1: alcohol intake greater than 20 g/day and less than 40 g/day; G2: alcohol intake less than 20 g/day; G3: no alcohol intake	MAC may have a protection effect against IR in severely obese patients but no effect on liver disease.	NASH Fibrosis
Dunn et al, 2012 [114]	682	NIH NASH Clinical Research Network	(1) drinking >20 g/day, (2) binge drinkers, or (3) non-drinkers with previous alcohol consumption were excluded	Reduced risk of NASH in modest drinkers vs. non-drinkers (OR 0.56 [95%CI 0.39-0.84]). Likelihood of NASH fell as alcohol consumption increased within the range of modest consumption. Modest drinkers had reduced fibrosis (OR 0.56 [0.41-0.77]), and hepatocellular injury (OR 0.66 [0.48-0.92]) than non-drinkers	NASH Fibrosis
Dunn et al, 2012 [220]	405	Adult car accident autopsies in 17 Kansas and Missouri counties from 2000 to 2010	The non-alcoholic group had undetectable blood alcohol concentration, while the alcoholic group had a blood alcohol concentration ≥0.08%.	Alcohol had 3.5-fold increase [95%CI, 2.0-5.9], while every 5 kg/m^2 BMI increase had 1.9-foldincrease [95%CI, 1.7-2.5] risk of a higher NAFLD Activity Score. Negative interaction between alcohol and BMI on fibrosis observed . Every 5 kg/m^2 increased BMI conferred 2.2-fold increased risk of fibrosis in non-alcoholics, but not in alcoholics.	NAS Fibrosis
Kwon et al, 2014 [113]	77	Adults >18 years of age with presumed NAFLD and alcohol consumption <40 g/week were enrolled	Alcohol consumption <40 g/week	On multivariable analysis, increasing age (OR 1.07 [95%CI 1.01-1.14]) associated with worse liver disease, but alcohol consumption ≥24 gram-years associated with less severe disease (OR 0.26 [95%CI 0.07-0.97])	

OR: Odds Ratio; 95%CI: 95% Confidence interval

Table 5: HCC Development in setting of NAFLD and Alcohol

Study	Study Number	Type of Study	Country	Obesity/Fatty liver	Alcohol consumption categories	Key reported findings
Lok et al, 2005 [138]	210	Case-controlled study	USA	Lean (BMI <25 kg/m^2), overweight (BMI 25.1–30 kg/m^2) or obese (BMI >30 kg/m^2	None (consumed <100 servings of alcohol during his/her lifetime, <1500 gram-years (mild-to-moderate) or ≧1500 gram-years (heavy),	6-fold HCC risk increase for alcohol (OR 5.7 [95%CI 2.4-13.7]), 5-fold for tobacco (OR 4.9 [2.2-10.6]), 4-fold with obesity (OR 4.3 [2.1–8.4])
Loomba et al, 2010 [133]	2260	Prospective cohort study from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–Hepatitis B Virus (REVEAL–HBV)	China	Normal BMI (<23), overweight (23–24.9), obese (25–29.9), and extremely obese (≥30)	<20 g/day , 20-39 g/day, 40-69 g/day, and ≥70 g/day	Risk of incident HCC increased in overweight (HR 2.4 [95% CI 1.3-4.4]), obese (2.0 [1.1-3.7]), and extremely obese (2.9 [1.0-8.0]) consumers of alcohol.
Ascha et al, 2010. [221]	510	Retrospective cohort	USA	Biopsy	"Never," "social" no more than two alcoholic drinks daily or three to six drinks daily on weekends. "Significant" more than two drinks daily or more than six drinks daily on weekends for the past 5 years. "Formerly significant" more than "social alcohol intake" within the past 5 years.	Age and alcohol consumption associated with HCC risk in NASH-cirrhosis. Patients with regular alcohol consumption at increased HCC risk (HR 3.6).
Loomba at el. 2013,[94]	23712	Prospective cohort study	China	Participants were categorized into normal (<23), overweight (23–24.9), obese (25–29.9), and extremely obese (≥30)	Alcohol drinkers were defined as those who had consumed alcohol at least 4 days per week for at least 1 year.	Alcohol use and obesity increased HCC risk in unadjusted analyses (HR 7.19 [95%CI 3.69-14.00]) and multivariable-adjusted analyses (age, sex, smoking, serum alanine aminotransferase, serum hepatitis B surface antigen, anti-hepatitis C virus antibody, and diabetes mellitus) (HR 3.82 [1.94-7.52])
Pais et al,	110	Retrospective Cohort	France	Liver Explant review	Alcoholic cirrhosis on	Obesity/T2DM in ALD transplant recipients increased

2015, [222]					explant	HCC risk (OR 6.23 [95% CI 2.47-15.76] and 4.63 [1.87-11.47] respectively).
Kawamura et al, 2016 [132]	9959	Multicentre retrospective analysis	Japan	Ultrasound	<20 g/day, 20-39 g/day, 40-69 g/day, and ≥70 g/day	Greater alcohol consumption associated with HCC incidence: 0.06% if 20-39 g/day ethanol (HR 1.54 [95%CI 0.34-7.04]), 0.16% if 40-69 g/day (HR 3.49 [1.50-8.12]),]0.22% if ≥70 g/day (HR 10.58 [5.06-22.13]), compared to consumption <20 g/day.

OR: Odds Ratio; HR: Hazard Ratio; 95%CI: 95% Confidence interval

References

[1] European Association for the Study of the Liver . Electronic address eee, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.

[2] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005-2023.

[3] Anstee QM, Seth D, Day CP. Genetic Factors That Affect Risk of Alcoholic and Nonalcoholic Fatty Liver Disease. Gastroenterology 2016;150:1728-1744 e1727.

[4] Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613-619.

[5] Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut 1997;41:845-850.

[6] Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-344.

[7] Global status report on alcohol and health. World Health Organisation 2014.

[8] Public health successes and missed opportunities. Trends in alcohol onsumption and attributable mortality in the WHO European Region, 1990-2014: World Health Organisation; 2016.

[9] Substance Abuse and Mental Health Services Administration (SAMHSA). 2013 National Survey on Drug Use and Health (NSDUH). Table 2.41B—Alcohol use in lifetime py, and past month among persons aged 18 or older, by demographic characteristics: percentages, 2012 and 2013. . Available at: http://wwwsamhsagov/data/ sites/default/files/NSDUH-DetTabsPDFWHTML2013/Web/ HTML/NSDUH-DetTabsSect2peTabs1to42-2013htm# tab241b 2013.

[10] Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2011;9:524-530 e521; quiz e560.

[11] Kraus L, Osthus S, Amundsen EJ, Piontek D, Harkonen J, Legleye S, et al. Changes in mortality due to major alcohol-related diseases in four Nordic countries, France and Germany between 1980 and 2009: a comparative age-period-cohort analysis. Addiction 2015;110:1443-1452.

[12] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol 2013;59:160-168.

[13] Global Status Report on noncommunicable diseases: World Health Organisation; 2014.

[14] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. Hepatology 2015.

[15] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2017;in press.

[16] Hayashi PH, Harrison SA, Torgerson S, Perez TA, Nochajski T, Russell M. Cognitive lifetime drinking history in nonalcoholic fatty liver disease: some cases may be alcohol related. The American journal of gastroenterology 2004;99:76-81.

[17] Wannamethee SG, Shaper AG. Alcohol, body weight, and weight gain in middle-aged men. The American journal of clinical nutrition 2003;77:1312-1317.

[18] Wannamethee SG, Field AE, Colditz GA, Rimm EB. Alcohol intake and 8-year weight gain in women: a prospective study. Obesity research 2004;12:1386-1396.

[19] Rissanen AM, Heliovaara M, Knekt P, Reunanen A, Aromaa A. Determinants of weight gain and overweight in adult Finns. European journal of clinical nutrition 1991;45:419-430.

[20] Bendsen NT, Christensen R, Bartels EM, Kok FJ, Sierksma A, Raben A, et al. Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. Nutrition reviews 2013;71:67-87.

[21] Traversy G, Chaput JP. Alcohol Consumption and Obesity: An Update. Current obesity reports 2015;4:122-130.

[22] Fazzino TL, Fleming K, Sher KJ, Sullivan DK, Befort C. Heavy Drinking in Young Adulthood Increases Risk of Transitioning to Obesity. American journal of preventive medicine 2017.
[23] Baumeister SE, Alte D, Meyer C, John U. [Health Risk drinking and problematic consumption of alcohol in Pomerania: comparative analysis of the Study of Health in Pomerania (SHIP) compared with the Federal German Health and Examination Survey in 1998]. Gesundheitswesen 2005;67:39-47.
[24] Kotronen A, Yki-Jarvinen H, Mannisto S, Saarikoski L, Korpi-Hyovalti E, Oksa H, et al. Non-alcoholic and alcoholic fatty liver disease - two diseases of affluence associated with the metabolic syndrome and type 2 diabetes: the FIN-D2D survey. BMC Public Health 2010;10:237.
[25] Soberg S, Sandholt CH, Jespersen NZ, Toft U, Madsen AL, von Holstein-Rathlou S, et al. FGF21 Is a Sugar-Induced Hormone Associated with Sweet Intake and Preference in Humans. Cell metabolism 2017;25:1045-1053 e1046.
[26] Forgione A, Miele L, Cefalo C, Gasbarrini G, Grieco A. Alcoholic and nonalcoholic forms of fatty liver disease. Minerva Gastroenterol Dietol 2007;53:83-100.
[27] Lieber CS. Metabolism of alcohol. Clin Liver Dis 2005;9:1-35.
[28] Nagata K, Suzuki H, Sakaguchi S. Common pathogenic mechanism in development progression of liver injury caused by non-alcoholic or alcoholic steatohepatitis. J Toxicol Sci 2007;32:453-468.
[29] Arteel GE. Oxidants and antioxidants in alcohol-induced liver disease. Gastroenterology 2003;124:778-790.
[30] Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. Gastroenterology 2002;122:1649-1657.
[31] Sakaguchi S, Takahashi S, Sasaki T, Kumagai T, Nagata K. Progression of alcoholic and non-alcoholic steatohepatitis: common metabolic aspects of innate immune system and oxidative stress. Drug Metab Pharmacokinet 2011;26:30-46.
[32] Diehl AM. Nonalcoholic fatty liver disease: implications for alcoholic liver disease pathogenesis. Alcohol Clin Exp Res 2001;25:8S-14S.
[33] Sabate JM, Jouet P, Harnois F, Mechler C, Msika S, Grossin M, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. Obes Surg 2008;18:371-377.
[34] Cope K, Risby T, Diehl AM. Increased gastrointestinal ethanol production in obese mice: implications for fatty liver disease pathogenesis. Gastroenterology 2000;119:1340-1347.
[35] Baker SS, Baker RD, Liu W, Nowak NJ, Zhu L. Role of alcohol metabolism in non-alcoholic steatohepatitis. PLoS One 2010;5:e9570.
[36] de Medeiros IC, de Lima JG. Is nonalcoholic fatty liver disease an endogenous alcoholic fatty liver disease? - A mechanistic hypothesis. Med Hypotheses 2015;85:148-152.
[37] Mezey E, Imbembo AL, Potter JJ, Rent KC, Lombardo R, Holt PR. Endogenous ethanol production and hepatic disease following jejunoileal bypass for morbid obesity. Am J Clin Nutr 1975;28:1277-1283.
[38] Baraona E, Julkunen R, Tannenbaum L, Lieber CS. Role of intestinal bacterial overgrowth in ethanol production and metabolism in rats. Gastroenterology 1986;90:103-110.
[39] Picot D, Lauvin R, Hellegouarc'h R. [Intra-digestive fermentation in intestinal malabsorption syndromes: relations with elevated serum activity of gamma-glutamyl-transpeptidase]. Gastroenterol Clin Biol 1997;21:562-566.
[40] Karahanian E, Quintanilla ME, Tampier L, Rivera-Meza M, Bustamante D, Gonzalez-Lira V, et al. Ethanol as a prodrug: brain metabolism of ethanol mediates its reinforcing effects. Alcohol Clin Exp Res 2011;35:606-612.
[41] Ye Q, Wang X, Wang Q, Xia M, Zhu Y, Lian F, et al. Cytochrome P4502E1 inhibitor, chlormethiazole, decreases lipopolysaccharide-induced inflammation in rat Kupffer cells with ethanol treatment. Hepatol Res 2013;43:1115-1123.
[42] Lindros KO, Stowell L, Vaananen H, Sipponen P, Lamminsivu U, Pikkarainen P, et al. Uninterrupted prolonged ethanol oxidation as a main pathogenetic factor of alcoholic liver damage: evidence from a new liquid diet animal model. Liver 1983;3:79-91.
[43] Kovach SJ, Sitzmann JV, McKillop IH. Inhibition of alcohol dehydrogenase blocks enhanced Gi-protein expression following ethanol treatment in experimental hepatocellular carcinoma in vitro. Eur J Gastroenterol Hepatol 2001;13:1209-1216.
[44] Wilson PA, Gardner SD, Lambie NM, Commans SA, Crowther DJ. Characterization of the human

[45] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008;40:1461-1465.
[46] Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. Journal of hepatology 2014;61:75-81.
[47] Valenti L, Al-Serri A, Daly AK, Galmozzi E, Rametta R, Dongiovanni P, et al. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 2010;51:1209-1217.
[48] Buch S, Stickel F, Trepo E, Way M, Herrmann A, Nischalke HD, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet 2015;47:1443-1448.
[49] Tian C, Stokowski RP, Kershenobich D, Ballinger DG, Hinds DA. Variant in PNPLA3 is associated with alcoholic liver disease. Nat Genet 2010;42:21-23.
[50] Stickel F, Buch S, Lau K, Meyer zu Schwabedissen H, Berg T, Ridinger M, et al. Genetic variation in the PNPLA3 gene is associated with alcoholic liver injury in caucasians. Hepatology 2011;53:86-95.
[51] Trepo E, Gustot T, Degre D, Lemmers A, Verset L, Demetter P, et al. Common polymorphism in the PNPLA3/adiponutrin gene confers higher risk of cirrhosis and liver damage in alcoholic liver disease. J Hepatol 2011;55:906-912.
[52] Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjaerg-Hansen A, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nature genetics 2014;46:352-356.
[53] Liu YL, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nature communications 2014;5:4309.
[54] Dongiovanni P, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozzi E, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology 2015;61:506-514.
[55] Kahali B, Liu YL, Daly AK, Day CP, Anstee QM, Speliotes EK. TM6SF2: catch-22 in the fight against nonalcoholic fatty liver disease and cardiovascular disease? Gastroenterology 2015;148:679-684.
[56] Anstee QM, Day CP. The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on PNPLA3 and TM6SF2. Semin Liver Dis 2015;35:270-290.
[57] Heba ER, Desai A, Zand KA, Hamilton G, Wolfson T, Schlein AN, et al. Accuracy and the effect of possible subject-based confounders of magnitude-based MRI for estimating hepatic proton density fat fraction in adults, using MR spectroscopy as reference. Journal of magnetic resonance imaging : JMRI 2016;43:398-406.
[58] Liangpunsakul S, Chalasani N. What should we recommend to our patients with NAFLD regarding alcohol use? Am J Gastroenterol 2012;107:976-978.
[59] Lazo M LB, Hernaez R, et al. Alcohol consumption and hepatic steatosis in the general US population. J Hepatol 2014;60:S13.
[60] O'Shea RS, Dasarathy S, McCullough AJ, Practice Guideline Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Alcoholic liver disease. Hepatology 2010;51:307-328.
[61] Farrell GC, Chitturi S, Lau GK, Sollano JD, Asia-Pacific Working Party on N. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol 2007;22:775-777.
[62] Chokshi DA, El-Sayed AM, Stine NW. J-Shaped Curves and Public Health. Jama 2015;314:1339-1340.
[63] Heianza Y, Arase Y, Saito K, Tsuji H, Fujihara K, Hsieh SD, et al. Role of alcohol drinking pattern in type 2 diabetes in Japanese men: the Toranomon Hospital Health Management Center Study 11 (TOPICS 11). Am J Clin Nutr 2013;97:561-568.
[64] Sato KK, Hayashi T, Harita N, Koh H, Maeda I, Endo G, et al. Relationship between drinking patterns and the risk of type 2 diabetes: the Kansai Healthcare Study. Journal of epidemiology and community health 2012;66:507-511.
[65] Hong SW, Linton JA, Shim JY, Kang HT. High-risk drinking is associated with a higher risk of

[66] Cullmann M, Hilding A, Ostenson CG. Alcohol consumption and risk of pre-diabetes and type 2 diabetes development in a Swedish population. Diabetic Med 2012;29:441-452.
[67] Wechsler H, Austin SB. Binge drinking: the five/four measure. Journal of studies on alcohol 1998;59:122-124.
[68] Barrio E, Tome S, Rodriguez I, Gude F, Sanchez-Leira J, Perez-Becerra E, et al. Liver disease in heavy drinkers with and without alcohol withdrawal syndrome. Alcoholism, clinical and experimental research 2004;28:131-136.
[69] Nanji AA, French SW. Relationship between pork consumption and cirrhosis. Lancet 1985;1:681-683.
[70] Nanji AA, Mendenhall CL, French SW. Beef fat prevents alcoholic liver disease in the rat. Alcohol Clin Exp Res 1989;13:15-19.
[71] Buettner R, Parhofer KG, Woenckhaus M, Wrede CE, Kunz-Schughart LA, Scholmerich J, et al. Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. J Mol Endocrinol 2006;36:485-501.
[72] Tipoe GL, Ho CT, Liong EC, Leung TM, Lau TY, Fung ML, et al. Voluntary oral feeding of rats not requiring a very high fat diet is a clinically relevant animal model of non-alcoholic fatty liver disease (NAFLD). Histol Histopathol 2009;24:1161-1169.
[73] Bergheim I, Weber S, Vos M, Kramer S, Volynets V, Kaserouni S, et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol 2008;48:983-992.
[74] Feldstein AE, Canbay A, Guicciardi ME, Higuchi H, Bronk SF, Gores GJ. Diet associated hepatic steatosis sensitizes to Fas mediated liver injury in mice. J Hepatol 2003;39:978-983.
[75] Johansen D, Friis K, Skovenborg E, Gronbaek M. Food buying habits of people who buy wine or beer: cross sectional study. Bmj 2006;332:519-522.
[76] Barefoot JC, Gronbaek M, Feaganes JR, McPherson RS, Williams RB, Siegler IC. Alcoholic beverage preference, diet, and health habits in the UNC Alumni Heart Study. Am J Clin Nutr 2002;76:466-472.
[77] Ruidavets JB, Bataille V, Dallongeville J, Simon C, Bingham A, Amouyel P, et al. Alcohol intake and diet in France, the prominent role of lifestyle. European heart journal 2004;25:1153-1162.
[78] Tjonneland A, Gronbaek M, Stripp C, Overvad K. Wine intake and diet in a random sample of 48763 Danish men and women. The American journal of clinical nutrition 1999;69:49-54.
[79] Becker U, Gronbaek M, Johansen D, Sorensen TI. Lower risk for alcohol-induced cirrhosis in wine drinkers. Hepatology 2002;35:868-875.
[80] Kasdallah-Grissa A, Mornagui B, Aouani E, Hammami M, Gharbi N, Kamoun A, et al. Protective effect of resveratrol on ethanol-induced lipid peroxidation in rats. Alcohol Alcohol 2006;41:236-239.
[81] Ajmo JM, Liang X, Rogers CQ, Pennock B, You M. Resveratrol alleviates alcoholic fatty liver in mice. Am J Physiol Gastrointest Liver Physiol 2008;295:G833-842.
[82] Kanuri G, Wagnerberger S, Landmann M, Prigl E, Hellerbrand C, Bischoff SC, et al. Effect of acute beer ingestion on the liver: studies in female mice. European journal of nutrition 2015;54:465-474.
[83] Obara K, Mizutani M, Hitomi Y, Yajima H, Kondo K. Isohumulones, the bitter component of beer, improve hyperglycemia and decrease body fat in Japanese subjects with prediabetes. Clin Nutr 2009;28:278-284.
[84] Pelletier S, Vaucher E, Aider R, Martin S, Perney P, Balmes JL, et al. Wine consumption is not associated with a decreased risk of alcoholic cirrhosis in heavy drinkers. Alcohol Alcoholism 2002;37:618-621.
[85] Holst C, Becker U, Jorgensen ME, Gronbaek M, Tolstrup JS. Alcohol drinking patterns and risk of diabetes: a cohort study of 70,551 men and women from the general Danish population. Diabetologia 2017.
[86] Bode C, Bode JC. Effect of alcohol consumption on the gut. Best practice & research Clinical gastroenterology 2003;17:575-592.
[87] Purohit V, Bode JC, Bode C, Brenner DA, Choudhry MA, Hamilton F, et al. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol 2008;42:349-361.
[88] Lieber CS, Jones DP, Decarli LM. Effects of Prolonged Ethanol Intake: Production of Fatty Liver Despite Adequate Diets. The Journal of clinical investigation 1965;44:1009-1021.

[89] Lieber CS, DeCarli LM. The feeding of ethanol in liquid diets. Alcoholism, clinical and experimental research 1986;10:550-553.
[90] Duly AM, Alani B, Huang EY, Yee C, Haber PS, McLennan SV, et al. Effect of multiple binge alcohol on diet-induced liver injury in a mouse model of obesity. Nutr Diabetes 2015;5:e154.
[91] Anstee QM, Goldin RD. Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. Int J Exp Pathol 2006;87:1-16.
[92] Kanuri G, Landmann M, Priebs J, Spruss A, Loscher M, Ziegenhardt D, et al. Moderate alcohol consumption diminishes the development of non-alcoholic fatty liver disease (NAFLD) in ob/ob mice. European journal of nutrition 2016;55:1153-1164.
[93] Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697-10703.
[94] Loomba R, Yang HI, Su J, Brenner D, Barrett-Connor E, Iloeje U, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. American journal of epidemiology 2013;177:333-342.
[95] McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. Journal of hepatology 2015;62:1148-1155.
[96] Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132:112-117.
[97] Ruhl CE, Everhart JE. Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2005;3:1260-1268.
[98] Alatalo PI, Koivisto HM, Hietala JP, Puukka KS, Bloigu R, Niemela OJ. Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. Am J Clin Nutr 2008;88:1097-1103.
[99] Loomba R, Bettencourt R, Barrett-Connor E. Synergistic association between alcohol intake and body mass index with serum alanine and aspartate aminotransferase levels in older adults: the Rancho Bernardo Study. Aliment Pharmacol Ther 2009;30:1137-1149.
[100] Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. Hepatology 1997;25:108-111.
[101] Raynard B, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology 2002;35:635-638.
[102] Ekstedt M, Franzen LE, Holmqvist M, Bendtsen P, Mathiesen UL, Bodemar G, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. Scand J Gastroenterol 2009;44:366-374.
[103] Liu B, Balkwill A, Reeves G, Beral V, Million Women Study C. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. Bmj 2010;340:c912.
[104] Hart CL, Morrison DS, Batty GD, Mitchell RJ, Smith GD. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. Brit Med J 2010;340.
[105] Aberg F, Helenius-Hietala J, Puukka P, Jula A. Binge drinking and the risk of liver events: A population-based cohort study. Liver Int 2017.
[106] Seitz HK, Mueller S, Hellerbrand C, Liangpunsakul S. Effect of chronic alcohol consumption on the development and progression of non-alcoholic fatty liver disease (NAFLD). Hepatobiliary Surg Nutr 2015;4:147-151.
[107] Klatsky AL, Udaltsova N, Li Y, Baer D, Nicole Tran H, Friedman GD. Moderate alcohol intake and cancer: the role of underreporting. Cancer causes & control : CCC 2014;25:693-699.
[108] Sookoian S, Castano GO, Pirola CJ. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut 2014;63:530-532.
[109] Hashimoto Y, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. J Gastroenterol Hepatol 2015;30:546-552.
[110] Petersen P. Fatty liver in patients with moderate alcohol consumption, diabetes mellitus and overweight. Scandinavian journal of gastroenterology 1977;12:781-784.

[111] 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;21:969-972.
[112] Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91-100.
[113] Kwon HK, Greenson JK, Conjeevaram HS. Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease. Liver Int 2014;34:129-135.
[114] Dunn W, Sanyal AJ, Brunt EM, Unalp-Arida A, Donohue M, McCullough AJ, et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). Journal of hepatology 2012;57:384-391.
[115] Hagstrom H, Nasr P, Ekstedt M, Kechagias S, Onnerhag K, Nilsson E, et al. Low to moderate lifetime alcohol consumption is associated with less advanced stages of fibrosis in non-alcoholic fatty liver disease. Scandinavian journal of gastroenterology 2017;52:159-165.
[116] Mukamal KJ. Alcohol consumption and self-reported sunburn: a cross-sectional, population-based survey. Journal of the American Academy of Dermatology 2006;55:584-589.
[117] Fillmore KM, Golding JM, Graves KL, Kniep S, Leino EV, Romelsjo A, et al. Alcohol consumption and mortality. I. Characteristics of drinking groups. Addiction 1998;93:183-203.
[118] La Vecchia C, Decarli A, Franceschi S, Ferraroni M, Pagano R. Prevalence of chronic diseases in alcohol abstainers. Epidemiology 1995;6:436-438.
[119] Ajmera VH, Terrault NA, Harrison SA. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review. Hepatology 2017;65:2090-2099.
[120] Suh B, Yun JM, Park S, Shin DW, Lee TH, Yang HK, et al. Prediction of future hepatocellular carcinoma incidence in moderate to heavy alcohol drinkers with the FIB-4 liver fibrosis index. Cancer 2015;121:3818-3825.
[121] Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. American journal of epidemiology 2013;178:38-45.
[122] Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol 2009;51:371-379.
[123] Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocr Rev 2008;29:777-822.
[124] Longato L, Ripp K, Setshedi M, Dostalek M, Akhlaghi F, Branda M, et al. Insulin resistance, ceramide accumulation, and endoplasmic reticulum stress in human chronic alcohol-related liver disease. Oxid Med Cell Longev 2012;2012:479348.
[125] Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut 2010;59:1410-1415.
[126] Bhagat V, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. Liver Transpl 2009;15:1814-1820.
[127] Yan AW, Schnabl B. Bacterial translocation and changes in the intestinal microbiome associated with alcoholic liver disease. World J Hepatol 2012;4:110-118.
[128] Szabo G. Gut-liver axis in alcoholic liver disease. Gastroenterology 2015;148:30-36.
[129] Finelli C, Tarantino G. What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? World J Gastroenterol 2013;19:802-812.
[130] Rogers CQ, Ajmo JM, You M. Adiponectin and alcoholic fatty liver disease. IUBMB Life 2008;60:790-797.
[131] Yi SW, Hong JS, Yi JJ, Ohrr H. Impact of alcohol consumption and body mass index on mortality from nonneoplastic liver diseases, upper aerodigestive tract cancers, and alcohol use disorders in Korean older middle-aged men: Prospective cohort study. Medicine (Baltimore) 2016;95:e4876.
[132] Kawamura Y, Arase Y, Ikeda K, Akuta N, Kobayashi M, Saitoh S, et al. Effects of Alcohol Consumption on Hepatocarcinogenesis in Japanese Patients With Fatty Liver Disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2016;14:597-605.

[133] Loomba R, Yang HI, Su J, Brenner D, Iloeje U, Chen CJ. Obesity and alcohol synergize to increase the risk of incident hepatocellular carcinoma in men. Clin Gastroenterol Hepatol 2010;8:891-898, 898 e891-892.
[134] Mirza MS. Obesity, Visceral Fat, and NAFLD: Querying the Role of Adipokines in the Progression of Nonalcoholic Fatty Liver Disease. ISRN Gastroenterol 2011;2011:592404.
[135] Singal AG, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am J Gastroenterol 2014;109:325-334.
[136] Salameh H, Raff E, Erwin A, Seth D, Nischalke HD, Falleti E, et al. PNPLA3 Gene Polymorphism Is Associated With Predisposition to and Severity of Alcoholic Liver Disease. Am J Gastroenterol 2015;110:846-856.
[137] Liu YL, Patman GL, Leathart JB, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 2014;61:75-81.
[138] Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. Journal of hepatology 2005;42:218-224.
[139] Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138-1153.
[140] Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S, et al. Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. Diabetes care 2009;32:2123-2132.
[141] Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes care 2015;38:1804-1812.
[142] Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes. A review. Nutrition, metabolism, and cardiovascular diseases : NMCD 2010;20:366-375.
[143] Huang J, Wang X, Zhang Y. Specific types of alcoholic beverage consumption and risk of type 2 diabetes: A systematic review and meta-analysis. Journal of diabetes investigation 2017;8:56-68.
[144] Sinn DH, Gwak GY, Cho J, Son HJ, Paik YH, Choi MS, et al. Modest alcohol consumption and carotid plaques or carotid artery stenosis in men with non-alcoholic fatty liver disease. Atherosclerosis 2014;234:270-275.
[145] Klatsky AL. Alcohol and cardiovascular diseases. Expert review of cardiovascular therapy 2009;7:499-506.
[146] Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW, Jr., et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. The New England journal of medicine 1997;337:1705-1714.
[147] Klatsky AL. Alcohol and cardiovascular diseases: where do we stand today? Journal of internal medicine 2015;278:238-250.
[148] Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. Addiction 2000;95:1505-1523.
[149] Marks P, Williams R. Calorie and alcohol consumption in nonalcoholic fatty liver disease. European journal of gastroenterology & hepatology 2012;24:527-530.
[150] Bell H, Tallaksen CM, Try K, Haug E. Carbohydrate-deficient transferrin and other markers of high alcohol consumption: a study of 502 patients admitted consecutively to a medical department. Alcoholism, clinical and experimental research 1994;18:1103-1108.
[151] Seitz HK. Additive effects of moderate drinking and obesity on serum gamma-glutamyl transferase. The American journal of clinical nutrition 2006;83:1252-1253.
[152] Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-1075.
[153] Nalpas B, Vassault A, Charpin S, Lacour B, Berthelot P. Serum mitochondrial aspartate aminotransferase as a marker of chronic alcoholism: diagnostic value and interpretation in a liver unit. Hepatology 1986;6:608-614.
[154] Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988;95:734-739.

[155] Nyblom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol 2004;39:336-339.
[156] McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265-1269.
[157] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-854.
[158] Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007;46:32-36.
[159] McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. The American journal of gastroenterology 2017;112:740-751.
[160] Mitchell MC, Jr., Teigen EL, Ramchandani VA. Absorption and peak blood alcohol concentration after drinking beer, wine, or spirits. Alcoholism, clinical and experimental research 2014;38:1200-1204.
[161] Chrostek L, Cylwik B, Gruszewska E, Tobolczyk J. The diagnostic power of direct carbohydrate-deficient transferrin immunoassay in alcoholics. Absolute or relative values? Alcohol 2012;46:69-73.
[162] Fagan KJ, Irvine KM, McWhinney BC, Fletcher LM, Horsfall LU, Johnson LA, et al. BMI but not stage or etiology of nonalcoholic liver disease affects the diagnostic utility of carbohydrate-deficient transferrin. Alcoholism, clinical and experimental research 2013;37:1771-1778.
[163] Stewart. Alcohol. Clin Exp Res 2013;1:150-155.
[164] Staufer K, Andresen H, Vettorazzi E, Tobias N, Nashan B, Sterneck M. Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. Hepatology 2011;54:1640-1649.
[165] Coulton S, Drummond C, James D, Godfrey C, Bland JM, Parrott S, et al. Opportunistic screening for alcohol use disorders in primary care: comparative study. Bmj 2006;332:511-517.
[166] Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88:791-804.
[167] Kaner E, Bland M, Cassidy P, Coulton S, Dale V, Deluca P, et al. Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. Bmj 2013;346:e8501.
[168] Hagedorn JC, Encarnacion B, Brat GA, Morton JM. Does gastric bypass alter alcohol metabolism? Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2007;3:543-548; discussion 548.
[169] Maluenda F, Csendes A, De Aretxabala X, Poniachik J, Salvo K, Delgado I, et al. Alcohol Absorption Modification After a Laparoscopic Sleeve Gastrectomy Due to Obesity. Obesity surgery 2010;20:744-748.
[170] Yoder R, MacNeela P, Conway R, Heary C. How Do Individuals Develop Alcohol Use Disorder After Bariatric Surgery? A Grounded Theory Exploration. Obesity surgery 2017.
[171] Mitchell JE, Lancaster KL, Burgard MA, Howell LM, Krahn DD, Crosby RD, et al. Long-term follow-up of patients' status after gastric bypass. Obesity surgery 2001;11:464-468.
[172] Ertelt TW, Mitchell JE, Lancaster K, Crosby RD, Steffen KJ, Marino JM. Alcohol abuse and dependence before and after bariatric surgery: a review of the literature and report of a new data set. Surgery for Obesity and Related Diseases 2008;4:647-650.
[173] Suzuki J, Haimovici F, Chang G. Alcohol use disorders after bariatric surgery. Obesity surgery 2012;22:201-207.
[174] King WC, Chen JY, Mitchell JE, Kalarchian MA, Steffen KJ, Engel SG, et al. Prevalence of alcohol use disorders before and after bariatric surgery. Jama 2012;307:2516-2525.
[175] King WC, Chen JY, Courcoulas AP, Dakin GF, Engel SG, Flum DR, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2017;13:1392-1402.

[176] Ostlund MP, Backman O, Marsk R, Stockeld D, Lagergren J, Rasmussen F, et al. Increased admission for alcohol dependence after gastric bypass surgery compared with restrictive bariatric surgery. JAMA surgery 2013;148:374-377.
[177] Conason A, Teixeira J, Hsu CH, Puma L, Knafo D, Geliebter A. Substance use following bariatric weight loss surgery. JAMA surgery 2013;148:145-150.
[178] Wee CC, Mukamal KJ, Huskey KW, Davis RB, Colten ME, Bolcic-Jankovic D, et al. High-risk alcohol use after weight loss surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2014;10:508-513.
[179] Barry D, Petry NM. Associations between body mass index and substance use disorders differ by gender: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Addictive behaviors 2009;34:51-60.
[180] Barry D, Pietrzak RH, Petry NM. Gender differences in associations between body mass index and DSM-IV mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Annals of epidemiology 2008;18:458-466.
[181] Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosomatic medicine 2008;70:288-297.
[182] Scott KM, Bruffaerts R, Simon GE, Alonso J, Angermeyer M, de Girolamo G, et al. Obesity and mental disorders in the general population: results from the world mental health surveys. Int J Obesity 2008;32:192-200.
[183] Abizaid A, Gao Q, Horvath TL. Thoughts for food: brain mechanisms and peripheral energy balance. Neuron 2006;51:691-702.
[184] Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet 2001;357:354-357.
[185] Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cerebral cortex 2000;10:318-325.
[186] Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine 1996;89:396-400.
[187] Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. Journal of addictive diseases 2004;23:39-53.
[188] Kiefer F, Jahn H, Jaschinski M, Holzbach R, Wolf K, Naber D, et al. Leptin: a modulator of alcohol craving? Biological psychiatry 2001;49:782-787.
[189] Cowan J, Devine C. Food, eating, and weight concerns of men in recovery from substance addiction. Appetite 2008;50:33-42.
[190] CDC. Cigarette smoking among adults and trends in smoking cessation -United States 2008. MMWR Morb Mortal;Wkly Rep. 2009:58:1227-1232.
[191] Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Annals of internal medicine 2010;152:10-17.
[192] Janzon E, Hedblad B, Berglund G, Engstrom G. Changes in blood pressure and body weight following smoking cessation in women. Journal of internal medicine 2004;255:266-272.
[193] Karsenty C, Ulmer M, Chanussot F, Ratanasavanh R, Debry G. Paradoxical effect of ethanol on liver lipogenesis in the genetically-obese Zucker rat. Br J Nutr 1985;54:15-20.
[194] Carmiel-Haggai M, Cederbaum AI, Nieto N. Binge ethanol exposure increases liver injury in obese rats. Gastroenterology 2003;125:1818-1833.
[195] Olleros ML, Martin ML, Vesin D, Fotio AL, Santiago-Raber ML, Rubbia-Brandt L, et al. Fat diet and alcohol-induced steatohepatitis after LPS challenge in mice: role of bioactive TNF and Th1 type cytokines. Cytokine 2008;44:118-125.
[196] Wang Y, Millonig G, Nair J, Patsenker E, Stickel F, Mueller S, et al. Ethanol-induced cytochrome P4502E1 causes carcinogenic etheno-DNA lesions in alcoholic liver disease. Hepatology 2009;50:453-461.
[197] Wang Y, Seitz HK, Wang XD. Moderate alcohol consumption aggravates high-fat diet induced steatohepatitis in rats. Alcohol Clin Exp Res 2010;34:567-573.
[198] Gabele E, Dostert K, Dorn C, Patsenker E, Stickel F, Hellerbrand C. A new model of interactive

[199] Xu J, Lai KK, Verlinsky A, Lugea A, French SW, Cooper MP, et al. Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK. J Hepatol 2011;55:673-682.
[200] Everitt H, Hu M, Ajmo JM, Rogers CQ, Liang X, Zhang R, et al. Ethanol administration exacerbates the abnormalities in hepatic lipid oxidation in genetically obese mice. Am J Physiol Gastrointest Liver Physiol 2013;304:G38-47.
[201] Nascimento AF, Ip BC, Luvizotto RA, Seitz HK, Wang XD. Aggravation of nonalcoholic steatohepatitis by moderate alcohol consumption is associated with decreased SIRT1 activity in rats. Hepatobiliary Surg Nutr 2013;2:252-259.
[202] Duryee MJ, Willis MS, Schaffert CS, Reidelberger RD, Dusad A, Anderson DR, et al. Precision-cut liver slices from diet-induced obese rats exposed to ethanol are susceptible to oxidative stress and increased fatty acid synthesis. Am J Physiol Gastrointest Liver Physiol 2014;306:G208-217.
[203] Minato T, Tsutsumi M, Tsuchishima M, Hayashi N, Saito T, Matsue Y, et al. Binge alcohol consumption aggravates oxidative stress and promotes pathogenesis of NASH from obesity-induced simple steatosis. Molecular medicine 2014;20:490-502.
[204] Alwahsh SM, Xu M, Schultze FC, Wilting J, Mihm S, Raddatz D, et al. Combination of alcohol and fructose exacerbates metabolic imbalance in terms of hepatic damage, dyslipidemia, and insulin resistance in rats. PLoS One 2014;9:e104220.
[205] Chang B, Xu MJ, Zhou Z, Cai Y, Li M, Wang W, et al. Short- or long-term high-fat diet feeding plus acute ethanol binge synergistically induce acute liver injury in mice: an important role for CXCL1. Hepatology 2015;62:1070-1085.
[206] Song M, Chen T, Prough RA, Cave MC, McClain CJ. Chronic Alcohol Consumption Causes Liver Injury in High-Fructose-Fed Male Mice Through Enhanced Hepatic Inflammatory Response. Alcohol Clin Exp Res 2016;40:518-528.
[207] Lau K, Baumeister SE, Lieb W, Meffert PJ, Lerch MM, Mayerle J, et al. The combined effects of alcohol consumption and body mass index on hepatic steatosis in a general population sample of European men and women. Aliment Pharmacol Ther 2015;41:467-476.
[208] Suzuki A, Angulo P, St Sauver J, Muto A, Okada T, Lindor K. Light to moderate alcohol consumption is associated with lower frequency of hypertransaminasemia. Am J Gastroenterol 2007;102:1912-1919.
[209] Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology 2008;47:1947-1954.
[210] Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, et al. Light and moderate alcohol consumption significantly reduces the prevalence of fatty liver in the Japanese male population. Am J Gastroenterol 2009;104:2189-2195.
[211] Yamada T, Fukatsu M, Suzuki S, Yoshida T, Tokudome S, Joh T. Alcohol drinking may not be a major risk factor for fatty liver in Japanese undergoing a health checkup. Dig Dis Sci 2010;55:176-182.
[212] Shen Z, Li Y, Yu C, Shen Y, Xu L, Xu C, et al. A cohort study of the effect of alcohol consumption and obesity on serum liver enzyme levels. Eur J Gastroenterol Hepatol 2010;22:820-825.
[213] Hiramine Y, Imamura Y, Uto H, Koriyama C, Horiuchi M, Oketani M, et al. Alcohol drinking patterns and the risk of fatty liver in Japanese men. J Gastroenterol 2011;46:519-528.
[214] Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, et al. Alcohol consumption appears to protect against non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2011;33:378-388.
[215] Hamaguchi M, Kojima T, Ohbora A, Takeda N, Fukui M, Kato T. Protective effect of alcohol consumption for fatty liver but not metabolic syndrome. World J Gastroenterol 2012;18:156-167.
[216] Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409-415.
[217] Taniai M, Hashimoto E, Tokushige K, Kodama K, Kogiso T, Torii N, et al. Roles of gender, obesity, and lifestyle-related diseases in alcoholic liver disease: Obesity does not influence the severity of alcoholic liver disease. Hepatol Res 2012;42:359-367.
[218] Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, et al. Roles of alcohol consumption in fatty liver: a longitudinal study. J Hepatol 2015;62:921-927.

[219] Takahashi H, Ono M, Hyogo H, Tsuji C, Kitajima Y, Ono N, et al. Biphasic effect of alcohol intake on the development of fatty liver disease. J Gastroenterol 2015;50:1114-1123.
[220] Dunn W, Zeng Z, O'Neil M, Zhao J, Whitener M, Yu-Jui Wan Y, et al. The interaction of rs738409, obesity, and alcohol: a population-based autopsy study. The American journal of gastroenterology 2012;107:1668-1674.
[221] Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-1978.
[222] Pais R, Lebray P, Rousseau G, Charlotte F, Esselma G, Savier E, et al. Nonalcoholic fatty liver disease increases the risk of hepatocellular carcinoma in patients with alcohol-associated cirrhosis awaiting liver transplants. Clin Gastroenterol Hepatol 2015;13:992-999 e992.