Food, alcohol, and obesity: Policy Statement on the coexistence of non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ARLD)

Recommendations

Research

- Consensus should be reached on (i) the appropriate terminology to be used for patients in whom both metabolic, non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ARLD) are present, and (ii) the definition of ARLD, with particular focus on whether it should include patients with obesity and diabetes with any level of alcohol intake, or those drinking above 20 g and 30 g/week, for women and men respectively.
- Research efforts and funding should be focused on improving understanding of the consequences of the joint diseases and developing effective measures for prevention and treatment.

Education

- Primary care practitioners and specialists should be educated or updated on the frequent coexistence of NAFLD and ARLD, and therefore the importance of screening for alcohol use in patients with NAFLD (for example, using CAGE and AUDIT-C), and dysmetabolism in patients with moderate or above levels of alcohol intake.
- The knowledge and skills of medical care providers about lifestyle (nutrition, physical activity, and smoking), and focused pharmacological treatment options for patients with NAFLD and ARLD, and engagement of patients for treatment should be expanded.

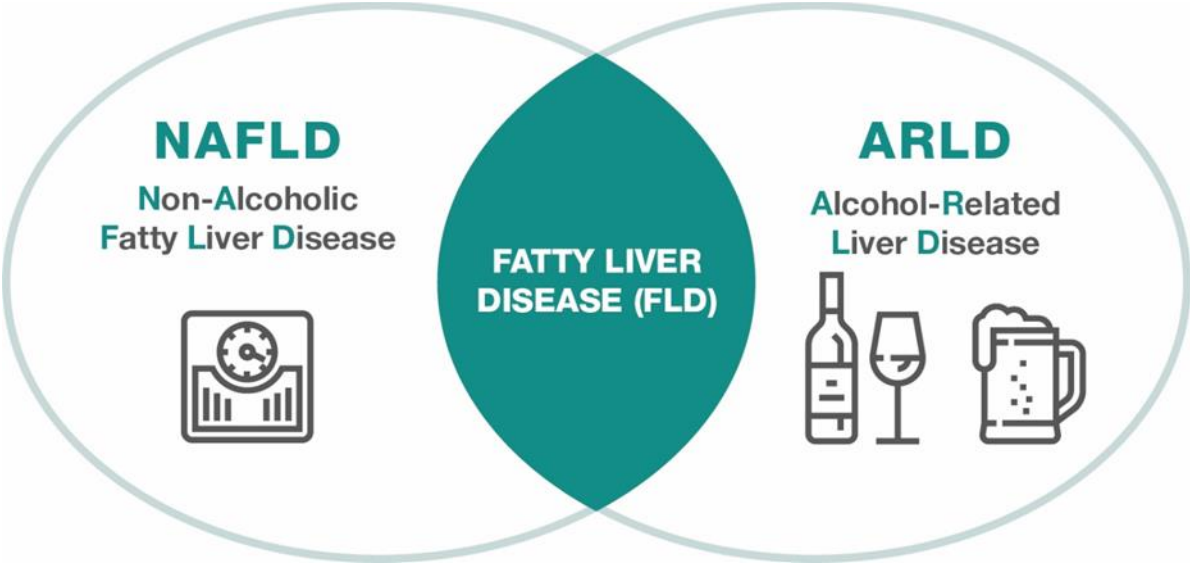
Public health policies

- Reducing the mortality and morbidity of alcohol- and metabolic-associated liver disease in Europe will require coordinated action to implement evidence-based health policies at local, national, and international levels as recommended by the World Health Organization (WHO). These include:

  - Increasing excise taxes on alcoholic and sugar-sweetened beverages (SSBs) as well as on tobacco products
  - Banning or creating comprehensive restrictions on marketing of alcoholic and SSBs
  - Restricting the physical availability of alcoholic and SSBs
  - Ensuring that healthy and nutritious choices are available and affordable to all consumers
- Educating the public on the harmful effect of alcohol use, combined with other unhealthy lifestyle behaviours including smoking and/or obesity, leading to advanced liver disease and mortality.
- Establishing holistic referral pathways and structured treatment programmes to deal with patients with diseases should be favoured.
- Clinical networks between general practitioners, endocrinologists, cardiologists, nutritionists, and hepatologists should ideally be able to provide a comprehensive management of both NAFLD and ARLD.
- Promoting the referral of patients with metabolic and alcohol-related fatty liver disease for smoking cessation programmes.

Nomenclature

- For those individuals with both metabolic and alcohol risk factors, we suggest the term "fatty liver disease" (FLD).



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Executive summary

Non-alcoholic fatty liver disease (NAFLD) affects 25% of the European population and most of the population with obesity or type 2 diabetes (T2DM), and is a major indication for liver transplantation. NAFLD is strongly linked with obesity. This is partly driven by excessive energy intake and an unhealthy diet, which is in part a consequence of advertising, increasing availability, and the low cost of industrially processed fast food and sugared-sweetened beverages (SSBs); in addition to low levels of physical activity. Alcohol-related liver disease (ARLD) accounts for nearly a third of deaths from liver disease worldwide. It is also the leading indication for liver transplantation in Europe. ARLD results from harmful levels of alcohol consumption and is therefore entirely preventable. The latest data suggest there is no safe level of alcohol consumption in terms of mortality, as the increase in the risk of cancer risk outweighs any protective cardiovascular benefit, even for low levels of intake (1).

The separation of both aetiologies is arbitrary; however, since many people with obesity can also have alcohol-induced liver damage and vice versa. Behavioural risk factors for NAFLD and ARLD frequently coexist, particularly among populations of a lower socioeconomic status.

Moreover, the presence of NAFLD and ARLD synergistically accelerates liver damage. There is therefore a pressing need to work to prevent and treat simultaneously these two leading causes for liver disease. Fiscal measure such as taxation of soft drinks, or a minimum unit price for alcohol have been shown to be effective at reducing consumption. Such measures, alongside public health campaigns highlighting the harmful effects of both diseases, supported by food and drink (including alcohol) labelling, restrictions on advertising including those embedded in movies, TV and social networks etc, and availability, can help tackle this major threat to global health.

Aim

The aim of this European Association for the Study of the Liver (EASL) policy statement is to,

firstly, inform politicians, policymakers, and the general population about the two leading causes of liver disease in Europe, NAFLD and ARLD, which often coexist and amplify the liver-related morbidity, mortality, and healthcare resource burden associated with each individually. Secondly, it aims to provide information about how behavioural risk factors may interact and lead to severe liver disease and should be the target of preventive interventions due to their modifiable nature.

Problem statement

Liver disease accounts for significant health and economic losses, with two-thirds of potential years of life lost being working years (2). The two leading risk factors for liver disease in Europe are ARLD and NAFLD. According to the Global Burden of Disease, 27% of deaths occurring worldwide due to liver disease in 2016 were attributable to alcohol (3). Liver mortality is determined for a large fraction by average population alcohol consumption (4), and the relationship between alcohol intake and cirrhosis is exponential for heavy drinkers (5). Age-standardised heavy drinking is highest in Europe and this may in part explain the increasing prevalence rates of cirrhosis experienced by several European countries (2). Mortality from ARLD is substantially greater for disadvantaged socio-economic classes, and the relative risk is particularly high for younger subjects (6). The WHO top three "best buys" for alcohol policy are all aimed at reducing population-level alcohol consumption and include increasing excise taxation, a ban on advertising, and reduced availability (7).

NAFLD, which represents the accumulation of excess fat in the liver, is now the commonest cause of liver disease in Western countries and reflects the rising levels of obesity and T2DM. (67,68). NAFLD refers to a spectrum of disease ranging from isolated steatosis to steatohepatitis (non-alcoholic steatohepatitis, NASH), and may evolve on to cirrhosis. NAFLD affects about 25–31% of the population of Europe (8), with the prevalence and severity rising further in individuals that are overweight and/or have T2DM, reflecting its strong association with the metabolic syndrome. Unhealthy behaviour, namely a lack of physical activity and excess calorie intake, together with high consumption of fructose and saturated fats (9–11) lead

to weight gain and/or ectopic fat deposition, which plays a major role in the development and progression of NAFLD in susceptible individuals (12).

Of note, SSBs are one of the largest sources of added sugar and an important contributor of calories with few, if any, other nutrients. Consequently, consumption of SSBs is now one of the leading causes of childhood and adult obesity (13, 14), and is associated with NAFLD incidence and increased liver damage (NASH and fibrosis) in NAFLD patients. Epidemiological data indicate that governmental measures aimed at increasing the cost of SSBs can reduce consumption and decrease weight (15). A WHO meta-review of 11 recent systematic reviews on the effectiveness of fiscal policies to reduce weight, improve diet, and prevent chronic non-communicable diseases concluded that the strongest evidence to date was for SSBs levies, reducing consumption by 20–50% (15).

NAFLD and ARLD have historically been treated as separate diseases, yet both conditions share several histopathological similarities characterised by fat deposits within hepatocytes, leading to steatohepatitis, progressive fibrosis and then cirrhosis in a proportion of individuals, which is heavily influenced by genetics (16, 17). Histopathology is frequently indistinguishable between the twin aetiologies and it is highly likely that pathogenetic mechanism are shared. These two conditions can be commonly referred to as "fatty liver disease" (FLD) (17). There are some important clinical differences, acute-on-chronic liver failure (alcoholic hepatitis) is common in ARLD and occurs rarely in NAFLD, and the course of progressive liver fibrosis is far more rapid in ARLD.

Important synergies are seen between alcohol and obesity on three levels: epidemiological or clinical, behavioural, and in implications for health policy. At the epidemiological level, the combination of alcohol and obesity increases the probability of developing and the severity of liver disease, reflecting a synergic effect on hepatic fat accumulation and lipotoxicity of both FLD triggers (18–21). A large cohort study from the US reported that patients with NAFLD who drink excessively (≥3 drinks/day for men, ≥2 for women) are three times more likely to have advanced fibrosis compared to those with NAFLD alone (18). In addition, adults with

hepatic steatosis or NAFLD who had excessive alcohol consumption have a greater overall mortality (27, 28). Importantly, even mild to moderate drinking (<210 g/ week) has been found to increase the risk of steatohepatitis, fibrosis, decompensated liver disease, mortality, and liver cancer among individuals with obesity and diabetes (19,26,29–33), although there is some disagreement among studies (28, 34, 35).

Other studies have also identified obesity as a risk factor for progression towards cirrhosis in patients drinking excessively; suggesting that obesity increases the hepatotoxicity of alcohol (22,23). Moreover, obesity is associated with a more than two-fold increase in short-term mortality in patients with alcoholic hepatitis (24). Similarly, concomitant metabolic syndrome has been shown to increase the ten-year cumulative risk of incident advanced liver disease from 0.3% to 1.4% in moderate drinkers (10–20 g/day for women, 10–30 g/day for men) and from 0.8% to 2.4% in risk drinkers (20–50 g/day for women, 30–50 g/day for men) (25).

Synergism has also been demonstrated between diabetes and high-risk drinking for liver-related morbidity and mortality (26). In terms of liver-related mortality, data from two prospective cohort studies with a median follow up of 29 years, revealed that among drinkers of 15 or more units (120 g) per week, being overweight or obese increases an individual's relative risk of liver disease mortality from 3.2 to 7.0 and 18.9 respectively; a synergistic interaction was also seen for individuals drinking just 1–14 units (8–112 g) per week in the presence of obesity (19).

All cirrhotic patients should avoid alcohol since any regular alcohol consumption puts them at significantly greater risk for hepatocellular carcinoma (HCC) (36). This is likely a result of the multiplicative interaction between alcohol use and obesity in this setting (37). The precise cellular mechanisms by which adiposity and alcohol interact to produce hepatic steatosis, steatohepatitis, and cirrhosis are unclear. Experimental studies suggest there is a combined pathological effect on hepatocellular lipid accumulation (excess alcohol drives hepatic lipogenesis via several mechanisms), hepatic inflammation, fibrosis and carcinogenesis

mediated via insulin resistance and pro-inflammatory cytokines (20, 38). There are also some genetic similarities (39).

Finally, NAFLD and ARLD are both associated with an increased risk of the metabolic syndrome, all-cause mortality, cardiovascular events, chronic kidney disease and extra-hepatic malignancy, yet little is known about the synergistic interaction of these co-morbidities in terms of their extra-hepatic manifestations. Data from two Finnish cohort studies suggests that even low levels of alcohol can increase the incident cancer risk for patients with NAFLD (32).

Smoking is a third risk factor accelerating progression of liver disease by itself and may act in synergism with the other risk factors. In a meta-analysis including 9 cross-sectional, 6 case-control, and 5 cohort studies; a significant but weak association was observed between smoking (current, former, and second-hand) and NAFLD (odds ratio 1.1) (40). Moreover, among current smokers, the risk of NAFLD increases with an increase in the amount of cigarettes smoked in a dose-response manner, and with increased levels of urinary cotinine (the main metabolite of nicotine) (41, 42). An interaction was observed between current heavy smoking and moderate drinking (80–210 g/week) in terms of developing NAFLD, where the combination of both behaviours led to the highest risk (43).

Importantly, smoking is associated with progression to fibrosis in patients with NAFLD. In a large prospective cohort study of young and middle-aged men and women, current smoking, pack-years, and urinary cotinine levels were positively associated with the risk of incident NAFLD and elevated fibrosis markers (44). In NAFLD patients who had undergone a liver biopsy, a smoking history of ≥10 pack-years was associated with a greater risk for advanced fibrosis, confirming that smoking may enhance the progression of NAFLD (45). In support of that, a large cohort study consisting of 406,770 persons with T2DM demonstrated that smoking is associated with a 60% increased risk for severe liver disease, defined as a diagnosis of HCC, cirrhosis, decompensation, liver failure, and/or death due to liver disease during follow-up (46). Not surprisingly, smoking is associated with a greater risk of cardiovascular disease among NAFLD patients; recently reported to be increased by 33% following adjustment for other risk factors (47). In contrast, there is a sparsity of data describing the effect of smoking on the

incidence and progression of ARLD, although the prospective data available does not report any such interaction (48).

Smoking is an extremely important risk factor for HCC (49, 50), with a similar impact to obesity (odds ratio smoking 1.6–1.9, obesity 1.8) (51). In the UK, the tobacco attributable fraction for primary liver cancer is 27% in men and 15% in women (52). A meta-analysis of 38 cohort studies and 58 case-control studies reported smoking as a risk factor for HCC across different regions, independent to alcohol consumption (relative risk 1.51) (50). While a prospective case-control study of 210 individuals reported that smoking acts synergistically with both alcohol and obesity to cause HCC (53), a more recent analysis of 14 prospective US-based cohort studies failed to find any interaction between smoking, obesity, and alcohol, although did report an interaction between alcohol and diabetes (54). Smoking also strongly synergises with alcohol in terms of extra-hepatic carcinogenesis, particularly for oropharyngeal cancer (55). Synergy between alcohol and smoking increases the risk of oesophageal cancer by three times, and of laryngeal cancer by 128 times (56,57).

The second level of synergy is behavioural. A substantial proportion of people drink too much and are obese. In the UK Midspan study, 28% of obese people were drinking above the UK's low-risk drinking guidelines of 14 units (112 g) per week, and of those drinking above the guideline, 49% were overweight or obese (19). Data from two Finnish studies, suggests that among individuals who develop advanced non-viral liver disease, 24% are heavy drinkers (ARLD), 37% are abstainers or light drinkers (NAFLD and other aetiologies), and 39% are moderate drinkers, of whom nearly all had at least one component of the metabolic syndrome (i.e. both NAFLD and alcohol are contributing towards liver injury). Alcohol energy content (7 kcal/g) can be a contributing factor to weight gain if not compensated for. In general, recent prospective studies show that light-to-moderate alcohol intake is not associated with adiposity gain while heavy drinking is more consistently related to weight gain (58, 59), suggesting that alcohol intake may be a risk factor for obesity in some individuals (58).

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Smoking is also more prevalent in individuals who display obesity-related behaviours and alcohol abuse (60). Cross-substance craving may play a role as nicotine increases alcohol cravings and vice versa (61). Smokers have been found to consume significantly higher levels of saturated fat, cholesterol, and alcohol, and lower levels of polyunsaturated fat, fiber, fruit and vegetables, and some vitamins than non-smokers (62, 63). Compared to never smokers, current smokers reported more frequent cravings for high-fat foods and fast food, after controlling for depression, stress, body mass index, and demographic factors. This translated to higher levels of consumption among smokers of unhealthy foods and fats (60).

Synergies also exist for health policy strategies in terms of tackling obesity-related behaviour, alcohol, and tobacco use. The most effective and cost-effective strategies for alcohol are identical to those for tobacco, namely fiscal policy and effective protection of children from tobacco and alcohol marketing (64). The evidence base for effective obesity policy is less developed, and no country has as yet turned the tide of childhood obesity. Recommendations from the WHO commission include controls on marketing and effective taxation of SSBs (65).

With increasing numbers of alcohol users who also have obesity, tackling the two problems simultaneously could make a significant contribution to improving public health (66). The occurrence of both risk factors in the same populations should be acknowledged and taken into consideration in health promotion and public health policies.

Future research

Gaps in knowledge include up to date prevalence rates of patients with NAFLD who also drink alcohol at light, moderate, and harmful levels; the impact of light and moderate levels of alcohol intake on the incidence of hepatic steatosis and disease progression; whether there is synergism in terms of the extra-hepatic manifestations of HCC and mortality in patients with both risk factors; and a better understanding of the role of non-invasive biomarkers, including liver damage and genetic markers, in this at-risk population. Large long-term prospective studies looking at both hepatic and extra-hepatic morbidity, and mortality endpoints are

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required to understand if there is a need to revise EASL's current drinking guidelines (<30 g/day men, <20 g/day women) for individuals with a raised body mass index (BMI). There is also a pressing need to expand our knowledge regarding evidence-based policies aimed at reducing obesity rates.

Conclusions

Alcohol and obesity are twin risk factors causing FLD with progressive liver fibrosis. They overlap to amplify hepatotoxicity in a substantial proportion of people. Therefore, the current dichotomic categorisation of NAFLD and ARLD is unhelpful and unrepresentative, and a new terminology is required highlighting the independent and often coexisting role of both FLD triggers. The addition of smoking to alcohol and obesity creates a detrimental triad.

Main messages

- Both diseases, ARLD and NAFLD, are preventable, with modifiable risk factors.
- Those communities most affected by NAFLD and ARLD – people with less formal schooling and living in lower-income, lower socio-economic settings – be protected by targeted prevention.
- SSBs and alcohol (sometimes mixed together) can both cause liver injury and, therefore fiscal policies can help defeat both.
- Smoking is a neglected modifiable risk factor for hepatocellular carcinoma.

For further information please contact: yoanna.nedelcheva@easloffice.eu

Written by:

- Prof. Shira Zelber-Sagi, BSc, RD, PhD, Associate Professor, Head of School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, the Tel-Aviv Medical Center, Department of Gastroenterology and Hepatology
- Nick Sheron, MD, FRCP, Head of clinical hepatology, Faculty of Medicine, University Hospital Southampton
- Dr Theresa Hydes, University Hospital Southampton

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