JOURNAL OF HEPATOLOGY

Non-alcoholic fatty liver disease – A global public health perspective

Zobair M. Younossi[1,2,*]

Summary

As the epidemics of obesity and type 2 diabetes mellitus increase worldwide, the prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing proportionately. The subtype of NAFLD which can be characterised as non-alcoholic steatohepatitis (NASH) is a potentially progressive liver disease that can lead to cirrhosis, hepatocellular carcinoma, liver transplantation, and death. NAFLD is also associated with extrahepatic manifestations such as chronic kidney disease, cardiovascular disease and sleep apnoea. NAFLD and NASH carry a large economic burden and create poor health-related quality of life. Despite this important burden, we are only beginning to understand its mechanisms of pathogenesis and the contribution of environmental and genetic factors to the risk of developing a progressive course of disease. Research is underway to identify appropriate non-invasive diagnostic methods and effective treatments. Although the risk of liver-related mortality is increased in patients with NAFLD and liver fibrosis stages F3 or F4, the leading cause of death is cardiovascular disease. Given the rapidly growing global burden of NAFLD and NASH, efforts must continue to find accurate non-invasive diagnostic and prognostic biomarkers, to develop effective treatments for individuals with advanced NASH and prevention methods for individuals at high risk of NAFLD and progressive liver disease.

Keywords: NAFLD; NASH; Epidemiology; HRQoL; Diabetes; Obesity.

Received 19 September 2018; received in revised form 24 October 2018; accepted 30 October 2018

[1]*Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, USA*;
[2]*Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA*

Introduction

Chronic liver disease (CLD) is a major cause of mortality, morbidity, and health care resource utilisation worldwide.[1] From 1980 through 2010, mortality related to CLD increased by 46% worldwide.[2] This increase was mostly observed in low- and low-middle-income countries of Asia and Africa.[3] The factors that contribute to increases in mortality vary in different parts of the world. In a recent study from the United States (US), the increase in liver mortality was associated with the increased prevalence of non-alcoholic fatty liver disease (NAFLD).[4] These trends are also observed in other parts of the world, where the burdens of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection could be positively impacted with effective HBV vaccination and potent antiviral regimens for both HBV and HCV.[1]

NAFLD

NAFLD is a liver disease associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, hyperlipidaemia, and metabolic syndrome. The subtype of NAFLD that is histologically categorised as non-alcoholic steatohepatitis (NASH) has a potentially progressive course leading to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation. All of these complications of NASH can pose significant health, economic, and patient-experience burdens to the patients, their families and the society.[5]

Risk factors for NAFLD

Obesity increases the risk of NAFLD.[6–16] Overweight has been defined by the World Health Organization (WHO) as a body mass index (BMI) greater than or equal to 25 and obesity is defined as a BMI greater than or equal to 30. BMI has been the most useful population-level measure to define overweight and obesity, because the measurement applies to both sexes and adults of all ages. Nevertheless, because of diverse populations in Asia, the WHO has classified the different BMI strata by risk. Patients with BMIs of 18.5–23 kg/m^2 are considered to have increasing but acceptable levels of risk for obesity-related conditions, patients with BMIs of 23–27.5 kg/m^2 have an increased risk for obesity-related conditions, and patients with BMIs of 27.5 kg/m^2 or higher have a high risk for obesity-related conditions.[6] Given the importance of visceral obesity as a risk factor for a number of complications of metabolic syndrome, assessment of waist circumference may be the more accurate. Nevertheless, the advantages and disadvantage of BMI *vs.* waist circumference measurements continue to be debated. In this context, it may be best to assess the risk and progression of NAFLD both based on BMI and waist circumference.[17,18]

Using these BMI cut-offs, the WHO determined in 2016 that worldwide overweight and obesity rates have nearly tripled since 1975 – more than 1.9 billion adults (18 years and older) are overweight, of whom 650 million are obese. It is estimated that 13% of the world's adult population is obese and 39% is overweight.[7] It is important to note that the prevalence of obesity in adults varies

Key point

To best assess the risk and progression of NAFLD, both measures of BMI and waist circumference should be used.

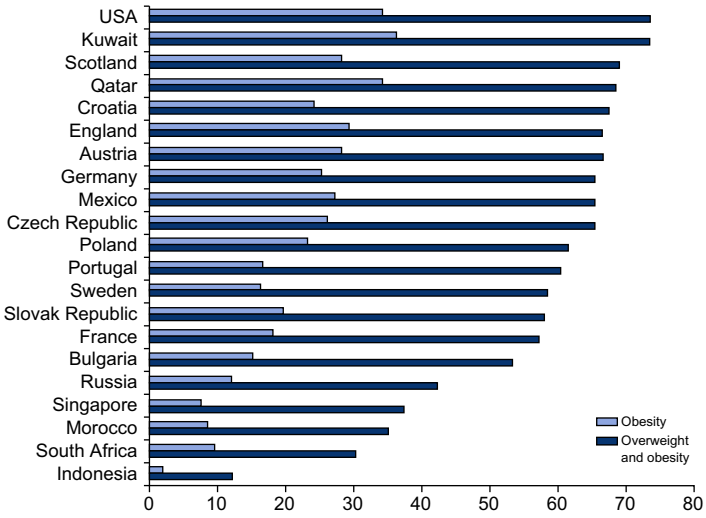

Fig. 1. Countries with the highest adult prevalence rate of overweight and obesity. (World Population: 7,505,257,673 and World Obesity Population: 774,000,000).[8,20]

among countries. Data from WHO indicates that the US has the most obese adults (109,342,839), followed by China (97,256,700 obese adults). Indonesia has the fewest obese adults (Fig. 1). The world region with the highest prevalence of obesity is the Oceania islands (Cook Islands, Samoa, Tonga, Nauru, Palau, Niue, and the Marshall Islands). The Middle East (Qatar, United Arab Emirates, Saudi Arabia, Libya, Oman, Jordan, Egypt, and Kuwait) has the second highest prevalence – as much as 75% of the population is considered obese or overweight. South America (Brazil, Mexico, Argentina, Peru, Chile) has the largest number of obese or overweight people. (Fig. 1).[8]

Even more troubling is that 41 million children under the age of 5 were overweight or obese, and that more than 340 million children and adolescents 5–19 years old were overweight or obese, in 2016. Most of the world's population live in countries where more people die as a result of being overweight or obese than being underweight. If these trends continue, more children and adolescents will be obese than moderately or severely underweight by 2022, according to a study led by Imperial College London and the WHO.[7] The prevalence values for overweight and obese children varied among countries for boys and girls, but Moldova had the lowest percentage of obese boys and girls. India, however, maintained its status as the country with the highest number of children considered to be underweight, though the percentage decreased from 1975 to 2016.

These increases in the rates of obesity have reached such proportions that the WHO has identified obesity as 1 of the 9 global noncommunicable diseases that must be addressed. In 2016, the World Health Assembly called upon all stakeholders to act at global, regional, and local levels to improve diets and physical activity patterns and identify and address obesogenic factors at the population level, to reduce relative obesity-related mortality by 25%.[14]

These data on the global epidemic of obesity are driving a number of obesity-related complications, including NAFLD.[5] In fact, the prevalence of NAFLD is proportional to the increase in BMI.[5] In this context, the prevalence of NAFLD in the general population is about 25% but it increases to over 90% for very obese individuals undergoing weight reduction procedures and surgeries.[5] This issue highlights the importance of including weight management in any strategy targeting the epidemic of NAFLD.

T2DM

Parallel to the high prevalence of obesity, T2DM is also on the rise worldwide. T2DM is another important risk factor for NAFLD and NASH. The International Diabetes Federation reports that more than 400 million people were living with diabetes as of 2015.[9] The WHO estimates that 90% of people who have diabetes worldwide have T2DM.[10] In 2012, diabetes caused an estimated 1.5 million deaths – more than 80% of these were in low- and middle-income countries. In developing nations, more than half of all diabetes cases go undiagnosed. The WHO anticipates that worldwide deaths from diabetes will double by 2030. By age, 0.26% of children (19 years and under) have diabetes whereas 12.3% of all adults (age 20 years or older) have diabetes, and 25.9% of adults aged 65 years or older have diabetes. However, adults aged 40 to 59 years comprise the group with the highest incidence of diabetes worldwide – this is expected to shift to adults 60 to 79 years old by 2030.[9,10]

Within the US, 29.1 million people are thought to have T2DM, with 8.1 million estimated to be undiagnosed and unaware of their condition. In addition, about 1.4 million new cases of diabetes are diagnosed in the US every year – now more than 10% of adults 20 years or older have diabetes. In seniors (65 years and older), the proportion is 25%, which cost an estimated $245 billion in healthcare resources in 2012, and these values continue to increase.[9] In the US, the risk of T2DM is higher in certain ethnic groups compared to non-Hispanic whites: Asian Americans have a 9% higher risk of diabetes, non-Hispanic blacks have a 13.2% higher risk, and Hispanics have a 12.8% higher risk. Among Hispanics, the rate of T2DM varies depending on country of origin – diagnoses of diabetes have been made for 8.5% of Hispanics from Central and South America, 9.3% of Cubans, 13.9% of Mexican Americans, and 14.8% of Puerto Ricans. However, native American adults in southern Arizona have the world's highest rate of T2DM – 33% of adults have diabetes.[9]

T2DM is rare in children of all racial and ethnic backgrounds, but the incidence is higher in some

* Address: Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042, USA. Tel.: +1 (703) 776 2540; fax: +1 (703) 776 4386.
E-mail address: zobair.younossi@inova.org.

minority groups than in Caucasians, particularly among Asian Pacific Islanders (ages 10–19 years). The risk of T2DM in children increases with age, especially as children reach puberty.[9,10] Indeed, across all ethnic groups the incidence of T2DM begins to increase around the age of puberty, especially in children who are overweight. According to the US Centers for Disease Control, among children 10 years and younger, the rate of new cases in 2008–2009 was 0.8 per 100,000, whereas for children 10–19 years old, the rate was 11 per 100,000.[11]

Although T2DM is tightly connected to obesity, its relevance in NAFLD is 2-fold. First the prevalence of NAFLD and NASH in patients with T2DM is over 60% (5–15,16). Second, presence of T2DM seems to accelerate the course of NAFLD and is a predictor of advanced fibrosis and mortality (16). In this context, careful consideration of T2DM in patients with NASH not only has prognostic implications, but also provides potential therapeutic options.

Prevalence and incidence of NAFLD

The prevalence of NAFLD is increasing at approximately the same rate as obesity.[12,13] In fact, the global prevalence of NAFLD in the general population has been estimated to be 25% whereas the global prevalence of NASH has been estimated to range from 3% to 5%.[15,16,19]

It is important to note that the prevalence of NAFLD varies across the globe.[12-36] The prevalence rate of NAFLD in South America seems to be higher than that reported for the US.[5,20] Specifically, the prevalence of NAFLD (based on ultrasound) for South America has been estimated at approximately 30.45%.[19] Most studies reporting the prevalence of NAFLD in South America were performed in Brazil.[21] Nevertheless, in a study from Chile, the prevalence of NAFLD (using ultrasound) was estimated to be 23%.[22] A study from Colombia, which also used ultrasound, reported a prevalence rate of 26.6% in males.[22] The same investigators estimated the prevalence of probable NAFLD (based on the rates of obesity in Peru, Argentina, Ecuador, Paraguay, and Uruguay) to range from 13% in Peru to 24% in Uruguay.[22] Although there are estimates for the prevalence of NAFLD in South America, data on the prevalence of NASH are scarce. Nevertheless, 61% of the patients with NAFLD in South America were found to have NASH, so the prevalence of NASH could range from 6% to 18%.[16,20,22,23] Rates of NAFLD and NASH are affected by different genetic factors in different populations.

The data regarding the burden of NAFLD in Asia is evolving. In the past 2 decades, urbanisation of many Asian countries has led to sedentary lifestyles and overnutrition, setting the stage for the epidemic of obesity and consequently NAFLD. The population prevalence of NAFLD in Asia is around 25%, and 8%–19% of the population is believed to have lean NAFLD.[12] The prevalence of NAFLD in China has doubled in the past 20 years; NAFLD is most prevalent (27%) in urban populations, where obesity and metabolic syndrome are more common. Obesity and metabolic syndrome are believed to be the most important risk factors for NAFLD in China.[24,35] However, there are regional variations; overall, the prevalence rate of NAFLD for adults in China has been estimated to be 15%. The prevalence of NAFLD is 2.1% in children and 68.2% in obese children.[24] The prevalence of NAFLD in Japan has also been increasing.[25] The overall prevalence of NAFLD in Japan was reported to be 29.7%, with a 3-fold difference in the mean prevalence between men (41.0%) and women (17.7%). NAFLD incidence increased linearly with BMI and levels of triglycerides and low-density lipoprotein cholesterol, even without obesity, so it seems that many people have lean NAFLD. The authors estimated the prevalence of NASH to range from 1% to 9%, based on the FIB-4 index, and to 2.7%, based on a BAAT (BMI, alanine aminotransferase, age, triglycerides) index score ≥3.[25]

In addition to East Asian countries, the prevalence of NAFLD and NASH is being reported from South Asia. In India, the NAFLD prevalence ranged from 8.7% to 32.6%, depending on whether patients were from rural or urban areas, respectively.[28] In urban Sri Lanka, the prevalence of NAFLD was reported to be 32.6%.[29]

In the Middle East, the prevalence of NAFLD is thought to range from 20% to 30%, but again this value varies among countries. Iran reports a NAFLD prevalence rate of 4.1% and a NASH prevalence of 2.9%, whereas Israel reports a NAFLD prevalence of 30% and Saudi Arabia a NAFLD prevalence of 16.6% (either report includes the prevalence of NASH).[16,20] In a recent unpublished epidemiological survey, the overall prevalence of NAFLD in Turkey was reported to be 48.3%, with the highest prevalence rates in people older than 50 years (65.6%), men (64.0%), and in individuals with a BMI >25 kg/m^2 (63.5%).

In Europe, the prevalence of NAFLD is around 24%.[5,20] In this context, there may be a gradient of higher prevalence from Southern Europe to Northern Europe.[5] In fact, in Greece, the prevalence of NAFLD was estimated to be 41%, but an analysis of autopsy reports from patients without known liver disease who died from ischaemic heart disease or traffic accidents found the prevalence of NASH to be 40%.[26] In a study conducted in Spain that assessed patients by ultrasound and excluded those with liver disease or high alcohol intake found the prevalence of NAFLD to be 33% in men and 20% in women.[27]

In Australia, the prevalence of NAFLD was reported to be 20%–30%. NAFLD is the most common liver disease in Australia. In New Zealand, the prevalence of NAFLD was reported to be only 13%.[28–30] These results should not be surprising since Australia has one of the highest burdens of

Key point

The prevalence of NAFLD is increasing in line with obesity, with an estimated global prevalence of 25%.

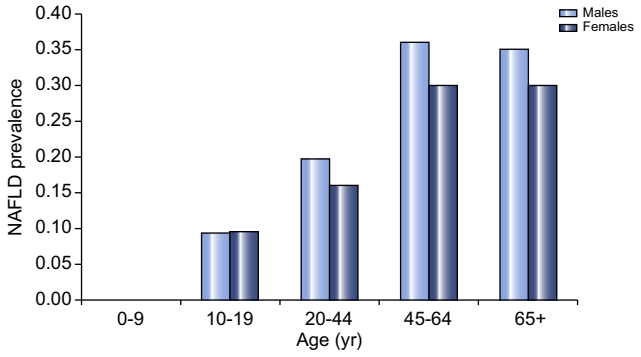

Fig. 2. Trends in the prevalence of NAFLD by age.[7,13] NAFLD, non-alcoholic fatty liver disease.

overweight or obese individuals globally.[31] NAFLD prevalence data are lacking for the other areas of the Pacific, including Micronesia, Melanesia, and Polynesia, but if the prevalence rates of T2DM and obesity are any indication, these countries will soon have a high burden of NAFLD.[9,13]

Finally, the data on the prevalence and incidence of NAFLD from Africa is quite scarce. It seems that the prevalence of NAFLD in North African countries mimic those reported from Middle East.[5] Meanwhile, a meta-analysis reported that the prevalence of NAFLD in Africa was about 13%, with lower prevalence reported from Nigeria (9%) and higher prevalence from Sudan (20%).[16,20]

Despite relatively robust data about the prevalence of NAFLD, the data about the incidence of NAFLD and NASH are quite scarce but ranges around 28.01 per 1,000 person-years to 52.34 per 1,000 people.[5,59,63] For more detail about the incidence of NAFLD and NASH, please refer to recent reviews.[5,60]

Age, sex, and ethnicity

As age increases so does the prevalence of NAFLD and NAFLD-related fibrosis.[16,18,31] This was confirmed in a retrospective study of a group of 351 patients with biopsy-proven NAFLD who were older (>60 years), middle-aged (>50 years to <60 years), or younger (<50 years).[31] In addition to higher prevalence of NAFLD, higher stage of fibrosis was observed in older individuals. In fact, these prevalence rates may be driven by a higher prevalence of metabolic conditions in older individuals.[31] Additional studies confirmed these results linking age to an increased risk of severe hepatic fibrosis, HCC, and T2DM.[32]

In addition to age, earlier studies of NAFLD suggested that female sex was associated with an increased risk of NAFLD.[5,17,18,36,57,60] Additionally, studies from Sri Lanka and Thailand reported female predominance. In fact, a study of 34,709 people in Thailand (27,073 women and 7,636 men) calculated the prevalence of NAFLD to be 22.9% in women and 18.3% in men. Investigators adjusted for age and the presence of T2DM, along with other diseases, and still found the prevalence of NAFLD to be 4.2% higher in women.[34] In contrast, a number of studies from the US, Southwest China, and Spain have reported a higher prevalence of NAFLD in men (Fig. 2).[17,25,27,33]

As noted previously, race and ethnicity can also be considered a risk for NAFLD.[5,16,20] The highest prevalence of NAFLD was observed in Hispanics, followed by non-Hispanic white individuals, and the lowest prevalence was observed in African Americans (10%).[5,16,20] However, an analysis of liver biopsies from patients undergoing bariatric surgery for obesity found that Hispanic and non-Hispanic white patients were significantly more likely than non-Hispanic black patients to have advanced steatosis, whereas non-Hispanic black patients and women were more likely to have NASH.[37] The researchers have proposed that age and levels of triglycerides and serpin family E member 1 (PAI-1, a marker of fibrosis) are only associated with NAFLD in Hispanic patients, whereas serum levels of adiponectin are associated with NAFLD in African Americans.[38,39] Other studies have shown that fructose malabsorption, which has a negative correlation with liver fat, is greater in African Americans than Hispanics.[40] These data suggest the impact of genetic and environmental factors in influencing the prevalence of NAFLD.

In addition to the studies related to race and ethnicity, there is evidence for familial clustering of NAFLD. In fact, as many as 27% of cases of NAFLD may be related to familial clustering.[39,40] This clustering suggests a genetic predisposition for development and progression of NASH.

One of the genetic markers is related rs738409 G (I148M) allele in the patatin like phospholipase domain containing 3 gene (*PNPLA3*), which encodes a triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes.[39–43] This allele has been associated with increased liver fat content and concentrations of serum aspartate aminotransferase. In the US, this allele is detected in higher proportions of Hispanics and lower proportions of African Americans. The rs738409 G allele has been associated with severe steatosis, NASH, and liver fibrosis in adults.[39,41] Other genetic variants significantly associated with NAFLD include those in *NCAN, GCKR,* and *LYPLAL1* as well as the polymorphisms C-482T and T-455C in APOC, which has also been associated with insulin resistance.[41,42]

Lean NAFLD

Although most patients with NAFLD are overweight or obese, some may have a BMI that is considered lean. Although patients with lean NAFLD are not obese, they may be metabolically abnormal compared to people who are not obese and do not have NAFLD.[44–53] It is important to note that lean NAFLD encompasses a heterogeneous spectrum of diseases arising from different aetiologies including dual alcoholic and non-

alcoholic fatty liver disease, congenital and acquired lipodystrophy (HIV treatment), genetic factors (polymorphisms in *PNPLA3*), congenital defects of metabolism (lysosomal acid lipase deficiency), endocrine disorders (polycystic ovarian syndrome, hypothyroidism, growth hormone deficiency), drug use (amiodarone, methotrexate, tamoxifen), jejunoileal bypass, starvation, or the receipt of total parental nutrition.[45,46]

The prevalence of lean NAFLD in the US was reported to be 7%, whereas the prevalence of lean NAFLD in rural areas of some Asian countries ranges from 25% to 30%.[16,20] However, there appears to be a gradient of lean to obese NAFLD in Asian countries – in contrast to rural areas, where lean NAFLD is more prevalent, patients in urban areas of Asia have NAFLD profiles similar to those of patients in Western countries. Patients with lean NAFLD from Asia seem to have lower rates of NASH, liver fibrosis, or metabolic abnormalities, after adjustment for severity of visceral obesity (waist circumference), whereas rates of clinical events and advanced fibrosis are similar between lean and obese patients with NAFLD.

The *PNPLA3* rs738409 GG allele is more common in Asians with lean NAFLD without metabolic syndrome, which could account for the observation that Asian and Caucasian populations have a similar prevalence of NAFLD, but Asians have a lower metabolic burden.[51–53] However, because of the heterogeneity in genetic factors, lifestyle, and economic status in Asia, further studies of NAFLD are required.

Although lean NAFLD is generally considered a less severe form of liver disease than NAFLD in obese patients,[49] this notion has recently been challenged.[50,51] Nevertheless, compared to overweight or obese patients with NAFLD, patients with lean NAFLD are younger and have a lower prevalence of metabolic syndrome (2%–48% *vs.* 22%–64% in overweight or obese patients).[51] However, recent data suggest that patients with lean NAFLD have higher mortality and more morbidities.[50] Additionally, patients with lean NAFLD were shown to have shorter survival times following liver transplantation.[16,50,52] An analysis of an international cohort study of patients with NAFLD, followed for a mean time of 11 years, determined that although patients with lean NAFLD have a healthier metabolic profile and less-advanced liver fibrosis, their median survival time without liver transplantation was significantly shorter than that of non-lean patients (18.1 years *vs.* 26.6 years) (52). The validity of these findings that suggest a more aggressive course for lean NAFLD must be further established.

Disease progression

Before an individual can be diagnosed with NAFLD, other liver diseases, such as alcoholic liver disease, must be ruled out. Alcohol-related liver disease can be contemplated in men who consume more than 30 g alcohol/day and women who consume more than 20 g alcohol/day.[54]

Although hepatic steatosis can occur when there is more than 5% fat in hepatocytes, progression can ensue if these fatty hepatocytes are exposed to insults or stress, which can then cause cell death, apoptosis, inflammation, and fibrosis, leading to NASH.[54,55] As NASH progresses, hepatic fibrosis develops, the liver becomes stiff and functionally impaired, which can lead to cirrhosis, HCC, decompensated cirrhosis, death, and/or liver transplantation (Fig. 3).[52,53]

This course of progression can take many years – 1 study found that each step takes an average of 7.7 years.[56] In the context of this long natural history, it will be clinically valuable to identify patients who are at risk of the progressive form of NAFLD. In fact, individuals with NAFLD and T2DM, especially those with an increasing number of components of metabolic syndrome are at increased risk of adverse long-term outcomes and should be carefully assessed using non-invasive tools.[54]

In studies of paired liver biopsies, researchers found that 30% of patients with NAFL and NASH had progressive fibrosis, whereas 20% with NASH showed regression, over 2.2–13.8 years.[55,56] These rates of progression or regression can be influenced by a number of genetic or environmental factors.[57,59–61] Interestingly, a meta-analysis of randomised controlled trials for the treatment of NASH found that 25% of the patients who received a placebo experienced an improvement in NAFLD activity score of 2 or more points, whereas at least 30% of the placebo patients experienced a 1 point decrease in steatosis as well as hepatocyte ballooning and lobular inflammation scores. A decrease in fibrosis scores was found in 21% of patients, though there was a substantial amount of heterogeneity among the findings. Nonetheless, investigators concluded that the placebo effect must be accounted for in the upcoming therapeutic trials for NASH to avoid the over-interpretation of disease progression or regression based solely on the therapeutic agent.[58] It is important to recognise that factors most strongly associated with NAFLD progression include older age (though this may be more related to the length of time exposure than actual age), the presence of visceral obesity, presence of T2DM or insulin resistance, and Hispanic ethnicity (this varies with ethnicity, because Mexican Hispanics have a higher prevalence of NAFLD than people from the Dominican Republic).[56] In contrast, factors associated with spontaneous regression of fibrosis in NASH have been clearly defined.

It is important to note that NAFLD is also associated with extrahepatic manifestations that can increase its disease burden. A meta-analysis found that 51% of patients with NAFLD were obese, 23% had T2DM, 69% had hyperlipidaemia, 39% had

Key point

Some patients with NAFLD are neither overweight nor obese and are considered to have lean NAFLD, which encompasses a heterogeneous spectrum of disease and is thought to be linked to worse outcomes.

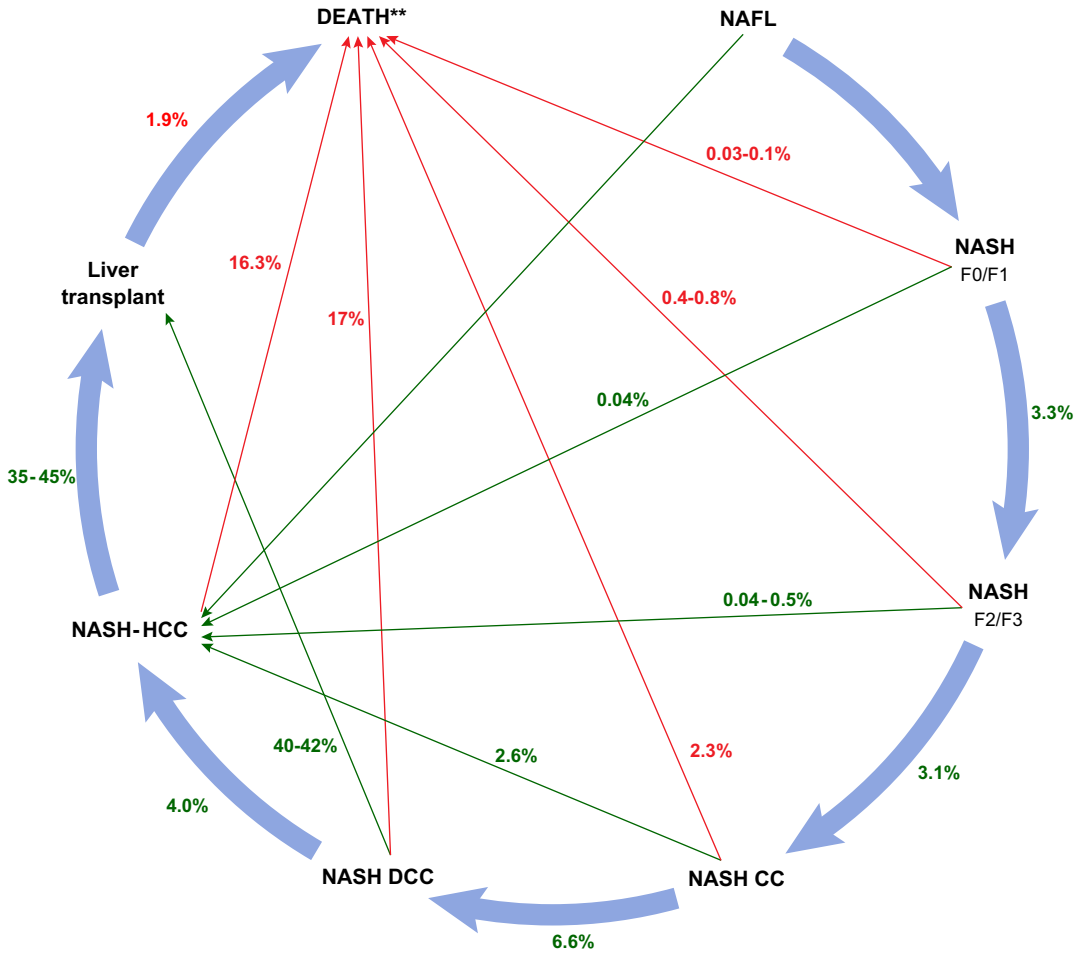

Fig. 3. Incidence of NAFLD by age group and sex. Modified from.[59] NAFLD, non-alcoholic fatty liver disease.

hypertension, and 42% had metabolic syndrome.[17] Renal impairment was also found to be more prevalent in patients with NAFLD than without. A meta-analysis of 33 studies associated NAFLD with a 2-fold increase in risk of chronic kidney disease (CKD). This study reported that patients with NASH, compared to those with with steatosis alone, had higher prevalence and incidence of CKD. Similarly, advanced fibrosis was associated with a higher prevalence and incidence of CKD than non-advanced fibrosis.[61]

Mortality, HCC and liver transplantation in NAFLD

The presence of metabolic syndrome, especially obesity and insulin resistance, can increase the rate of liver fibrosis progression, leading to cirrhosis, HCC, and/or death. In fact, the more components of metabolic syndrome, the higher the risk of mortality.[62–87]

Liver-specific mortality among patients with NAFLD was reported to be 0.77 per 1,000 person-years, and among patients with NASH it was reported to be 11.77 per 1,000 person-years.[16,20] Overall mortality per 1,000 person-years was reported to be 15.44 for patients with NAFLD and 25.56 for patients with NASH. Researchers associated NASH (adjusted hazard ratio, 9.16), age (adjusted hazard ratio, 1.06), and the presence of T2DM (adjusted hazard ratio, 2.09) with increased all-cause and liver-related mortality, after controlling for other variables.[69]

However, the stage of fibrosis associated with risk of severe liver disease: hazard ratios ranged from 1.9 for patients with F0 fibrosis to 104.9 for patients with F4 fibrosis.[70–72] Furthermore, fibrosis stages F3–F4 were associated with overall mortality. In fact, overall mortality was 3-fold greater in patients with F3–F4 fibrosis than in those without liver disease. Therefore, it is the stage of fibrosis and not steatosis that is directly related to overall mortality in patients with NAFLD.[72]

Despite these data, the most common cause of death among patients with NAFLD, especially among those with lean NAFLD, is cardiovascular disease.[73–75] It has been estimated that 5%–10% of patients with NAFLD die from cardiovascular disease. Patients with NAFLD have a 2-fold increase in risk of cardiovascular disease.[71,74] Although

there is evidence of endothelial dysfunction in patients with NAFLD, little is known about its causes or the effects of other factors. In this context, T2DM, very low-density lipids, hepatic overproduction of glucose, inflammatory factors, C-reactive protein, coagulation factors, and insulin resistance are all common in patients with NAFLD and increase the risk of death from cardiovascular disease.[81–83] Although the presence of hepatic steatosis can indicate a risk of insulin resistance, recent data suggest that the stage of fibrosis may be associated with cardiovascular disease. In this context, the underlying pathophysiology that hastens the development of fibrosis in NAFLD may also promote the development of cardiovascular disease. Despite these data, further research on this linkage is needed.[80]

As noted previously, metabolic syndrome in the presence of NAFLD has also been associated with increased mortality. A recent study found that the number of metabolic syndrome components increases the risk of death in patients with NAFLD.[59] In this study investigators collected data from the US National Health and Nutrition Examination Surveys (NHANES) and followed patients with NAFLD over 19 years, comparing outcomes to a set of control patients. They found that the presence of just 1 metabolic syndrome component doubled the risk of mortality (8-year, 2.6% for controls *vs.* 4.7% for patients with NAFLD; 16-year, 6% *vs.* 11.9%). In multivariate analyses, having all metabolic syndrome components was associated with overall, cardiac, and liver-specific mortality. So, as the number of metabolic syndrome components increase, the odds of survival decrease.[62]

In addition to cirrhosis and associated mortality, HCC is an important complication of CLD and NAFLD. HCC has become the third-leading cause of cancer death worldwide.[68] HBV is the leading cause of HCC worldwide, followed by HCV. However, a recent study on the global trends of HCC found incidence to be increasing in Northern and Central Europe, North America, and Latin America whereas East Asia had reductions. However, mortality in East Asia was 2- to 5-fold higher than in most European countries and the Americas. Better control of HBV and HCV infection are believed to be reducing HCC incidence in Asia but increases in obesity and alcohol use are hindering the control of HCC. Incidences of alcohol-related and NAFLD-related HCC are expected to increase.[68]

The incidence rate for HCC among patients with NAFLD was reported to be 0.44 per 1,000 person-years. Patients with NAFLD fibrosis stages F3 and F4 had an almost 7-fold increase in risk of HCC compared to people without liver disease.[19] An analysis of data from the Surveillance, Epidemiology and End Results registries (2004–2009) linked to Medicare files assessed the prevalence and mortality of patients with NAFLD-associated HCC. Of the 4,929 identified cases of HCC, 54.9% were related to HCV, 16.4% to alcoholic liver disease, 14.1% to NAFLD, and 9.5% to HBV. However, there was a 9% annual increase in NAFLD-associated HCC. Additionally, patients with NAFLD-associated HCC were older, had shorter survival times, more heart disease, and were more likely to die from their primary liver tumour; only 5% of the patients who received a liver transplant had NAFLD-associated HCC. Finally, patients with NAFLD-associated HCC had a 1.2-fold higher risk of death within 1 year than patients with HCCs of other aetiologies – especially older patients with lower incomes and unstaged tumours. The researchers concluded that NAFLD-associated HCC carries a high mortality burden and is poised to become a major contributor to HCC in the US.[81]

Although most patients with HCC have underlying cirrhosis, there is evidence that a small proportion of cases of NAFLD can progress directly to HCC before fibrosis has developed.[64] Interestingly, data has suggested that patients with NAFLD without cirrhosis, with no or mild fibrosis, are at some risk of developing HCC due to insulin resistance, hyperinsulinemia, increased TNF signalling, and alterations in cellular lipid metabolism.[63] In fact, a recent meta-analysis that characterised the pooled risk of HCC in patients with NAFLD without cirrhosis confirmed this concept.[64] The authors determined that the prevalence of HCC in patients with NASH without cirrhosis was 38.0%, whereas among patients with HCC without cirrhosis from other liver aetiologies, the prevalence rate was only 14.2%. Patients with non-cirrhotic NASH had an almost 3-fold increased risk of developing HCC than non-cirrhotic individuals with other types of liver disease (OR 2.61; 95% CI 1.27–5.35; $p = 0.009$). This increase in the risk of HCC disappeared when both cirrhotic and non-cirrhotic patients were combined.[64] Despite these interesting results, further studies are needed to identify risk factors for HCC in patients with NASH without cirrhosis.

Finally, it is important to recognise that NAFLD and NASH are rapidly becoming a major indication for liver transplantation in the US.[83] A recent analysis of the US Scientific Registry of Transplant Recipients from 2012 to 2016 found that NASH was the fastest increasing indication for liver transplantation among those listed, positioning NASH to become the most common indication for liver transplantation in the near future.[82,84,85] Additionally, another study of the same dataset that restricted the analysis to those listed for liver transplantation for HCC showed that NASH is the fastest growing cause of HCC in those listed.[85] Most disturbing, though, is that patients with NASH are the least likely to be surveyed for the development of HCC, and the most likely to die while awaiting a liver transplant.[85–87]

Key point

NAFLD is associated with an increased risk of liver-related mortality, HCC and the need for liver transplant, even though the most common cause of death in these patients is cardiovascular disease.

Changing profile of CLD

An analysis of the US NHANES (1988–2008 data) found that that the prevalence rates for CLD

increased from 11.78% in 1988–1994 to 14.78% in 2005–2008. The prevalence rates of HBV-related, HCV-related, and alcohol-related liver disease remained generally stable, but the prevalence rate of NAFLD doubled; obesity was an independent predictor of NAFLD.[88] However, it is important to keep in mind that aetiologies of CLD vary worldwide. Prevalence values are affected by external factors such as comorbidities and the availability of HBV vaccination and alcohol and drug use prevention programmes.[1]

Variations are also observed in CLD-related mortality. An analysis of data from the US Census and National Center for Health Statistics mortality records found HCV-related mortality to be decreasing, associated with the use of direct-acting antiviral therapies, which have high rates of sustained viral responses. Meanwhile, the mortality rate of patients with alcoholic liver disease or NAFLD increased over the same period; minorities in the US had disproportionately high CLD-related mortality (4). A separate study of data from the US showed that mortality from CLD and liver cancer increased substantially from the 1980s to the 2010s. In 2010, the age-adjusted rates of death associated with CLD and liver cancer were 23.67 and 16.57 per 100,000 people, respectively.[89] Interestingly, there was a decrease in HBV and HCV infections and a large increase in the prevalence of NAFLD.[89]

Key point

Modelling suggests that the global burden of NAFLD will continue to increase, with the largest increase in prevalence expected in China.

CLD mortality in the US varies between regions, ranging from 6.4 to 17.0 per 100,000 liver-related deaths. The Southern and Western Regions of the US have the highest rates of CLD-associated mortality.[90] Being of Hispanic ethnicity, having viral hepatitis, or having lower household income increase CLD mortality.[90] As expected prevalence of HCV infection was higher in non-Hispanic whites, whereas the prevalence of HBV infection was higher in Asian Americans, especially among individuals who had immigrated to the US from Vietnam or China. Alcoholic liver disease-related mortality was highest in Japanese-Americans, whereas HCC-related mortality was found to be highest in Vietnamese, Japanese, and Korean Americans compared to non-Hispanic whites.

Although these studies used data from the US, similar findings have been reported in European countries. In Europe, the HEPAHEALTH project assessed CLD in 35 European countries.[91] It found substantial geographical differences in aetiologies of CLD. In northern Europe, increases in cirrhosis and liver cancer were associated with excessive alcohol consumption, whereas viral hepatitis was most likely to cause cirrhosis and liver cancer in Eastern and Southern European countries. Furthermore, given the increasing incidence of obesity across Europe, NAFLD was projected to become a serious cause of CLD in Europe.[91] The most common cause of cirrhosis in Germany is fatty liver disease, related to metabolic syndrome and alcoholism.[92]

In Asia, there is geographical variation in the aetiology of CLD.[89] In India, HBV is the most common overall cause of CLD.[93] HBV is the most common cause of CLD in the eastern and southern parts of India, whereas HCV infection is more common in the northern region. Furthermore, alcoholic liver disease is most common in the northeastern regions of the country, whereas NAFLD is most common in the western and central regions of the country, where diabetes is also most prevalent.[93]

Finally, in the Asia-Pacific region, chronic viral hepatitis, excessive alcohol consumption, and NAFLD are all major causes of CLD.[94] However, the expanding implementation of HBV vaccination has been effective in reducing the incidence of HBV and liver cancer, especially in China. Nevertheless, further efforts are required to tackle the prevalence of HCV infection in this region, despite the introduction of direct-acting antiviral agents – these agents have not been widely used in some regions because of access issues. At the same time, the prevalence of NAFLD is increasing in the Asia-Pacific region, as in Western countries, especially in urban populations.[94]

Future projections

The global epidemic of NAFLD appears to be increasing at the same rate as epidemics of obesity and diabetes, so researchers used mathematical modelling analyses to estimate the future disease burden associated with NAFLD in the US. Their results indicate increases in cases of advanced liver disease and liver-related mortality in the coming years.[44] More specifically, if the prevalence of obesity and diabetes level off from 2016 through 2030, there will be only a modest increase in the total number of NAFLD cases (increases of 0 to 30%). Globally, the largest increase in prevalence of NAFLD is expected to occur in China, because of urbanisation. Meanwhile, the worldwide prevalence of NASH will increase 15%–56%, with liver mortality and advanced liver disease doubling as the population ages. Within Europe, Germany had the highest prevalence of NAFLD in 2016, but by 2030 the highest prevalence is predicted to be in Italy (29.5%) and the lowest in France (23.6%). The largest number of cases is estimated to occur in individuals who are 55–59 years old, followed by people who are 50–54 years old.[44]

In addition, in 2016 the highest proportion of NASH cases with advanced disease was estimated to be in Italy (22%), whereas the smallest proportion was in China (12%). By 2030, the highest prevalence of NASH-related advanced disease is predicted to be in Spain (29.5%) whereas China will have the lowest (6.5%). Interestingly, for every country studied, the number of advanced fibrosis cases increased to a greater extent than cases of early fibrosis. By 2030 for the US, 21% of NASH

cases will have stage F3 or F4 fibrosis or advanced liver disease.[44]

Economic burden

The huge clinical burden of NAFLD is associated with a large economic burden.[95–101] In an analysis of data from the US Medical Expenditure Panel Survey (2004–2013) conducted to determine the effects of CLD (including NAFLD) on worker productivity, researchers found that, compared to people without CLD, patients with CLD were significantly less likely to be employed, due to illness/disability.[92] People with CLD had more health care use, generating higher health care expenses ($19,390 *vs.* $5,567/year without CLD). These findings held after multivariate analyses controlled for sociodemographic factors and comorbidities; patients with CLD were 40% more likely to be unemployed and incurred annual health care expenditures of $9,503 ± $2,028. Patients with CLD-related cancer had health care expenditures of $17,278 ± $5,726 per year.[96]

A study quantified total health care cost and resource utilisation associated with NAFLD, comparing the results to those of patients with similar metabolic comorbidities but without NAFLD. The researchers used a large national administrative claims database to collect longitudinal health data from more than 100 million enrolees in private and Medicare Advantage health plans.[97] The authors found the total annual cost of care per NAFLD patient with private insurance to be $7,804 (interquartile range, $3,068–$18,688) for a new diagnosis and $3,789 (interquartile range, $1,176–$10,539) for long-term management, significantly higher than for matched controls ($2,298; interquartile range, $681–$6,580). The study found that liver biopsies, imaging evaluations, and hospitalisations accounted for the increased costs for patients with NAFLD compared to matched controls.[97]

In another study, researchers developed a steady-state prevalence model to quantify the expected increase in the economic burden of NAFLD.[59] Using real-world data and data from published studies or expert opinions and a series of interlinked Markov models, the authors transitioned patients with NAFLD across 9 liver disease states: NAFL, non-NASH, NASH-fibrosis, NASH compensated cirrhosis, NASH decompensated cirrhosis, HCC, liver transplantation, post-liver transplant, and death. Their models predict that more than 39 million people will have NAFLD, with annual direct medical costs of approximately $62 billion ($1,584 per patient) in the US. In Germany, France, Italy, and the United Kingdom, the model projects that there will be 30 million people with NAFLD, with an annual cost of about €19 billion (from €345 to €1,115 per patient). Overall, the costs were found to be highest for 45–65-year old patients. The burden is significantly higher when societal costs are included.[59]

Another recent Markov model was used to estimate the economic burden of all stages of NASH in the US, based on inpatient, outpatient, professional services, emergency department, and drug costs.[101] The authors estimated that in 2017, 6.65 million adults in the US had NASH, and that 232,000 of these were incident cases. The lifetime costs for these patients with NASH were estimated to be $222.6 billion, and the costs for patients with NASH and fibrosis stage F >3 were estimated to be $95.4 billion.[101]

In addition to economic modelling, administrative databases such as the Medicare database have provided additional evidence related to the economic burden of NAFLD. Using data from 30,000 Medicare beneficiaries (2005–2010), researchers quantified outpatient costs for patients with NAFLD.[98] In these patients, comorbidities of cardiovascular disease, diabetes, hyperlipidaemia, and hypertension increased significantly, along with mean inflation-adjusted yearly charge and the mean inflation-adjusted yearly payment, from $2,624 ± $3,308 and $561 ± $835 to $3,608 ± $5,132 and $629 ± $1,157; respectively. After multivariate analysis, the total number of outpatient visits and the comorbidities studied accounted for most of the yearly charges and yearly payments.[98]

Data from Medicare beneficiaries (2010) were also used to assess the economic burden of NAFLD, based on resource utilisation (total charges and total provider payments) for inpatients and outpatients.[99] The authors found that for inpatients, the median total hospital charge was $36,289. Patients with NAFLD and cirrhosis had higher charges than patients with NAFLD without cirrhosis ($61,151 *vs.* $33,863) and payments ($18,804 *vs.* $10,146 respectively). The median total charges for outpatients was $9,011 – again, patients with NAFLD and cirrhosis incurred higher charges than patients with NAFLD without cirrhosis ($12,049 *vs.* $8,830) and had higher payments ($2,586 *vs.* $1,734, respectively). The variables most highly associated with increased inpatient resource utilisation were inpatient mortality, decompensated cirrhosis, and cardiovascular disease. In outpatients, cardiovascular disease, obesity, and hypertension were all significantly associated with increased resource utilisation.[99] The estimated 10-year economic burden of managing NAFLD complications is $908 billion.[100]

Patient-reported outcomes

Patient-reported outcomes (PROs) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else".[102] Therefore, the tools

used to measure PROs attempt to provide patients a platform to explain what they are able to do and how they feel doing what they are doing through a series of questions that assess patients' perception of their physical and mental health as well as their social well-being.[102] Some of the tools more commonly used to measure PROs in patients with NAFLD include the generic health-related quality of life (HRQoL) tool, the SF-36, and the disease specific tool the Chronic Liver Disease Questionnaire (CLDQ).[103,104] However, due to the exponential increase in NAFLD and NASH cases, specific disease HRQoL tools have been developed, such as the CLDQ NASH, which measure the specific areas of abdominal symptoms, activity, emotional, fatigue, systemic symptoms, and worry.[105,106]

In addition to HRQoL impairments, other comorbidities can impact these patients' health and well-being. In fact, depression has been reported in 27.2% of patients with NAFLD, a value 4-fold higher than the rate of 6.7% reported by the National Institute of Mental Health in the adult population of the US, and is an important confounder in measurements of HRQoL.[107,108] Other important confounders that affect HRQoL in patients with NAFLD are the presence of T2DM and obesity. In assessing HRQoL in patients with NAFLD, it is important to address the effects of these confounders.[106]

Key point

It has been shown that patients with NAFLD have reduced HRQoL compared to healthy individuals and patients with liver disease of other aetiologies.

Researchers have found that patients with NAFLD have reduced HRQoL compared with controls. In an analysis of data from the NHANES, patients with NAFLD were compared to healthy individuals and patients with HCV infection. Thirty percent of patients with HCV reported their health as fair or poor compared to 20% of patients with NAFLD and 10% of healthy controls. However, after adjustment for age, sex, race, and BMI, patients with NAFLD were 18%–20% more likely to report days when their physical health was not good or when they were unable to perform daily activities.[109] Researchers used the CLDQ tool to compare patients with NAFLD to patients with HBV or HCV infection, and found that patients with NAFLD had the lowest HRQoL.[110] Encouragingly, patients with NAFLD who obtained at least a 5% weight loss through a lifestyle modification programme reported a significant increase (a 5-point decrease in BMI led to a 10% adjusted improvement) in HRQoL, compared to their baseline scores prior to the weight loss. Most importantly, nondiabetic patients with NASH but without advanced fibrosis were most likely to increase HRQoL following weight loss.[111]

In a study of the ability of a selective inhibitor of apoptosis signal regulating kinase 1 (selonsertib) to reduce fibrosis in patients with NASH, researchers measured PRO scores.[112] At baseline all patients reported their physical health to be significantly worse than that of the population. However, over the course of the study, PRO scores increased in patients with a ≥2 decrease in NAFLD activity score or ≥1-stage reduction in fibrosis, as well as a relative reduction in liver collagen of 50% or more. Patients with NASH who had >17% increase in their baseline collagen levels had lower PRO scores than patients without this increase in collagen. In addition, investigators found that increased baseline serum levels of CK-18, IL6, and C-reactive protein were correlated with lower PRO scores.[112]

Impact of NAFLD on patients with other liver diseases

There are concerns about the effects of NAFLD on the outcomes of other liver diseases. NAFLD and HCV infection are each associated with development of T2DM. The combined effects of NAFLD and HCV on T2DM could create a cycle of poor health that eventually increases all-cause mortality and liver-related and cardiovascular complications. Conversely, reducing fatty liver and eradicating HCV with direct-acting antiviral agents might reduce risk of T2DM and improve patient outcomes. Further studies are needed to confirm preliminary findings.[113]

The relationship between NAFLD and HBV infection is complicated. In patients with NAFLD infection, HBV infection might actually slow fatty liver-associated disease progression. However, following HBV seroclearance (through treatment or spontaneous), fatty liver-induced liver disease progresses. Further studies are needed, because NAFLD and seroclearance are each associated with older age.[114,115]

Finally, a recent study of NHANES suggests that the impact of excessive alcohol use on mortality is exacerbated by the presence of metabolic syndrome.[116] These data suggest a significant overlap between alcohol-related liver disease and NAFLD.

In addition to these liver diseases, it is important to mention that NAFLD also encompasses patients with cryptogenic cirrhosis.[5,15,16] Although controversial, recent biopsy data suggested that patients with cryptogenic cirrhosis are a part of the spectrum of NASH but may experience worse outcomes.[117]

Strategies to decrease NAFLD prevalence

Despite our increasing knowledge of NAFLD, many questions remain about progression, staging, diagnosis, and management. As we move forward, research should focus on identification of biomarkers that can be measured noninvasively, clarification of pathogenic pathways, development of screening guidelines, and determination of clinical endpoints, which are necessary to effectively assess the safety of new therapeutic agents.[118,119] Until then, we must push forward the global initiative to decrease obesity, increase awareness about liver diseases associated with metabolic abnormalities, encourage a diet lower in fat and fructose, and promote exercise routines that com-

bine conditioning and strengthening exercises. Bariatric surgery and newer endoscopic procedures can only be considered for morbidly obese individuals who are candidates for these interventions.[118–122]

In addition, we must also consider the social determinants of health when developing strategies to combat the development of NAFLD. In this context, social determinants are broadly defined as the external factors which can separate the health status of one area from another. Recently, the WHO quantified the effect of environmental factors, such as pollution, occupational risks, agricultural methods, climate change, and food contamination on the burden of disease and found that the US experienced a higher burden of disease than other comparable countries.[123] Although environmental factors do have an impact on NAFLD and its progression, there is a gap in our current knowledge about the social determinants impacting NAFLD. In this context, the impact of advertisement of food, the location of and quality of food provided by local grocery stores as well as access to outdoor and indoor space for recreational activities along with other determinants may have a profound impact on NAFLD and should be included in the comprehensive treatment strategy for NAFLD. This perspective emphasises the complexity of treating NAFLD and NASH which cannot be solved with a simple treatment strategy that only includes drug regimens.[123]

Conclusions

Due to the increasing prevalence of obesity and T2DM in children and adults, along with the world's aging population, the prevalence of NAFLD is increasing. The rate of NAFLD-related HCC is also increasing, along with demand for livers for transplantation, of which there are not enough. NAFLD decreases patients' HRQoL and causes a significant economic burden. Although agents are being tested in clinical trials for their ability to reverse the effects of fatty liver, the only proven treatments are weight loss and increased physical activity, which are hard to sustain. Additionally, NAFLD is associated with a significant economic burden to Medicare, while the presence of cirrhosis and cardiovascular disease are associated with increased resource utilisation. Global awareness programmes are needed not only to raise cognisance of NAFLD but also the disorders associated with NAFLD, so that worldwide strategies can be instituted to change the course of disease.

Conflict of interest

The author declares no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Acknowledgement

The author thanks Linda Henry PhD for medical writing and editorial assistance.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.033.

References

[1] Marcellin P, Kutala BK. Liver diseases: a major, neglected global public health problem requiring urgent actions and large-scale screening. Liver Int 2018;38 (Suppl 1):2–6. https://doi.org/10.1111/liv.13682.
[2] Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12:145, Pmid: 25242656.
[3] Stepanova M, De Avila L, Afendy M, Younossi I, Pham H, Cable R, et al. Direct and indirect economic burden of chronic liver disease in the United States. Clin Gastroenterol Hepatol 2017;15. https://doi.org/10.1016/j.cgh.2016.07.020, 759–766.e5 Epub 2016 Jul 25.
[4] Kim D, Li AA, Gadiparthi C, Khan MA, Cholankeril G, Glenn JS, et al. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. Gastroenterology 2018. https://doi.org/10.1053/j.gastro.2018.07.008.
[5] Younossi Z, Tacke F, Arrese M, Sharma BC, Mostafa I, Bugianesi E, et al. Global perspectives on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Hepatology 2018. https://doi.org/10.1002/hep.30251.
[6] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies Obtained from:. Lancet 2004:363. Available from: http://www.who.int/nutrition/publications/bmi_asia_strategies.pdf.
[7] Tenfold increase in childhood and adolescent obesity in four decades: new study by Imperial College London and WHO 11 October 2017 News Release LONDON- http://www.who.int/news-room/detail/11-10-2017-tenfold-increase-in-childhood-and-adolescent-obesity-in-four-decades-new-study-by-imperial-college-london-and-who.
[8] World Obesity Facts. Obtained from the world wide web at: https://renew-bariatrics.com/obesity-rank-by-countries/.
[9] Type 2 Diabetes Mellitus-International Diabetes Federation. IDF diabetes atlas. 8th ed. 2017 obtained from the world wide web at http://www.diabetesatlas.org/.
[10] WHO Diabetes Fact Sheets. Obtained from the world wide web at: http://www.who.int/news-room/fact-sheets/detail/diabetes.
[11] Centers for Disease Control. Rates of new diagnosed cases of type 1 and type 2 diabetes on the rise among children, teens. Obtained from the world wide web at: https://www.cdc.gov/media/releases/2017/p0412-diabtes-rates.html.
[12] Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017;67:862–873. https://doi.org/10.1016/j.jhep.2017.06.003, Epub 2017 Jun 19.
[13] World Health Organization (WHO). Obesity and overweight. Obtained from the world wide web at: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
[14] World Health Assembly. Action plan to reduce global obesity. Obtained from the world wide web at: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
[15] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274–285.
[16] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20. https://doi.org/10.1038/nrgastro.2017.109, Epub 2017 Sep 20. Review.
[17] Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity 2011;19:402–408.
[18] Mongraw-Chaffin M, Golden SH, Allison MA, Ding J, Ouyang P, Schreiner PJ, et al. The sex and race specific relationship between anthropometry and body fat composition determined from computed tomography: evidence from the multi-ethnic study of atherosclerosis. PLoS One 2015;10 e0139559.

[19] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016 Jul;64:73–84. https://doi.org/10.1002/hep.28431.

[20] Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the united states and the rest of the world. Clin Liver Dis 2016;20:205–214.

[21] Cotrim HP, Parise ER, Figueiredo-Mendes C, Galizzi-Filho J, Porta G, Oliveira CP. Nonalcoholic Fatty Liver Disease Brazilian Society of Hepatology consensus. Arq Gastroenterol 2016 Apr-Jun;;53:118–122.

[22] López-Velázquez JA, Silva-Vidal KV, Ponciano-Rodríguez G, Chávez-Tapia NC, Arrese M, Uribe M, Méndez-Sánchez N. The prevalence of nonalcoholic fatty liver disease in the Americas. Ann Hepatol 2014;13:166–178.

[23] Andrade GC, Fujise LH, Santana JE Filho, Oliveira C, Silva Rde. Non-alcoholic fatty liver disease (NAFLD) in different populations: a clinical and epidemiological study – sample of São José do Rio Preto. Rev Assoc Med Bras (1992) 2016;62:218–226.

[24] Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 2013;28:11–17.

[25] Eguchi Y, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. J Gastroenterol 2012;47:586–595.

[26] Zois CD, Baltayiannis GH, Bekiari A, Goussia A, Karayiannis P, Doukas M, et al. Steatosis and steatohepatitis in postmortem material from Northwestern Greece. World J Gastroenterol 2010;16:3944–3949. https://doi.org/10.3748/wjg.v16.i31.3944.

[27] Caballería L, Pera G, Auladell MA, Torán P, Muñoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. Eur J Gastroenterol Hepatol 2010;22:24–32.

[28] Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology 2010;51:1593–1602.

[29] Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. J Gastroenterol Hepatol 2009;24:1284–1288.

[30] Association TGSoAAL. The economic cost and health burden of liver diseases in Australia. Sydney: Deloitte Access Economics; 2012.

[31] National Health Survey: First Results, 2014–15. http://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001.

[32] Coppell KJ, Miller JC, Gray AR, et al. Obesity and the extent of liver damage among adult New Zealanders: findings from a national survey. Obes Sci Pract 2015;1:67–77.

[33] Frith J, Day CP, Henderson E, Burt AD, Newton JL. Non-alcoholic fatty liver disease in older people. Gerontology 2009;55:607–613.

[34] 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.

[35] Li H, Wang YJ, Tan K, Zeng L, Liu L, LIU FJ, et al. Prevalence and risk factors of fatty liver disease in Chengdu, Southwest China. Hepatobiliary Pancreat Dis Int 2009;8:377–382.

[36] Summart U, Thinkhamrop B, Chamadol N, Khuntikeo N, Songthamwat M, Kim CS. Gender differences in the prevalence of nonalcoholic fatty liver disease in the Northeast of Thailand: a population-based cross-sectional study. F1000Research 2017;6:1630. https://doi.org/10.12688/f1000research.12417.2.

[37] Messiah SE, Vidot DC, Baeker B, Jordan A, Kristopher L, Khorgami Z, De La Cruz-Muñoz N. Ethnic and gender differences in the prevalence of nonalcoholic steatohepatitis among bariatric surgery patients. Bariatr Surg Pract Patient Care 2016;11. https://doi.org/10.1089/bari.2016.0018.

[38] Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011;53:1883–1894.

[39] Kalia HS, Gaglio PJ. The prevalence and pathobiology of nonalcoholic fatty liver disease in patients of different races or ethnicities. Clin Liver Dis 2016;20:215–224.

[40] Walker RW, Lê KA, Davis J, Alderete TL, Cherry R, Lebel S, Goran MI. High rates of fructose malabsorption are associated with reduced liver fat in obese African Americans. J Am Coll Nutr 2012;31:369–374.

[41] Kotronen A, Johansson LE, Johansson LM, Roos C, Westerbacka J, Hamsten A, et al. A common variant in PNPLA3, which encodes adiponutrin, is associated with liver fat content in humans. Diabetologia 2009;52:1056–1060.

[42] Sharma M, Mitnala S, Vishnubhotla RK, Mukherjee R, Reddy DN, Rao PN. The riddle of nonalcoholic fatty liver disease: progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis. J Clin Exp Hepatol 2015;5:147–158. https://doi.org/10.1016/j.jceh.2015.02.002.

[43] Dongiovanni P, Anstee QM, Valenti L. Genetic predisposition in NAFLD and NASH: impact on severity of liver disease and response to treatment. Curr Pharm Des 2013;19:5219–5238.

[44] Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD Disease Burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol 2018;69:896–904. https://doi.org/10.1016/j.jhep.2018.05.036, pii: S0168-8278(18)32121-4 [Epub ahead of print].

[45] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012;91:319–327.

[46] Kumar R, Mohan S. Non-alcoholic fatty liver disease in lean subjects: characteristics and implications. J Clin Transl Hepatol 2017;5:216–223. https://doi.org/10.14218/JCTH.2016.00068.

[47] Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism. 2013;62:352–360.

[48] Feldman A, Denkmayr L, Strasser M, Ruhaltinger S, Strebinger M, Huber-Schönauer U, et al. Liver-related mortality and morbidity of lean NAFLD is higher compared to overweight and obese NAFLD patients. J Hepatol 2017;66 (Supplement):S149.

[49] Otgonsuren M, Stepanova M, Gerber L, Younossi ZM. Anthropometric and clinical factors associated with mortality in subjects with nonalcoholic fatty liver disease. Dig Dis Sci 2013;58:1132–1140. https://doi.org/10.1007/s10620-012-2446-3, Epub 2012 Nov 10.

[50] Dela Cruz AC, Bugianesi E, George J, Day CP, Liaquat H, Charatcharoenwitthaya P, et al. 379 characteristics and longterm prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology 2014;146:S909.

[51] Wei JL, Leung JC, Loong TC, Wong GL, Yeung DK, Chan RS, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol 2015;110:1306–1314.

[52] Hu X, Huang Y, Bao Z, Wang Y, Shi D, Liu F, et al. Prevalence and factors associated with nonalcoholic fatty liver disease in Shanghai work-units. BMC Gastroenterol 2012;12:123.

[53] Chan WK, Treeprasertsuk S, Imajo K, Nakajima A, Seki Y, Kasama K, et al. Clinical features and treatment of nonalcoholic fatty liver disease across the Asia Pacific region-the GO ASIA initiative. Aliment Pharmacol Ther 2018;47:816–825.

[54] Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 2016;65:1017–1025. https://doi.org/10.1016/j.metabol.2016.01.012, Epub 2016 Jan 29. Review.

[55] McPherson S et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62:1148–1155.

[56] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13, 643–654.e1-9.

[57] Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol 2013;59:550–556.

[58] Han MAT, Altayar O, Hamdeh S, Takyar V, Rotman Y, Etzion O, et al. Rates of and factors associated with placebo response in trials of pharmacotherapies for nonalcoholic steatohepatitis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018, in press.

[59] Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577–1586. https://doi.org/10.1002/hep.28785, Epub 2016 Sep 26.

[60] European Association for the Study of the Liver (EASL)European Association for the Study of Diabetes (EASD)European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402. https://doi.org/10.1016/j.jhep.2015.11.004, Epub 2016 Apr 7. PubMed PMID: 27062661.

[61] Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med 2014;11 001680.

[62] Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). Medicine (Baltimore) 2018;97 e0214.

[63] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357. https://doi.org/10.1002/hep.29367, Epub 2017 Sep 29. Review. PubMed PMID: 28714183.

[64] Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is

associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14, 124-131.e1.
[65] Seyda Seydel G, Kucukoglu O, Altinbasv A, Demir OO, Yilmaz S, Akkiz H, et al. Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries. Ann Hepatol 2016;15:662–672.
[66] Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 2012;56:1384–1391.
[67] Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018.
[68] Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 2017;67:302–309.
[69] Stepanova M, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci 2013;58:3017–3023.
[70] Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265–1273.
[71] Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547–1554.
[72] Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoen-witthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149, 389–397.e10.
[73] Younossi ZM, Stepanova M, Rafiq N, et al. Nonalcoholic steatofibrosis independently predicts mortality in nonalcoholic fatty liver disease. Hepatol Commun 2017;1:421–428. https://doi.org/10.1002/hep4.1054.
[74] Spahillari A, Mukamal KJ, DeFilippi C, Kizer JR, Gottdiener JS, Djoussé L, et al. The association of lean and fat mass with all-cause mortality in older adults: The Cardiovascular Health Study. Nutr Metab Cardiovasc Dis 2016;26:1039–1047.
[75] Stepanova M, Younossi Z. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. CGH 2012;10:646–650.
[76] Saponaro C, Gaggini M, Gastaldelli A. Curr Diab Rep 2015;15:34. https://doi.org/10.1007/s11892-015-0607-4.
[77] Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013;5:1544–1560.
[78] Bugianesi E, Gastaldelli A. Hepatic and cardiac steatosis: are they coupled? Heart Fail Clin 2012 Oct;8:663–670. https://doi.org/10.1016/j.hfc.2012.06.010. Epub 2012 Aug 9.
[79] Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330–344.
[80] Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology 2018;155, 443–457.e17.
[81] Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730. https://doi.org/10.1002/hep.28123, Epub 2015 Oct 24.
[82] Kim D, Li AA, Perumpail BJ, Gadiparthi C, Kim W, Cholankeril G, et al. Changing trends in etiology- and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2018.
[83] Younossi ZM. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Implications for liver transplantation. Liver Transpl 2018;24:166–170. https://doi.org/10.1002/lt.25003, PubMed PMID: 29272073.
[84] Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri, et al. Liver transplantation for nonalcoholic steatohepatitis in the us: temporal trends and outcomes. Dig Dis Sci 2017;62:2915–2922.
[85] Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Non-alcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2018.
[86] Tavakoli H, Robinson A, Liu B, Bhuket T, Younossi Z, Saab S, et al. Cirrhosis patients with nonalcoholic steatohepatitis are significantly less likely to receive surveillance for hepatocellular carcinoma. Dig Dis Sci 2017;62:2174–2181.
[87] Young K, Aguilar M, Gish R, Younossi Z, Saab S, Bhuket T, et al. Lower rates of receiving model for end-stage liver disease exception and longer time to transplant among nonalcoholic steatohepatitis hepatocellular carcinoma. Liver Transpl 2016;22:1356–1366.
[88] 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. Clin Gastroenterol Hepatol 2011;9, 524–530.e1.
[89] Kim Y, Ejaz A, Tayal A, Spolverato G, Bridges JF, Anders RA, et al. Temporal trends in population-based death rates associated with chronic liver disease and liver cancer in the United States over the last 30 years. Cancer 2014;120:3058–3065. https://doi.org/10.1002/cncr.28843, Epub 2014 Jun 10.
[90] Desai AP, Mohan P, Roubal AM, Bettencourt R, Loomba R. Geographic variability in liver disease-related mortality rates in the United States. Am J Med 2018;131:728–734.
[91] Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. J Hepatol 2018;69:718–735. https://doi.org/10.1016/j.jhep.2018.05.011, Epub 2018 May 17.
[92] Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: Part 1 of a series on liver cirrhosis. Dtsch Arztebl Int 2013;110:85–91. https://doi.org/10.3238/arztebl.2013.0085.
[93] Mukherjee PS, Vishnubhatla S, Amarapurkar DN, et al. Etiology and mode of presentation of chronic liver diseases in India: a multi centric study. Ray R, ed.. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0187033, e1087033.
[94] Wong M, Huang J, George J, Huang J, Leung C, Eslam M, et al. The changing epidemiology of liver diseases in the Asia-Pacific region. Nat Rev Gastroenterol Hepatol 2018.
[95] Younossi ZM, Henry L, Bush H, Mishra A. Clinical and economic burden of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Clin Liver Dis 2018;22:1–10.
[96] Stepanova M, De Avila L, Afendy M, Younossi I, Pham H, Cable R, Younossi ZM. Direct and indirect economic burden of chronic liver disease in the United States. Clin Gastroenterol Hepatol 2017;15. https://doi.org/10.1016/j.cgh.2016.07.020, 759–766.e5. Epub 2016 Jul 25.
[97] Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large US claims database. Hepatology 2018. https://doi.org/10.1002/hep.30094, [Epub ahead of print].
[98] Younossi ZM, Zheng L, Stepanova M, Henry L, Venkatesan C, Mishra A. Trends in outpatient resource utilizations and outcomes for Medicare beneficiaries with nonalcoholic fatty liver disease. J Clin Gastroenterol 2015;49:222–227.
[99] Sayiner M, Otgonsuren M, Cable R, et al. Variables associated with inpatient and outpatient resource utilization among Medicare beneficiaries with nonalcoholic fatty liver disease with or without cirrhosis. J Clin Gastroenterol 2017;51:254–260.
[100] Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. Ann Gastroenterol 2018;31:288–295. https://doi.org/10.20524/aog.2018.0240. Epub 2018 Feb 23.
[101] Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of illness and economic model for patients with non-alcoholic steatohepatitis (NASH) in the United States. Hepatology 2018. https://doi.org/10.1002/hep.30254, [Epub ahead of print].
[102] Patient Reported Outcomes obtained from the world wide web at: https://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx, CDC 2017. Last accessed on July 16, 2018
[103] Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405–413, discussion 415–420.
[104] Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 1999;45:295–300.
[105] Younossi ZM, Stepanova M, Henry L, Racila A, Lam B, Pham HT, et al. A disease-specific quality of life instrument for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: CLDQ-NAFLD. Liver Int 2017;37:1209–1218.
[106] Chawla KS, Talwalkar JA, Keach JC, Malinchoc M, Lindor KD, Jorgensen R. Reliability and validity of the Chronic Liver Disease Questionnaire (CLDQ) in adults with non-alcoholic steatohepatitis (NASH). BMJ Open Gastroenterol 2016;3 e000069.
[107] National Institute of Mental Health. Depression. Obtained from the world wide web at: https://www.nimh.nih.gov/health/topics/depression/index.shtml.
[108] Weinstein AA, Kallman Price J, Stepanova M, Poms LW, Fang Y, Moon J, et al. Depression in patients with nonalcoholic fatty liver disease and chronic viral hepatitis B and C. Psychosomatics 2011;52:127–132. https://doi.org/10.1016/j.psym.2010.12.019.
[109] Golabi P, Otgonsuren M, Cable R, Felix S, Koenig A, Sayiner M, et al. Non-alcoholic Fatty Liver Disease (NAFLD) is associated with impairment of Health Related Quality of Life (HRQOL). Health Qual Life Outcomes 2016;9:18.
[110] Dan AA, Kallman JB, Wheeler A, Younoszai Z, Collantes R, Bondini S, et al. Health-related quality of life in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2007;26:815–820.
[111] Tapper EB, Lai M. Weight loss results in significant improvements in quality of life for patients with nonalcoholic fatty liver disease: a prospective cohort study. Hepatology 2016;63:1184–1189. https://doi.org/10.1002/hep.28416, Epub 2016 Feb 22.

[112] Younossi ZM, Stepanova M, Lawitz E, Charlton M, Loomba R, Myers RP. Improvement of hepatic fibrosis and patient-reported outcomes in non-alcoholic steatohepatitis treated with selonsertib. Liver Int 2018.
[113] Ballestri S, Nascimbeni F, Romagnoli D, Baldelli E, Targher G, Lonardo A. Type 2 diabetes in non-alcoholic fatty liver disease and hepatitis C virus infection—liver: the "musketeer" in the spotlight. Int J Mol Sci 2016;17:355.
[114] Joo EJ, Chang Y, Yeom JS, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. Hepatology 2017;65:828–835.
[115] Cheng YL, Wang YJ, Kao WY, Chen PH, Huo TI, Huang YH, et al. Inverse association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0072049. eCollection 2013 e72049.
[116] Younossi Z, Stepanova Z, Ong J, Yilmaz Y, Duseja A, Eguchi Y, et al. Non-alcoholic Fatty Liver Disease (NAFLD) and Alcoholic Fatty Liver Disease (AFLD): The Impact of Alcohol Consumption and Metabolic Syndrome on Mortality. American Association for the Study of Liver Annual Meeting 2018, San Francisco, CA.
[117] Younossi Z, Stepanova M, Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, et al. The conundrum of cryptogenic cirrhosis: adverse outcomes without treatment options. J Hepatol 2018;69:1365–1370. https://doi.org/10.1016/j.jhep.2018.08.013, pii: S0168-8278(18)32295-5 [Epub ahead of print] PubMed PMID: 30144554.
[118] Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. Ann Gastroenterol 2018;31:288–295. https://doi.org/10.20524/aog.2018.0240, Epub 2018 Feb 23.
[119] Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2018;68:361–371.
[120] Golabi P, Bush H, Younossi ZM. Treatment strategies for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Clin Liver Dis 2017;21:739–753.
[121] Younossi ZM. Patient-reported outcomes and the economic effects of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis – the value proposition. Hepatology 2018. https://doi.org/10.1002/hep.30125, [Epub ahead of print] Review. PubMed PMID: 30070714.
[122] Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67:829–846. https://doi.org/10.1016/j.jhep.2017.05.016, Epub 2017 May 23.
[123] Kamal R, Cox C, Blumenkranz E, The Kaiser Family Foundation. What do we know about social determinants of health in the U.S. and comparable countries? Chart Collections Health & Wellbeing. Posted: November 21, 2017. Accessed on 10/23/2018 at https://www.healthsystemtracker.org/chart-collection/know-social-determinants-health-u-s-comparable-countries/#item-u-s-highest-environmental-burden-disease-compared-high-income-countries.