Review

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Changing epidemiology, global trends and implications for outcomes of NAFLD

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Summary

Non-alcoholic fatty liver disease (NAFLD) has rapidly become the most common liver disease globally and is currently estimated to affect 38% of the global population. Only a minority of patients with NAFLD will progress to cirrhosis or hepatocellular carcinoma, but from this vast population the total number of patients who are at risk of such severe outcomes is increasing. Worryingly, individuals are increasingly being affected by NAFLD at an earlier age, meaning there is more time for them to develop severe complications. With considerable changes in dietary composition and urbanisation, alongside the growth in obesity and type 2 diabetes in the global population, in particular in developing countries, the global proportion of persons affected by NAFLD is projected to increase further. Yet, there are large geographical discrepancies in the prevalence rates of NAFLD and its inflammatory component non-alcoholic steatohepatitis (NASH). Such differences are partly related to differing socio-economic milieus, but also to genetic predisposition. In this narrative review, we discuss recent changes in the epidemiology of NAFLD and NASH from regional and global perspectives, as well as in special populations. We also discuss the potential consequences of these changes on hepatic and extrahepatic events.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide. According to a recent systematic review and meta-analysis, the global prevalence of NAFLD increased from 25.3% in 1990-2006 to 38.0% in 2016-2019.[1] In parallel, non-alcoholic steatohepatitis (NASH), the more active form of NAFLD characterised by the presence of hepatic steatosis, inflammation, and hepatocyte ballooning, is emerging as one of the leading causes of cirrhosis, cirrhotic complications, hepatocellular carcinoma (HCC) and liver-related death.[2] NASH is also the most rapidly rising indication for liver transplantation in the United States, and a rapidly increasing indication elsewhere.[3–5] The reasons for this increasing trend are multifactorial. Urbanisation and the resulting unhealthy eating habits and sedentary lifestyle are often blamed,[6] but rising BMI in rural areas is an important driver of the global obesity trend.[7] In addition, the prevalence of NAFLD increases with age, particularly in post-menopausal women.[8] All chronic liver diseases progress over a long period of time, meaning that severe liver disease is more common in older populations.[9,10] Against this background, with improved survival from other diseases such as cardiovascular disease and cancer, population aging will further fuel the epidemic of NAFLD, including the more severe forms with NASH and cirrhosis. Modelling studies suggest that cirrhosis, hepatic decompensation, HCC and deaths from NAFLD will increase in most countries from 2015 to 2030.[11] Additionally, an increased prevalence of obesity in younger populations suggests that many patients will be exposed to NAFLD from an earlier timepoint, and thus have a longer duration of disease. Hence, more people are likely to develop progressive fibrosis eventually resulting in cirrhosis, without first dying from competing causes such as cardiovascular disease. Obesity early in life, and thus a high risk of having NAFLD, is an independent risk factor for progression to cirrhosis and liver cancer later in life.[12–15] Indeed, NAFLD is the main driver of an increase in chronic liver disease among adolescents and young adults.[16] Another worrying observation is that children of obese mothers seem to be at a higher risk of developing NAFLD potentially of a more advanced severity.[17,18] (Table 1, Figs. 1 and 2)

Because of the close association between NAFLD and metabolic syndrome, cardiovascular disease and extrahepatic malignancies remain the leading causes of death in patients with NAFLD.[10,19,20] Although the strong link between NAFLD

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Key points:

- NAFLD is estimated to be present in around one-third of the global population.
- The prevalence is increasing in most countries, in parallel with an increase in obesity and type 2 diabetes.
- NAFLD prevalence and severity is higher in patients with metabolic risk factors, suggesting such populations might be appropriate to target for case-finding of hepatic fibrosis due to NAFLD.
- The increase in NAFLD prevalence has already affected the prevalence of cirrhosis and its complications, and roughly twice as many persons are estimated to suffer from NAFLD-related cirrhosis in 2030 compared to 2016.
- Incidence and prevalence estimates often come from studies with heterogenous designs and selected populations, hence initiatives should be undertaken to harmonise future study designs to enhance comparability.

and these systemic and extrahepatic complications is firmly established, a causal relationship remains largely elusive due to methodological challenges in separating the individual components and their severity in most study settings.[21,22] By contrast, hepatic complications are the leading causes of death in patients with NAFLD who have developed cirrhosis.[23] This highlights the importance of identifying patients with NAFLD at a high risk of having, or developing, cirrhosis – especially from a hepatologists' perspective. From a holistic point of view, it would be best to have treatments that reduce both cardiovascular and hepatic risk. Otherwise, accurate prediction of the likelihood of different competing events would guide clinicians to choose the right treatment for the right patient.

There have been numerous narrative and systematic reviews on the epidemiology of NAFLD.[1,24–28] The purpose of this narrative review is to focus on changes in the epidemiology and outcomes of NAFLD over the past few decades, both globally and in different regions. We consider both hepatic and extrahepatic outcomes and aim to provide information that could guide strategies to mitigate the impact of this challenging condition.

Changing epidemiology

Overview

The global prevalence of NAFLD has grown immensely over the last few decades, in parallel with the epidemics of obesity and type 2 diabetes.[1,25,26,29] There are, however, remarkable geographical differences in the rates of increase in the prevalence of NAFLD, as well as the severity of NAFLD, NASH, and the related complications across ethnicities because of various genetic and sociodemographic determinants. Globally, the prevalence of NAFLD has increased by more than 50% over the last three decades, from 25.3% in 1990-2006 to 38.0% in 2016-2019 according to a recent systematic review (Fig. 1).[1]

The improvement in socio-economic status in regions with low or middle sociodemographic index (SDI) is strongly linked to access to unhealthy diets.[30] NAFLD-related adverse outcomes are attributed to the overconsumption of sugar/fructose-laden foods in Latin American, independent from the increasing prevalence of obesity and type 2 diabetes, while a Mediterranean diet has been adopted as one of the interventions to prevent or treat NAFLD in some parts of the

Table 1. Global epidemiology of NAFLD and NASH.

	Ultrasound	MRI	CAP	CT	Liver biopsy
Prevalence of NAFLD (%)[1,24,26]					
Overall	30	–	–	–	–
North America	31	38	38	34	–
South America	44	–	–	–	–
Europe	25	–	–	–	–
Asia-Pacific	28	28	–	25	–
Middle East and North Africa	37	–	–	–	–
Sub-Saharan Africa	14	–	–	–	–
Incidence of NAFLD (per 1,000 person-years)[25]					
Overall	46.9	–	–	–	–
China	47.3	–	–	–	–
Hong Kong	–	34.4	–	–	–
Japan	39.5	–	–	–	–
South Korea	60.2	–	–	–	–
Israel	28.0	–	–	–	–
Prevalence of NASH (%)[1]					
North America	–	–	–	–	5.0
South America	–	–	–	–	7.1
Western Europe	–	–	–	–	4.0
Middle East and North America	–	–	–	–	5.9
South Asia	–	–	–	–	5.4
South-East Asia	–	–	–	–	5.3
East Asia	–	–	–	–	4.8
Asia-Pacific	–	–	–	–	4.5

Figures represent summary statistics from the quoted systematic reviews and, in some cases, individual studies.

CAP, controlled attenuation parameter; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

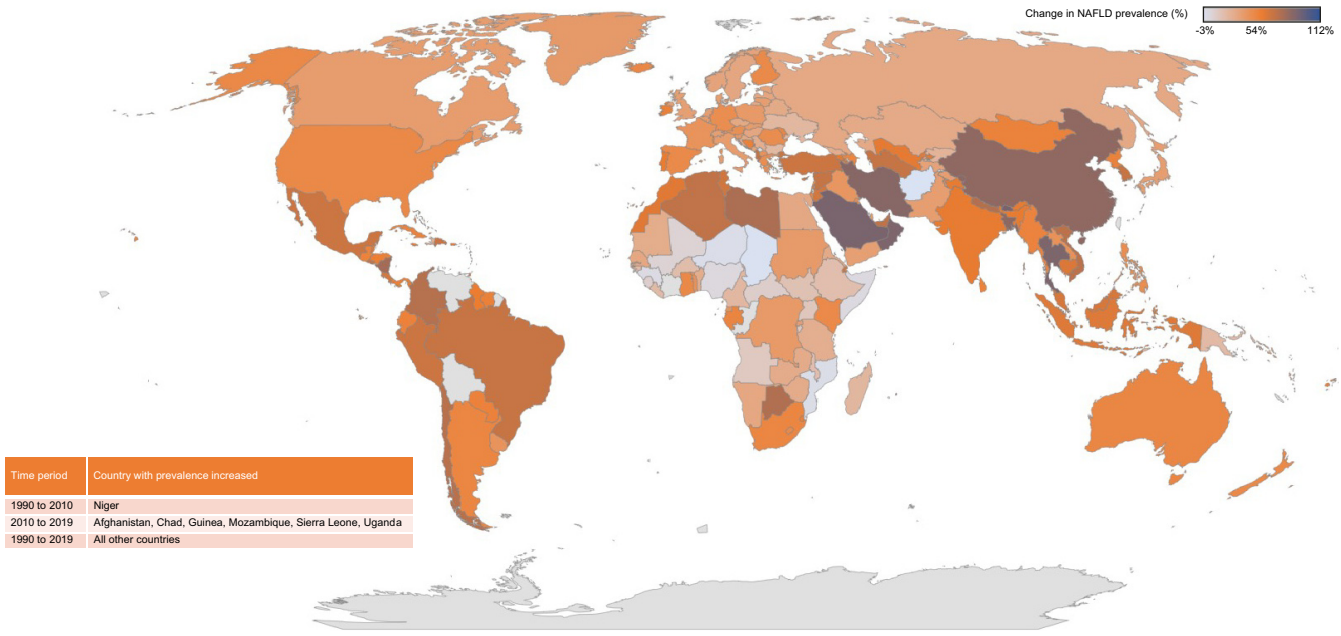

Fig. 1. Global heat-map of changing NAFLD prevalence. The prevalence of NAFLD increased from 1990 to 2019 in all countries, except Niger (decreased from 2010 to 2019), Afghanistan, Chad, Guinea, Mozambique, Sierra Leone and Uganda (decreased from 1990 to 2010). [22] NAFLD, non-alcoholic fatty liver disease.

world, like Southern Europe.[31] Ceramides, which are promoted as being good for skin care in the West, are free fatty acids and lipotoxic agents which may increase the risk of NAFLD independently of BMI and fasting glucose levels.[32] Westernised urban lifestyles may increase the number of deaths attributable to NAFLD-HCC, as the increase in age-standardised death rates for NAFLD-HCC from 2010 to 2019 was most prominent in the populations from middle SDI, followed by those from high-middle and high SDI countries [2].

It is challenging to accurately estimate the changing epidemiology of NAFLD from a global perspective, as we do not have access to high-quality data on the epidemiology of NAFLD in some parts of the world, for example most African countries. Epidemiological studies of NAFLD are often

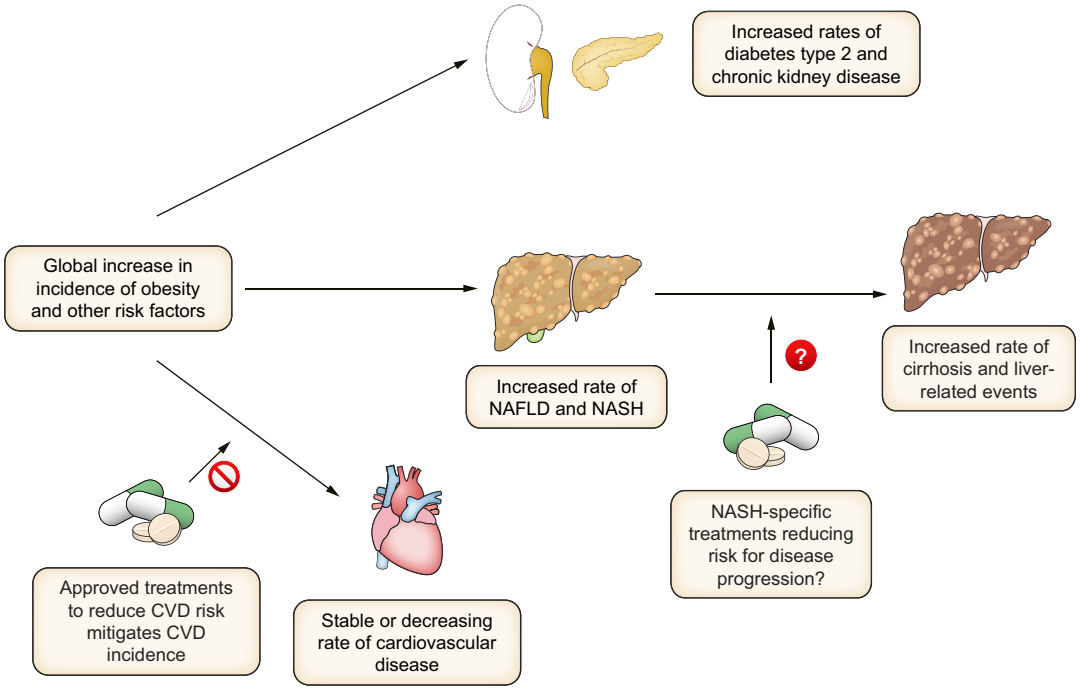

Fig. 2. Implications of an increase in the prevalence of NAFLD on clinical outcomes. NAFLD, non-alcoholic fatty liver disease.

dominated by a North American perspective. Study populations and diagnostic modalities also contribute to variations in reported prevalence rates, which range from 5% to 46%.[24] A clear goal for further research is to generate high-quality prevalence and incidence estimates for NAFLD, using similar methodologies across different countries. The varying epidemiology of NAFLD across different continents is discussed in the following sections.

Global trends

In this section, we review changing trends in NAFLD epidemiology in different geographical regions. It should be noted, however, that there is much heterogeneity among studies (Table 1). True population studies are scarce. Community studies have often adopted convenient sampling rather than random sampling, thus resulting in potential selection bias. In addition, because of differences in test performance, studies using different diagnostic modalities can yield very different results. At one extreme, studies using diagnosis codes and raised liver enzymes to define NAFLD reported the lowest prevalence rates due to undercoding and the well-recognised phenomenon of normal liver enzymes among patients with NAFLD, respectively. MRI-based quantification of hepatic steatosis can be considered the gold standard for diagnosing NAFLD, but it is expensive.[33] Studies utilising this technique inevitably have smaller sample sizes but report higher prevalence estimates.

Trends in Asia-Pacific

Several issues distinguish the Asia-Pacific region from other areas. According to the United Nations, Asia-Pacific is home to 62 countries and a population of 4.8 billion people.[34] In fact, China and India are the two most populous countries worldwide. With such a huge population, a 1% change in the prevalence of any disease would mean tens of millions of patients. Second, economic growth in Asia began several decades later than in Western countries. That shapes the secular trend of NAFLD. The number of patients with cirrhosis and HCC related to NAFLD is expected to peak much later.[35] Third, there is much diversity in genetic background, economic background, healthcare coverage, diet and physical activity levels in people from the Asia-Pacific region.[36] For example, the at-risk G allele of the *PNPLA3* gene is more common in East Asian than South Asian, non-Hispanic White and Black individuals.[24] This may explain the high prevalence of NAFLD in East Asia despite a relatively healthy metabolic profile. Westernisation of dietary habits and lack of physical activity are often mentioned as key drivers of the NAFLD pandemic in this region, though regional differences are substantial.[6] In any case, the urban-rural divide in metabolic disorders including NAFLD has been decreasing rapidly in the past two decades;[37,38] compared with the contribution of urbanisation (0-11%), changes in BMI in rural areas have contributed more to the rise in BMI in the past 30 years (Central Asia, Middle East and North Africa: 48% in men and 59% in women; East and Southeast Asia: 67% in men and 73% in women; Oceania: 90% in men and 81% in women; South Asia: 86% in men and 80% in women, respectively).[39]

According to a recent systematic review and meta-analysis by Younossi and colleagues, the pooled prevalence of NAFLD in 1990-2019 was 33.8% in South Asia, 33.1% in Southeast Asia, 29.7% in East Asia, and 28.0% in Oceania.[1] Taking the population size into consideration, these prevalence estimates translate into 375 million prevalent cases of NAFLD in East Asia, 325 million in South Asia, 109 million in Southeast Asia, and 46 million in Oceania.[1] While estimates for NASH are limited by the need for histology, the prevalence of NASH was 5.4% in South Asia, 5.3% in Southeast Asia, 4.8% in East Asia and 4.5% in Oceania.[1] Another systematic review and meta-analysis by Li and colleagues yielded a similar pooled prevalence of NAFLD of 29.6% in Asia.[40] The prevalence increased from 25.3% in 1999-2005, to 28.5% in 2006-2011 and then to 33.9% in 2012-2017. The pooled incidence of NAFLD was 50.9 cases per 1,000 person-years. Among patients with NAFLD, the annual incidence of HCC was 1.8 cases per 1,000 person-years.

In China, the prevalence of NAFLD increased from 25.4% in 2008-2010, to 26.1% in 2011-2014, and then to 32.3% in 2015-2018.[37] NAFLD was more common in males and the prevalence peaked at 50-69 years of age. There were considerable regional differences in NAFLD prevalence, ranging from 19.3% in Southwest China to 33.8% in the Northwest. A U-shaped relationship between income and NAFLD prevalence was observed – the prevalence was the lowest in regions with a per capita gross domestic product of 70,000-80,000 yuan (24.2%), and highest in regions with a per capita gross domestic product <50,000 yuan (29.7%) and >100,000 yuan (32.1%). In Japan, the pooled NAFLD prevalence was 25.5% and had been increasing by 0.64% per year from 1983 to 2012, being 29.61% in the 2011–2016 period.[41]

Because Asians tend to develop NAFLD and other metabolic complications at a lower BMI, most studies on lean or non-obese NAFLD come from this region, though available data suggest that lean NAFLD is by no means rare in the West.[36,42,43] By region, the prevalence of NAFLD among non-obese individuals was 11.7% in East Asia and 10.0% in South Asia.[38] Among patients with NAFLD, the proportion who were non-obese was 37.8% in East Asia, 40.9% in South Asia, 12.9% in Southeast Asia and 52.9% in West Asia.

Childhood obesity is also emerging in the Asia-Pacific region. The pooled prevalence of NAFLD was 5.4% in Asian children and 7.3% in adolescents.[44] NAFLD was more common in males and increased with BMI. The prevalence was 4.4% in 2002-2010 and 7.1% in 2010-2020.

Apart from rapid changes in the prevalence and incidence of NAFLD during the past two to three decades, changes in the epidemiology of other chronic liver diseases also have a major impact on the relative importance of NAFLD. In particular, the prevalence of chronic hepatitis B has been decreasing in the Asia-Pacific region through universal birth dose vaccination and perinatal antiviral prophylaxis.[45] From 1990 to 2019, the prevalence of chronic hepatitis B has decreased from 4.8% to 3.2% in Central Asia, 3.6% to 2.8% in South Asia, 11.9% to 9.2% in East Asia, 7.1% to 4.4% in Southeast Asia, and 9.3% to 4.9% in Oceania.[46] Meanwhile, concomitant chronic hepatitis B and fatty liver is associated with an increased risk of cirrhosis and HCC.[47]

The biggest increase in alcohol consumption from 1990 to 2017 was observed in lower-middle income countries, including many countries in the Asia-Pacific region.[48] During this period, per capita alcohol consumption increased by 104% in Southeast Asia and 54% in the Western Pacific region. Data

on the effect of modest to moderate alcohol consumption on NAFLD in this region are limited, though studies elsewhere suggest accelerated disease progression in patients with dual aetiologies.[49,50]

Trends in Europe

As elsewhere, the prevalence and incidence of NAFLD in Europe is closely associated with the change in underlying risk factors, most importantly overweight, obesity and type 2 diabetes. Such conditions are heterogenous within and between countries, and the incidence and prevalence of NAFLD depends on the prevalence of such risk factors in a population. According to EuroStat, the mean proportion of overweight adults in the EU was 53% in 2019, but varied between 37% in Italy and 58% in Croatia for women, and between 53% in France and 73% in Croatia for men[51]. Similarly, about 32.3 million adults were diagnosed with diabetes in the EU in 2019, an increase from an estimated 16.8 million adults in 2000.[52] Several meta-analyses have estimated the prevalence of NAFLD in Europe to figures between 23.7%[26] and 26.9%.[53] This appears to have increased to 30.9% in a more recent meta-analysis with data updated until 2019.[28] Nonetheless, the prevalence rates for NAFLD reported in individual studies are highly heterogeneous, ranging between 5% and 48%, which can be attributed to differences in period of observation, country and ethnicity, inclusion setting, various characteristics of the studied population, and diagnostic approaches for hepatic steatosis.[24]

For single studies, prevalence estimates depend highly on the mode of diagnosis and the examined population. A study from the Rotterdam cohort found a NAFLD prevalence of 35% when defining NAFLD by abdominal ultrasound.[54] A study from the UK biobank reported a prevalence of hepatic steatosis of 19.9% when using MRI.[55] By contrast, when using increased alanine aminotransferase levels as the definition of NAFLD, a prevalence of only 4.7% was reported from Norway, despite more than 50% of the sampled population being overweight or obese.[56] Similarly, a large cross-sectional study based on administrative ICD codes found that a formal diagnosis of NAFLD is only made in around 2% of patients in a primary care setting.[57]

Incidence data on NAFLD and NASH from Europe are scarce. A recent meta-analysis on the topic found no studies investigating the incidence of NAFLD from Europe.[1] An unpublished Swedish report based on ICD codes found an annual increase of 8.0% in the incidence of diagnosed NAFLD between 2005 and 2019, reaching an incidence rate of 15.2/100,000 person-years in 2019.[58] It is likely that increased awareness of NAFLD among clinicians contributed to this steep increase, but the increase in the underlying risk factors suggests a true increase in the incidence and prevalence of NAFLD.

The prevalence of NASH can only be estimated on a population level since unbiased general population studies using liver biopsy are impractical. A recent meta-analysis suggested the prevalence of NASH in Europe to be 4.0%.[26] This figure is certainly different depending on the underlying population. For instance, in patients undergoing bariatric surgery where a liver biopsy was performed, the prevalence of NASH is between 63-78%.[59] In the paediatric population, a meta-analysis estimated the prevalence of NAFLD to be 2.7% in unselected and 31.6% in obese/overweight children/adolescents.[53]

Trends in Americas

The US was one of the first countries to have a severe obesity epidemic. Already in 1980, the number of overweight individuals exceeded 40%. Since then, the proportion of persons who are overweight or obese has grown substantially. The proportion of obese individuals between 1980 and 2015 increased from 10.7% to 30.7%.[60] The total proportion of overweight or obese individuals in the US was 73.6% in 2017-18 according to data from the Centers for Disease Control and Prevention.[51] Furthermore, between 1999-2000 and 2013-2014 the prevalence of central obesity in the National Health and Nutrition Examination Surveys (NHANES) studies increased from 45.2% to 56.7%.[61] In Canada, there was only a modest increase in the proportion of overweight individuals between 1999-2000 and 2013-2014 (41.6% to 42.7%), though this was from a high starting level.[60] Given the strong association between obesity and NAFLD, it is reasonable to extrapolate that changes in NAFLD will mirror changes in obesity.

Even more alarming than the high number of obese individuals in adults is the steady increase of obesity among children and adolescents. In a recent survey, almost 20% of American children (age 2–19 years) were obese,[62] and at least a quarter of these children will also have NAFLD.[63] Data from Southern California using public health records showed a 62%increase in NAFLD incidence in children between 2009 and 2018 (36.0 per 100,000 to 58.2 per 100,000, respectively).[64]

NAFLD prevalence estimates in North America mostly come from studies in the US; in 2016, the pooled prevalence was 24%,[26] which had increased to 31.2% (including Australia) in the meta-analysis.[26] A series of studies from the NHANES, which represent the general US population, illustrate a steady increase in NAFLD prevalence over the last three decades: 19% in 1988-1994, 32% in 1999-2016, and 54% in 2005-2016.[24] The increasing NAFLD prevalence might have been partly attributable to the different diagnostic tools used: ultrasonography in the earliest years and serum-based formulae in more recent years. In the recent NHANES 2017-2018 cycle, the prevalence of NAFLD was estimated to be 57% and 38% using controlled attenuation parameter scores of ≥248 dB/m and ≥285 dB/m, respectively, on vibration-controlled transient elastography.[24]

The rapid increase in obesity is a global phenomenon and the situation is not different in South America. There is a general trend that the rates of increase are highest in low to low-middle income countries, probably since the number of individuals that are not yet obese is greater. For instance, between 1980 and 2015, the number of overweight individuals increased in Argentina (42.0% to 43.5%), Bolivia (25.3% to 36.5%), Chile (41.4% to 47.3%), Colombia (17.8% to 36.7%), Guatemala (19.8% to 33.6%), and Venezuela (20.0% to 39.6%).[60] Nowhere can a decrease in obesity be seen.

It is well-recognised that NAFLD disproportionately affects Latin Americans in the US; yet there are scant data about NAFLD prevalence in South America. Previous studies have reported a prevalence of 35.2% in Brazil, 23% in Chile, 17% in

Mexico, and 26.6% in Colombia.[65] The latest systematic review reported that the highest NAFLD prevalence rate was observed in Latin America (44.4%).[66] Studies in individual countries (*e.g.* Brazil, Chile), districts or populations in South America reported NAFLD prevalence estimates ranging from 19.2% to 35.2% in the community, and 24% in a hospital cohort.[24]

Trends in Africa and the Middle East

Incidence and prevalence data on NAFLD from sub-Saharan Africa are largely missing and are thus a topic for future studies. A recent meta-analysis investigating NAFLD prevalence found no studies from the sub-Saharan region.[26] Nevertheless, it can be assumed that the burden of NAFLD and NASH will increase in Africa in the coming decades. The prevalence of diabetes was estimated to be at least 4.7% in 2019 and is expected to increase to at least 5.2% in 2045.[67] While some primary data sources are available, most have limitations. In a study from Sudan, researchers used ultrasound in relatives of patients admitted to a gastroenterology ward and found a prevalence of hepatic steatosis of 20%.[68] The role of genetics, with a lower prevalence of the G risk allele of the *PNPLA3* gene in persons of African heritage is well known;[69] indeed, a study from South Africa has shown that liver steatosis is less common in African women compared to women of Indian heritage.[70] As elsewhere, the prevalence of NASH is difficult to estimate on a population level given the risk for selection bias. One study found that in patients with NAFLD from South Africa who underwent liver biopsy, 36% had NASH and 17% had advanced fibrosis.[71]

By contrast, there is more epidemiological data from the Middle East and North Africa (MENA) region. Worryingly, the rate of increase in obesity has been faster in the MENA region compared to the global average.[72] The prevalence of diabetes was approximately 10.8% in 2017, the highest figure globally.[72] A recent meta-analysis suggested a high prevalence of NAFLD at 36.5% in the MENA region.[26] A few examples from specific countries, with varying methodologies, reported prevalence estimates of 33.3% in Kuwait, and 33.9% in Iran.[73]

The scant available data suggest the prevalence of NAFLD in the general population is comparatively lower in Africa than globally, but the prevalence in individuals with type 2 diabetes is similar to that reported by other countries. With a general increase of wealth and gradual adoption of a sedentary lifestyle, the incidence and prevalence of NAFLD in sub-Saharan Africa is likely to continue to increase. Meanwhile, the very high prevalence of NAFLD in the MENA countries serves as an example of what a rapid increase in obesity is likely to lead to on a population level.

NAFLD in special populations

The prevalence and severity of NAFLD is considerably higher in certain populations. Among patients with type 2 diabetes, the prevalence of NAFLD is around 56%, with an estimated prevalence of NASH of 37%.[74] The risk of developing cirrhosis and HCC is also around twice as high in those with type 2 diabetes compared to non-diabetic populations.[75,76] This increased prevalence and risk is now acknowledged in international guidelines with recommendations to actively investigate the presence and severity of NAFLD in those with type 2 diabetes.[77] Similarly, the prevalence of NAFLD is significantly higher in populations with traits of the metabolic syndrome, such as overweight/obesity where more than 70% may have NAFLD, and 7% may have advanced fibrosis.[78] In polycystic ovarian syndrome, the prevalence of NAFLD is also considerable at around 43%.[79] Similar figures are seen for patients with other diseases related to the metabolic syndrome, with the common theme being a high prevalence of obesity and insulin resistance. Other populations at an increased risk of developing NAFLD are people living with HIV, in whom 22-42% may have NAFLD.[80] Finally, there seems to be an interaction between alcohol consumption and NAFLD, where patients at risk for both conditions have higher stages of fibrosis at presentation, and worse prognosis.[50,81–83]

Implications for outcomes

The number of liver-related complications, namely cirrhosis, HCC, hepatic decompensation and liver-related death, attributable to NAFLD has been increasing worldwide. Amidst the global epidemics of obesity and diabetes, a parallel increase in the epidemic of NAFLD-related complications has been observed. While pharmacotherapies are available to reduce the complications of cardiovascular and other diseases also releated to obesity and diabetes, it will remain to be seen if future approved therapies for NAFLD and NASH will reduce the numbers of liver-related outcomes (Fig. 2). The burden of complications related to NAFLD and NASH might be easier to estimate given the inherent problems of accurately studying NAFLD and NASH. An analysis of the global incidence trends in primary liver cancer, including HCC, between 1990 and 2017 found that, in most parts of the world, the incidence of primary liver cancer due to NASH was increasing, especially in older age groups. This is important since life expectancy is steadily increasing,[84] and proportionally more cases of cirrhosis and primary liver cancer are likely to be attributed to NASH in the coming years.

A parallel problem is that the prognosis of NAFLD, in particular liver-related outcomes, are highly dependent on the stage of liver fibrosis.[19,85–87] Therefore, methods to measure or preferably indirectly estimate the severity of liver fibrosis are essential to predicting the risk of liver-related outcomes. Such methods today mainly rely on different forms of transient elastography or expensive patented serum tests.[88,89] Scaling up such methodologies to expanded use in primary care or developing new methods or biomarkers to estimate the severity of liver fibrosis, and hence prognosis, is a key area for ongoing research efforts.

Cirrhosis and its complications

The true burden of NAFLD-related cirrhosis and its complications has traditionally been underestimated, as NAFLD-related cirrhosis is often labelled as “cryptogenic cirrhosis” and “other cirrhosis”, which are often burned-out NASH in reality.[90] A crude estimation of the presence of advanced fibrosis (stage 3-4 on liver biopsy) can be made using the FIB-4 score.[91] By this definition, prevalence can be estimated in larger populations, with contemporary estimates of 1.0% in Germany,[92] 1.7% in the US,[93] and 2.2% in the UK,[94] for example. Differences in study populations and exclusion criteria are likely to influence these estimates. Future studies with similar methodologies and

random sampling should be performed to determine longitudinal trends and enable geographical comparisons.

NAFLD-related cirrhosis and its complications accounted for only 0.8% of all hospitalisations in 2005; this rate more than tripled to 2.8% in 2018 in Germany, with ascites being the most common complication of cirrhosis.[95] Data from the Global Burden of Disease 2009-2019 revealed an increase from 2009 to 2019 in incident liver complications related to NAFLD from 1.78 to 2.51 per 100,000 population globally, and an increase in MENA from 1.88 to 2.23 per 100,000 population.[96] MENA together with Asia regions accounted for nearly half of the global burden of NAFLD-related liver complications.[96] Modelling studies have estimated that both compensated and decompensated cirrhosis related to NAFLD will double in most countries between 2016 and 2030, with an increase ranging from +64% in Japan to +156% in France.[11,35]

Hepatocellular carcinoma

The global epidemiology of HCC is shifting away from a disease predominated by chronic viral hepatitis, with an increasing share of new cases now attributable to NAFLD.[97] It is challenging to estimate the changing epidemiology of NAFLD-HCC because of the heterogeneous definitions for NAFLD, differential proportions of patients with metabolic syndrome and referral bias; the impact of NAFLD on the epidemiology of HCC is thus likely to be underestimated.[97]

The increasing importance of NAFLD as the underlying aetiology of HCC was first supported by a small single-centre study in the UK, in which NAFLD had caused none of the HCC cases in 2000-2002 but nearly one-third of HCC cases in 2010.[98] NAFLD has increasingly been identified as the cause of HCC, accounting for 0-3% of cases in the 1990s to 12-29% in the 2010s in other European studies.[99,100] According to the trajectories in Italy, fatty liver disease will already be the top aetiology of HCC in 2023.[101]

The aetiologies of HCC in Asia are also undergoing a change from viral to non-viral causes – predominantly NAFLD.[102] Non-viral HCC accounted for 10.0% of HCC cases in the early 1990s compared to 32.5% in the mid 2010s in Japan.[103] More specifically, the proportion of HCC cases attributable to NAFLD has tripled from 3.8% in 2001-2005 to 12.2% in 2006-2010 in Korea.[104] The trajectories in Asia demonstrate notable increases of 86% and 82% in prevalent and incident HCC cases in China, respectively, through year 2016-2030; whereas projected incident HCC cases will increase by 65%, 80%, 80%, and 85% in Hong Kong, Singapore, South Korea, and Taiwan, respectively.[35]

In a recent report from six countries in South America, NAFLD is now the most common aetiology of liver disease in HCC cases.[105] The proportion of HCC cases attributable to NAFLD increased from 9% to 37% in little more than a decade. The increased proportion of NAFLD-related HCC is partly due to the decrease in HCV-HCC cases, but there is no doubt that NAFLD is making its mark on liver-related outcomes in North and South America, with the largest increase in cases likely to be seen in South America.

Liver transplantation and liver-related death

The global shift from viral hepatitis towards fatty liver disease as the major driver of chronic liver disease is clearly demonstrated in the setting of liver transplantation. In the US, NAFLD is today the most common indication for liver transplantation in women and the elderly and is the most rapidly rising aetiology overall.[106,107] In the European Liver Transplantation Registry, NAFLD-related cirrhosis represented up to 8.4% of liver transplantations for cirrhosis in 2016.[108] The growing relevance of NAFLD in the transplant setting is a global phenomenon,[109–111] and is a clear link between the increasing prevalence of obesity and its impact on NAFLD. A growing concern in the transplant setting is the increasing number of cases of post-transplant NAFLD recurrence.[112]

Mortality due to cirrhosis has increased in the US. In younger age groups this is mainly attributed to increased alcohol consumption, but in the middle aged and the elderly this is mostly due to NAFLD.[113] The number of liver-related deaths in the US is expected to increase by 178% to an estimated 78,300 deaths in 2030.[11] A challenge when interpreting registry data is the difficulty in differentiating between alcohol-related and non-alcohol-related aetiologies. The amount of liver fibrosis is the strongest predictor of liver-related events and mortality.[114] There is a risk that the projections for the future overestimate the coming numbers of liver-related events since most predictions are based on hospital series in which the percentage of individuals with significant or advanced fibrosis is higher. In studies from the general population or primary care, the number of patients with fibrosis is lower. But, even if only a minority of patients go on to develop liver-related complications, due to the vast number of patients, NAFLD will be a significant issue for the healthcare system in the future.[115,116]

Extrahepatic outcomes

It is well known that NAFLD is associated with a higher risk of developing cardiovascular outcomes.[22,117–119] Indeed, the most common cause of death in patients with NAFLD is cardiovascular disease.[19] Evidence suggests that with increasing stages of fibrosis, liver-related causes of death in NAFLD gradually become more common.[23] Patients with NAFLD are also at a higher risk of presenting with, or developing, several obesity-related comorbidities such as type 2 diabetes, obstructive sleep apnoea, polycystic ovarian syndrome, and several non-hepatic malignancies.[120–125] It is methodologically challenging to tease out the individual effect of NAFLD on the risk of such comorbidities on top of other components of the metabolic syndrome. The increasing prevalence of NAFLD nevertheless suggests that such comorbidities will also become more common in the future.

Conclusions

Existing data firmly demonstrate that NAFLD is not only a common but also a rapidly growing disease. Growth in its incidence and prevalence are also being seen in younger populations, who are being exposed earlier to the primary risk factors for NAFLD (obesity and insulin resistance). Because chronic liver disease takes time to progress, any rise in the NAFLD prevalence will be paralleled by an increase in cirrhosis, cirrhotic complications, and HCC one to two decades later. Despite regional differences, the healthcare burden is and will be tremendous, and the importance of prevention, case identification, clinical care pathways and

effective treatments cannot be overemphasised.[126] Unfortunately, a recent survey in 102 countries indicated that no country has a national or subnational strategy for NAFLD.[29] NAFLD is not even listed among the non-communicable diseases on the World Health Organisation agenda. For a long time, NAFLD research has been largely liver-centric, attracting relatively little attention from outside the hepatology field, as exemplified by the number of research articles published in gastroenterology and hepatology journals *vs*. general medical and endocrinology journals, and the number of NAFLD presentations at liver meetings *vs.* elsewhere. However, given that primary care physicians and colleagues from other medical disciplines are seeing the vast majority of patients with NAFLD, communication and collaboration across disciplines is of paramount importance,[127] as are the development and implementation of simple-to-follow models of care that can be used to direct which patients will need specialist evaluation, or treatment.[128] There are currently no widely approved pharmacological treatments available to treat patients with fibrosis due to NAFLD, although this is expected to change within the coming years.[129] It then remains to be seen if the introduction of such therapies can stem the expected tide of hepatic complications due to NAFLD. Nevertheless, as a community, we should engage patients, the public and policymakers to develop and apply strategies to combat this growing epidemic.

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Abbreviations

HCC, hepatocellular carcinoma; MENA, Middle East and North Africa; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Surveys; SDI, sociodemographic index.

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Conflict of interest

Vincent Wong served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, and TARGET PharmaSolutions; and a speaker for Abbott, AbbVie, Gilead Sciences, and Novo Nordisk. He has received a grant from Gilead Sciences for fatty liver research and is a co-founder of Illuminatio Medical Technology Limited. Grace Wong has served as an advisory committee member for Gilead Sciences and Janssen; and a speaker for Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen and Roche. She has also received research grants from Gilead Sciences. Hannes Hagström's institutions have received research grants from Astra Zeneca, EchoSens, Gilead, Intercept, MSD and Pfizer. Hagström further reports consulting for Astra Zeneca and being part of a hepatic events adjudication committee for KOWA and GW Pharma.

Authors' contributions

All authors contributed to the conception, literature review and drafting and critical revision of this review article. They all approved the final version of this manuscript.

Supplementary data

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