**Global Perspectives on Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis**

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## Abstract

Over the past 2 decades, nonalcoholic fatty liver disease (NAFLD) has grown from a relatively unknown disease to the most common cause of CLD in the world. In fact, 25% of the world's population is currently thought to have NAFLD. Non-alcoholic steatohepatitis (NASH) is the subtype of NAFLD that can progress to cirrhosis, hepatocellular carcinoma,

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and death. NAFLD and NASH are found in not only adults—there is a high prevalence in children and adolescents. Due to NAFLD's close association with type 2 diabetes (T2DM)

and obesity, the latest models predict the prevalence of NAFLD and NASH will increase, causing a tremendous clinical and economic burden and poor patient-reported outcomes. Nonetheless, there is no accurate non-invasive method to detect NASH and treatment is limited to life style modifications. To examine the state of NAFLD among different regions and understand the global trajectory of this disease, an international group of experts came together during 2017 AASLD Global NAFLD Forum. We provide a summary of this forum and an assessment of the current state of NAFLD and NASH worldwide.

## Introduction

Over the past three decades, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have gone from obscure liver diseases with histologic features similar to alcoholic liver disease to the most prominent cause of CLD worldwide (1,2). In fact, after its first description, there was initial skepticism that NASH was a real liver disease (3). In the 1990s, it became evident that NASH was part of the NAFLD spectrum, but with specific histopathology and potential for progression (4).

Over the next decade, it became increasingly clear that NASH is the hepatic manifestation of metabolic syndrome and is highly prevalent in obese and diabetic subjects (5). Additionally, the increasing number of components of metabolic syndrome appear to increase the risk of progression to NASH (6,7). In contrast to NAFLD from Western countries, data from Asia indicate that a proportion of patients with NASH, especially from the rural regions, do not meet the criteria for obesity and have “lean NAFLD” (8).

In 2018, it is estimated that about 25% of the world population has NAFLD (9) **(Figure 1)**. Several studies investigated progression of NAFLD and its subtypes (4, 10-19). Although most studies have concluded that NASH is the progressive form, recent data indicate that a small subset of NAFLD without histologic features of NASH can develop progressive liver

disease (11). NASH is already considered among the top etiologies for hepatocellular carcinoma (HCC) and indications for liver transplantation (LT) in the United States (U.S.) (1,20-21).

Progression of NASH does not seem to be linear or simple—patients seem to have spontaneous progression and regression of liver disease over a long period of time (11). Although factors related to metabolic syndrome, especially presence of T2DM, seem to promote progression (3, 6), factors independently associated with spontaneous regression of NASH and NASH-related fibrosis are not fully described. However, the most current data indicate a tight association between increasing prevalence of T2DM and progressive NASH. In fact, given the increasing global epidemic of obesity and T2DM, a recent model has estimated a 178% increase in liver deaths related to NASH by 2030 (13).

In addition to liver-related mortality and morbidity, NAFLD and NASH are associated with several extrahepatic manifestations, adding to the burden of disease (Figure 2) (16). As our clinical and epidemiologic understanding increases, clinical burden of NAFLD and NASH related to its prevalence, incidence, and progressiveness must be coupled with its tremendous economic burden, and its negative effects on patient-reported outcomes (PROs) (14). Currently, there is no approved drug regimen to treat NASH (17). As a consequence of the lack of treatment and the growing global epidemic of obesity, the prevalence of NAFLD is likely to increase, creating a serious health crisis in the next few decades. Given this global burden, we summarize the data on NAFLD and NASH from different global regions.

**Prevalence in the Americas**

The prevalence of NAFLD in the general population of North America has been estimated to be approximately 24% (9, 18). In contrast, the prevalence of NAFLD in South America is

32% (9). The prevalence of NAFLD varies among countries in Central and South America, depending on the prevalence of obesity. The lowest prevalence of NAFLD in this region has been reported from Peru (12.5%) with only 15% of the population being obese, while the highest prevalence is reported from Belize at 29% with 35% being obese (9).

In addition to obesity, other factors may contribute to the prevalence and outcomes of NAFLD such as genetic factors, including those associated with Native American and Hispanic heritage. (1-8) A study that compared NAFLD in Hispanics of Mexican origin vs those of Caribbean origin (Dominican Republic and Puerto Rican) reported that Hispanics of Mexican origin had a higher prevalence of NAFLD (33%) than Hispanics of Dominican origin (16%) or Puerto Rican origin (18%), ($P$<.01). After controlling for age, sex, body mass index (BMI), waist circumference, hypertension, serum level of high-density lipoprotein, levels of triglyceride and C-reactive protein, and insulin resistance, Hispanics of Mexicans remained more likely to have NAFLD than those of Dominican or Puerto Rican origin (23). A high prevalence of a polymorphism in the gene encoding patatin-like phospholipase domain-containing 3 (*PNPLA3*; rs738409 C/G, M148I) in Hispanics has been proposed to contribute to the high prevalence of NAFLD (1). Nonetheless, given the increasing trends of obesity, T2DM, and the pediatric NAFLD in the Latin America, it is expected that the NAFLD-associated liver disease burden will increase significantly.

Because of histologic requirements, we do not have accurate data on the prevalence of NASH. In the general US population, the prevalence of NASH is estimated between 1.5% to 6.45% (9). Although there are substantial efforts in the U.S. to understand NASH, its biomarkers and drug treatment, a great number of challenges remains. Some of the efforts are undertaken by AASLD, FDA, NIH, Liver Forum and chronic liver disease foundations to address end points and biomarkers in NASH. Nevertheless, the most important challenge in

the U.S. is developing a national policy to address the epidemic of obesity, the main culprit that fuels the growing burden of NAFLD.

**Prevalence in Europe**

The prevalence of NAFLD has been estimated at 20%–30% in the European Union, with approximately 3% having NASH. (9) NAFLD prevalence rates varies from different European countries. A population-based study from the North-Eastern rural part of Germany determined the prevalence of fatty liver by ultrasound to be 29.9%. Only15.9% of these patients had increased levels of serum alanine aminotransferase, supporting the concept that prevalence of NAFLD can vary with diagnostic methods (22). Similar rates have been described in the general population of Northern Italy with 25% having NAFLD by ultrasound (23). Again, 5.9% to 54% of NAFLD had increased alanine aminotransferase (24). In addition, similar rates have been reported from Spain (25.8%) (25) and UK (26.4%) (26).

In Eastern Europe, the prevalence of NAFLD by ultrasound was 22.6% in Hungary (27) and 20% in Romania (28). Similar to other regions, prevalence of NAFLD in Europe increases with BMI, 25% (BMI<25kg/m2), 67% (BMI 25–30 kg/m2) and 91% (BMI ≥30 kg/m2). (29) Similarly, risk factors for NAFLD (obesity or T2DM) are increasing in Europe, fueling its complications of cirrhosis and HCC (30-36).

In Europe, the most urgent challenge is to establish a set of biomarkers that, singly or in combination, can enable the detection and monitoring of disease progression or regression in NASH. The “Liver Investigation: Testing Marker Utility in Steatohepatitis” (LITMUS) project has been funded and brings together clinicians and scientists from academic centers across Europe and the European Federation of Pharmaceutical Industries and Associations (EFPIA) to deal with this challenge. The common goal of this group is to develop validate

and qualify biomarkers for NAFLD, NASH and related fibrosis. In this context, LITMUS will specifically seek biomarkers that (i) separate cases with non-NASH NAFLD from NASH; (ii) track disease progression and/or monitor response to treatment; and (iii) predict those at greatest risk of future progression to NASH, advanced liver fibrosis or liver-related morbidity. It is expected that the LITMUS project can make important contribution the field of NAFLD.

**Prevalence in Asia**

The NAFLD prevalence in Asia ranges from 15% to 40%, while NASH ranges from 2% to 3% (37,38). In this context, prevalence of NAFLD in India increased from 28% in 2015 to 31% in 2016 and is estimated to be 30.7% in the rural region of Haryana (39). The reported prevalence of fatty liver has also increased in many regions of China (40) increased from 3.87% in 1995 to 14.04% in 2002, 17.3% in 2005, and 43.65% in 2015 among Shanghai adults (4145). Additionally, about 5.0% of 7229 school children from the Yangtze River delta region in

China had NAFLD (7.5% in boys, 2.5% in girls, 5.6% in subjects with peripheral obesity, 12.9% in those with abdominal obesity and 44.8% in those with mixed obesity) (47).

Furthermore, prevalence of NAFLD from Korea and Taiwan ranges from 24% to 40% and 15% to 27%, respectively (9). In contrast, lower prevalence rates of 9% to 18% have been reported from Japan (9).

Similar to the other regions of the world, accurate data on the prevalence of NASH from Asia is lacking. Nevertheless, it is estimated that NASH affects 1.9% to 2.2% of general population in Shanghai, China (46).

It is interesting that lean NAFLD seems to be more common in Asian countries than in

Western countries **(Figure 3).** There are differences in the profiles of Western vs Asian NAFLD (48), and a gradient of lean to obese NAFLD is observed in Asian countries. It appears that the rural areas in Asian countries have a lower prevalence of NAFLD while the profile is more consistent with lean NAFLD, whereas in urban areas of Asia NAFLD prevalence and risk profiles are similar to Western countries. (49) Although 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, the clinical events and rates of advanced fibrosis are similar between lean and obese patients with NAFLD (49). Interestingly, *PNPLA3*rs738409 GG genotype is more common in Asian NAFLD patients without metabolic syndrome [50]. Since Asians are more likely to harbor the GG genotype than Caucasians, this may explain why the two populations have similar prevalence of NAFLD even though Asians lower metabolic burden. Finally, similar to the West, the extrahepatic manifestations of NAFLD in Asia include complications of the cardiovascular, gastrointestinal, and renal systems (37).

Because Asia is a vast continent with much heterogeneity in genetic background, lifestyle and economic status, it is important to study and compare the epidemiology and natural history of NAFLD across different Asian countries. To this end, The Gut and Obesity Asia (GO ASIA) Workgroup has been established to serve as a platform for NAFLD researchers in Asia to collaborate, expand the knowledge and understanding of NAFLD and NASH by collecting real-world data from representative countries [51].

**Prevalence in the Middle East and Turkey:**

The prevalence of adult NAFLD in Middle Eastern countries has not been systematically investigated. A recent meta-analysis suggested that the prevalence of NAFLD in the Middle East is 31.79% (9). Additionally, data from Iran suggest that 33.9% of population have NAFLD (52).

In addition to these meta-analyses, a cross-sectional population-based study from Israel (N=352) suggest a prevalence of 30% for NAFLD detected by ultrasound and several components of the metabolic syndrome were the main risk factors (53). Another crosssectional study from the central part of Iran (n=483) reported 39.3% prevalence of NAFLD (54). These rates are significantly higher than the 15.3% reported from the rural Fars province of Iran (55).

In addition to data from Israel and Iran, there is also growing evidence about the increase of NAFLD prevalence in Turkey. Until recently, the prevalence of NAFLD in Turkey has been reported from single-center, small-sized studies (56-58), reporting prevalence rates of 19.8% (56), 23.2% (57), and 10.6% (58). These low rates may be explained by the fact that these studies were conducted either in rural parts of the country (56) or in young individuals (57,58). In a recent unpublished epidemiological survey conducted in 113,239 apparently healthy subjects, the overall prevalence of NAFLD in Turkey was 48.3%. The prevalence was higher in those older than 50 (65.6%), males (64.0%), and in those with BMI>25 $kg/m^2$ (63.5%). There are also geographical differences with the Central and Eastern Anatolia regions showing the highest prevalence of NAFLD (57.1% and 55.7%). Importantly, the prevalence of NAFLD in the region has increased by 22% from 43.5% (2007) to 53.1% (2016) (*YY 2018*.) These findings indicate a rapidly increasing prevalence of NAFLD related to the epidemic of obesity and T2DM in these regions. It is noteworthy that in a hospitalbased study, the prevalence of lean NAFLD in Turkey was 7.6% (59) while an autopsy-based study of 330 children and adolescents suggested a prevalence of 6% with higher rates in overweight than in normal-weight subjects (10.6% *versus* 4.9%) (59, 60)

Despite these emerging data from Israel, Turkey and Iran, there is a significant paucity of data from the rest of the Middle East. Nonetheless, it is important to note that the rates of

obesity and T2DM in the region are rapidly increasing which could certainly fuel the burden of NAFLD. Similar to the other reports from Asia, it is highly likely that the differences in the prevalence rates for this region can be explained by differences between urban and rural areas, as well as by the increasing burden of obesity over the years. Therefore, it can be hypothesized that a westernized diet and a sedentary lifestyle have led to an increase in the prevalence of obesity and NAFLD in the region.

The Middle East is expected to face major challenges with NAFLD, but there is no systematic approach to deal with these challenges. Future large, multicenter, collaborative epidemiological studies are needed to more thoroughly investigate the burden of NAFLD in this region. A multi-prong approach leveraging social media to educate and spread awareness about the burden of obesity, DM and its complications such as NAFLD are necessary to help the region implement strategies to deal with the serious disease burden.

**Prevalence in Africa**

The burden of NAFLD in Africa appears to vary widely, although finding accurate data is difficult. In contrast to North America, Europe and Asia, there are very few studies on the epidemiology of NAFLD from Africa. A meta-analysis estimated the prevalence of NAFLD in Africa to be 13.48% (9). Given the paucity of data and the need to collect additional information about NAFLD, a member of the Global Forum sent surveys to 37 medical providers in 21 African and Middle Eastern countries. Based on the survey results, the prevalence of NAFLD appears to range from 5% (in Ethiopia) to 30% (in Saudi Arabia).

Currently, there is no established program to provide a systematic approach to study NAFLD in Africa. Nevertheless, the issue of NAFLD in Africa may be important not only for its own risk of progressive liver disease but also because NAFLD could potentially worsen the course

of viral hepatitis which is quite prevalent in Africa. Future research programs to be better understand NAFLD in different regions of Africa are needed.

**Prevalence in Australia and Pacific Countries:**

Consistent with data from other industrialized societies, a commissioned report noted that NAFLD is the commonest liver disease in Australia, affecting a third of the population (5.5 million people; 40% of adults ≥ 50 years of age and 15% of school children) (61), and 13% of the population of New Zealand (62). This is not surprising since Australia has one of the highest burdens of overweight and obesity (63.4% of adults in 2014-15) (63).

A recent nationwide population-based survey of 9,447 individuals reported NAFLD is the commonest cause of abnormal liver tests. Further, 47% of the population had elevated ALT attributable to truncal obesity (64). Over the last decades, there has been an increasing appreciation of NAFLD in Australia and New Zealand by primary care physicians, with diagnosis and referral prompted by obesity, features of the metabolic syndrome, the detection of elevated liver enzymes, or a bright liver on ultrasound.

For much of the remainder of Oceania and the Pacific, including Micronesia, Melanesia and Polynesia (roughly 22 nations and 10 million people), data on NAFLD/NASH prevalence are lacking. However, if T2DM and obesity prevalence data are any indication, this region will be a hotbed of NAFLD. For example, a global burden of disease study indicated that obesity prevalence in men exceeded 50% in Tonga and in women from Kiribati, the Federated States of Micronesia, Tonga, and Samoa (67). More worrisome, Pacific Island nations have the highest global prevalence of diabetes, including 7 of the top 10 countries and all of the top six [Tokelau (37.5%), Federated States of Micronesia, Marshall Islands, Kiribati, Cook Islands

and Vanuatu) where, in 2013, diabetes prevalence ranged from 37.5% in Tokelau to 24% in Vanuatu (68).

While there are no coordinated plans to deal specifically with the challenge of NAFLD in Australia and New Zealand, the parallel rises in obesity and T2DM prevalence is viewed as a national health priority. Frequent campaigns have been undertaken by Federal and State agencies promoting healthy food intake and physical activity, while obesity and T2DM research is targeted for research funding. Such efforts have borne some fruit as Australian national nutrition surveys between 1995 and 2011 reported for 12,000 participants' positive changes, including the consumption of more fruit, vegetables, peas, beans, nuts, seeds, pulses, brown and wholegrain cereals, as well as reduced intake of sugars (65). Consistently, shorter- and longer-term declines in the availability and intake of added sugars and sugar-sweetened beverages has been reported (66). Major efforts are now underway to reduced sedentary behavior by encouraging physical activity. At an investigator-led level, consortiums are being formed (often as part of international collaborations) to study NAFLD natural history, pathophysiology, and to establish biobanks for biomarker development.

**Global Incidence of NAFLD**

here are few accurate data on NAFLD incidence in the general population. Some rates have been estimated to range from 28.01 per 1000 person-years to 52.34 per 1000 person- (9). For more details, please see supplementary material.

**Clinical Outcomes**

Complications of NAFLD/NASH have been reported worldwide. The rate of cirrhosis is lower in Asia compared to Western countries. In Hong Kong, 3.7% of NAFLD patients had

fibrosis or cirrhosis. In biopsy-proven NAFLD from mainland China 1.97%-2.97% reported cirrhosis. (71-72) In India, 2% of NAFLD patients had cirrhosis, while in Japan, 2.1% had significant fibrosis (73).

In contrast, an estimated 10-15% of NAFLD patients from US and Europe have advanced fibrosis (9). A study using NHANES (1999–2002 and 2009–2012 cycles) reported a 2.5-fold increase in the prevalence of NASH-associated cirrhosis and 2-fold increase in the prevalence of NAFLD-associated advanced fibrosis. The authors then predicted a 6% increase in NAFLD and >100% increase in advanced liver diseases over the next 15 years. (74) *Liver-related mortality*

Patients with NAFLD have an increased risk of liver-specific death—primarily those with histologically proven NASH. In a study of 289 NAFLD patients who were followed for 150 months, those with NASH had >6-fold higher risk of liver-related death than NAFLD without NASH (75). Liver related mortality was increased 2-fold if T2DM and or histologic NASH was present. (75) Other studies have independently associated insulin resistance and MS with all-cause, liver-specific, and cardiovascular mortality (6-9). Although NASH is associated with increased liver-related mortality, it is the stage of fibrosis that increases the risk of death in NAFLD patients. (12, 76-79)

lthough cardiovascular disease is the leading cause of death in NAFLD, a recent multicenter study suggests that this is true for non-cirrhotic cases [80]. Among 458 patients with biopsyproven NAFLD from Europe, Asia, Australia and America, 37 died during a mean follow-up of 5.5 years. Liver complications accounted for 50% of the deaths in patients with F3 fibrosis, 73% in those with early cirrhosis, and 100% in those with advanced cirrhosis. This suggests that in NAFLD patients with advanced fibrosis, liver mortality will dominate.

*Cardiovascular disease*

The cause of death for most patients with NAFLD is related to cardiovascular diseases. (81) When patients with NAFLD and liver fibrosis (stages 3 or 4) were followed for an average of 26 years, they had a 1.55-fold increase in risk for cardiovascular disease compared to individuals without NAFLD (81-85). Similarly, 117 NAFLD patients and 507 controls from South China were followed for 4 years showing higher rates of cardiovascular mortality in NAFLD, especially if MS was present (0.19% and 0.17%, P=0.005). (86)
There has been intense research to understand the underlying mechanisms connecting NAFLD to cardiovascular diseases (87). Prospective, long-term studies are needed to determine whether the presence of NAFLD, NASH, or advanced NASH (stage 3 and 4) is independently associated with cardiovascular mortality and if treatment of these liver diseases can modify the cardiovascular outcomes.

*HCC*

AFLD is the third-most common cause of cancer-related death worldwide and seventh-most common cause in the US (88). In a study of the Surveillance, Epidemiology, and End Results database, investigators found that among the 4949 patients with HCC, 701 patients had NAFLD, providing a prevalence of NAFLD-associated HCC of 14.1% (19).The cumulative incidence of HCC among patients with NAFLD and cirrhosis has been reported to range from 2.4% to 12.8% over a median follow-up period of 3.2 to 7.2 years (89, 90). For more details regarding HCC, please see supplementary material.

*Liver Transplantation*

NASH is the most rapidly growing indication for LT in the US (20,94-99). Despite the resurgence of ALD, NASH is the second-leading indication for LT. For more detail about LT and NASH, please see supplementary material.

## Special Topics in Epidemiology of NAFLD

*NAFLD in Diabetics*

A recent systematic review of studies, comprising 88,978 persons with diabetes from 28 countries, found the overall global prevalence of NAFLD among persons with diabetes to be 57.80%. The highest rate was in Europe (66.19%) and the lowest was in Africa (13.20%) (100). In this study, the overall prevalence of NASH among diabetic patients from whom biopsies were available was 65.26%. In addition, the prevalence of advanced fibrosis (≥ F3) was 15.05% (100). In addition, prevalence of NAFLD diabetics can range from 42.6% in UK patients (30) to 60-70% in Italy (31). In the absence of biopsy, the prevalence of NAFLD and advanced fibrosis in diabetics (N=1918), as determined by vibration controlled transient elastography, is estimated to be 72.8% and 17.7% [102]. Furthermore, a community-based study from Netherlands estimated that significant fibrosis by elastography was present in 8.4% of NAFLD subjects which was associated with T2DM (32). These and other studies have confirmed the high prevalence of NAFLD, NASH and advanced in patients with T2DM (100-101).

*Interactions between NAFLD and metabolic syndrome*

In addition to T2DM, patients with NAFLD have a high prevalence of metabolic syndrome (MS) and patients with MS have a high prevalence of NAFLD. This phenomenon has led some to consider NAFLD as the hepatic manifestation of MS. Findings from many studies worldwide corroborate this strong and reciprocal association.

A study conducted in Asia reported that the incidence of fatty liver increased by 14% in patients with at least 3 components of MS compared to patients with fewer than 3 features (37). Prevalence of MS among lean NAFLD was 36.1% in Shanghai, China, and fatty liver appears to be a better predictor than overall obesity and abdominal obesity for the clustering

of risk factors for MS **(**43**).** In east China, 358 NAFLD patients and 788 matched controls were followed for 6 years. Incidence of obesity (47.6% vs 19.5%), hypertension (69.6% vs 16.3%), hypertriglyceridemia (39.1% vs 16.3%), hypercholesterolemia (24.5% vs 17.3%), T2DM (20.3% vs 5.2%) and MS (56.3% vs 16.3%) were significantly higher in NAFLD group than controls. (42)

These data were confirmed in a systematic review which reported a prevalence of 34% for MS in patients with NAFLD (9). In fact, similar rates are reported worldwide. Of patients with NAFLD in Asia, Europe, the Middle East, North America, and South America, 34%, 62%, 31%, 33%, and 37% have been reported to have MS (9).

n addition to high reciprocal prevalence rates, patients with NAFLD with multiple features of MS are also at higher risk for advanced fibrosis and death than patients with NAFLD without MS (100-106). A multivariate analysis of biopsies from 432 patients with NAFLD independently associated increases in aspartate and alanine aminotransferases, presence of diabetes, male sex, and Caucasian ethnicity with the presence of moderate to severe histologic fibrosis ($P<.0001$). Additionally, an increase in the number of MS components (T2DM, hypertension, and visceral obesity) increased the likelihood of advanced fibrosis in a stepwise fashion- finding confirmed using NHANES III data. (101,106).

In addition to higher risk for advanced fibrosis in patients with NAFLD, the presence of MS increases the risk for liver-related mortality and all-cause mortality (7). Other analysis of NHANES III data determined MS independently increased liver-related mortality and overall mortality (7, 75). These data indicate that not only the presence of metabolic derangement but also its severity have negative effects on long-term outcomes of patients with NAFLD.

*NAFLD in non-obese or lean individuals*

Although NAFLD is closely linked to obesity and MS, approximately 5%–8% of patients with NAFLD in Western countries are considered lean (8,107). These NAFLD patients still have abnormal glucose tolerance, and about one-third have a diagnosis of diabetes (64). Interestingly, a higher proportion of lean individuals with NAFLD have the *PNPLA3* rs738409 GG genotype and low serum concentrations of adiponectin, compared to controls (107). These data indicate that lean patients with NAFLD have dysregulated glucose metabolism and adipose tissue, as well as the *PNPLA3* rs738409 GG genotype (107).

The similarities of lean NAFLD to obese or overweight NAFLD indicate a spectrum of metabolic abnormalities in such a way that obese patients with NAFLD might have more severe abnormalities whereas lean NAFLD patients have less severe metabolic defects. A recent systematic review concluded that lean and obese patients with NAFLD have a common altered metabolic profile but lean persons with NAFLD have excess abdominal adipose tissue (108).

Lean NAFLD in Asia appears to differ from that of the West. Approximately 20% of the Asian population has lean NAFLD (37). In China, patients with lean NAFLD had a lower BMI and waist circumstance than obese NAFLD, but these were higher than individuals without NAFLD (109). Furthermore, patients with lean NAFLD also had a significantly higher visceral adiposity index and greater odds for having T2DM, hypertension, MS, and central obesity than individuals without NAFLD (66). Similar findings have reported from Korea, India, Iran, and Turkey. (110-112)

Despite the spectrum of metabolic abnormalities in patients with lean or obese NAFLD, it is likely that other genetic and environmental factors affect risk. Studies are needed to investigate the role of gut microbiota and environmental factors, including exposures to antibiotics, in development and progression of NAFLD.

*Pediatric NAFLD*

Based on analyses of surrogate makers, the prevalence of NAFLD in children has been estimated to range from 2.6% to 17.3%. (113) In an autopsy series study of children, investigators determined the overall prevalence of NAFLD to be 9.6%, but rates increased with age. NAFLD was more common in boys, but the highest rate was in Hispanic children (11.8%), while the lowest rate was in African-American children (1.5%). (114)

A longitudinal study of NHANES data estimated that the prevalence of NAFLD in adolescents increased from 3.9% in 1988–1994 to 10.7% in 2007–2010 ($P<.0001$), affecting all race/ethnic groups and both sexes. (115) Again, the prevalence of NAFLD increased with age, BMI, Mexican-American ethnicity, and male sex. However, among obese adolescences, the odds of NAFLD were higher with increased age, BMI, Mexican-American ethnicity, and male sex. In 2007–2010, 48.1% of all obese male adolescents and 56.0% of obese Mexican-American male adolescents were suspected to have NAFLD. (116)

Children seem to have a different presentation of advanced NAFLD than adults. In a crosssectional study of 813 children from the Nonalcoholic Steatohepatitis Clinical Research Network with biopsy-proven NAFLD, researchers found that children with zone 1 steatosis (18%) had significantly more advanced fibrosis and were younger than children without zone 1 steatosis. In children with steatosis in zone 3 (32%), a higher proportion had steatohepatitis (30%) than children with steatosis in zone 1 (6%) ($P<.001$) (114). It is also important to note that presence and progression of NASH in pediatric patients accelerates with T2DM (117-

Since there are few data from long-term studies (> 2 years) or studies with liver biopsy data, the current pediatric data may not represent real-world pediatric patients. Additionally,

noninvasive fibrosis scoring systems designed for adults do not adequately predict which children will develop liver fibrosis. Thus, pediatric markers are needed to determine risk of fibrosis in children.

**Patient Reported Outcomes in NAFLD**

In addition to clinical outcomes, PROs are important to consider for NAFLD patients (120). NAFLD has been found to cause a significant decrease in quality of life as measured by various tools (16,120-122). In addition, some PRO impairment may be associated with NAFLD comorbidities such as depression or the stage of fibrosis (123-125).

Although NASH itself can reduce HRQL scores, treatment of NASH can also affect HRQL. Preliminary data from selonsertib in NASH suggested that reductions in hepatic fibrosis and the amount of collagen were associated with improvements in HRQL (124). Although generic HRQL instruments have been used to study NAFLD and NASH, a disease-specific HRQL instrument (CLDQ NAFLD-NASH) was recently developed and validated (122, 126). CLDQ-NAFLD-NASH was developed using an established rigorous methodology (patients' interviews, focus groups, item reduction, factor analysis, and psychometric testing). As such, the CLDQ-NAFLD-NASH is now being used in clinical trials of NASH to capture patients' perspectives about their disease and treatment. (126).

**Economic effects of NAFLD and NASH**

NAFLD is also associated with a significant economic burden. For details regarding the Economic burden of NAFLD, please see the supplementary material.

**Conclusions**

The prevalence of NAFLD as well as the genetic and environmental factors that determine its associated risk varies worldwide. The progressive form of NAFLD or NASH is associated

with liver-related mortality, reduced HRQL, and substantial economic burdens. In the context of growing burden of NASH worldwide, there is a lack effective treatment regimen and validated non-invasive diagnostic, prognostic and dynamic biomarkers. For details about authors' statement about future of NAFLD/NASH, please see supplementary material.

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**Figure 1**

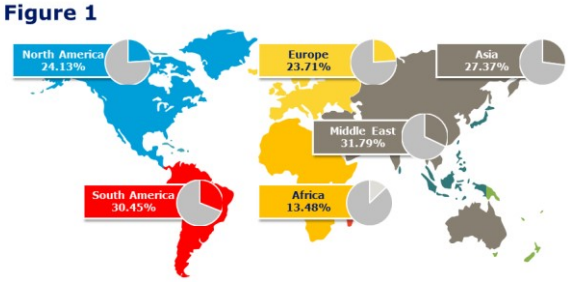


**Figure 2**

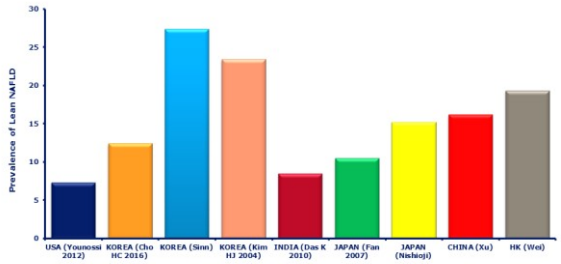


**Figure 3**