Editorial Commentary

Up-to-date global epidemiology of nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is known as the most prevalent cause of chronic liver disease globally, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which can lead to advanced fibrosis and cirrhosis. The burden of NAFLD is projected to increase over the next decade because of the lack of effective approved medications and continued increases in obesity and diabetes. Individuals with NAFLD are left with the challenge of 'lifestyle modification', which is difficult to implement or maintain in a predictably effective fashion. The impact on public health will likely be profound as NAFLD and NASH progress further into cirrhosis with all of its accompanying complications, such as bleeding varices, hepatic encephalopathy, and increased risk of infections. Therefore, there is an unmet need to figure out the contemporary burden of NAFLD.

The recent article published by Younossi *et al.* (1) sheds light on the contemporary health burden of NAFLD. This meta-analysis assessed 92 studies, including over 9 million individuals all over the globe, and reported that NAFLD has a global prevalence of 30.1% [95% confidence interval (CI): 27.9–32.3%], with a prevalence rising over the three decades [1990–2019]. Global prevalence of NAFLD increased by 50.4% from 25.3% (95% CI: 21.6–29.3%) in 1990–2006 to 38.2% (95% CI: 33.7–42.9%) in 2016–2019. This rise in NAFLD parallels the rise in the prevalence of obesity and diabetes while the prevalence of chronic viral hepatitis continues to trend down overall (2). An earlier meta-analysis by Riazi *et al.* published in 2022 looking at 72 studies and 1,030,160 individuals reported a global NAFLD prevalence of 32.4% (3), similar to the 30.1% reported by Younossi *et al.* despite the smaller sample size. However, the study by Riazi *et al.* did not include individuals from the Middle East and Africa as they did not find any studies that met their inclusion criteria, limiting a truly global representation of the conclusions. Notably, both of these studies had a high degree of heterogeneity among their included studies.

The findings from Younossi *et al.* should be taken into a broader context and compared to other studies looking at more narrowly defined populations (*Table 1*). A study found that the prevalence of NAFLD was around 40% among individuals without obesity (5). There was significant variability across the regions, with Europe having a nonobese NAFLD prevalence of 51.3% and East Asia showing a nonobese NAFLD prevalence of 37.8%. These findings slightly differ from the regional prevalence reported by Younossi *et al.*, which is not limited to the nonobese population, with the highest NAFLD prevalence

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Table 1 Recent epidemiological studies of NAFLD

Study	Country	Total Population	Findings
Zou *et al.* [2019], (4)	10 countries	19 studies; 5,620 individuals	Pooled prevalence of NAFLD in patients with IBD was 27.5%
Ye *et al.* [2020], (5)	24 countries	93 studies; 10,530,308 individuals	Prevalence of nonobese NAFLD among individuals with NAFLD was 40.8% Prevalence of lean NAFLD among individuals with NAFLD was 19.2%
de Vries *et al.* [2020], (6)	17 countries	20 studies; 3,901 patients with type 1 diabetes	Pooled NAFLD prevalence in type 1 diabetes was 19.3%
Riazi *et al.* [2022], (3)	17 countries	72 studies; 1,030,160 individuals	Global NAFLD prevalence was 32.4% Prevalence rose from 25.5% in or before 2005 to 37.8% in 2016 or later
Le *et al.* [2022], (7)	25 countries	245 studies; 5,399,254 individuals	Global NAFLD prevalence was 29.8% Prevalence rose from 21.9% in 1991 to 37.3% in 2019, with an annual increase of 0.7%
Quek *et al.* [2023], (8)	35 countries	151 studies; 101,028 individuals	NAFLD prevalence in the overweight population was 70.0% NAFLD prevalence in the obese population was 75.3%
Hartmann *et al.* [2023], (9)	Worldwide	Data from the Global Burden of Disease study on individuals aged 10 to 19 years	Global NAFLD prevalence in adolescents rose from 3.73% in 1990 to 4.71% in 2019 (a relative increase of 26.27%)

NAFLD, nonalcoholic fatty liver disease; IBD, inflammatory bowel disease.

of 44.4% (95% CI: 30.7–59.0%) in Latin America, 36.5% (95% CI: 19.0–51.0%) in Middle East and North Africa, 29.7% (95% CI: 26.0–33.8%) in East Asia and the lowest prevalence of 25.1% (95% CI: 21.0–30.3%) in Western Europe. Another meta-analysis reported that the prevalence of NAFLD in the overweight population was nearly 70%, with the region of the Americas at 75% and the African region at 48%, demonstrating regional differences (8). Current evidence suggests heterogeneous and various prevalence of NAFLD across the region, race/ethnicity, and obesity status. Therefore, researchers should consider body mass index or waist circumferences, geographical location, and race/ethnicity for epidemiologic research of NAFLD.

Interestingly, due to differences in the definition of alcohol consumption across the studies, this study categorized the studies into three groups: (I) standard: cutoff of 20 g/day for males and 10 g/day for females (28 studies, n=167,164); (II) above standard: cutoff greater than 20 g/day for males and 10 g/day for females (45 studies, n=9,124,741); (III) no specific definition for significant alcohol consumption (19 studies, n=69,811). Although studies that used more strict definitions of significant alcohol consumption reported a numerically lower prevalence of NAFLD, the effect of the different categories of alcohol consumption in the meta-regression model was insignificant. These findings need to be re-evaluated in the context of the condition as metabolic dysfunction-associated steatotic liver disease (MASLD), which includes cardiometabolic criteria (10). The cutoff to define MASLD is an average of 30 g/day (210 g/week) in males and 20 g/day (140 g/week), which is more liberal than the cutoffs the authors used as their standard. Also, recent consensus suggests MetALD (MASLD and increased alcohol intake) as individuals who met both steatotic liver disease with metabolic criteria and consumed 140–350 g/week (females) and 210–420 g/week (males). We assumed that some of the individual studies in the second group utilized cutoffs more aligned with the values presented in the new MASLD definition, though ultimately, no significant difference was found between the prevalence in the three groups. Future studies to assess the prevalence of MASLD are needed, which are unlikely to change the conclusions of the meta-analysis (11).

The weaknesses in this study merit some attention. First, the prevalence of NASH was not directly assessed but was an estimate obtained by multiplying the assessed prevalence of NASH in the group of patients that underwent liver biopsies with the total number of individuals with NAFLD. Therefore, the estimated global NASH prevalence of 5.27% may not be accurate and should be interpreted with caution.

Markov modeling estimates that the prevalence of NASH will continue to increase, with 27 million cases expected by 2030 in the United States alone, and the prevalence of advanced fibrosis is also slated to rise (12). Second, possible oversampling of countries in Asia is possible due to their higher publication rates. Of the 92 studies analyzed, 46 are from Asia, 9 are from the Middle East and North Africa, and only 3 are from Latin America. Research in these less-represented regions must be encouraged, and global support will be essential to ensure that patients residing in these regions receive the global standard of care in NAFLD. Epidemiological data is vital to both discover disparities in the current state of healthcare delivery and to assess the outcomes of interventions designed to overcome those disparities, and a genuinely international picture that is impartial without mirroring known socioeconomic discrepancies among countries is instrumental in achieving these aims.

Given the rising prevalence of NAFLD, the risk factors of NAFLD and its causes of mortality should be understood. Specific treatment of the commonly known predisposing factors of diabetes, dyslipidemia, or hypertension and lifestyle modification against decreased physical activity, obesity, and unhealthy nutrition are undoubtedly essential. In addition, awareness of lesser-known risk factors such as hypothyroidism and sarcopenia should be spread to inculcate a comprehensive approach (2,12). Cardiovascular disease inflicts the highest mortality among patients with NAFLD, with extrahepatic cancers and liver-related conditions following (2). Although cirrhosis is the end-stage phenotype of liver disease, regardless of the underlying etiology, cardiovascular disease affects patients with NAFLD more than alcohol-associated liver disease and viral hepatitis (2). Advanced fibrosis in NAFLD does increase the risk of all-cause and cardiovascular mortality (13), proving that while the rise in NAFLD prevalence needs to be blunted, the patients with NAFLD also need to be monitored and treated to prevent disease progression of liver disease and cardiovascular disease.

Awareness of the prevalence of NAFLD is essential, but timely action is required. A well-known correlation exists between NAFLD and obesity and diabetes, components of the metabolic syndrome (2). Correction of just one of the facets may improve biochemical parameters but is unlikely to dramatically impact global mortality rates attributable to the global epidemic, requiring a management plan to address all factors involved. In addition, specific populations are at higher risk of deleterious liver-specific outcomes, such as persons GG homozygous for the patatin-like phospholipase domain-containing 3 (*PNPLA3*) *rs738409* G allele, commonly seen in Hispanic Americans (2). In addition, ultrasound-based epidemiologic studies show that Hispanic and Asian children have a higher prevalence of NAFLD than white children (14). These specific populations will likely experience the rising prevalence of NAFLD, but their mortality outcomes may be disproportionately higher, forcing them to be more vulnerable than the general population. The need to curb the NAFLD epidemic is pressing, not only due to the breadth of the disease but also to protect these at-risk populations.

While NAFLD is an asymptomatic condition, its evolution into advanced fibrosis, cirrhosis, and predisposition to hepatocellular carcinoma can contribute to significant morbidity and mortality. Future research will need to address the global trends in the incidence and prevalence of advanced fibrosis. However, the biggest challenge will be comparatively limited access to noninvasive methods of diagnosis, such as vibration-controlled transient elastography, and selection bias when analyzing data obtained from liver biopsies. Overcoming these challenges is a public health necessity and an opportunity for ongoing investigation.

This article by Younossi *et al.* is an essential step in advancing understanding of NAFLD as it currently exists and provides convincing data to back the authors' call for national public health responses to the NAFLD epidemic. Concern is growing that if a response is not timely or proportionate, the downstream effects may involve significant morbidity and mortality despite NAFLD being a medical condition for which evidence-based management guidelines exist, though a cure remains elusive. While several agents are under investigation and hopefully will be powerful tools in the clinician's repertoire, nonpharmacologic approaches currently form the cornerstone of management, and these should continue to be publicized to combat the NAFLD epidemic.

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