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Prevalence trends in non-alcoholic fatty liver disease at the global, regional and national levels, 1990–2017: a population-based observational study

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ABSTRACT

Objective Non-alcoholic fatty liver disease (NAFLD) is the leading cause of end-stage liver diseases worldwide. Understanding NAFLD prevalence and trends over time at the global, regional and national levels is critical to understanding the NAFLD disease burden and creating more tailored prevention strategies.

Design Population-based observational study.

Setting The study was global, including 21 regions and 195 countries or territories.

Main outcomes measure The estimated annual percentage change for NAFLD prevalence.

Results Worldwide, cases of NAFLD have increased from 391.2 million in 1990 to 882.1 million in 2017, with the prevalence rate increasing from 8.2% to 10.9% during the same period. The increasing trends were consistent across sexes. Case numbers were highest in East Asia, followed by South Asia, then North Africa and the Middle East. The highest prevalence of NAFLD was observed in North Africa and the Middle East, while the greatest increase was detected in Western Europe, followed by Tropical Latin America, then high-income North America.

Conclusion Nearly all countries or territories worldwide have experienced a significant increase in NAFLD prevalence. The greatest increase was observed in Oman. Almost all countries showed a significant increasing trend in NAFLD prevalence over the past three decades. This drastic increase is alarming and suggests that NAFLD has emerged as a new public health concern worldwide. As such, more efficient prevention strategies are urgently needed.

Strengths and limitations of this study

► Our study comprehensively investigated temporal trends in non-alcoholic fatty liver disease (NAFLD) prevalence at the global, regional and national levels.
► We assessed secular trends in NAFLD risk factors, according to the Global Burden of Disease study.
► All data used in our study were derived from mathematical estimates rather than surveillance data.

South America and the Middle East, followed by Asia, the USA, and Europe; NAFLD is less common in Africa.[4]

In line with the worldwide increases in obesity and type 2 diabetes,[5 6] in recent years, NAFLD has shown novel epidemics in both developed and developing countries. Understanding temporal trends in NAFLD prevalence is vital to better understanding its disease burden and preventing additional cases of NAFLD. Previous studies have either focused on individual regions had limited time frames.[3 7 8] Fortunately, the Global Burden of Disease (GBD) study, which provides a tool for quantifying health losses caused by hundreds of diseases, injuries and risk factors, fills the gap when actual data on disease burden is sparse or unavailable, providing an unprecedented opportunity to learn more about NAFLF epidemiology. This study uses the data from the GBD study to comprehensively describe NAFLD prevalence and to quantify its temporal trends between 1990 and 2017 at the global, regional and national levels. Our results are instrumental in raising awareness of NAFLD and will be invaluable in the establishment of updated prevention strategies.

INTRODUCTION

Over the past three decades, non-alcoholic fatty liver disease (NAFLD) has gone from an obscure liver disorder to the most prominent chronic liver disease worldwide.[1 2] NAFLD is a growing cause of end-stage liver disease and has been recognised as an aetiology of hepatocellular cancer (HCC), even in the absence of underlying cirrhosis.[3] NAFLD is highly prevalent across nearly all continents and is geographically heterogeneous in its prevalence from country to country, with the highest rates, for example, being reported in

MATERIALS AND METHODS

Prevalence data for NAFLD by sex, region, and age were retrieved using the online

Global Health Data Exchange query tool.[9] We used data from five Sociodemographic Index (SDI) regions (low, low-middle, middle, high-middle and high), 21 GBD geographically defined regions (eg, East Asia) and a total of 195 countries and territories. The SDI is a composite average of the rankings of residents' incomes per capita, average educational attainment and fertility rates in all areas for their respective regions, according to the GBD study. Prevalence (or the prevalence rate) is a commonly used Epidemiological Index that quantifies the degree to which a disease or condition exists within a population at a particular point in time. We calculated annual NAFLD prevalence as: $Prevalence = \frac{case\ number}{population\ size}$, where the case number denotes the number of NAFLD cases diagnosed at the end of that year. The general methods used in the GBD for creating estimates have been detailed in the previous studies.[10] NAFLD is an umbrella term for a range of liver conditions affecting people who drink little to no alcohol and is identified by International Classification of Disease (ICD)10 code K76.0. NAFLD prevalence was estimated by conducting a systematic literature review of PubMed, and then adopting DisMod-MR 2.1 models. The following inclusion criteria were used: (1) a sample size greater than 100; (2) representative of locale or area and sufficient methods; (3) does not exclude comorbidities and (4) NAFLD diagnosed by ultrasound scan (USS) or other imaging diagnostic. Any hospital or claims data that severely underestimated NAFLD prevalence were excluded. Data were outliered or excluded if we found that they differed significantly when compared with the regional, superregional or global rates. Studies using serum diagnostics or fatty liver indices and scores to diagnose NAFLD were also excluded. We also retrieved data from the National Human Development Index (HDI), a composite index created by the World Bank (www.world-bank.org) that measures average achievement in three basic dimensions of human development—a long and healthy life, knowledge and a decent standard of living. To assess secular trends in NAFLD risk factors, we retrieved prevalence data for type 2 diabetes from the GBD online database and prevalence data for obesity (and overweight status) from the WHO (http://apps.who.int/gho/data/view.main.GLOBAL2461A?lang=en). The obesity dataset includes estimates of the prevalence of overweight men and women aged 18 and over by country, region and globally. A person is defined as overweight if he or she has a body mass index (BMI) equal to or greater than 25. BMI is calculated by dividing a person's weight in kilograms by his or her height in metres. We retrieved data spanning 1990–2016.

Estimated annual percentage change (EAPC) was used to quantify trends in the prevalence of NAFLD, stratified by sex, nation and age, between 1990 and 2017. As described elsewhere, EAPC can be calculated using a regression line fitted to the natural logarithm of the rates, that is, $y = \alpha + \beta x + \varepsilon$, where $y = \ln(rate)$, and $x = $ calendar year.[11] All statistical analyses were performed using the R program (V.3.3.3, R Core Team, Vienna, Austria).

A p value of less than 0.05 was considered statistically significant.

Patient and public involvement

No patients or members of the public were involved in designing, conducting, reporting on or dissemination information related to our research.

RESULTS
Prevalence in case numbers and prevalence rates of NAFLD globally

Worldwide, the prevalence of NAFLD increased from 391.2 million in 1990 to 882.1 million in 2017, with the prevalence rate increasing from 8.2% to 10.9% during this same period (EAPC=1.05, 95% CI 1.04 to 1.07, p<0.001) (table 1; figures 1 and 2). Men accounted for approximately two-thirds of all cases; however, women experienced a greater increase in NAFLD prevalence than men (table 1). All five SDI regions saw increase in both NAFLD prevalence in case numbers and prevalence rate. The most pronounced increase was in the high-middle SDI region, with the greatest prevalence seen in 2017 (table 1; figures 1 and 2). The increasing trends in both NAFLD prevalence in absolute case numbers and in prevalence rates were consistent across different age groups. Younger people (aged 15–49 years) accounted for nearly 50% of the total number of cases and accounted for the greatest increase in NAFLD prevalence between 1990 and 2017 (EAPC=1.25, 95% CI 1.22 to 1.28, p<0.001) (table 1).

Prevalence in case numbers and prevalence rates of NAFLD regionally

A total of 21 GBD regions were included in our analysis. The prevalence in terms of case numbers was highest in East Asia, followed by South Asia, then North Africa and the Middle East. In these three regions, absolute case numbers exceeded 0.1 billion in 2017. The highest NAFLD prevalence was observed in North Africa and the Middle East (19.3%), followed by Oceania, Southeast Asia and Central Latin America (table 1). Between 1990 and 2017, all 21 regions experienced significant increases in NAFLD prevalence (figure 3). The greatest increase was detected in Western Europe, followed by Tropical Latin America and then high-income North America (table 1; figure 3).

Prevalence in case numbers and prevalence rates of NAFLD nationally

Globally, NAFLD prevalence varied from country to country, ranging from 5.2% in Rwanda to 24.9% in Qatar in 2017 (figure 4A). The highest prevalence rates were observed in Qatar, Kuwait, Saudi Arabia and Oman. Relatively lower prevalence was found in parts of Africa and Europe, including Uganda, Mozambique, France and Denmark. China, India, Indonesia, Brazil and the USA had the heaviest burden of NAFLD in terms of absolute case numbers, with case numbers above 20 million

Table 1 The changing trends of number of prevalent cases and prevalence rate of NAFLD from 1990 to 2017

	1990		2017		1990–2017*
	No. of cases (×1 million)	Prevalence (%)‡	No. of cases (×1 million)	Prevalence (%)	EAPC (95% CI)
Overall	391.2	8.2	882.1	10.9	1.05 (1.04 to 1.07)
Sex					
Male	236.4	10.0	524.0	13.2	1.00 (0.99 to 1.02)
Female	154.8	6.4	358.1	8.7	1.12 (1.10 to 1.13)
Sociodemographic Index					
High	76.2	6.7	137.4	9.0	1.14 (1.06 to 1.21)
High-middle	100.2	9.4	224.5	13.1	1.21 (1.17 to 1.25)
Middle	120.0	9.4	282.3	12.2	0.94 (0.92 to 0.96)
Middle-low	62.3	8.0	157.1	10.5	1.01 (1.00 to 1.02)
Low	30.4	6.5	76.2	7.9	0.74 (0.70 to 0.79)
Age (years)†					
15–49	241.5	8.8	489.1	12.5	1.25 (1.22 to 1.28)
50–69	109.1	15.9	281.5	21.4	1.06 (1.04 to 1.08)
≥70	40.7	20.0	111.4	25.7	0.93 (0.89 to 0.96)
GBD region					
Andean Latin America	2.5	8.8	7.1	12.0	1.13 (1.10 to 1.16)
Australasia	1.5	6.4	3.1	8.6	1.16 (1.04 to 1.28)
Caribbean	2.8	9.2	5.8	11.7	1.03 (0.98 to 1.07)
Central Asia	3.8	6.7	7.4	8.5	0.91 (0.81 to 1.01)
Central Europe	9.5	6.7	13.1	8.0	0.70 (0.67 to 0.73)
Central Latin America	12.7	10.5	36.5	14.4	1.17 (1.14 to 1.21)
Central sub-Saharan Africa	2.3	6.5	6.2	7.5	0.58 (0.50 to 0.67)
East Asia	111.8	9.6	242.8	12.6	0.88 (0.82 to 0.95)
Eastern Europe	18.4	7.0	23.7	8.4	0.73 (0.64 to 0.82)
Eastern sub-Saharan Africa	7.1	6.0	18.0	7.0	0.58 (0.55 to 0.60)
High-income Asia Pacific	11.4	5.7	18.7	7.0	0.78 (0.75 to 0.82)
High-income North America	23.1	7.2	44.0	9.6	1.17 (1.06 to 1.29)
North Africa and Middle East	35.0	14.3	108.0	19.3	1.12 (1.10 to 1.15)
Oceania	0.6	12.8	1.6	16.3	0.90 (0.87 to 0.92)
South Asia	53.6	6.4	131.2	8.0	0.81 (0.78 to 0.83)
Southeast Asia	39.5	10.9	98.5	14.5	1.12 (1.08 to 1.15)
Southern Latin America	3.1	6.5	6.3	8.6	1.05 (1.01 to 1.08)
Southern sub-Saharan Africa	3.7	9.3	8.1	11.4	0.73 (0.69 to 0.77)
Tropical Latin America	9.8	8.0	26.7	11.1	1.17 (1.15 to 1.19)
Western Europe	30.9	6.5	52.1	8.9	1.17 (1.05 to 1.29)
Western sub-Saharan Africa	8.4	6.5	23.2	8.0	0.69 (0.63 to 0.75)

*The prevalence has been standardised by age.
†Crude prevalence rate for each age group.
‡P values of all EAPCs were <0.001.
EAPC, estimated annual percentage change; GBD, Global Burden of Disease; NAFLD, non-alcoholic fatty liver disease.

in each of these five countries (figure 4B). Between 1990 and 2017, nearly all countries or territories experienced a significant increase in NAFLD prevalence rates (figure 4C). The greatest increase was observed in Oman (EAPC=2.12, 95% CI 1.97 to 2.26, p<0.001), followed by Finland, Equatorial Guinea and Nicaragua (figure 4C; online supplementary table). Only one country, Bulgaria, remained stable in terms of NAFLD prevalence for the
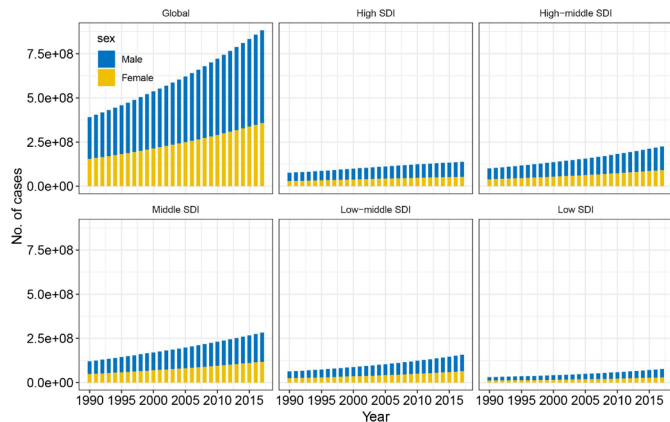
Figure 1 Changing trends in case numbers for non-alcoholic fatty liver disease between 1990 and 2017, by sex and SDI. SDI, Sociodemographic Index.

study period. These increasing trends were consistent across both sexes and all three age groups at national levels (online supplementary table).

Correlations between NAFLD prevalence and risk factors

We assessed the correlations between NAFLD prevalence and the prevalence of overweight and diabetic status at the national level (online supplementary figure S1). There were significant positive correlations between these categories, with a r of 0.664 and 0.354, respectively. We also tested the correlations for EAPCs of NAFLD prevalence with HDIs at the national level. As shown in figure 5A, we found a significant positive correlation between these two indices (r=0.310, p<0.001). Over the last three decades, more than 90% of countries or territories experienced a significant increase in overweight prevalence, while more than 80% experienced increases in diabetes prevalence. This positive correlation was observed between temporal trends in NAFLD and the same trends in overweight status and diabetes (figure 5B,C).
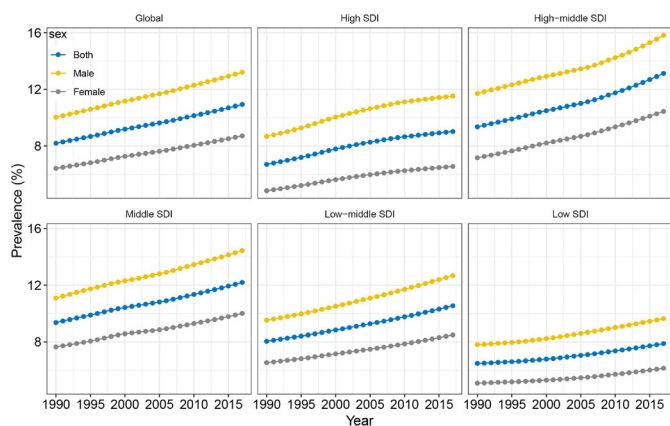

Figure 2 Temporal trends in the prevalence of non-alcoholic fatty liver disease between 1990 and 2017, by sex and SDI. SDI, Sociodemographic Index.
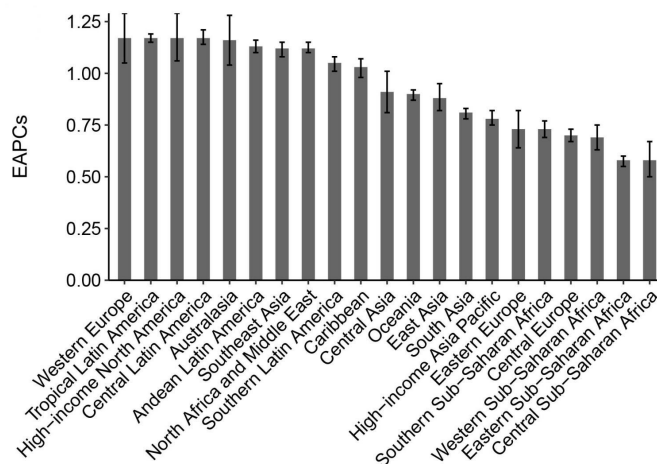

Figure 3 Prevalence trends in non-alcoholic fatty liver disease at the Global Burden of Disease regional level. The error bar denotes a 95% CI. EAPCs, estimated annual percentage changes.

DISCUSSION

NAFLD and its histological subtype, non-alcoholic steatohepatitis (NASH), have emerged as the most common forms of chronic liver disease in most regions worldwide.
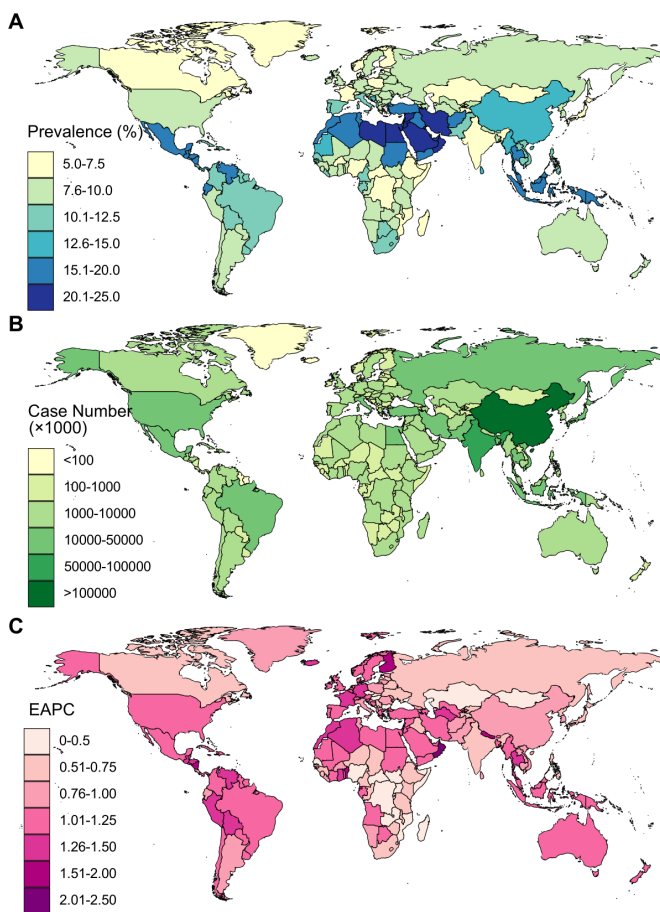

Figure 4 Age-standardised prevalence rates (A), case numbers (B) and trends (C) in non-alcoholic fatty liver disease between 1990 and 2017 at the national level. EAPC, estimated annual percentage change.
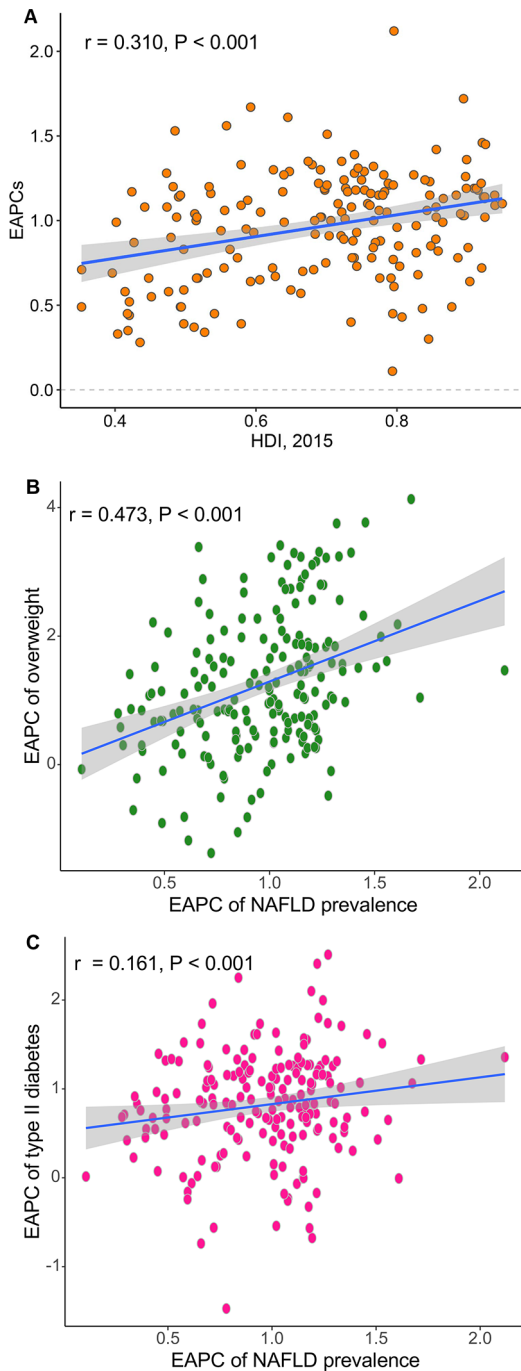
Figure 5 Association of prevalence trends in non-alcoholic fatty liver disease (NAFLD), quantified by estimated annual percentage changes (EAPCs), with Human Development Index (HDI) (A), trends in overweight prevalence (B) and trends in diabetes prevalence (C) at the national level. The correlation coefficient was derived from a Pearson correlation test.

This study comprehensively describes NAFLD prevalence and temporal trends in NAFLD prevalence over the past three decades at the global, regional and national levels. In general, we found that NAFLD prevalence was heterogeneous across the globe, with almost all countries demonstrating significantly increasing trends between 1990 and 2017. These increases have been consistent across sexes

and age groups. The highest prevalence overall was observed in countries located in North Africa and the Middle East. The most significant increases in prevalence were observed in Western European countries.

According to a recent study, the estimated prevalence of overweight status was highest in several countries North African and Middle Eastern countries (including Qatar, Libya and Kuwait) across both sexes.[6] The distribution of overweight status lines up significantly with NAFLD prevalence, as demonstrated in this and other studies.[12] The greatest increase in NAFLD prevalence was found in Western Europe, which may primarily be ascribed to the rapid increase in overweight status in these countries.[6] This striking increase in NAFLD prevalence has prompted investigators to explore the disease's risk factors. So far, well-established risk factors for NAFLD include obesity, type 2 diabetes, an unhealthy diet (eg, high intake of red meat and processed meat) and physical inactivity.[13–17] Of these, an unhealthy lifestyle is deemed to be the most important contributor to NAFLD.[18] Key lifestyle parameters include an increased intake of glucose, fructose, and saturated fat, induced hepatic de novo lipogenesis, subclinical inflammation in the adipose tissue and liver, and insulin resistance in adipose tissue, the liver, and skeletal muscle. These parameters are also accompanied by an increased risk of type 2 diabetes.[19]

Additionally, gut dysbiosis, which is induced in most cases by an unhealthy diet, is believed to be a major contributor to the accumulation of fat in the liver and to the pathogenesis of NASH. There is a set of clinical trials currently underway that focuses on liver-specific and extrahepatic targets, including the microbiome and gut–liver signalling axis, as well as other organs that contribute to metabolic syndrome, especially muscle and adipose tissue.[20] Although there is a great deal of activity in terms of drug development targeting NASH—for example, with an farnesoid X receptor (FXR) agonist (obeticholic acid), a peroxisome proliferator-activated receptor (PPAR)α and PPARδ agonist (elafibrinor) and a C-C chemokine receptor (CCR)2 and CCR5 antagonist (cenicriviroc)—it is too early to prioritise these drugs or mechanisms based on which seems most promising. It will take time to translate the findings of all these studies into long-term safety and efficacy.[20] For these reasons, the primary preventative steps in terms of the abovementioned risk factors, including adherence to a healthy lifestyle and maintaining a healthy BMI, remain the optimal approach to preventing NAFLD.

Our study found that approximately 0.9 billion people suffered from NAFLD in 2017. What sets NAFLD apart from other common liver diseases is the sheer number of patients worldwide. Unfortunately, we also observed increasing trends in NAFLD prevalence globally. Consequently, the complications and sequelae of NAFLD might also be on the rise. For example, this increasing prevalence of NAFLD is accompanied by increasing prevalence of other non-communicable diseases, including cardiovascular disease, obesity-associated and type 2

diabetes-associated cancer and advanced liver diseases such as hepatic cirrhosis and HCC.[21] As the clinical consequences of NAFLD grow, so too will the economic repercussions. One model based on the populations of the USA and four European countries (Germany, France, Italy and the UK) estimated the annual burden associated with all incident and prevalent NAFLD cases at US$103 billion in the USA (or US$1613 per patient) and €35 billion in these four European countries (from €354 to €1163 per patient).[22] Unfortunately, as our results show, we found significant increases in both obesity and diabetes prevalence in most countries over the last decade. If the annual rate of increase in NAFLD-related costs parallels annual growth in the prevalence of obesity—and taking into account an ageing population—then the expected 10-year burden for NAFLD could increase to an estimated US$1.005 trillion in the USA and €334 billion in these Europe countries.[22] Interestingly, we also found a significant positive correlation between national HDI and increase magnitude in NAFLD prevalence. This result suggests a striking increase in NAFLD risk factors, particularly in developed countries; these factors likely include an ever-growing ageing population, physical inactivity, increases in consumption of red meat and processed meat and other unhealthy lifestyles choices that contribute to NAFLD.[16 23] Given the observable increases in obesity and diabetes prevalence, NAFLD prevalence is anticipated to continue to increase in the near future if no effective interventions are introduced.[3] Moreover, this persistent increase in NAFLD also indicates an increasing need for medical facilities and improved health systems in these countries, given that more NAFLD patients will continue to be diagnosed.

NAFLD prevalence has also persistently increased in developing regions, including the sub-Saharan Africa, a region where NAFLD had previously been a less frequent diagnosis. This increase might be ascribed to the increasing availability of healthcare and the concomitant rise in accurate NAFLD diagnosis, as well as to transitions in lifestyle. Increased awareness and urgent action is needed if we want to control the NAFLD pandemic worldwide. Specifically, (1) our governments should play a strong leadership role in reinforcing the importance of addressing obesity and establishing more effective prevention strategies; (2) funds should be allocated specifically to create a culture that promotes healthy eating and an active lifestyle, especially for children and adolescents; (3) we must create multifaceted interventions aimed at motivating behavioural changes, including setting-based health promotion and education programmes (eg, in preschools, schools, workplaces, religious settings and hospitals), mass media campaigns, social marketing to share knowledge and skills within our communities and routine primary healthcare and counselling appointments to facilitate obesity prevention and management.[24]

Our study has several limitations that should be noted. First, the data we used were derived from mathematical models rather than surveillance. Differences in data processing approaches between the GBD study and previous studies might also contribute to disparities in the NAFLD prevalence rates proposed in our study when compared with those from the previous meta-analyses.[4 25] For example, Younossi *et al* reported that the global prevalence of NAFLD derived from a meta-analysis was 25.24%, which is significantly higher than the estimates in our study.[4] We assume that this difference can be explained as follows: (1) Most studies included in the meta-analysis were conducted in Europe, Asia and North America, where NAFLD prevalence is relatively high. In Africa and Australia, where NAFLD is not a major public health concern, studies on NAFLD are rare. However, in the GBD study, NAFLD prevalence was estimated from country to country using mathematical models; (2) The GBD study included a wider study population, ranging in age from 0 to ≥85 years. Children, adolescents and young adults are relatively less afflicted by NAFLD than middle-aged people and elderly people[26] and (3) To ensure the robustness of its estimates, NAFLD prevalence rates that were significantly higher than the regional, superregional, or global rates were excluded from the GBD study.

Second, NAFLD is a complex and heterogeneous disease. The scarcity of histological and stage data in the GBD database made it difficult to describe the NAFLD disease burden in detail. This type of descriptive study also lacks information at the individual level. For example, the GBD study did not include information on hepatic fibrosis evaluations, which are a key determinant of NAFLD outcomes. Future studies assessing the NAFLD disease burden should also take these histological and pathological data into account. Third, NAFLD prevalence was estimated using a mathematical model that included patients who were diagnosed only by USS or another imaging diagnostic tool. Since there are few effective diagnostic methods available in daily clinical practice—and because we excluded NAFLD diagnosed using other methods (eg, non-invasive scores)—our data may underestimate the NAFLD disease burden.

In summary, NAFLD prevalence is increasing worldwide and the disease is being diagnosed in all parts of the world. The highest prevalence was observed in North Africa and the Middle East, while the greatest increase was detected in Western Europe and North America. This dramatic and significant increase in NAFLD prevalence is alarming and suggests that NAFLD has emerged as a new public health concern worldwide. More efficient prevention strategies are urgently needed.

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