Journal Pre-proof

Global Burden of Metabolic Dysfunction-Associated Liver Disease, 2010 to 2021☆

Gong Feng, Giovanni Targher, Christopher D. Byrne, Yusuf Yilmaz, Vincent Wai-Sun Wong, Cosmas Rinaldi Adithya Lesmana, Leon A. Adams, Jerome Boursier, Georgios Papatheodoridis, Mohamed El-Kassas, Nahum Méndez-Sánchez, Silvia Sookoian, Laurent Castera, Wah-Kheong Chan, Feng Ye, Sombat Treeprasertsuk, Helena Cortez-Pinto, Hon Ho Yu, Won Kim, Manuel Romero-Gomez, Atsushi Nakajima, Khin Maung Win, Seung Up Kim, Adriaan G. Holleboom, Giada Sebastiani, Ponsiano Ocama, John D. Ryan, Monica Lup□or-Platon, Hasmik Ghazinyan, Mamun Al-Mahtab, Saeed Hamid, Nilanka Perera, Khalid Alswat, Qiuwei Pan, Michelle T. Long, Vasily Isakov, Man Mi, Marco Arrese, Arun Sanyal, Shiv Kumar Sarin, Nathalie Carvalho Leite, Luca Valenti, Philip N. Newsome, Hannes Hagström, Salvatore Petta, Hannele Yki-Jarvinen, Jörn M. Schattenberg, Marlen I. Castellanos Fernández, Isabelle Leclercq, Gulnara Aghayeva, Abdel-Naser Elzouki, Ali Tumi, Ala I. Sharara, Asma Labidi, Faisal M. Sanai, Khaled Matar, Maen Al-Mattooq, Maisam Waid Akroush, Mustapha Benazzouz, Nabil Debzi, Maryam Alkhatry, Salma Barakat, Said A. Al-Busafi, John Rwegasha, Wah Yang, Agyei Adwoa, Christopher Kenneth Opio, Mohammadjavad Sotoudeheian, Yu Jun Wong, Jacob George, Ming-Hua Zheng

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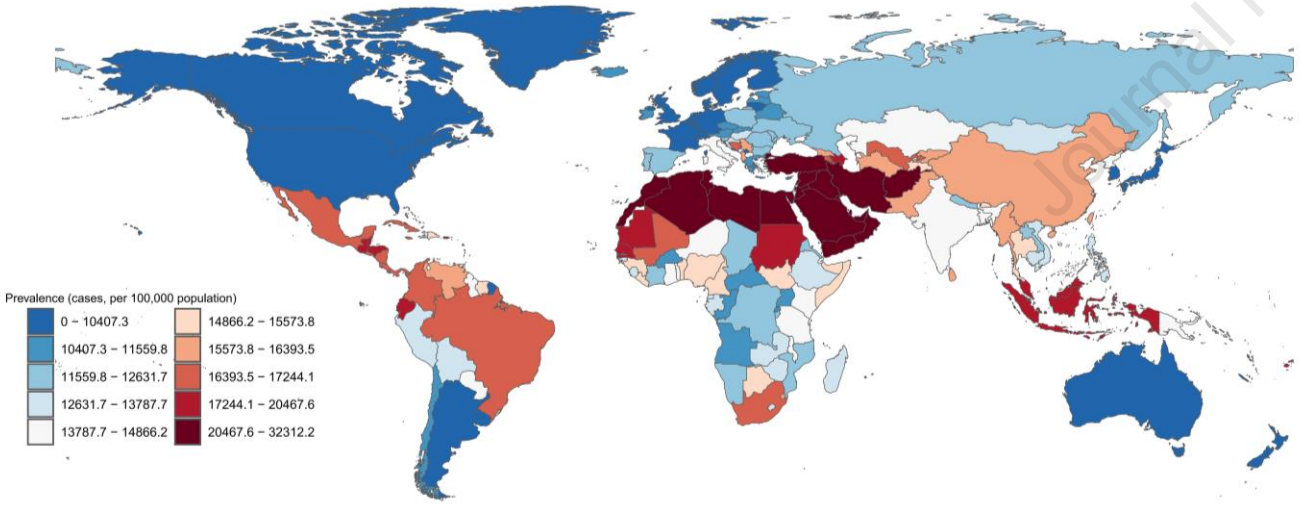
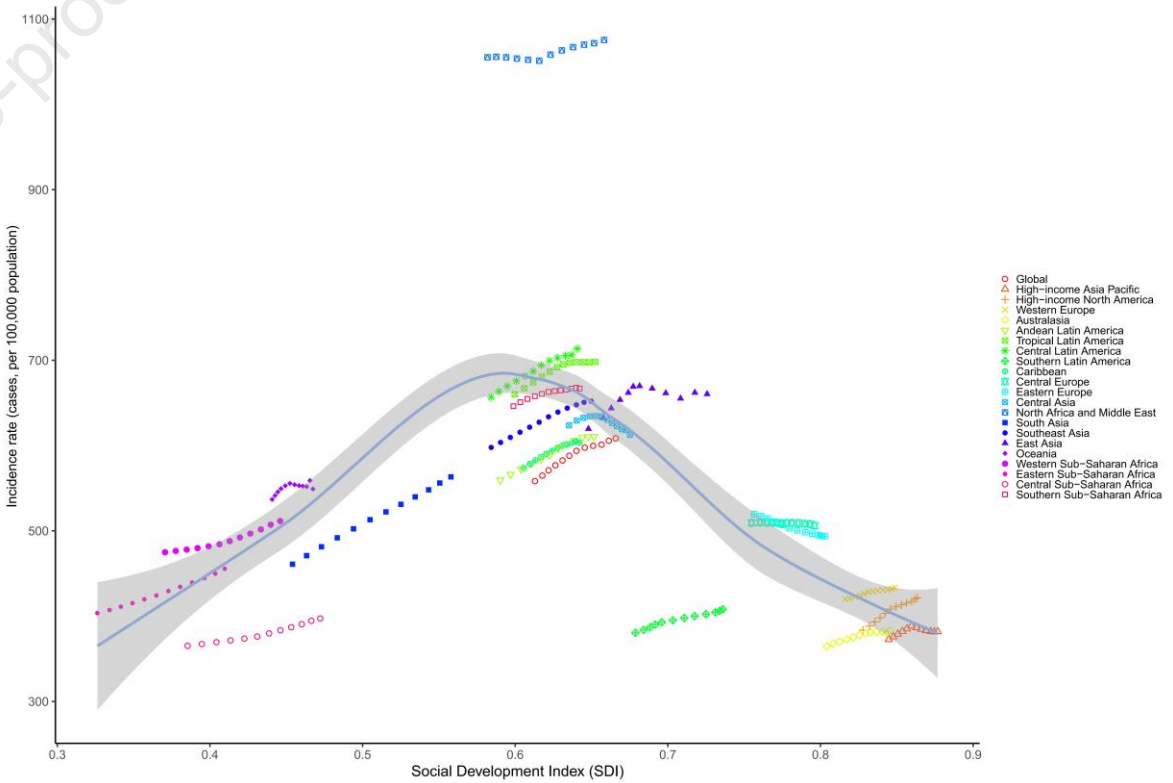
Global, Regional, and National Burden of Metabolic Dysfunction-Associated Liver Disease: A Systematic Analysis of the Global Burden of Disease Study 2021

Age-standardized point prevalence rates of MASLD per 100,000 population in 2021 by country



Age-standardized incidence rates of MASLD per 100,000 population for 21 GBD regions by SDI between 2010 and 2021



Global Burden of Metabolic Dysfunction-Associated Liver Disease, 2010 to 2021☆

Short Title: Global Burden of MASLD (2010-2021)

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Conflict of interest statement

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advisory board member for Abbott, Roche, Abbvie, Boehringer Ingelheim and Novo Nordisk; and a speaker for Abbott, Novo Nordisk, Echosens, Viatris and Hisky Medical. **John D. Ryan** received consultancy fees from Falk, Gilead, Pfizer and a speaker honorarium from Takeda. **Luca Valenti** reports consulting fees from Gilead, Pfizer, Astra Zeneca, Novo Nordisk, Intercept pharmaceuticals, Diatech Pharmacogenetics, IONIS, Viatris; honoraria from MSD, Gilead, AlfaSigma, AbbVie, Resalis, grants from Gilead. **Jörn M. Schattenberg** serves as a consultant for Akero, Alentis Therapeutics, Astra Zeneca, Apollo Endosurgery, Boehringer Ingelheim, GSK, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi and Siemens Healthineers. He has received research funding from Gilead Sciences, Boehringer Ingelheim and Siemens Healthcare GmbH. He holds stock options in AGED diagnostics and Hepta Bio. He has also received speaker honorarium from Gilead Sciences, Advanz, Echosens, MedPublico GmbH. **Manuel Romero-Gomez** reported receiving personal fees from Echosens. **Seung Up Kim** reported personal fees from Gilead Sciences, GSK, Bayer, Eisai, AbbVie, Echosens, MSD, Bristol-Myers Squibb, AstraZeneca, and grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences. **Philip N Newsome** reported receiving grants from Novo Nordisk, advisory board and personal consulting fees, honoraria for lectures and travel expenses from Novo Nordisk, personal consulting and advisory board fees from Boehringer Ingelheim, Gilead, Intercept, Poxel Pharmaceuticals, Bristol-Myers Squibb, Pfizer, MSD, Sun Pharma, Eli Lilly, Madrigal, GSK, and nonfinancial support for educational events from AiCME. **Arun**

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Abstract

Background & Aims: This study used the Global Burden of Disease data (2010-2021) to analyze the rates and trends of point prevalence, annual incidence, and years lived with disability (YLDs) for metabolic dysfunction-associated steatotic liver disease (MASLD) in 204 countries.

Methods: Total numbers and age-standardized rates per 100,000 population for MASLD prevalence, annual incidence, and YLDs were compared across regions and countries by age, sex, and sociodemographic index (SDI). Smoothing spline models were used to evaluate the relationship between the burden of MASLD and SDI. Estimates were reported with uncertainty intervals (UI).

Results: Globally, in 2021, the age-standardized rates per 100,000 population of point prevalence of MASLD were 15018.1 cases (95% UI 13,756.5 to 16,361.4), annual incidence rates were 608.5 cases (598.8-617.7), and YLDs were 0.5 (0.3 to 0.8) years. MASLD point prevalence was higher in men than women (15731.4 vs. 14310.6 cases per 100,000 population). Prevalence peaked at ages 45-49 for men and 50-54 for women. Kuwait (32,312.2 cases per 100,000 people; 95% UI: 29,947.1-34,839.0), Egypt (31,668.8 cases per 100,000 people; 95% UI: 29,272.5-34,224.7), and Qatar (31,327.5 cases per 100,000 people; 95% UI: 29,078.5-33,790.9) had the highest prevalence rates in 2021. The largest increases in age-standardized point prevalence estimates from 2010 to 2021 were in China (16.6%, 95% UI 14.4-18.6%), India (12.5%, 95% UI 11.3-13.6%), and Sudan (12.4%, 95% UI 8.9-15.8%). MASLD incidence varied with SDI, peaking at moderate SDI levels.

Conclusions: MASLD is a global health concern, with the highest prevalence reported in Kuwait, Egypt, and Qatar. Raising awareness about risk factors and prevention is essential in every country, especially in China, India, and Sudan, where disease incidence and prevalence are rapidly increasing.

Keywords: Metabolic dysfunction-associated fatty liver disease, Non-alcoholic fatty liver disease, Metabolic dysfunction-associated steatotic liver disease, Epidemiology

Impact and implications

This research provides a comprehensive analysis of the global burden of MASLD, highlighting its rising prevalence and incidence, particularly in countries with varying sociodemographic indices. The findings are significant for both clinicians and policymakers, as they offer critical insights into the regional disparities in MASLD burden, which can inform targeted prevention and intervention strategies. However, the study's reliance on modeling and available data suggests cautious interpretation, and further research is needed to validate these findings in clinical and real-world settings.

Introduction

Non-alcoholic fatty liver disease (NAFLD), recently renamed as metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD), has rapidly become the most common chronic liver disease worldwide, with an estimated 38% of the global adult population currently affected.[1,2] For simplicity, we opted for using the term MASLD throughout this manuscript. MASLD is closely linked to obesity, type 2 diabetes, hypertension, and other metabolic risk abnormalities.[3] MASLD may progress from metabolic dysfunction-associated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with varying levels of fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[4]

The Global Burden of Diseases (GBD) study is an important epidemiological research project led by the Institute for Health Metrics and Evaluation at the University of Washington, USA.[5,6] The GBD study is considered one of the most extensive burden-of-disease studies conducted to date.[7] While Paik et al. have recently utilized the GBD database to investigate the disease burden of MASLD, it is important to underline that their analysis was conducted using the previous 2019 GBD data and did not explore the relationships between the sociodemographic index (SDI) and the disease burden of MASLD.[8]

The global incidence and prevalence rates of MASLD have notably increased in the

last decades. This increase in the global prevalence and incidence rates of MASLD is closely linked to modern dietary patterns, decreased physical activity, and rapid urbanization. MASLD is not only associated with liver disease but data suggests that it is also contributing to various extrahepatic complications, such as cardiovascular disease, type 2 diabetes, chronic kidney disease and certain types of extrahepatic cancers, which further increase the patient's risk of disability.[9-11] MASLD is recognized as a significant risk factor likely to be attributed to the rise in years lived with disability (YLDs), but needs further research to provide evidence for these hypotheses.[12] Genetic susceptibility also plays a role in MASLD development, with some genetic variants, such as Patatin-like phospholipase domain-containing protein 3, Transmembrane 6 superfamily member 2, and Membrane-bound O-acyltransferase domain-containing 7, identified as risk factors for increased hepatic fat accumulation and disease progression.[13] The most updated data from the GBD 2021 was published in mid-May 2024, offering detailed information on various diseases and injuries over different time frames.[14] Utilizing the GBD 2021 dataset can enhance our understanding of the updated global, regional and national burden of MASLD.

Methods

Data sources

Data for this study were obtained from the GBD 2021 database. The database draws from 328,938 data sources and disaggregates data by key demographic variables such as age, sex, location, and socioeconomic groups. Health disparities can be identified

through further analysis. GBD 2021 encompasses the global burden of disease assessments for 204 countries (or regions) from 1990-2021. The data were generated from the GBD study results, publicly available at https://vizhub.healthdata.org/gbd-results/. This study used the GBD data (2010-2021) to analyze the rates and trends of point prevalence, annual incidence, and YLDs for MASLD in 204 countries.

Definition

The study employs various disease burden indicators, including the rates of prevalence, incidence, mortality, and years lived with disability (YLDs), to illustrate the impact of diseases on population health and the extent of their lethal hazards. Incidence refers to the frequency of new cases, reflecting the effect of the disease on population health. YLDs are a measure of the burden of disease that quantifies the effects of health conditions on an individual's life. The calculation method for YLDs involves multiplying the number of people with a specific disease or health condition within a given period by the disability weight of that disease or health condition. Therefore, YLDs provide an indicator of the burden of disease, reflecting the impact of specific diseases or health conditions on the quality of life. The GBD study incorporates global disease burden data from 2010 to 2021. NAFLD is defined by the presence of hepatic steatosis (>5% hepatic steatosis) without significant alcohol consumption or other known liver disease causes. In 2020, the term MAFLD was proposed by a group of researchers to emphasize the disease's link with metabolic dysfunction, requiring hepatic steatosis along with criteria such as overweight/obesity,

type 2 diabetes, or metabolic dysregulation.[15] In 2023, the term MASLD was proposed by three pan-national scientific associations. MASLD is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factor(s), and the absence of harmful alcohol intake.[1] The GBD study employs the sociodemographic index (SDI) as a composite measure to quantify the health-related socioeconomic development of regions. This index is derived from three key indicators: fertility rates among young women (under 25 years), educational attainment (average years of schooling for individuals ≥15 years), and economic prosperity (lag-distributed income per capita).[16] The SDI is computed as the geometric mean of these three components, each normalized to a scale of 0 to 1. To facilitate comparative analyses, the GBD 2021 study categorizes the 204 countries into five quintiles — low, low-middle, middle, high-middle, and high — based on their SDI values in 2021.[16]

Statistical methods

The prevalence and trends of MASLD were assessed through a range of statistical analysis methods. Initially, the point prevalence of MASLD per 100,000 population was calculated to indicate disease prevalence at a specific time; annual incidence was used to track new cases annually; and YLDs, determined by disease prevalence and associated disability weights, gauged the impact on quality of life. Disability weights, which represent the magnitude of health loss associated with specific health outcomes, are used to calculate YLDs for these outcomes in each population. The

weights are measured on a scale from 0 to 1, where 0 equals a state of full health and 1 equals death (https://ghdx.healthdata.org/record/ihme-data/gbd-2021-disability-weights). All estimates were accompanied by a 95% uncertainty interval (UI) to account for statistical variability in the forecast. Ul is widely used in GBD research, as it not only captures statistical uncertainty (such as sampling error) but also includes other sources of uncertainty (such as model selection and parameter estimation). Subsequently, a regression model was employed to analyze the changing burden of MASLD from 2010 to 2021, identifying countries and regions with notable growth or decline. Furthermore, a comparison of MASLD burden across different countries and regions was conducted, evaluating variations among age groups, sexes, and sociodemographic index (SDI) levels to investigate the effect of economic development and lifestyle changes on the rates of prevalence, incidence, and YLDs of MASLD. Smoothing spline models were used to evaluate the relationship between the burden of MASLD and SDI for the 21 regions and 204 countries and territories. The expected values were determined through a calculation that considers the SDI and disease rates across all locations.[16] We fitted smooth splines using the Locally Weighted Scatterplot Smoothing (LWSS) method, which automatically determines the degree, number, and location of nodes (knots) based on the data and the span parameter.[16] The statistical computing software R (Version 3.5.2) was utilized to perform procedures for analysis and graphic representation.

Results

Global level for MASLD

Table 1 shows the prevalence, incidence, and YLD rates of MASLD in the general population for males and females in 2021. Additionally, it shows the percentage change in age-standardized rates (ASRs) per 100,000 population between 2010 and 2021 across various GBD regions. The global prevalence of MASLD in 2021 was approximately 1.27 billion (95% UI 1,157,934,071 to 1,380,435,423) with an ASR of 15,018.1 cases (95% UI 13,756.5 to 16,361.4) per 100,000 population, representing an 11.2% increase (95% UI 10.5% to 11.8%) in ASRs from 2010 to 2021. The global incidence of MASLD was about 48.35 million (95% UI 47,612,534 to 49,094,010) with an ASR of 608.5 cases (95% UI 598.8-617.7) per 100,000 population, reflecting a 3.2% increase (95% UI 2.1% to 4.2%). YLDs were reported at 44,089 (95% UI 29,048 to 65,849) with an ASR of 0.5 years (95% UI 0.3 to 0.8) per 100,000 population **(Table 1).**

Regional level for MASLD

In 2021, the highest age-standardized point prevalence rates of MASLD per 100,000 population were in North Africa and the Middle East (27,686.7 cases (95% UI 25,586.9 to 29,914.6)), Central Latin America (16,984.0 cases (95% UI 15,536.5 to 18,533.6)), and Tropical Latin America (16,662.7 cases (95% UI 15,244.9 to 18,205.5)). The lowest age-standardized rates per 100,000 population of MASLD were in High-income North America (10056.0 cases (95% UI 9187.3 to 10925.6)), Australasia (9468.2 cases (95% UI 8665.5 to 10349.4)), and high-income Asia Pacific

(8885.7 cases (95% UI 8148.4 to 9666.7)) (**Table 1**). High-income North America refers specifically to the United States and Canada. The high-income Asia-Pacific region refers to economically developed countries and territories within the Asia-Pacific area. These nations typically have high per capita income levels and well-established healthcare systems. Specific countries and regions in this category include Japan, South Korea, and Singapore.

Similarly, the highest age-standardized incidence rates per 100,000 population were in North Africa and the Middle East (1075.5 cases (95% UI 1049.6-1103.8)), Central Latin America (713.6 cases (95% UI 691.5-734.9)), and Tropical Latin America (698.1 cases (95% UI 624.4-797.7)). The lowest incidence rates per 100,000 population of MASLD were observed in Central Sub-Saharan Africa (397.2 cases (95% UI 333.7-486.3)), Australasia (383.2 cases (95% UI 368.0-400.4)), and high-income Asia Pacific (381.9 cases (95% UI 367.1-397.2)) (**Table 1**).

The highest age-standardized rates of YLDs per 100,000 population were in Andean Latin America (1.7 years (95% UI 1.0 to 2.4)), Central Latin America years (1.5 (95% UI 1.0 to 2.3)), and Eastern Europe (1.1 years (95% UI 0.7 to 1.8)). The lowest age-standardized rates of YLDs per 100,000 population were in East Asia (0.3 years (95% UI 0.2 to 0.4)), Central Sub-Saharan Africa (0.3 years (95% UI 0.2 to 0.5)), and Oceania (0.2 years (95% UI 0.1 to 0.3)) **(Table 1**).

The highest percentage change in the age-standardized prevalence rate of MASLD per 100,000 population from 2010 to 2021 was an increase observed in East Asia (+16.6% (95% UI 14.5% to 18.5%)), South Asia (+12.0% (95% UI 10.9% to 12.9%)) and Southern Latin America (+7.2% (95% UI 4.3%-9.9%)). The highest percentage change in the age-standardized annual incidence of MASLD per 100,000 population from 2010 to 2021 was an increase observed in East Asia (+10.7% (95% UI 9.1%-12.6%), Southern Latin America (+8.9% (95% UI 5.6%-12.1%), and Western Europe (+6.4% (95% UI 5.0%-8.0%). In addition, the highest increase in age-standardized years lived with disability from MASLD per 100,000 population from 2010 to 2021 was in Central Asia (+16.3% (95% UI 8.5%-24.4%)), Central Latin America (+14.2% (95% UI 8.1%-20.9%)), and Southern Latin America (+9.6% (95% UI -2.6%-23.4%) (**Table 1**).

National level for MASLD

The national age-standardized point prevalence rates of MASLD in 2021 ranged from 8,133.5 to 32,312.2 cases per 100,000 population. The countries with the highest age-standardized point prevalence rates per 100,000 population in 2021 were Kuwait (32312.2 cases (95% UI 29,947.1-34,839.0)), Egypt (31,668.8 cases (95% UI 29,272.5-34,224.7)), and Qatar (31,327.5 cases (95% UI 29,078.5-33,790.9)), whereas Canada (8,492.3 cases (95% UI 7,739.8-9,305.5)), Finland (8,358.5 cases (95% UI 7,620.0-9,180.6)), and Japan (8,133.5 cases (95% UI 7,457.7-8,837.4)) had the lowest age-standardized point rates of MASLD (**Figure 1** and **Supplementary Table 1**).

The highest national age-standardized annual incidence rates per 100,000 population of MASLD in 2021 were observed in Brazil (1,407.1 cases (95% UI 1221.7 to 1,659.1)), Qatar (1358.6 cases (95% UI 1,284.0 to 1,448.6)), and Saudi Arabia (1,333.3 cases (95% UI 1,187.2 to 1,516.0)), with the lowest national age-standardized annual incidence rates reported in Japan (349.0 cases (95% UI 330.3 to 371.7)), Finland (336.1 cases (95% UI 311.9 to 369.9)), and Canada (333.4 cases (95% UI 316.0 to 350.6)) **(Figure 2** and **Supplementary Table 2**). In addition, the highest age-standardized rates of YLDs per 100,000 population were in Mexico (2.2 years (95% UI 1.4 to 3.4)), Mongolia (2.1 years (95% UI 1.3 to 3.2)), and Ecuador (1.9 years (95% UI 1.2 to 2.8)). The lowest age-standardized rates of YLDs per 100,000 population were in Timor-Leste (0.2 years (95% UI 0.1 to 0.2)), Yemen (0.1 years (95% UI 0.1 to 0.2)), and Papua New Guinea years (0.1 (95% UI 0.1 to 0.2)) **(Supplementary Figure 1** and **Supplementary Table 3**).

The percentage change in age-standardized point prevalence rates per 100,000 population from 2010 to 2021 differed substantially between countries, with the largest increases in China (16.6% (95% UI 14.4% to 18.6%)), India (12.5% (95% UI 11.3% to 13.6%)), and Sudan (12.4% (95% UI 8.9% to 15.8%)) (**Supplementary Figure 2 and Supplementary Table 4**). The largest increases for percentage change in age-standardized annual incidence rates per 100,000 population from 2010 to 2021 were in China (10.1% (95% UI 8.5% to 12.0%)), Sudan (9.3% (95% UI 6.6% to

12.3%)), and India (8.9% (95% UI 7.8% to 10.0%)) (**Supplementary Figure 3 and Supplementary Table 5**). The largest increases for percentage change in age-standardized rates of YLDs per 100,000 population in 204 countries and territories between 2010 and 2021 were in Turkmenistan (39.2% (95% UI 21.2% to 56.5%)), Nepal (38.5% (95% UI 26.5% to 53.4%)), and Turkey (36.8% (95% UI 23.1% to 52.2%)) (**Supplementary Figure 4 and Supplementary Table 6**).

Age and sex patterns

In 2021, the global age-standardized point prevalence rates of MASLD were higher in men (15,731.4 cases (95% UI 14,392.7 to 17167.4) per 100,000 population) than women (14,310.6 cases (95% UI 13,114.9 to 15,573.6) per 100,000 population). The number of prevalent cases also rose with age, peaking in the 45-49 age group for men and in the 50-54 age group for women, and then decreased as age advanced in both sexes (**Figure 3 and Supplementary Table 7).** Regarding the number of incident cases and incidence rates at different ages in MASLD, the number and incidence rates for men peaked at ages 15-19 years, then gradually declined; for women, these numbers peaked at ages 20-24, followed by a gradual decline (**Supplementary Figure 5 and Supplementary Table 8)**. Regarding the number of YLD cases and YLD rates across different ages in MASLD, the number and YLD rates for men peaked at ages 65-69. Similarly, for women, these values also reached their highest at ages 65-69, followed by a gradual decline thereafter (**Supplementary Figure 6 and Supplementary Table 9)**.

Observed burden of MASLD compared with expected by sociodemographic index

The incidence rates of MASLD peaked at moderate levels of social development and were lower at both low and high levels of social development. Some regions, such as North Africa and the Middle East, had higher-than-expected incidence rates, while more developed regions, like Australasia, had lower-than-expected incidence rates (**Figure 4).** The observed MASLD incidence rates were higher than expected, indicating that in certain regions, the actual incidence surpassed the rates predicted based on the region's SDI and disease rates. Similarly, for countries, MASLD incidence rates peaked at moderate levels of social development and were lower at both low and high levels of social development. Countries like Afghanistan, Yemen, and Sudan showed higher-than-expected incidence rates, whereas Australia, Canada, and Finland had lower-than-expected rates (**Figure 5).**

Supplementary Figure 7 shows the age-standardized prevalence rates of MASLD from 2010 to 2021 across GBD regions, grouped by the SDI. The overall trend indicates that MASLD prevalence rates peaked at moderate levels of social development and were lower at both low and high levels. Some regions, such as North Africa and the Middle East, showed higher-than-expected prevalence rates of MASLD, while Southern Latin America showed lower-than-expected prevalence rates. Similarly, countries, such as Egypt, Kuwait, and Qatar, had higher-than-expected prevalence rates of MASLD, whereas Japan, Canada, and Finland had

lower-than-expected rates (**Supplementary Figure 8)**.

Supplementary Figure 9 illustrates the age-standardized YLD rates from MASLD per 100,000 population across GBD regions, grouped by the SDI for 2010-2021. The trends indicate that YLD rates also peaked at moderate levels of social development and decreased at lower and higher levels. Some regions, such as Central Latin America, had higher-than-expected YLD rates, while East Asia showed lower-than-expected YLD rates. Similarly, countries like Egypt, Mexico, and Qatar had higher-than-expected YLD rates, whereas Japan, Singapore, and Sweden had lower-than-expected YLD rates (**Supplementary Figure 10)**.

Discussion

This study utilizes data from the GBD 2021 to examine the point prevalence and annual incidence of MASLD across 204 countries and regions from 2010 to 2021, along with trends in YLDs. The analysis of the GBD 2021 study highlights global prevalence patterns of MASLD and offers detailed insights into the burden of the disease across different sexes, ages, and SDI groups. Thus, the present analysis investigates the disease burden of MASLD using data from the most recent GBD period (2010-2021), providing an up-to-date analysis of this important health issue.

Our study offers several advantages over previously published research using the GBD database. Firstly, regarding data scope and time, Zhang et al. selected the period

from 1990 to 2021, while Pojsakorn et al. focused on 2000 to 2019.[17,18] We chose the period from 2010 to 2021 because the global burden of MASLD has significantly changed over the past decade. Selecting this time frame allows us to capture these changes. While GBD data has been available since 1990, MASLD-related data before 2010 is often scarce or lower in quality, so we focused on a more reliable period. Secondly, Zhang et al. reported only on MASLD-related DALYs and mortality, which is entirely different from our study's focus on the rates of incidence, prevalence, and YLDs of MASLD.[17] Pojsakorn et al. did not analyze incidence and YLDs.[18] Allen et al. provided a comprehensive review without specifically reporting updated rates of incidence, prevalence, or YLDs for MASLD.[19] Lastly, regarding the geographical scope, our study provides a more detailed and updated analysis of MASLD burden in 204 countries and emphasizes the differences in disease prevalence and incidence among countries with different SDI levels.

In 2021, the global age-standardized point prevalence rate of MASLD was 15,018.1 cases per 100,000 people, with an annual incidence rate of 608.5 cases per 100,000. These findings highlight MASLD as a growing public health concern globally. Kuwait, Egypt, and Qatar have the highest prevalence of MASLD. This high prevalence of MASLD could be attributed to specific dietary habits, lifestyle factors, and genetic susceptibility in these regions. Furthermore, China, India, and Sudan experienced the most significant increases in MASLD prevalence from 2010 to 2021. The rapid economic development and lifestyle changes in these countries might be the

618 primary drivers for the rising prevalence of MASLD.

619

620 The present study reported a higher prevalence of MASLD in men than in women. In
621 2021, the global age-standardized point prevalence rate of MASLD for men was
622 15,731.4 cases per 100,000 individuals, whereas for women, it was 14,310.6 cases per
623 100,000 individuals. A recent meta-analysis revealed that the global prevalence of
624 MASLD is higher than previously estimated and continues to rise at an alarming
625 rate.[20] There is a notably higher incidence and prevalence of MASLD in men than
626 women.[20] Sex-related differences in MASLD prevalence and incidence could be
627 attributed to various factors, such as different plasma hormone levels, menopausal
628 status, body fat distribution, and coexisting metabolic traits.[21] This study also shows
629 that MASLD prevalence peaked at different ages for men and women. In men, the
630 prevalence of the disease peaked in the 45-49 age group and gradually decreased. For
631 women, the prevalence of MASLD reached its highest value in the 50-54 age group.
632 This age disparity might indicate distinct physiological changes in metabolic function
633 and hepatic lipid accumulation between men and women. Moreover, the disparity
634 observed between affected ages in men and women might also be due to the
635 menopausal status, as menopause is associated with an increased risk for many
636 metabolic diseases.[22] In our study, women had higher MASLD-related YLDs than
637 men. Studies have shown that compared to men, women tend to report a more
638 pronounced decline in the quality of life and a greater symptom perception when
639 facing chronic diseases.[23] Women have greater amounts of visceral and subcutaneous

fat depots, especially in the post-menopausal period, which may be associated with higher levels of inflammatory biomarkers related to MASLD, thereby exacerbating disease progression and quality of life impairment.[24]

SDI is a composite indicator that assesses the socioeconomic development level of a country or region, considering factors such as per capita income, education level, and fertility rate. The GBD study indicates that SDI levels may significantly influence the incidence rates of MASLD. Generally, MASLD is most prevalent in countries with intermediate SDI levels, likely due to the impact of economic growth and lifestyle changes. Conversely, in countries with high SDI levels, the incidence of MASLD tends to be lower, possibly due to improved health education and preventive strategies. The study by Wu et al. suggested that the prevalence of MASLD exhibited varying trends worldwide from 1990 to 2019. MASLD prevalence was the highest in the moderate SDI group and the lowest in the low SDI group.[25]

The analysis of GBD 2021 data in our study can substantially support policymakers and public health experts. Firstly, it is essential to enhance health education to increase public awareness about MASLD and its major cardiometabolic risk factors. Encouraging a healthy diet, promoting physical activity, and reducing obesity rates may effectively lower the incidence rates of MASLD from common sense. However, further research is needed to confirm this relationship. Secondly, the healthcare system should focus on early screening and diagnosis of MASLD. Thirdly, we must

pay attention to the clinical complications related to MASLD.[26] This condition is not only associated with severe liver-related outcomes, such as cirrhosis and HCC, but it is also closely linked to the development of cardiovascular disease.[27] Therefore, management of MASLD should focus on maintaining and restoring liver health and including a comprehensive assessment and intervention of the patient's cardiovascular health status to reduce overall health risks. Furthermore, advocating for and implementing effective treatments, such as lifestyle intervention and pharmacotherapies, may represent a reasonable approach to potentially reduce symptoms and risk of long-term complications in people with MASLD. The recent FDA approval of resmetirom, a liver-targeted thyroid hormone receptor-β selective drug, offers hope for the treatment of adults with non-cirrhotic MASH and moderate to advanced fibrosis.[28] Resmetirom has shown efficacy in reducing hepatic fat content, improving liver histology, and ameliorating liver damage biomarkers while favorably affecting plasma lipid profile. Implementing resmetirom treatment will require careful patient selection and reliance on non-invasive liver fibrosis tests, marking a significant advancement in MASLD/MASH treatment and highlighting the need for ongoing research and therapeutic development.[29] While the data in the present study illustrate the magnitude of the problem and the increasing trends of MASLD over time, these findings could also inform policy decisions. With appropriate actions, it is possible that the observed global, regional and national trends of MASLD could be reversed, improving the individual's quality of life and reducing the overall health burden. However, it is essential to acknowledge that these outcomes

remain hypothetical at this stage, as further evidence is needed to support these conclusions.

This study has certain limitations that are strictly inherent to the GBD database and need to be acknowledged. Firstly, the accuracy and completeness of GBD database could be hindered by variations in data collection and reporting standards across different countries and regions. This variability might impact the comparability and interpretability of the data. Secondly, while the SDI utilized in the study is a composite measure, it may not entirely capture the socioeconomic status of diverse regions and its implications on MASLD. Thirdly, the GBD study, which estimates etiology-specific liver deaths through proportion models, has been criticized for its potential inaccuracies in measuring the trends of MASLD mortality.[30] Low-income countries may underreport the incidence and prevalence rates of MASLD, which could underestimate the exact rates in this group. That said, we chose to use the GBD model because of its comprehensive global scope and the ability to provide standardized comparisons across different regions and periods, which are essential for analyzing broad epidemiological patterns and informing public health strategies. In the future, we plan to conduct more detailed analyses considering these risk factors to provide a more comprehensive explanation of the epidemiological characteristics of MASLD. Fourthly, although the data used in this study primarily originate from the NAFLD era, it is important to acknowledge the highly consistent overlap between NAFLD and MASLD nomenclatures. NAFLD and MASLD are not two terms

entirely identical, as MASLD always incorporates metabolic dysfunction in its definition, but due to the consistent overlap between the two conditions, using MASLD as the primary term for this study is justified. Fifthly, no stratification considering cardiovascular risk factors has been made throughout the study. While Zhang et al.'s study does mention cardiovascular risk factors, their analysis of these factors is not specific to the MASLD population.[17] Instead, it encompasses the general population as a whole. This broad approach lacks specificity and may fail to elucidate the unique characteristics of cardiovascular risk factors within the MAFLD cohort.[17] We recognize that cardiovascular risk factors may provide additional insights into the observed differences. In future studies, we plan to explicitly integrate these cardiovascular risk factors to better clarify their specific role in the differences in the rates of MASLD observed between countries and regions. Additionally, our data presentation format is aligned with the style used in most current GBD studies. Although the GBD database contains relevant data on type 2 diabetes and obesity, these data cannot be correlated or matched with MASLD, meaning that a subgroup analysis of MASLD epidemiological data based on diabetes and obesity is not feasible.

Future research should leverage the granular data provided by this study to delve deeper into the regional disparities in MASLD prevalence and incidence.[4] Understanding the underlying causes of these differences, particularly the socioeconomic factors driving MASLD prevalence in countries with varying SDI

levels, could reveal more about the U-shaped relationship between economic development and MASLD burden. Moreover, identifying region-specific risk factors, such as genetic predispositions, dietary habits, or healthcare access, could help design more targeted public health interventions.[2] Additional research should also evaluate the effectiveness of socioeconomic policies to reduce MASLD risk in intermediate SDI regions, where the disease burden is most pronounced. Additionally, future studies should uncover the impact of lifestyle interventions and new pharmacological therapies, such as resmetirom, on the long-term outcomes of MASLD.[28] Understanding how these metabolic disorders may influence MASLD onset and progression will be key to refining treatment and prevention strategies.

In conclusion, this updated analysis of the GBD study examines the global burden of MASLD from 2010 to 2021, revealing a significant increase in the prevalence and incidence and YDL rates of this metabolic liver disease. Countries with intermediate SDI levels show the highest burden, likely due to rapid economic and lifestyle changes. China, India, and Sudan also showed substantial increases. Men exhibit a higher prevalence of MASLD than women, though women are more affected in terms of YLDs, with the peak age of prevalence of MASLD differing between sexes. Despite limitations like data variability, we believe that the study can offer important insights into MASLD's global trends, guiding public health strategies and early intervention efforts in high-burden regions.

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Table legend

Table 1. Prevalence, incidence, and years lived with disability (YLDs) of MASLD in the global population in 2021 for men and women, and percentage change of age-standardized rates (ASRs) per 100,000 population between 2010 and 2021 by Global Burden of Disease regions (generated from data available at https://vizhub.healthdata.org/gbd-results/)

Figure legends

Figure 1. Age-standardized point prevalence rates of MASLD per 100,000 population in 2021 by country.

Figure 2. Age-standardized annual incidence rates of MASLD per 100,000 people in 2021 by country.

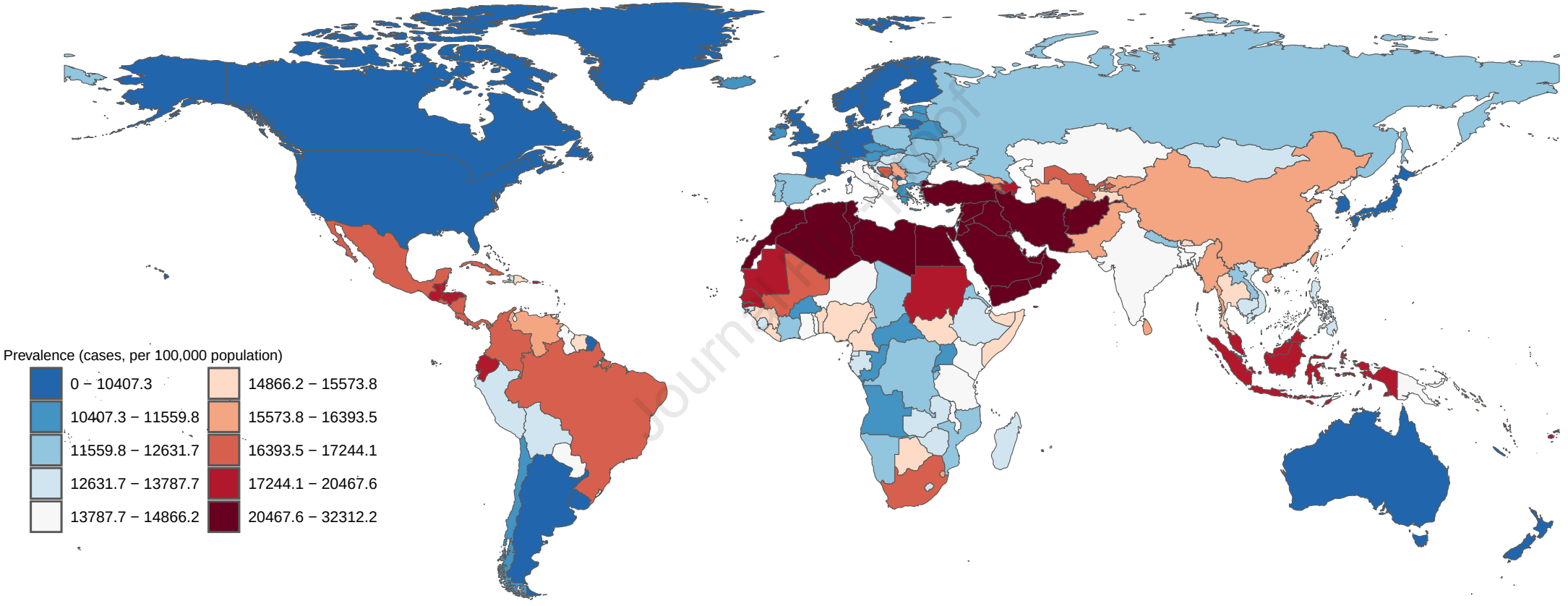
Figure 3. Total number of prevalent cases and age-standardized point prevalence rates of MASLD per 100,000 population by age and sex in 2021.

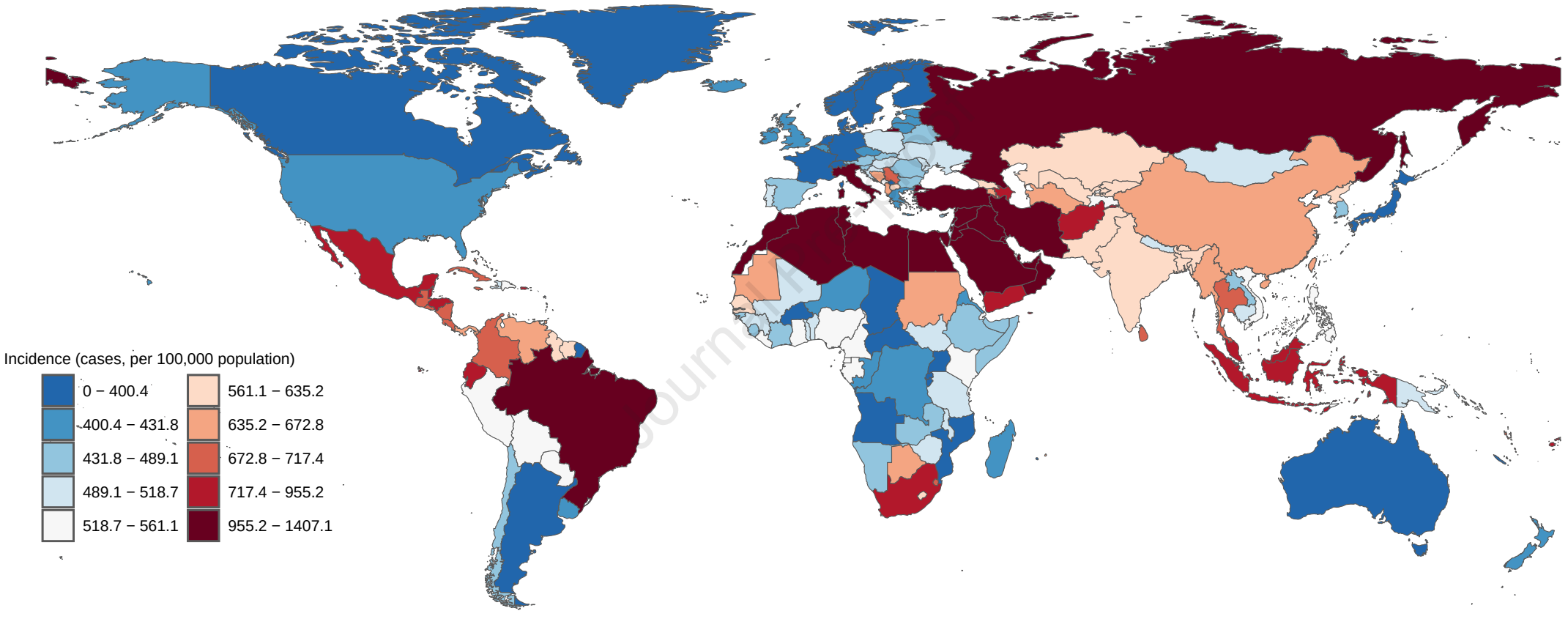
(A) Prevalence and rate of disease by age and sex. Dashed lines indicate 95% upper and lower uncertainty intervals (UI). (B) Age and sex distribution of disease prevalence. (C) Regional distribution of disease prevalence by sex.

Figure 4. Age-standardized incidence rates of MASLD per 100,000 population for 21 Global Burden of Disease regions by sociodemographic index (SDI) between 2010 and 2021. The purple line represents expected values based on the sociodemographic index and incidence rates in all locations. Twelve points are plotted for each Global Burden of Disease region and show the observed age-standardized incidence rates for

that region from 2010 to 2021.

Figure 5. Age-standardized incidence rates of MASLD per 100,000 population by 204 countries and sociodemographic index (SDI) in 2021. The black line represents expected values based on the sociodemographic index and incidence rates in 204 countries. Each point shows observed age-standardized incidence rates for a specified country in 2021.





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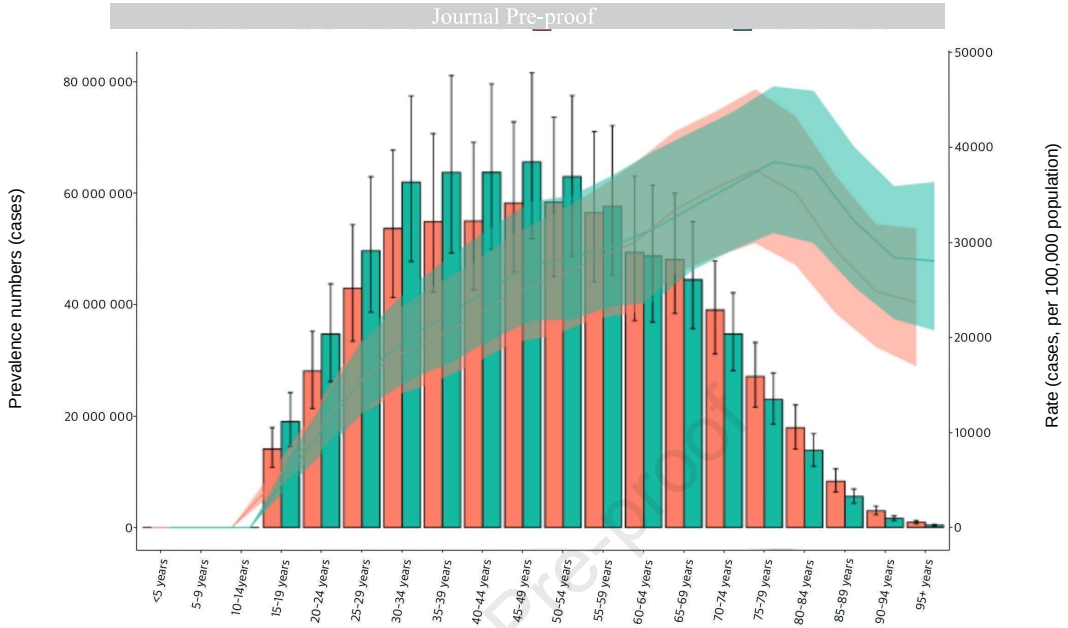

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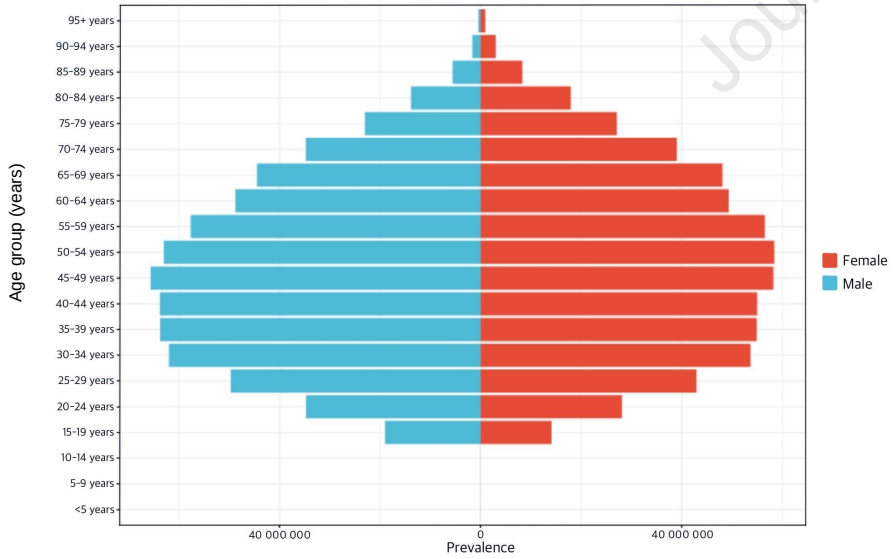

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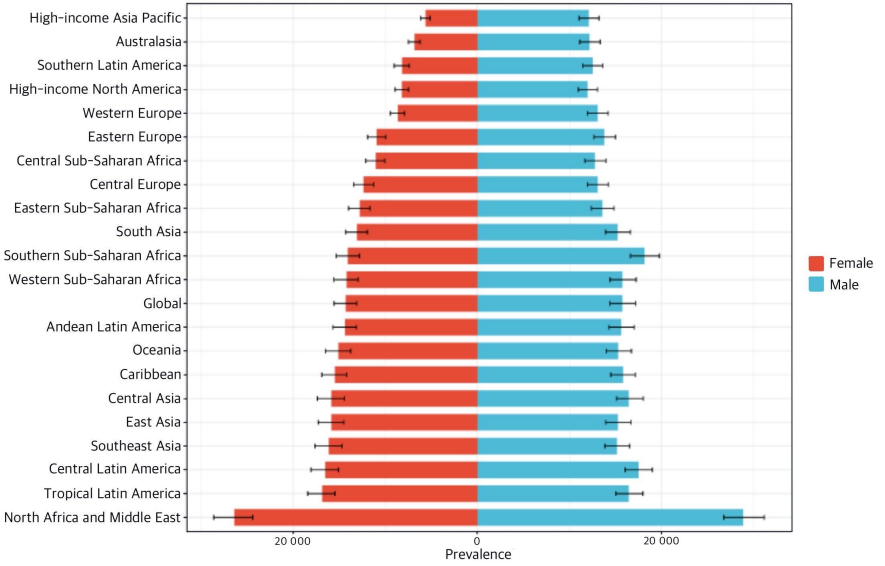

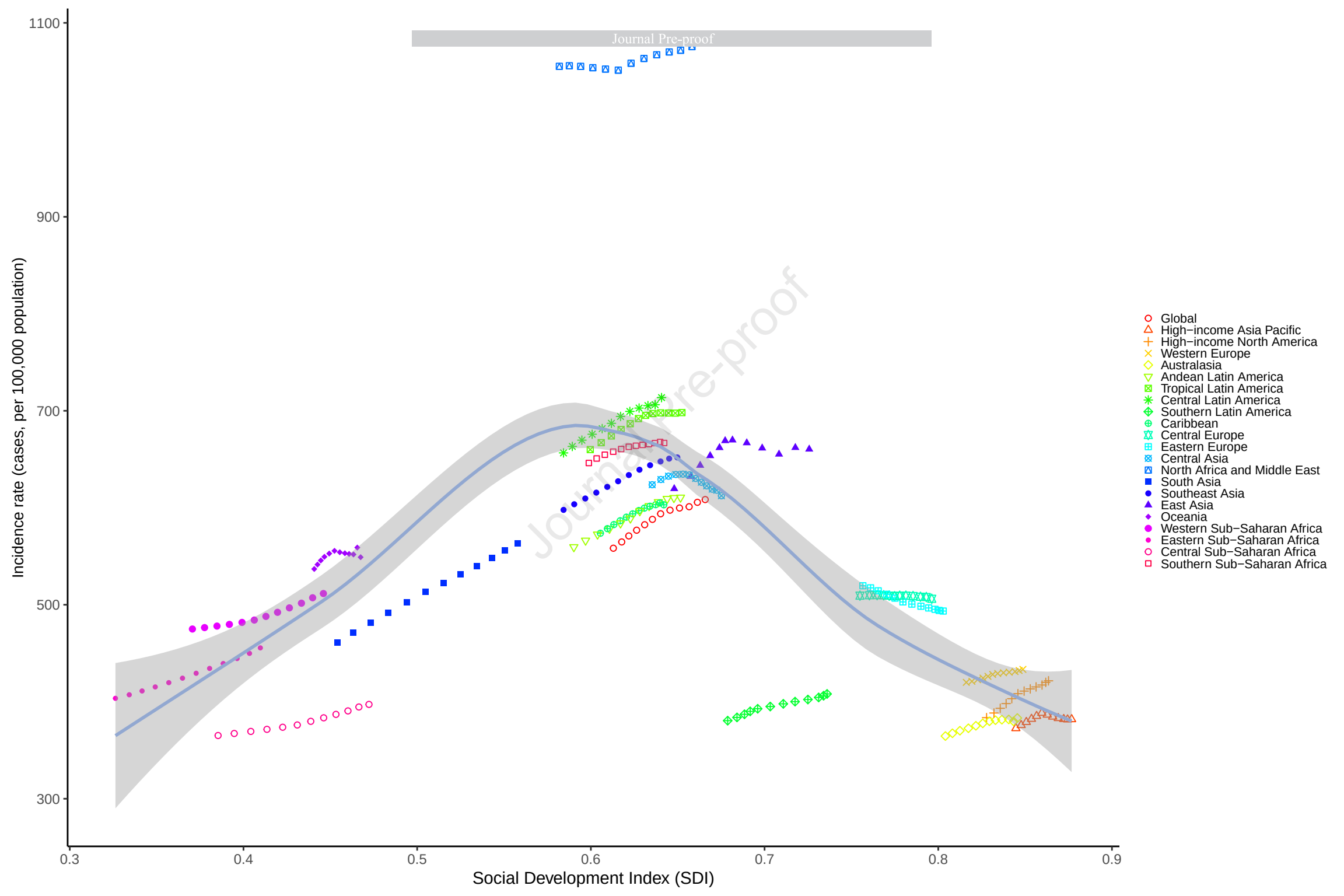

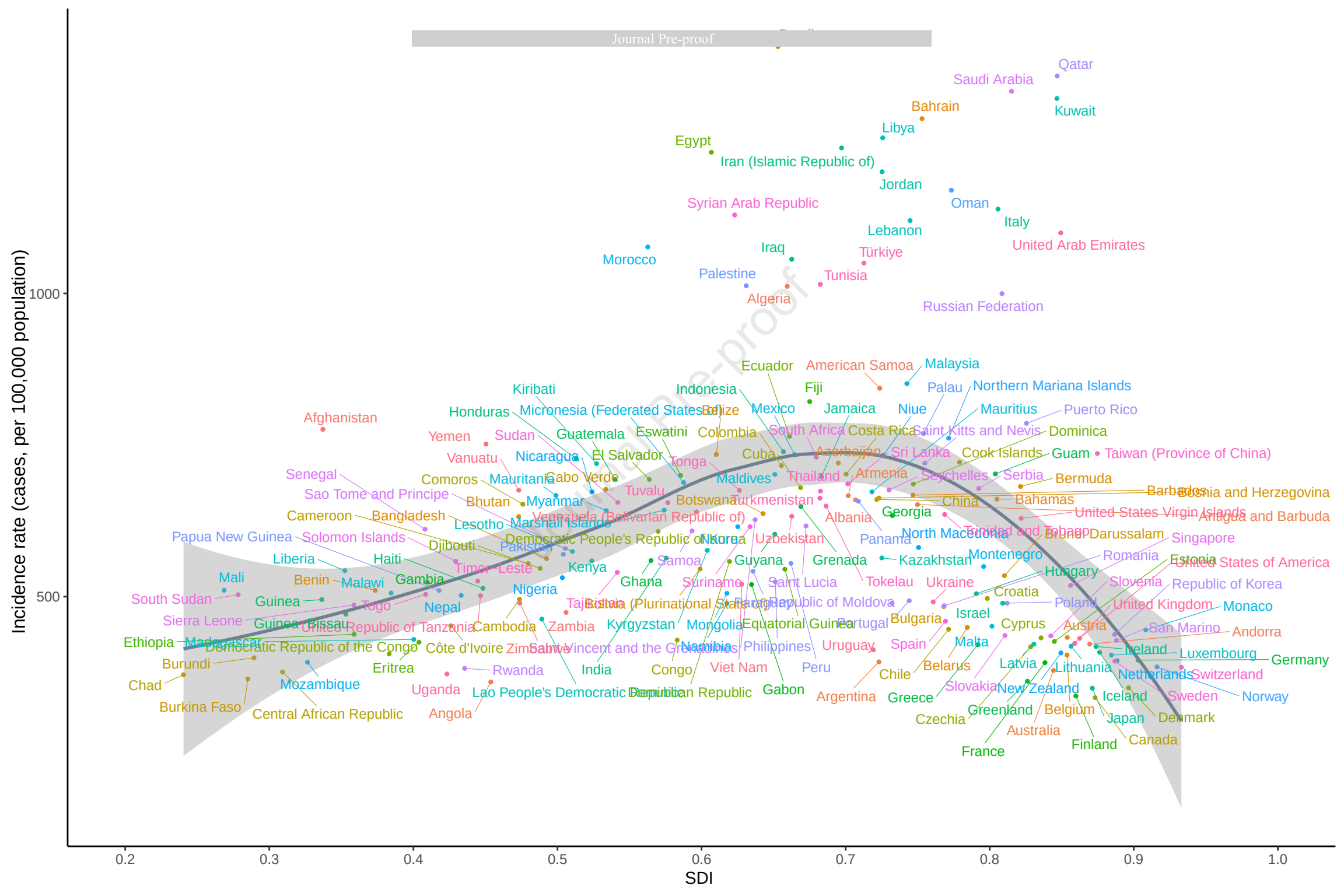

Highlights:

- MASLD is a global health concern, with the highest prevalence reported in Kuwait, Egypt, and Qatar.
- Men have a higher prevalence of MASLD than women, with the peak age of prevalence differing between sexes.
- Women are more affected in terms of years lived with disability.
- Raising awareness about MASLD risk factors and prevention is crucial worldwide, particularly in China, India, and Sudan.

Table 1. Total numbers and global and regional rates of prevalence, incidence, and years lived with disability (YLDs) from MASLD in the general population in 2021 for males and females, and percentage changes of age-standardized rates (ASRs) per 100,000 population between 2010 and 2021 by Global Burden of Disease regions (generated from data available at https://vizhub.healthdata.org/gbd-results/)

	Prevalence			Incidence			YLDs		
Regions	**No (95% UI, cases)**	**ASRs per 100,000 population (95% UI, cases)**	**Percentage change in ASRs per 100,000 population (95% UI, %)**	**No (95% UI, cases)**	**ASRs per 100,000 population (95% UI, cases)**	**Percentage change in ASRs per 100,000 population (95% UI, %)**	**No (95% UI, years)**	**ASRs per 100,000 population (95% UI, years)**	**Percentage change in ASRs per 100 000 population (95% UI, %)**
Global	1,267,867,998 (1157934071 to 1380435423)	15018.1 (13756.5 to 16361.4)	11.2 (10.5-11.8)	48353272 (47612534 to 49094010)	608.5 (598.8-617.7)	3.2 (2.1-4.2)	44089 (29048 to 65849)	0.5 (0.3 to 0.8)	0.8 (-2.4-3.9)
Andean Latin America	9737655 (8884038 to 10649706)	14984.8 (13708.4 to 16361.5)	4.1 (1.9-6.1)	399223 (393163 to 405283)	610.6 (583.1-647.4)	-2.8 (-5.8-0.5)	996 (627 to 1467)	1.7 (1.0 to 2.4)	8.1 (-2.2-18.4)
Australasia	3778619 (3457855 to 4124388)	9468.2 (8665.5 to 10349.4)	5.8 (3.2-8.7)	117958 (116015 to 119902)	383.2 (368.0-400.4)	5.4 (1.7-9.2)	261 (169 to 372)	0.5 (0.4 to 0.8)	16.6 (9.0-24.6)
Caribbean	8111960 (7440860 to 8804729)	15650.7 (14340.1 to 16986.2)	3.4 (1.9-4.9)	287884 (283459 to 292309)	603.1 (568.1-639.4)	3.5 (0.3-6.5)	453 (295 to 675)	0.9 (0.6 to 1.3)	15.6 (8.8-23.2)
Central Asia	15204171 (13885517 to 16673758)	16120.1 (14735.3 to 17604.5)	7.1 (5.6-8.6)	583559 (574644 to 592474)	612.4 (563.3-673.7)	-6.1 (-9.3--2.7)	908 (572 to 1379)	1.1 (0.7 to 1.6)	16.3 (8.5-24.4)
Central Europe	20606023 (18822096 to 22372105)	12731.5 (11618.6 to 13852.6)	5.2 (3.9-6.4)	569426 (560221 to 578631)	506.2 (492.2-522.3)	-7.4 (-8.9--5.7)	1211 (763 to 1851)	0.6 (0.4 to 1.0)	6.8 (0.6-12.4)
Central Latin America	44693566 (40900171 to 48782244)	16984.0 (15536.5 to 18533.6)	6.2 (4.8-7.6)	1786200 (1759467 to 1812932)	713.6 (691.5-734.9)	-1.4 (-3.0-0.3)	3929 (2514 to 5904)	1.5 (1.0 to 2.3)	14.2 (8.1-20.9)
Central Sub-Saharan Africa	10850618 (9833003 to 11986283)	11870.6 (10844.9 to 12943.4)	5.6 (3.1-8.5)	549883 (541760 to 558005)	397.2 (333.7-486.3)	-0.4 (-4.0-3.6)	183 (118 to 298)	0.3 (0.2 to 0.5)	11.2 (-0.8-23.3)
East Asia	301408386 (274406342 to 328824040)	15596.2 (14262.4 to 16999.3)	16.6 (14.5-18.5)	9905423 (9743925 to 10066921)	660.4 (625.4-699.0)	10.7 (9.1-12.6)	6226 (4124 to 9154)	0.3 (0.2 to 0.4)	-1.6 (-10.0-8.9)
Eastern Europe	34696290 (31695847 to 37763371)	12293.9 (11254.5 to 13359.2)	4.3 (2.3-6.0)	1035050 (1017952 to 1052148)	493.5 (454.6-543.7)	-7.8 (-10.0--5.6)	3298 (2028 to 5370)	1.1 (0.7 to 1.8)	-3.2 (-9.3-4.1)
Eastern Sub-Saharan Africa	37304081 (34041055 to 41466666)	13162.1 (12037.1 to 14400.2)	6.5 (5.5-7.5)	1953106 (1925028 to 1981184)	455.5 (440.7-471.3)	-0.9 (-2.4-0.6)	841 (566 to 1240)	0.5 (0.3 to 0.7)	6.1 (-2.3-14.8)
High-income Asia Pacific	24694242 (22636602 to 26784254)	8885.7 (8148.4 to 9666.7)	6.4 (3.5-8.9)	728246 (715952 to 740540)	381.9 (367.1-397.2)	5.8 (3.5-8.1)	1933 (1260 to 2786)	0.4 (0.3 to 0.7)	-20.1 (-24.6--15.0)
High-income North America	48995594 (44673054 to 53423290)	10056.0 (9187.3 to 10925.6)	4.5 (3.0-5.8)	1635646 (1609457 to 1661835)	421.6 (402.2-444.2)	-0.6 (-2.0-0.9)	3833 (2450 to 5799)	0.7 (0.4 to 1.0)	21.1 (15.9-26.3)
North Africa and Middle East	164312589 (151441885 to 179050648)	27686.7 (25586.9 to 29914.6)	6.0 (5.3-6.9)	6578946 (6480051 to 6677840)	1075.5 (1049.6-1103.8)	-2.8 (-4.6--0.9)	2600 (1703 to 3871)	0.6 (0.4 to 0.8)	23.5 (14.3-31.7)
Oceania	1625693 (1483817 to 1796525)	15182.7 (13936.2 to 16584.7)	2.1 (-0.0-4.4)	76654 (75506 to 77802)	549.0 (507.1-603.1)	-5.8 (-9.5--1.6)	18 (12 to 28)	0.2 (0.1 to 0.3)	-3.7 (-11.8-3.8)
South Asia	249790702 (227865117 to 273237523)	14158.3 (12940.9 to 15445.1)	12.0 (10.9-12.9)	10765351 (10602018 to 10928683)	563.3 (518.2-614.2)	1.3 (-0.5-3.4)	4838 (3193 to 7249)	0.3 (0.2 to 0.5)	20.8 (15.0-26.6)
Southeast Asia	115103788 (104841848 to 125940613)	15691.7 (14308.3 to 17127.2)	5.7 (4.6-6.7)	4606197 (4535042 to 4677353)	651.9 (635.1-669.3)	-0.7 (-2.1-0.6)	2553 (1682 to 3822)	0.4 (0.3 to 0.6)	8.2 (-1.2-17.0)
Southern Latin America	8080745 (7374984 to 8823030)	10292.5 (9394.6 to 11265.4)	7.2 (4.3-9.9)	283022 (278411 to 287634)	408.1 (377.8-443.1)	8.9 (5.6-12.1)	511 (315 to 788)	0.6 (0.4 to 0.9)	9.6 (-2.6-23.4)

Southern Sub-Saharan Africa	11781789 (10763174 to 12907446)	15937.2 (14572.6 to 17388.0)	7.1 (5.6-8.8)	532714 (524679 to 540749)	666.8 (616.9-722.6)	1.9 (-0.5-4.3)	346 (232 to 499)	0.6 (0.4 to 0.8)	-1.0 (-7.9-6.1)
Tropical Latin America	42870510 (39161072 to 46852272)	16662.7 (15244.9 to 18205.5)	3.8 (2.2-5.7)	1584118 (1559329 to 1608907)	698.1 (624.4-797.7)	-3.0 (-5.1--0.9)	1306 (823 to 2056)	0.5 (0.3 to 0.8)	11.0 (5.0-16.2)
Western Europe	66258939 (60940043 to 71561630)	10841.8 (9939.0 to 11802.0)	7.0 (5.9-8.2)	1871635 (1841743 to 1901527)	433.3 (426.6-441.9)	6.4 (5.0-8.0)	6556 (4227 to 9738)	0.8 (0.5 to 1.3)	-12.2 (-16.2--7.7)
Western Sub-Saharan Africa	47962036 (43856187 to 53002936)	14936.8 (13659.3 to 16347.6)	6.2 (5.3-7.2)	2501856 (2465846 to 2537866)	511.6 (490.5-534.7)	4.3 (2.5-6.1)	1289 (889 to 1875)	0.6 (0.4 to 0.9)	9.0 (-2.4-19.0)