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Exploring the landscape of steatotic liver disease in the general US population

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Abstract

Background and Objective: The aim of the present study is to explore the epidemiologic impact of the definition of steatotic liver disease (SLD) proposed by a multisociety (American Association for the Study of the Liver-the European Association for the Study of Liver Diseases-Asociación Latinoamericana para el Estudio del Hígado) Delphi consensus statement.

Methods: This is a cross-sectional study of US adults participating in the 2017–2020 cycles of the National Health and Nutrition Examination Survey who were evaluated by vibration-controlled transient elastography. Hepatic steatosis and fibrosis were diagnosed by the median value of controlled attenuation parameter and liver stiffness measurement using cut-offs of 274 dB/m and 8.0 kPa, respectively. Recently proposed criteria for metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD (MASLD + significant alcohol consumption), MASLD-Viral hepatitis and cryptogenic SLD were applied.

Results: SLD was present in 42.1% (95% CI: 40.3–43.9) of the 3173 included participants. Among patients with SLD, 99.4% met the metabolic dysfunction definition. Moreover, 89.4%, 7.7%, 2.4%, 0.4% and 0.1% were defined as MASLD, MetALD, MASLD-Viral, alcoholic liver disease (ALD) (significant alcohol consumption without metabolic dysfunction) and cryptogenic, respectively. No patients without metabolic dysfunction had significant liver fibrosis, which was present in 15.2%, 9.5% and 19.5% of patients with MASLD, MetALD and MASLD-viral, respectively. Approximately, 90% of the overall adult US population could be diagnosed with metabolic dysfunction according to the consensus criteria. A high degree of concordance was found between MASLD and the previously proposed metabolic dysfunction-associated fatty liver disease definition.

Conclusions: Metabolic dysfunction is present in almost all patients with SLD in the United States. The new change in diagnostic criteria did not significantly impact disease prevalence.

Abbreviations: CAP, controlled attenuation parameter; MAFLD, metabolic-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.

KEYWORDS
Fibroscan, MAFLD, MASLD, steatotic liver disease

1 | INTRODUCTION

Although the connection between liver fat content and the development of liver fibrosis has been recognized for over five decades,[1] it was in 1980 that Ludwig and colleagues identified it as a separate diagnostic condition.[2] These researchers observed histological characteristics similar to those typically associated with alcoholic hepatitis in a group of middle-aged individuals with elevated liver enzymes, despite their minimal or no alcohol consumption. They coined the term non-alcoholic steatohepatitis (NASH) to describe this condition. Subsequently, it became evident that NASH represented a more aggressive subtype of non-alcoholic fatty liver disease (NAFLD), which encompasses the excessive accumulation of fat within liver cells, without any other identifiable causes of liver steatosis or chronic liver disease.[3]

Simultaneously, the close correlation between NAFLD and visceral obesity, insulin resistance, type 2 diabetes (T2D) and metabolic syndrome (MS) was clarified.[4–6] Considering the escalating rates of obesity and T2D in the general population, NAFLD has emerged as the most prevalent chronic liver condition worldwide, affecting approximately 30% of individuals.[7–9] In recent years, experts in the field have engaged in a lively discussion concerning the terminology and diagnostic criteria associated with liver steatosis. Some authors have expressed the view that the current diagnostic criteria for NAFLD categorize it as a diagnosis of exclusion, failing to acknowledge its strong connection to metabolic dysfunction and insulin resistance. Additionally, there has been a consideration that referring to alcohol use in relation to NAFLD may contribute to potential stigmatization.

To address these limitations, a group of specialists introduced a new disease entity known as metabolic (dysfunction)-associated fatty liver disease (MAFLD), accompanied by a set of criteria that facilitate a positive diagnosis rather than an exclusionary one.[10,11] MAFLD encompasses individuals with liver steatosis and metabolic dysfunction, irrespective of their alcohol consumption. Although many Authors and institutions have embraced the new definition,[12] certain concerns have been raised. These include the persistent use of the term "fatty," which could be perceived as stigmatizing by some individuals, as well as potential negative consequences on the development of biomarkers and therapies due to variations in the diagnostic criteria.[13,14]

Recently, the American Association for the Study of the Liver, the European Association for the Study of Liver Diseases and the Asociación Latinoamericana para el Estudio del Hígado collaborated extensively to address these concerns and establish a consensus on the terminology and diagnostic criteria for this condition.[15] They employed a Delphi process involving multiple stakeholders. As a result, the term "steatotic liver disease" (SLD) was selected as a comprehensive term encompassing all causes of liver steatosis. Furthermore, the consensus group decided to replace the term NAFLD with "metabolic dysfunction-associated steatotic liver disease" (MASLD). To diagnose MASLD, the identification of metabolic dysfunction in accordance with newly established diagnostic criteria is deemed necessary.

Lay summary

In the present study, we evaluated how the new definition of metabolic dysfunction-associated steatotic liver disease impacted disease epidemiology in the United States. We show that while prevalence of disease was similar compared with previous definitions, 9 out of 10 US adults meet the new criteria for metabolic dysfunction.

In this context, the primary objective of the present study is to evaluate the impact of the proposed change in diagnostic criteria to SLD in the general US population. Ancillary objectives are to evaluate the proportion of US adults meeting the new definition of metabolic dysfunction and comparing the epidemiology of MASLD with those of MAFLD and NAFLD. To this aim, we conducted a cross-sectional study based on the 2017–2020 cycles of the National Health and Nutrition Examination Survey (NHANES).

2 | MATERIALS AND METHODS

The current analysis utilizes publicly available data obtained from the National Center for Health Statistics. The data can be accessed at https://wwwn.cdc.gov/nchs/nhanes/default.aspx. The analysis focuses on the 2017–2020 cycles of NHANES, which is a comprehensive survey conducted in the United States by the National Center for Health Statistics. NHANES is an ongoing cross-sectional complex survey that aims to include individuals from the general population of all ages who are not institutionalized. To achieve this, NHANES employs a stratified, multistage, clustered probability sampling design. The survey deliberately oversamples certain demographic groups, such as non-Hispanic black and Hispanic individuals, those with low income, and older adults. The survey process involves a structured interview conducted in the participants' homes, followed by a standardized health examination that includes both physical examinations and laboratory tests. Detailed information on the data collection methodology can be found elsewhere.[16]

The coronavirus disease 2019 pandemic required suspension of the NHANES 2019–2020 field operations in March 2020. Therefore, the partial 2019–2020 data were combined with the full data set from the previous cycle (2017–2018) to create nationally representative 2017-March 2020 pre-pandemic data files. All analyses reported in this study were performed according to specific guidance from the NCHS.[17] The original NHANES survey received

approval from the Centers for Disease Control and Prevention Research Ethics Review Board, and written informed consent was obtained from all adult participants. The present analysis, utilizing a completely de-identified dataset, was determined to be exempt from review by the Institutional Review Board at our institution.

2.1 | Clinical and laboratory data

Participants provided self-reported information on their age, sex, race-ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other), education, smoking status and previous medical history. During the mobile examination centre (MEC) visit, body measurements, such as height (cm), weight (kg), and waist circumference (cm) were recorded. Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Trained physicians obtained blood pressure measurements using a mercury sphygmomanometer and an appropriately sized cuff. After a 5-min seated resting period, three consecutive auscultatory blood pressure readings were taken. The average of these three measurements represented both systolic and diastolic blood pressure values.

Detailed laboratory methods for measuring total cholesterol, high-density lipoprotein (HDL) cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase, platelet count, creatinine and albumin are described elsewhere.[18] The presence of a current Hepatitis C virus infection was determined by the detection of viral RNA and/or a confirmed antibody test. For hepatitis B virus infection, a positive surface antigen test confirmed the presence of the infection.[18] Estimated glomerular filtration rate (eGFR) was computed according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[19] and CKD was defined as an eGFR <60 mL/min/1.73 m^2. Alcohol consumption was estimated based on self-reported data on the amount and frequency of alcohol use within the previous year. It was considered significant if >210 g/week for men and >140 g/week for women.[20] Diagnoses of heart failure, coronary artery disease and stroke were established based on self-reporting. Cardiovascular disease was considered present if the participant reported a previous history of one of these events. For the identification of advanced liver fibrosis, we applied the Fibrosis-4 index (FIB-4), according to the following formula[21]: [Age × AST]/[Platelets × √ALT]). A FIB-4 value <1.3 excluded the presence of advanced liver fibrosis, while a value ≥2.67 was considered indicative of advanced liver fibrosis.[22]

2.2 | Vibration-controlled transient elastography

In the 2017–2020 cycles, vibration-controlled transient elastography (VCTE) was performed by NHANES technicians after a 2-day training program with an expert technician, using the FibroScan® model 502 V2 Touch (Echosens) equipped with a medium (M) and extra-large (XL) probes. The M probe was used initially unless the machine indicated use of the XL probe. Inter-rater reliability between health technicians and expert FibroScan® technicians (tested on 32 subjects) was 0.86 for stiffness (mean difference 0.44 ± 1.3 kPa) and 0.94 for controlled attenuation parameter (CAP) (mean difference 4.5 ± 19.8 dB/m).

Exams were considered reliable only if at least 10 liver stiffness measurements (LSM) were obtained after a fasting time of at least 3 h, with an interquartile range/median <30%. Median CAP values ≥274 dB/m were considered indicative of steatosis in accordance with a landmark study by Eddowes et al.[23] A median LSM ≥8.0 kPa was considered indicative of significant (≥F2) fibrosis.[24]

2.3 | Subtypes of SLD

As recommended by the recent Delphi consensus, all patients with elastographic evidence of liver steatosis were diagnosed with SLD. Among these patients, a diagnosis of metabolic dysfunction was performed in the presence of at least one of the following criteria[15]:

(i) BMI ≥25 kg/m^2 or waist circumference ≥94 cm (males) and ≥80 cm females
(ii) Fasting plasma glucose ≥100 mg/dL OR HbA1c ≥5.7% OR a previous diagnosis of T2D OR treatment for T2D
(iii) BP ≥130/85 mmHg OR treatment for hypertension
(iv) Triglycerides ≥150 mg/dL or lipid lowering therapy
(v) HDL-C <40 mg/dL (males) OR <50 mg/dL (females) OR lipid lowering therapy

If the patient did not report any other form of liver disease and did not have viral hepatitis or significant alcohol consumption, a diagnosis of MASLD was performed. In the presence of metabolic dysfunction and significant alcohol consumption, a diagnosis of MASLD and increased alcohol consumption (MetALD) was made. If the patient had metabolic dysfunction and viral hepatitis, a diagnosis of MASLD-Viral hepatitis was made. If the patient did not have metabolic dysfunction and reported a history of significant alcohol consumption, a diagnosis of alcoholic liver disease (ALD) was made. Finally, in the absence of metabolic dysfunction, significant alcohol intake or viral hepatitis a diagnosis of cryptogenic SLD was made.

We also applied the definition of MAFLD using the criteria proposed by Eslam et al.[10]

2.4 | Statistical analysis

All analyses were conducted using Stata version 17 (StataCorp), taking into account the complex design of NHANES. We used weighting for each analysis, as suggested by the NCHS to obtain estimates that

were generalizable to the general adult US population. Data are expressed as weighted proportions (Standard Error [SE]) for categorical variables and as weighted means (SE) for continuous variables. Participants' features according to the presence or absence of liver steatosis (i.e. SLD) were compared using linear regression for continuous variables and the design-adjusted Rao-Scott chi-square test for categorical variables. A two-tailed value of $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

A total of 8965 participants aged ≥18 years attended a MEC visit. We initially excluded individuals without a reliable VCTE examination, leading to a population of 7768 participants. Among these, 4057 were excluded as they were not assigned to a morning session, precluding data on fasting plasma glucose and triglycerides. Among the remaining 3711 participants, 538 were excluded because of missing data on at least one variable included in the definition of metabolic dysfunction, leading to a final sample of 3173 individuals (Figure 1). Mean age was 46.8 years (95% confidence interval [CI] 44.9–48.1) and 48.7% were female.

Prevalence of SLD in the overall population was 42.1% (95% CI 40.3–43.9). Features of the study population according to the presence or absence of SLD are shown in Table 1. Patients with SLD were significantly older, with a higher proportion of males and Hispanic participants and a lower proportion of non-Hispanic blacks. They had a higher BMI and waist circumference, higher liver enzymes, a higher HOMA-IR and higher prevalence of CKD, cardiovascular disease and significant liver fibrosis according to both LSM and FIB-4. No significant differences were identified in platelet count, prevalence of viral hepatitis, cigarette smoke and significant alcohol consumption.

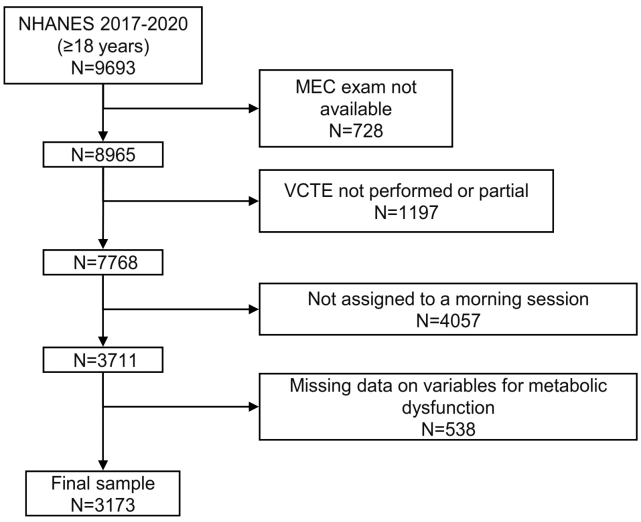

FIGURE 1 Flow chart of the study participants. MEC, mobile examination centre; NHANES, National Health and Nutrition Examination Survey; VCTE, vibration-controlled transient elastography.

3.2 | Subtypes of SLD

The distribution of study participants according to specific SLD subtypes are shown in Figure 2. Among the 1347 participants with SLD, 1339 (99.4%) met the definition of metabolic dysfunction. In particular, 89.4% had MASLD (single aetiology), 7.7% had MetALD and 2.4% had MASLD-Viral. Among the 8 participants with SLD but without metabolic dysfunction, 5 had significant alcohol consumption (ALD), while 3 were diagnosed with cryptogenic SLD.

As shown in Table 1, metabolic dysfunction defined according to the new criteria was present in 91.2% of the general US population and also by 68.7% of normal-weight US adults. In contrast, only 16.3% of normal-weight individuals showed signs of insulin resistance (HOMA-IR ≥2.5). While the prevalence of metabolic dysfunction was higher in patients with SLD, it was also present in 85.2% participants without elastographic evidence of steatosis. Figure 3 shows the prevalence of each component of the definition of metabolic dysfunction, as well as the proportion of insulin resistance in participants with and without SLD according to BMI. In the overall population, the most frequently met criteria were elevated BMI and waist circumference, while the less frequently met was reduced HDL. All abnormalities increased progressively with increasing BMI values (panels A through C), and within each BMI category, were significantly more common in participants with SLD.

Features of participants according to the specific SLD subtype are shown in Table 2. The few participants without metabolic dysfunction (ALD and cryptogenic) were younger normal-weight individuals (mean age 32.5 and 20.4 years, respectively) and none of them had evidence of significant liver fibrosis either with LSM or FIB-4. Age was similar across the other three groups. HOMA-IR was higher in MASLD and MASLD-Viral compared with MetALD. Prevalence of significant fibrosis according to VCTE was not higher in patients with MetALD compared with MASLD, while trend towards a higher prevalence was present in MASLD-Viral. MASLD-Viral patients also showed the highest prevalence of advanced fibrosis estimated through FIB-4 (9.7% vs. 6.3% in MetALD and 1.5% in MASLD).

3.3 | Comparison between MAFLD, MASLD and NAFLD

Prevalence of MAFLD, MASLD and NAFLD in different ethnic groups according to specific criteria in the overall population is shown in Figure 4. For all three conditions prevalence was highest among Hispanic participants and lowest among Non-Hispanic Blacks, with non-Hispanic whites and participants of other ethnicities at

TABLE 1 Features of the study population with and without steatotic liver disease.

	Total	No steatosis	SLD	*p* value
N (weighted prevalence)	3173 (100.0)	1821 (57.9)	1352 (42.1)	
Age (years)	46.8 (0.8)	43.9 (0.9)	50.8 (0.9)	<0.001
Female (%)	48.7 (1.5)	52 (1.8)	44.2 (2.1)	0.003
Race-ethnicity (%)				0.002
Non-Hispanic White	64.1 (2.1)	63.7 (2.2)	64.6 (2.4)	
Hispanic	15.8 (1.6)	14.2 (1.5)	18 (1.9)	
Non-Hispanic Black	10.3 (1.4)	11.9 (1.5)	8.1 (1.2)	
Other	9.8 (1.1)	10.2 (1.2)	9.3 (1.2)	
BMI (kg/m^2)	29.3 (0.2)	26.5 (0.2)	33.1 (0.3)	<0.001
AST (IU/L)	21.9 (0.3)	21.1 (0.4)	23.1 (0.6)	0.009
ALT (IU/L)	22.8 (0.4)	19.9 (0.5)	26.8 (0.7)	<0.001
GGT (IU/L)	28.6 (0.6)	24.2 (0.8)	34.7 (1.2)	<0.001
Albumin (g/dL)	4.1 (0.0)	4.1 (0.0)	4.0 (0.0)	<0.001
Platelet count ($10^9/L$)	241.3 (2.2)	240.0 (2.4)	243.1 (2.8)	0.314
HOMA-IR	3.9 (0.2)	2.5 (0.1)	5.9 (0.4)	<0.001
Elevated glucose (%)	65.3 (1.4)	54.1 (1.8)	80.8 (1.5)	<0.001
Elevated waist circumference (%)	74.9 (1.5)	61.6 (2.3)	93.3 (1.1)	<0.001
Elevated BMI (%)	72 (1.1)	56.7 (1.7)	93 (1.2)	<0.001
Elevated triglycerides (%)	25.7 (1.6)	14.5 (1)	41 (3)	<0.001
Low HDL-C (%)	27.9 (1.3)	20.9 (1.5)	37.7 (1.6)	<0.001
Elevated BP (%)	40.9 (1.8)	30.9 (1.9)	54.8 (3.1)	<0.001
Metabolic dysfunction (%)	91.2 (1.0)	85.2 (1.7)	99.5 (0.2)	<0.001
Cigarette smoke (%)				0.171
Never	57.1 (1.3)	58.5 (2.1)	55 (2.4)	
Former	26.5 (1.2)	24 (1.7)	30.1 (2)	
Current	16.4 (1.1)	17.5 (1.9)	14.9 (1.8)	
CKD (%)	5.5 (0.7)	4 (0.6)	7.5 (1.1)	0.001
CVD (%)	8.1 (0.9)	5.7 (0.7)	11.4 (1.8)	<0.001
HCV (%)	2.2 (0.7)	2.3 (0.6)	2.1 (1.4)	0.885
HBV (%)	0.2 (0)	0.2 (0.1)	0.3 (0.1)	0.745
Significant alcohol consumption (%)	7.7 (0.9)	7.4 (1.2)	8.1 (1)	0.682
LSM >8 kPa (%)	8.6 (0.8)	4.1 (0.5)	14.8 (1.8)	<0.001
CAP (dB/m)	263.3 (1.4)	220.9 (1.3)	321.6 (1.8)	<0.001
FIB4 (%)				0.048
<1.3	76.2 (1.5)	78.3 (1.7)	73.3 (2)	
1.3–2.67	22 (1.3)	20.1 (1.5)	24.7 (1.9)	
>2.67	1.8 (0.3)	1.7 (0.4)	2.1 (0.4)	

Note: Data are expressed as weighted proportions (Standard Error [SE]) for categorical variables and as weighted means (SE) for continuous variables. Linear regression and the design-adjusted Rao-Scott chi-square test were applied to evaluate the differences between groups in the distribution of continuous and categorical variables, respectively.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body Mass Index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CVD, cardiovascular disease; GGT gamma-glutamyltranspeptidase; HDL, high-density lipoprotein.

intermediate risk. No differences were found in the prevalence of MAFLD compared with MASLD in the overall population or in specific ethnic groups. The degree of agreement between the two definitions was high (99.2%) with a Cohen's *k* of 0.984. Finally, NAFLD had a similar distribution but its prevalence was lower than that of MAFLD and MASLD in all considered groups.

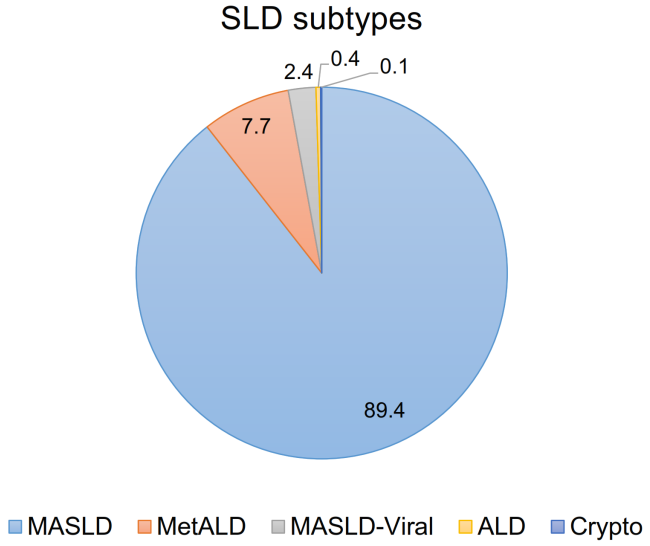

FIGURE 2 Distribution of the subtypes of steatotic liver disease in the studied population. ALD, alcohol-related steatotic liver disease; MASLD, metabolic (dysfunction)-associated steatotic liver disease.

4 | DISCUSSION

While several studies investigated epidemiological implications of introducing MAFLD criteria, this is to our knowledge the first study reporting the impact of the recently proposed MASLD definition in a general population setting. We made a series of observations. One, prevalence of SLD is alarmingly high in US adults with the highest rates found in Hispanic participants, as previously reported.[8] Two, MASLD criteria are met by 99% of US patients with elastographic evidence of liver steatosis (e.g. patients with SLD), with elevated BMI or waist circumference being the most commonly met criteria. Three, even among participants without SLD, metabolic dysfunction as defined by the recent Delphi consensus was extremely common in the general US population, with a prevalence of ~85%. Four, we did not find a significant difference in liver fibrosis between patients with MASLD and patients with MetALD, while a trend was evident for a higher prevalence of fibrosis in patients with MASLD and chronic viral hepatitis. Five, even though numbers were low, no participants with SLD but without metabolic dysfunction had evidence of significant liver fibrosis by either VCTE or FIB-4. Finally, the degree of agreement between the MAFLD and MASLD definitions was very high in the general population and the prevalence of the condition was not affected by the change in diagnostic criteria. On the other hand, both definitions were able to include more patients with steatosis compared with the NAFLD definition in all race-ethnic groups.

While each of the other components used in the definition of metabolic dysfunction is tightly linked with clinical outcomes such as cardiovascular disease and mortality, the most frequently met criterion for metabolic dysfunction in the United States was related to excess adiposity. In a population with a prevalence of overweight or obesity of >70%,[25] the probability of missing some individuals with lean SLD is quite limited. Nonetheless, some authors have criticized

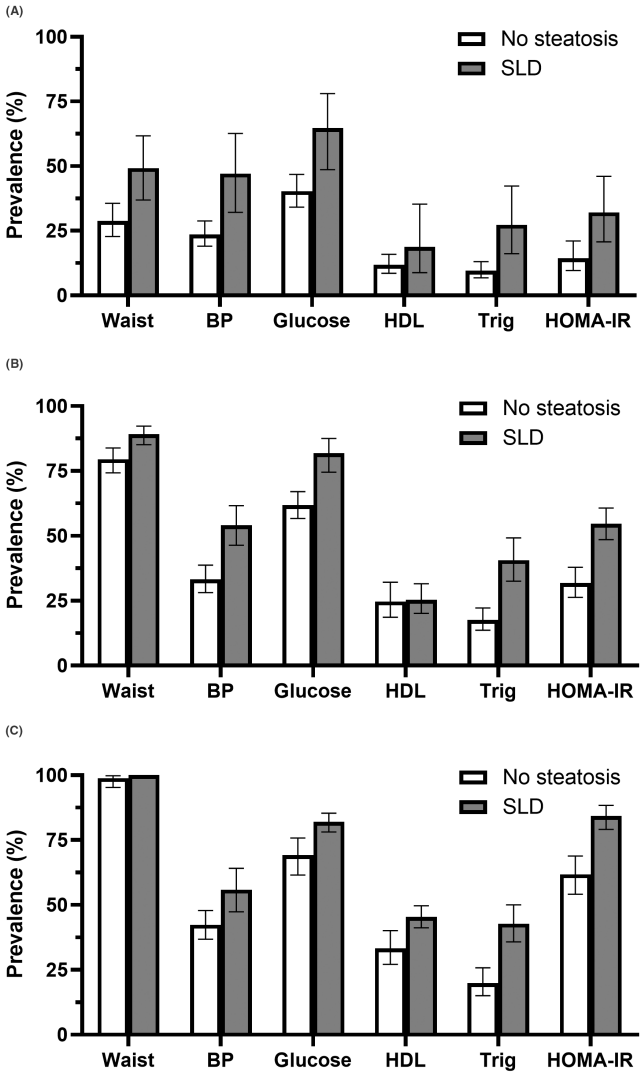

FIGURE 3 Weighted prevalence of single criteria for metabolic dysfunction and of insulin resistance in the general US population with and without steatotic liver disease. (A) Normal-weight individuals; (B) overweight individuals; (C) obese individuals. BMI, elevated body mass index; BP, elevated blood pressure; waist, elevated waist circumference; HDL, low HDL levels; Trig, elevated triglycerides levels; HOMA-IR represents the proportion of subjects with a HOMA-IR value ≥2.5. Specific cut-offs for each of the metabolic dysfunction criteria is described in the main text.

the over-emphasis given to weight, particularly in studies performed in Asian populations, in which metabolic dysfunction and obesity are less common, even in the context of liver steatosis.[26] It is disconcerting to acknowledge that ~90% of the general US population can be considered affected by metabolic dysfunction by meeting at least one of the criteria proposed in the recent Delphi consensus document. One can judge these results in two ways. The recently proposed criteria might be considered too strict and biased towards sensitivity rather than specificity. Indeed, while the considered variables are quite similar, the classical definition of the MS is based on the recognition of at least three, rather than one, diagnostic criteria.[27] Moreover, BMI is not considered in the MS definition and

TABLE 2 Features of patients according to the subtype of steatotic liver disease.

	MASLD	MetALD	MASLD-Viral	ALD	Crypto
N (weighted proportion)	1229 (89.4)	86 (7.7)	23 (2.4)	5 (0.4)	3 (0.1)
Age (years)	50.8 (0.9)	51.3 (2.4)	56.9 (1.3)	32.5 (6.4)	20.4 (0.9)
Female	43.9 (2.4)	46.1 (11.4)	51.4 (6.5)	15.2 (15)	41.6 (30)
Race-ethnicity					
Non-Hispanic White	63.3 (2.9)	73.7 (5.3)	79.7 (13.4)	96.6 (3.8)	0 (0)
Hispanic	18.9 (2.1)	12 (3.2)	5.4 (4.5)	0 (0)	22.3 (21.2)
Non-Hispanic Black	8.3 (1.3)	7.1 (2)	4.1 (3)	3.4 (3.8)	77.7 (21.2)
Other	9.5 (1.3)	7.2 (3.6)	10.8 (7.3)	0 (0)	0 (0)
BMI (kg/m^2)	33.6 (0.3)	29.6 (0.7)	30.2 (0.6)	22.6 (0.7)	22.0 (0.7)
AST (IU/L)	22.1 (0.4)	31.8 (2.9)	32.3 (1.6)	28.3 (5.8)	18.8 (1.7)
ALT (IU/L)	26.3 (0.7)	32.4 (2.2)	28.8 (1.4)	23.3 (4.8)	16.0 (4.4)
GGT (IU/L)	33.2 (1.2)	53.6 (7.0)	32.8 (3.5)	23.2 (3.7)	15.5 (1.0)
Albumin (g/dL)	4.0 (0.0)	4.0 (0.0)	4.1 (0.1)	4.3 (0.1)	4.0 (0.1)
Platelet count (10^9/L)	242.2 (3.1)	243.6 (8.1)	266.8 (17.2)	284.8 (13.3)	215.3 (11.9)
HOMA-IR	6.2 (0.4)	3.1 (0.5)	6.2 (0.7)	1.3 (0.1)	1.3 (0.2)
Elevated glucose (%)	82 (1.8)	66.3 (4.5)	96.5 (2.9)	0 (0)	0 (0)
Elevated waist circumference (%)	93.4 (1.1)	96.7 (1.8)	98 (1.9)	0 (0)	0 (0)
Elevated BMI (%)	94.3 (1.2)	82.4 (5.5)	98 (1.9)	0 (0)	0 (0)
Elevated triglycerides (%)	41.5 (2.8)	47.3 (5.5)	10.4 (7.1)	0 (0)	0 (0)
Low HDL-C (%)	40.1 (1.5)	17.4 (5.8)	21 (14.5)	0 (0)	0 (0)
Elevated BP (%)	55 (3.1)	53 (11.7)	60.6 (5.7)	0 (0)	0 (0)
Cigarette smoke (%)					
Never	58.9 (2.2)	23.7 (7.4)	8.2 (5.8)	46 (25.8)	100 (0)
Former	29.8 (2.1)	41 (11.4)	6.9 (5.4)	35.9 (26.7)	0 (0)
Current	11.3 (1.3)	35.3 (6.9)	84.9 (9.8)	18.1 (15.2)	0 (0)
CKD (%)	8.2 (1.1)	2.1 (1.8)	1.9 (2.1)	0 (0)	0 (0)
CVD (%)	12.3 (2)	4.7 (2.4)	2.7 (2.3)	0 (0)	0 (0)
HCV (%)	0 (0)	0 (0)	88.7 (7.6)	0 (0)	0 (0)
HBV (%)	0 (0)	0 (0)	11.3 (7.6)	0 (0)	0 (0)
Significant alcohol consumption (%)	0 (0)	100 (0)	0 (0)	100 (0)	0 (0)
LSM >8 (%)	15.2 (1.7)	9.5 (3.4)	19.5 (13.7)	0 (0)	0 (0)
CAP (dB/m)	322.5 (1.8)	313.3 (4.1)	281.6 (2.9)	287.9 (5.3)	318.7 (2.5)
FIB4 (%)					
<1.3	74.8 (2)	62 (7.3)	50.2 (7.9)	81.3 (15.7)	100 (0)
1.3–2.67	23.7 (2)	31.8 (6.5)	40.2 (5.5)	18.7 (15.7)	0 (0)
>2.67	1.5 (0.3)	6.3 (3.3)	9.7 (9)	0 (0)	0 (0)

Note: Data are expressed as weighted proportions (Standard Error [SE]) for categorical variables and as weighted means (SE) for continuous variables.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, Body Mass Index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CVD, cardiovascular disease; GGT, gamma-glutamyltranspeptidase; HDL, high-density lipoprotein.

waist circumference cut-offs are higher for western people (102 cm for men and 88 for women). By applying these more restrictive criteria, a previous NHANES study found a prevalence of MS in the US of 36.9% in 2015–2016,[28] quite lower than the one reported in the present study.

This is also in line with results obtained in the present study in terms of insulin resistance estimated through the HOMA-IR. Indeed, while one might ascribe this high prevalence to the very high prevalence of overweight and obesity in the US, even within normal weight, the new definition would label 68.7% of US adults as having metabolic dysfunction, while only 16.3% showed signs of insulin resistance when the HOMA-IR was applied.

On the other hand, more inclusive criteria are able to capture almost all individuals with SLD, leading to a low proportion

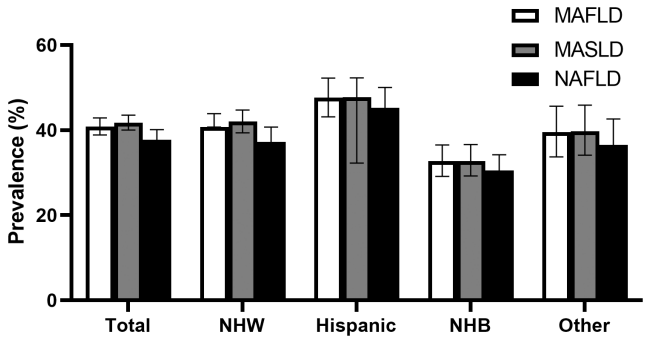

FIGURE 4 Prevalence of MAFLD, MASLD and NAFLD diagnosed according to a Controlled Attenuation Parameter ≥274 dB/m. Data show the combined prevalence of single and multiple-aetiology of MAFLD and MASLD. MAFLD, metabolic-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NHB, non-Hispanic Black; NHW, non-Hispanic White.

of cryptogenic cases of SLD (below 1% in the present study). Moreover, in the absence of all recently proposed criteria, no participants had evidence of significant or advanced liver fibrosis (even in the presence of significant alcohol consumption), suggesting a high negative predictive value for this important histologic outcome.

Given the extremely high degree of concordance between the MAFLD and MASLD definitions, it is likely that the major impact of this new definition will not be an epidemiological one. Nonetheless, we agree with the consensus panel that a unified global approach to nomenclature and disease definition is critical for increasing disease awareness, identifying those at risk and facilitating diagnosis and access to care.[15] In this sense, the proposed change to SLD as an umbrella term might help reduce stigma and promote awareness of liver steatosis while also keeping the focus on other concomitant forms of chronic liver disease.

Our study possesses several strengths. Firstly, it is a large-scale investigation conducted on a diverse and inclusive sample of adults in the United States, encompassing individuals of different genders and ethnic backgrounds. Additionally, our reliance on NHANES data ensures a high degree of external validity, as the survey aims to be representative of the overall US population. The acquisition of clinical, laboratory, and anthropometric data followed standardized and homogeneous protocols.

However, it is important to acknowledge several limitations. The absence of liver biopsy data necessitated the use of CAP obtained through VCTE as a surrogate measure for identifying steatosis. While the performance of CAP is considered adequate for diagnostic purposes, false-positive and false-negative results might have occurred. In particular, it is possible that obesity itself might lead to overestimating the degree of liver steatosis, thereby increasing the proportion of obese subjects among those with SLD. Given that there are no universally accepted cut-offs for CAP, we used the ones proposed by Eddowes et al. since they were derived from a large cohort in a western country and are also recommended by recent guidelines.[29] In that study, the AUROC of CAP compared with liver biopsy was 0.87 (95% CI: 0.82–0.92) for S ≥ S1. Still, future studies applying more accurate techniques such as MRI-PDFF are needed to corroborate our results.

Furthermore, as the aim of the survey is not specifically focused on liver health, but rather on general health, precise definition of less frequent causes of liver disease was missing. Indeed no specific tests were performed to exclude autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, steatosis related to malnutrition or to specific endocrine disorders. While inclusion of these alternative causes of chronic liver disease might have affected the number of participants with dual-aetiology SLD, estimates on its overall prevalence and on the prevalence of metabolic dysfunction would not be affected.

Finally, being a cross-sectional analysis, our study cannot evaluate whether the new proposed criteria are able to better capture the future occurrence of hepatic or extra-hepatic complications of SLD. Future cohort studies with adequate follow-up are needed to evaluate this crucial aspect.

In conclusion, our findings show that SLD affects approximately 40% of US adults. The vast majority of patients with SLD meet the newly proposed metabolic dysfunction criteria, as it is also the case for US adults without steatosis. This led to a very few number (0.1%) of patients with SLD being labelled as cryptogenic. On the other hand, no significant differences in prevalence were found between MAFLD and MASLD. Further studies are needed to evaluate whether results are consistent in populations with a lower prevalence of overweight or obesity.

AUTHOR CONTRIBUTIONS

Stefano Ciardullo and Gianluca Perseghin designed the study, wrote, reviewed and edited the manuscript. Marco Carbone and Pietro Invernizzi reviewed and edited the manuscript. Stefano Ciardullo researched and analysed data. All authors approved the final version of the manuscript to be published. Stefano Ciardullo is the guarantor of this work. The manuscript was written by the authors without any external writing assistance.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

All data used for the present study are freely available online at the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

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