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Clinical characteristics of MASLD/MetALD/MAFLD/NAFLD and the relative risk analysis on metabolic disorders

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Abstract

Objectives Our objective was to compare the clinical features of Metabolic dysfunction-associated steatotic liver disease (MASLD) /metabolic alcohol-related liver disease (MetALD)/metabolic associated fatty liver disease (MAFLD)/nonalcoholic fatty liver disease (NAFLD) and the relative risk analysis of metabolic disorders.

Methods The National Health and Nutrition Examination Survey for the 2017–2018 cycle was used to screen the participants. Multivariate-adjusted logistic regression models were applied to explore the difference in relative risk analysis between NAFLD/MAFLD/MASLD/MetALD and metabolic disorders.

Results Among the 1,862 eligible individuals, 358(44.84%) had MASLD, 213(11.44%) had MetALD, 841(45.17%) had MAFLD, and 1,125(60.42%) had NAFLD. Positive associations with the risk of hypertension were discovered for MASLD (OR = 2.892, 95%CI = 2.226–3.756), MetALD (OR = 1.802, 95% CI = 1.355–2.398), MAFLD (OR = 3.455, 95%CI = 2.741–4.354) and NAFLD (OR = 1.983, 95%CI = 1.584–2.484). Positive associations with the risk of T2DM were discovered for MASLD (OR = 6.360, 95%CI = 4.440–9.109), MAFLD (OR = 7.026, 95%CI = 4.893–10.090) and NAFLD (OR = 3.372, 95%CI = 2.511–4.528). We discovered similar results for hyperlipidemia. Compared to mild steatosis, moderate to severe steatosis in patients with MASLD (OR = 3.924, 95%CI = 2.399–6.419), MAFLD (OR = 3.814, 95%CI = 2.367–6.144), NAFLD (OR = 4.910, 95%CI = 2.983–8.080) has a higher risk for T2DM.

Conclusion The proposed definitions of MASLD and MetALD are valuable and deserve further exploration. Our findings suggest that MAFLD is a more effective indicator for identifying patients at increased risk for metabolic disorders.

Keywords MASLD, MetALD, Metabolic disorders, Hypertension, T2DM, Steatosis severity.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the number one chronic liver disease worldwide, with a prevalence rate of 32.4% [1]. NAFLD is able to cause cirrhosis and hepatocellular cancer, and increase the risk of a variety of extrahepatic diseases, which is a serious danger to human health and increases the burden on society [2]. The pathogenesis of NAFLD is complex and closely associated with various factors, including age, gender, genetics, and gut microbiota dysbiosis [3]. It is worth emphasizing that, more and more studies have shown that the development of NAFLD has a strong association with obesity and type 2 diabetes mellitus (T2DM) [4]. As the role of metabolic disorders in NAFLD has been increasingly widely emphasized and recognized with in-depth studies on the pathogenesis of the disease, some scholars have begun to doubt whether the name "NAFLD" fully and accurately describes the diversity and complexity of the disease.

An international expert consensus was proposed in 2020, suggesting the renaming of NAFLD to Metabolic Associated Fatty Liver Disease (MAFLD) and clarifying the criteria for a positive diagnosis [5]. Although MAFLD is accepted by some scholars, there are also scholars with reservations due to their concerns about mixed etiology, stigmatization of the term fatty, and changes in drinking habits. For this reason, in June 2023, 53 experts from around the world put forward a proposal to change the name of NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD), replacing the term "fatty" with "steatotic", and proposing a new diagnostic criterion [6]. This change has resulted in a lower diagnostic threshold for metabolism-related steatosis, making it easier to diagnose patients with MASLD. At the same time, the consensus proposes a new subgroup of metabolic alcohol-related liver disease (MetALD), a group in which metabolic risk and excessive alcohol consumption coexist. However, the differences in investigator characteristics under different definitions are unclear, and it is unclear whether the new diagnostic criteria for MASLD can identify and capture more potential patients.

T2DM, hypertension, and hyperlipidemia are common clinical metabolic disorders that have also been shown to be important risk factors for the progression of NAFLD to non-alcoholic steatohepatitis, advanced fibrosis, and even severe liver disease outcomes, including cirrhosis, cirrhotic complications, or liver-related death [7–10]. MASLD and MetALD are recently proposed new definition whose utility and scientific validity have not been examined and assessed. In-depth investigation of the relationship and differences between NAFLD, MAFLD, MASLD, MetALD and the risk of metabolic diseases is important for delaying the disease process and improving the prognosis of patients. However, it is not clear whether MASLD and MetALD are more advantageous than NAFLD and MAFLD in predicting the risk level of the metabolic diseases above.

Based on the above pending questions, we aim to deeply analyze the characteristics of current studies on different definitions of fatty liver and the differences between these characteristics. We will also further explore the association between the severity of steatosis and the risk of metabolic diseases by using data from the National Health and Nutrition Examination Surveys (NHANES) for 2017–2018. This study aims to provide a clearer perspective and more scientifically based guidance for the early diagnosis, treatment, and prevention of fatty liver disease.

Materials and methods

Study design

According to the STROBE guidelines for observational studies, a cross-sectional study was designed to:

1. analyze and compare investigator characteristics and intercharacteristic differences under different definitions regarding fatty liver disease: NAFLD, MAFLD, MASLD, and MetALD;
2. explore differences in the efficacy of different definitions and diagnostic criteria for predicting hazard risk classes for other metabolic diseases;
3. investigate the relationship between steatosis severity and the likelihood of developing metabolic diseases.

Study population

This is a retrospective cross-sectional study of individuals aged ≥ 20 years utilizing NHANES 2017–2018. The NHANES 2017–2018 dataset and more NHANES details are accessible to the general audience.

(https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2017). Online Resource 1 illustrates the specific details of patient registration. From a total of 9,254 individuals, we eliminated participants under the aged of 20 (n = 3,685), missing data of liver ultrasound transient elastography (FibroScan®) (n = 700), missing important data to diagnosis MASLD/MetALD/MAFLD/NAFLD (n = 1,319), such as body mass index (BMI), waist circumference (WC), fasting blood glucose (FBG), and missing important data to diagnosis hypertension/T2DM/ hyperlipidemia, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, triglycerides (TG) (n = 1,688). Finally, 1,862 participants were analyzed in the study (Figure S1). The NHANES protocol was reviewed and approved by the Research Ethics Review Board at the National Center for Health Statistics. All participants signed a written declaration of informed consent. The diagnostic criteria for NAFLD, MAFLD, MASLD and MetALD are shown in Online Resource 2 (Table S1).

Statistical analysis

In keeping with the research criteria of NHANES, we used sampling weights in our evaluations and computed variances by clustering and stratification. Binary or categorical variables were shown by number (%), while continuous variables were shown by mean ± standard deviation when normally distributed, otherwise, median (interquartile range, IQR) was used. Binary or categorical data were presented as number (%), and continuous data were expressed as mean ± standard deviation for normal distributions, or as median (interquartile range, IQR) otherwise.

The Rao-Scott Chi-square test, Wilcoxon rank-sum test, and Student's t-test were used to assess the variations in population characteristics for categorical and continuous variables, respectively.

In order to explore the association between NAFLD/MAFLD/MASLD/MetALD and the risk of hypertension/T2DM/ hyperlipidemia, multivariate-adjusted logistic regression models were used. We calculated the odds ratio (OR) and relevant 95% confidence intervals (95% CIs) in three models. Only independent variables were present in Model 1. Model 2 also accounted for additional factors including gender, age, ethnicity, family income-poverty ratio, and education level. Model 3 was further adjusted for the smoking and physical activity (PA). Smokers were identified as those consumed at least 100 cigarettes in the past. Nonsmokers were identified as those consumed less than 100 cigarettes or never smoked in the past. The amount of physical activity was classified with metabolic equivalent of task (MET)-minutes/week: MET = 0 as sedentary, 0 < MET ≤ 500 as insufficient, 500 < MET ≤ 1000 as moderate, and MET > 1000 as high. The NHANES website provides further information on the characteristics mentioned above. With a similar research methodology, we explored the relationship between the steatosis severity of NAFLD/MAFLD/MASLD/MetALD and the risk of T2DM/HTN/ hyperlipidemia. The participants were categorized into two groups according to the severity of steatosis, with mild steatosis as a reference.

All statistical analyses were carried out with R 3.6.2 and the "survey" package. Statistical significance was defined as $P < 0.05$ for a two-tailed test.

Results

Characteristics of the participants

There were 835 patients with MASLD (44.84%) and 213 with MetALD (11.44%) among the 1,862 participants (Table 1; Fig. 1). The population consisted of 50.21% males and 49.79% females. The median age was 57 years in participants with MASLD and 46 years in those with MetALD. Participants with MASLD had a greater likelihood of being older, having hypertension/T2DM/hyperlipidemia, and having higher FIPR/BMI/WC/FBG/Hb1Ac/SBP/TG/HOMA-IR levels than those without it. Compared to participants without MetALD, those with MetALD had a higher likelihood of being male, younger, smokers, and having higher BMI/WC/FBG/DBP/TG/HOMA-IR levels, and lower PIR/education/HDL-C levels.

There were 841 individuals with NAFLD (45.17%) and 1,125 with MAFLD (60.42%) among the 1,862 participants (Table 2; Fig. 1). The median age was 57 years in participants with NAFLD and 56 years in those with MAFLD. Individuals with NAFLD/MAFLD tended to be older, have hypertension/T2DM/hyperlipidemia, and have higher BMI/WC/FBG/Hb1Ac/SBP/TG/HOMA-IR levels.

The association between MASLD/MetALD/MAFLD/NAFLD and the risk of hypertension/T2DM/ hyperlipidemia

The ORs and 95% CIs for the association between MASLD, MetALD, MAFLD, and NAFLD and the risk of hypertension, T2DM, and hyperlipidemia were presented in Fig. 2. After adjusting for all covariates, positive associations with the risk of hypertension were discovered for MASLD (OR = 2.892, 95% CI = 2.226–3.756), MetALD (OR = 1.802, 95% CI = 1.355–2.398), MAFLD (OR = 3.455, 95% CI = 2.741–4.354) and NAFLD (OR = 1.983, 95% CI = 1.584–2.484). Also, positive associations with the risk of T2DM were discovered for MASLD (OR = 6.360, 95% CI = 4.440–9.109), MAFLD (OR = 7.026, 95% CI = 4.893–10.090) and NAFLD (OR = 3.372, 95% CI = 2.511–4.528). We discovered similar results for hyperlipidemia. However, we found that there was no association between MetALD and the risk of T2DM/hyperlipidemia.

Relationship of steatosis grade and hypertension/T2DM/hyperlipidemia

The multi-variate adjusted OR and 95% CIs for the association between steatosis grade and the risk of hypertension, T2DM, and hyperlipidemia were presented in Fig. 3. For MASLD/MAFLD/NAFLD, the degree of liver steatosis was strongly and independently correlated with the existence of T2DM in all models. Compared to mild steatosis, the moderate to severe steatosis in patients with MASLD (OR = 3.924, 95% CI = 2.399–6.419), MAFLD (OR = 3.814, 95% CI = 2.367–6.144), NAFLD (OR = 4.910, 95% CI = 2.983–8.080) have higher risk for T2DM. However, the grade of liver steatosis for MetALD was not associated with the presence of T2DM (OR = 2.399, 95% CI = 0.560–10.274, $P > 0.05$). What was a surprise was that the grade of liver steatosis in MASLD/MetALD/MAFLD/NAFLD was also unrelated to the risk of hypertension and hyperlipidemia.

Table 1 Basic characteristics of participants by MASLD and MetALD in NHANES 2017–2018

	Total (*n* = 1,862)			**Total (*n* = 1,862)**		
	Non-MASLD (*n* = 1,027)	**MASLD (*n* = 835)**	***P*-Value**	**Non-MetALD (*n* = 1,649)**	**MetALD (*n* = 213)**	***P*-Value**
NAFLD$^+$, *n*(%)	6 (0.6%)	835 (100%)	**< 0.001**	841 (51%)	0 (%)	**< 0.001**
MAFLD$^+$, *n*(%)	307 (70%)	818 (98%)	**< 0.001**	916 (56%)	209 (99%)	**< 0.001**
MASLD$^+$, *n*(%)	/	/		835 (51%)	0 (%)	**< 0.001**
MetALD$^+$, *n*(%)	213 (21%)	0 (%)	**< 0.001**	/	/	
Gender, *n*(%)			0.730			**0.028**
Female	515 (50%)	412 (49%)		836 (51%)	91 (43%)	
Male	512 (50%)	423 (51%)		813 (49%)	122 (57%)	
Age (year)	47 (32, 62)	57 (45, 66)	**< 0.001**	54 (37, 64)	46 (34, 58)	**< 0.001**
Ethnicity, *n*(%)			**0.024**			**< 0.001**
Mexican American	142 (14%)	132 (16%)		209 (13%)	65 (31%)	
Non-Hispanic Black	268 (26%)	175 (21%)		409 (25%)	34 (16%)	
Non-Hispanic White	319 (31%)	297 (36%)		537 (33%)	79 (37%)	
Other	298 (29%)	231 (28%)		494 (30%)	35 (16%)	
FIPR	2.15 (1.20, 4.17)	2.64 (1.52, 4.65)	**< 0.001**	2.49 (1.38, 4.62)	1.85 (1.11, 3.32)	**< 0.001**
Education, *n*(%)			0.217			**< 0.001**
College or above	589 (57%)	511 (61%)		1,005 (61%)	95 (45%)	
High school or equivalent	254 (25%)	183 (22%)		369 (22%)	68 (32%)	
Less than high school	184 (18%)	140 (17%)		274 (17%)	50 (23%)	
Smoking, *n*(%)			**0.006**			**< 0.001**
Nonsmoker	564 (55%)	511 (61%)		996 (60%)	79 (37%)	
Smoker	463 (45%)	324 (39%)		653 (40%)	134 (63%)	
Physical Activity			**0.016**			0.133
Sedentary	498 (49%)	448 (54%)		826 (50%)	120 (56%)	
Insufficient	131 (13%)	114 (14%)		213 (13%)	32 (15%)	
Moderate	112 (11%)	93 (11%)		186 (11%)	19 (8.9%)	
High	285 (28%)	178 (21%)		421 (26%)	42 (20%)	
BMI (kg/m^2)	27 (24, 32)	31 (27, 36)	**< 0.001**	28 (25, 33)	33 (29, 37)	**< 0.001**
WC (cm)	94 (84, 105)	106 (97, 117)	**< 0.001**	98 (88, 111)	108 (99, 119)	**< 0.001**
FPG (mg/dl)	101 (95, 110)	107 (100, 120)	**< 0.001**	103 (96, 113)	108 (100, 119)	**< 0.001**
Hb1Ac (%)	5.50 (5.20, 5.90)	5.90 (5.50, 6.70)	**< 0.001**	5.60 (5.30, 6.20)	5.70 (5.30, 6.18)	0.633
SBP (mmHg)	121 (111, 134)	127 (116, 138)	**< 0.001**	123 (112, 137)	125 (115, 136)	0.201
DBP (mmHg)	73 (66, 80)	74 (67, 81)	0.089	73 (66, 79)	76 (69, 85)	**< 0.001**
TG (mg/dl)	79 (59, 108)	99 (72, 129)	**< 0.001**	84 (62, 115)	99 (78, 133)	**< 0.001**
HDL-C (mg/dl)	54 (44, 66)	48 (41, 57)	**< 0.001**	51 (43, 61)	47 (39, 59)	**< 0.001**
HOMA-IR	1.99 (1.50, 2.65)	2.48 (1.81, 3.17)	**< 0.001**	2.12 (1.59, 2.82)	2.40 (1.65, 3.06)	**0.045**
Hypertension, *n*(%)			**< 0.001**			0.521
No	496 (48%)	241 (29%)		657 (40%)	80 (38%)	
Yes	531 (52%)	594 (71%)		992 (60%)	133 (62%)	
T2DM, *n*(%)			**< 0.001**			0.822
No	807 (79%)	447 (54%)		1,112 (67%)	142 (67%)	
Yes	220 (21%)	388 (46%)		537 (33%)	71 (33%)	
Hyperlipidemia, *n*(%)			**< 0.001**			0.066
No	206 (20%)	64 (8%)		248 (15%)	22 (10%)	
Yes	821 (80%)	771 (92%)		1,401 (85%)	191 (90%)	

NAFLD, non-alcoholic fatty liver disease; MAFLD, Metabolic Associated Fatty Liver Disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic alcohol-related liver disease; FIPR, family income-poverty ratio; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; T2DM, type 2 diabetes mellitus

Discussion

NAFLD has been an important challenge that poses a serious threat to public health. Due to the heterogeneity of NAFLD pathogenesis, an increasing number of experts believe that existing definitions of NAFLD and related terms often fail to accurately reflect the nature of the disease. Therefore, renaming this group of diseases is on the agenda in order to improve disease-related

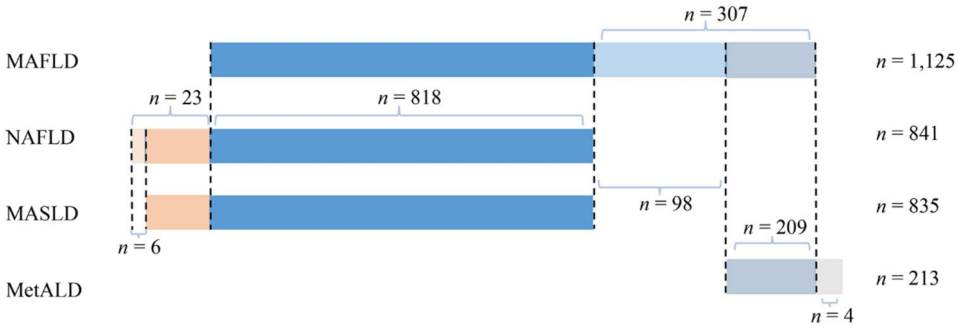

Fig. 1 Schematic diagram of the relationship between MASLD, MetALD, MAFLD and NAFLD

awareness, better prevent the disease, and guide non-invasive diagnosis and new drug development. NAFLD, MAFLD, and MASLD are three different definitions that currently exist, accompanied by different diagnostic criteria. However, it is not known which of the three better reflects the clinical features of the disease or the natural history of the disease. As far as we are aware, this is the initial research to comprehensively compare the manifestations of patients with MASLD, MetALD, MAFLD, and NAFLD.

Key findings

According to NHANES 2017–2018 data, the prevalence of MASLD, MAFLD, NAFLD and MetALD were 44.84%, 60.42%, 45.17% and 11.44%, respectively in U.S adults. 73% of participants with MAFLD can be classified as MASLD, 98% of participants with MASLD can be classified as MAFLD. Participants with MASLD/MAFLD/NAFLD/MetALD had higher BMI/WC/FBG/TG/HOMA-IR levels than those without. MASLD/MAFLD/NAFLD is associated with an increased risk of hypertension, T2DM and hyperlipidemia. The risk of T2DM was strongly and independently correlated with the severity of hepatic steatosis for the participants with MASLD/MAFLD/NAFLD. MetALD is associated with an increased risk of hypertension. These results suggest that the nomenclature of MASLD has certain clinical significance, which may help to improve the detection rate of the disease and provide a reference for the early prevention and treatment of the disease.

The renaming of MASLD is reasonable

Contributing to the improvement of disease detection rates and awareness

In the US population, we found that metabolism-related steatotic liver diseases show high prevalence rates, with MASLD at 44.84%, MAFLD at 60.42%, NAFLD at 45.17%, and MetALD at 11.44%. Unhealthy dietary habits, a sedentary lifestyle, and a lack of exercise have significantly contributed to the increasing prevalence of metabolic disorder-related diseases in recent years. Despite the fact that steatotic liver disease is a potentially important health problem that is closely associated with serious consequences such as cardiovascular disease, cirrhosis, and hepatocellular carcinoma [11, 12], it has not yet received sufficient attention from the patient population, and a large number of patients with steatotic liver disease still remain untreated by timely interventions and treatments [13]. One survey showed that public awareness of NAFLD in the United States was only 2.4–3.1% [14, 15]. Another survey of 29 European countries showed a widespread absence of an integrated public health strategy to address NAFLD [16]. Research into NAFLD has not kept pace with the disease's rapid advancement. Therefore, there is a need to establish an efficient approach to making people more aware of and attentive to NAFLD among the general public and the scientific community.

When adopting the diagnostic criteria for MASLD, the indicators align more closely with clinical practice, thereby simplifying the diagnostic process. Compared with MAFLD, MASLD may include more people at lower metabolic risk. According to the MASLD criteria, patients only need to meet one of the five metabolic cardiovascular risk factors. This approach does not rely on measurements like insulin levels or high-sensitivity C-reactive protein, which are not standard in clinical routine tests, thus aiding in increasing the disease detection rate. Ramírez-Mejía et al. found that MASLD has a higher capture of lean patients compared to MAFLD [17]. Although MAFLD identifies patients with significant hepatic fibrosis better than MASLD [18].

Furthermore, it is important to emphasize that liver biopsy, as the gold standard for the diagnosis of steatotic liver, is invasive and potentially harmful, making it unsuitable for patients with mild to moderate steatotic liver. It is also not feasible for widespread clinical use. Therefore, the search for more convenient diagnostic markers with higher sensitivity and specificity remains a significant research challenge for the future.

The new expert consensus recognizes metabolically combined alcohol impairment as a separate group named MetALD [6]. Our study further reveals that this group is

Table 2 Basic characteristics of participants by NAFLD and MAFLD in NHANES 2017–2018

	Total (*n* = 1,862)			**Total (*n* = 1,862)**		
	non-NAFLD (*n* = 1,021)	**NAFLD (*n* = 841)**	***P*-Value**	**Non-MAFLD (*n* = 737)**	**MAFLD (*n* = 1,125)**	***P*-Value**
NAFLD$^+$, *n*(%)	**/**	/		23 (3.1%)	818 (73%)	
MAFLD$^+$, *n*(%)	307 (30%)	818 (97%)	**< 0.001**	/	/	**< 0.001**
MASLD$^+$, *n*(%)	0 (%)	835 (99%)	**< 0.001**	17 (2.3%)	818 (73%)	**< 0.001**
MetALD$^+$, *n*(%)	213 (21%)	0 (%)	**< 0.001**	4 (0.5%)	209 (19%)	**< 0.001**
Gender, *n*(%)			0.662			**0.013**
Female	513 (50%)	414 (49%)		393 (53%)	534 (47%)	
Male	508 (50%)	427 (51%)		344 (47%)	591 (53%)	
Age (year)	47 (32, 62)	57 (45, 66)	**< 0.001**	44 (30, 61)	56 (43, 65)	**< 0.001**
Ethnicity, *n*(%)			**0.022**			**< 0.001**
Mexican American	140 (14%)	134 (16%)		76 (10%)	198 (18%)	
Non-Hispanic Black	267 (26%)	176 (21%)		206 (28%)	237 (21%)	
Non-Hispanic White	318 (31%)	298 (35%)		231 (31%)	385 (34%)	
Other	296 (29%)	233 (28%)		224 (30%)	305 (27%)	
FIPR	2.16 (1.20, 4.17)	2.64 (1.51, 4.64)	**< 0.001**	2.43 (1.24, 4.56)	2.43 (1.35, 4.40)	0.994
Education, *n*(%)			0.200			0.409
College or above	585 (57%)	515 (61%)		448 (61%)	652 (58%)	
High school or equivalent	253 (25%)	184 (22%)		170 (23%)	267 (24%)	
Less than high school	183 (18%)	141 (17%)		119 (16%)	205 (18%)	
Smoking, *n*(%)			**0.007**			0.061
Nonsmoker	561 (55%)	514 (61%)		445 (60%)	630 (56%)	
Smoker	460 (45%)	327 (39%)		292 (40%)	495 (44%)	
Physical Activity			**0.043**			**< 0.001**
Sedentary	497 (49%)	449 (54%)		331 (45%)	615 (55%)	
Insufficient	131 (13%)	114 (14%)		90 (12%)	155 (14%)	
Moderate	112 (11%)	93 (11%)		86 (12%)	119 (11%)	
High	280 (27%)	183 (22%)		229 (31%)	234 (21%)	
BMI (Kg/m^2)	27 (24, 32)	31 (27, 36)	**< 0.001**	25 (22, 29)	31 (28, 36)	**< 0.001**
WC (cm)	94 (84, 105)	106 (96, 117)	**< 0.001**	89 (81, 98)	106 (98, 117)	**< 0.001**
FPG (mg/dl)	101 (95, 110)	107 (100, 120)	**< 0.001**	99 (93, 106)	108 (100, 121)	**< 0.001**
Hb1Ac (%)	5.50 (5.20, 5.90)	5.85 (5.50, 6.70)	**< 0.001**	5.40 (5.20, 5.70)	5.80 (5.50, 6.60)	**< 0.001**
SBP (mmHg)	121 (111, 134)	126 (116, 138)	**< 0.001**	118 (108, 131)	127 (117, 138)	**< 0.001**
DBP (mmHg)	73 (66, 80)	74 (67, 81)	0.122	71 (65, 78)	75 (67, 82)	**< 0.001**
TG (mg/dl)	79 (58, 108)	99 (72, 129)	**< 0.001**	71 (55, 100)	100 (73, 130)	**< 0.001**
HDL-C (mg/dl)	54 (44, 66)	48 (41, 57)	**< 0.001**	57 (47, 68)	48 (41, 57)	**< 0.001**
HOMA-IR	1.99 (1.50, 2.65)	2.48 (1.81, 3.17)	**< 0.001**	1.90 (1.42, 2.48)	2.47 (1.83, 3.16)	**< 0.001**
Hypertension, *n*(%)			**< 0.001**			**< 0.001**
No	490 (48%)	247 (29%)		411 (56%)	326 (29%)	
Yes	531 (52%)	594 (71%)		326 (44%)	799 (71%)	
T2DM, *n*(%)			**< 0.001**			**< 0.001**
No	801 (78%)	453 (54%)		634 (86%)	620 (55%)	
Yes	220 (22%)	388 (46%)		103 (14%)	505 (45%)	
Hyperlipidemia, *n*(%)			**< 0.001**			**< 0.001**
No	203 (20%)	67 (8.0%)		185 (25%)	85 (7.6%)	
Yes	818 (80%)	774 (92%)		552 (75%)	1,040 (92%)	

not uncommon among adults in the United States, with a prevalence of up to 11.44%. In the past, this particular group has often been overlooked and difficult to study as a separate population. In addition, due to the asymptomatic nature of early-stage ALD and the lack of systematic and routine screening, many patients are diagnosed at an advanced stage of the disease, thus missing out on optimal treatment [19]. Meanwhile, after additional adjustment for ALD, MAFLD was no longer a significant risk factor for liver disease-related deaths in patients with fatty liver disease [20], suggesting that the role of excessive alcohol consumption in disease progression and poor prognosis in patients with MAFLD is complex and that coexisting ALD may be a major cause of increased

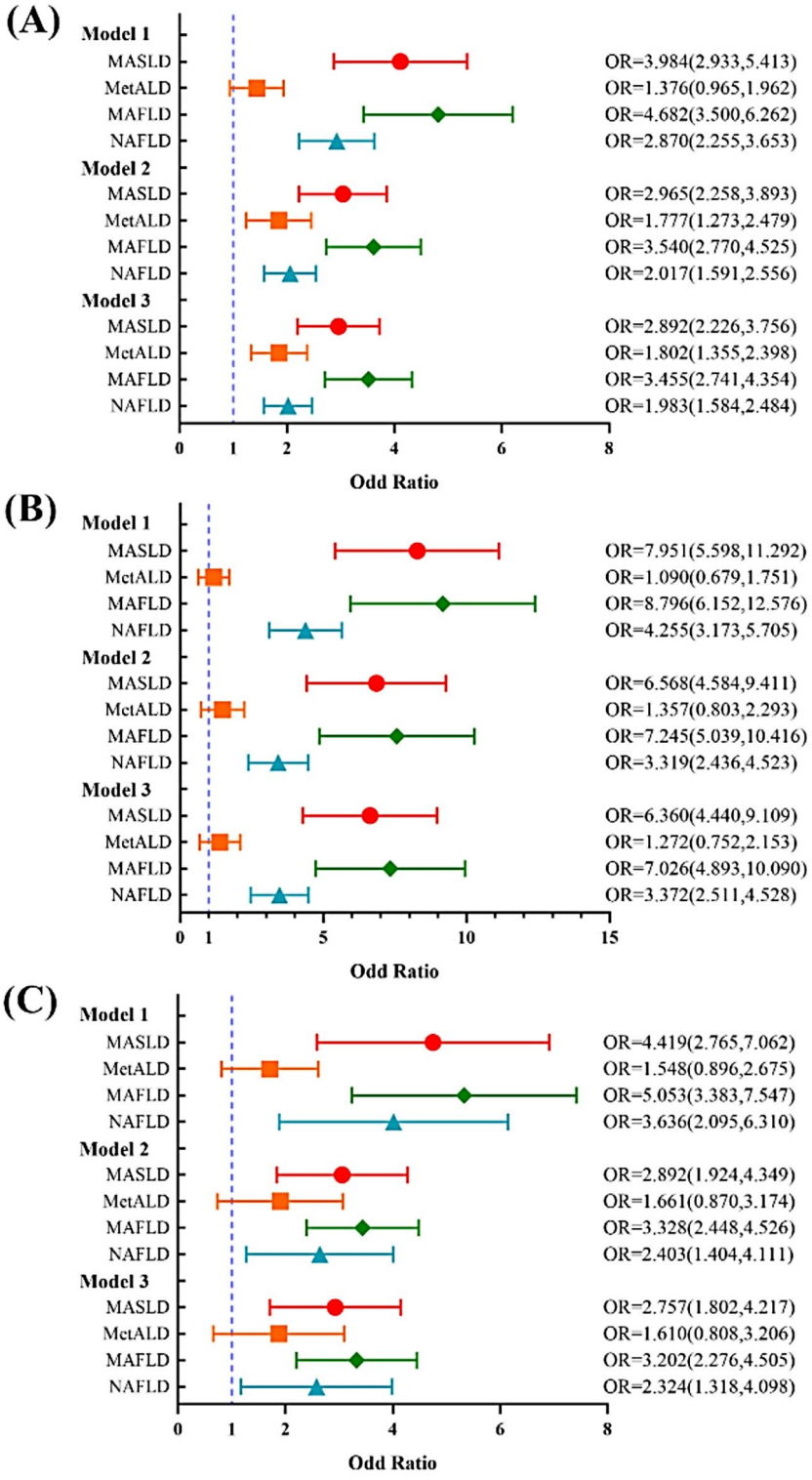

Fig. 2 Multi-variate adjusted odds ratio (95% CIs) for the relationship between MASLD/MetALD/MAFLD/NAFLD and the risk of hypertension (**A**), T2DM (**B**), and hyperlipidemia (**C**) among participants in NHANES 2017–2018. Model 1 contains only independent variables; Model 2 was additionally adjusted for gender, age, ethnicity, FIPR, and education level; and Model 3 was further adjusted for smoking and physical activity. Reference category: without MASLD/MetALD/MAFLD/NAFLD

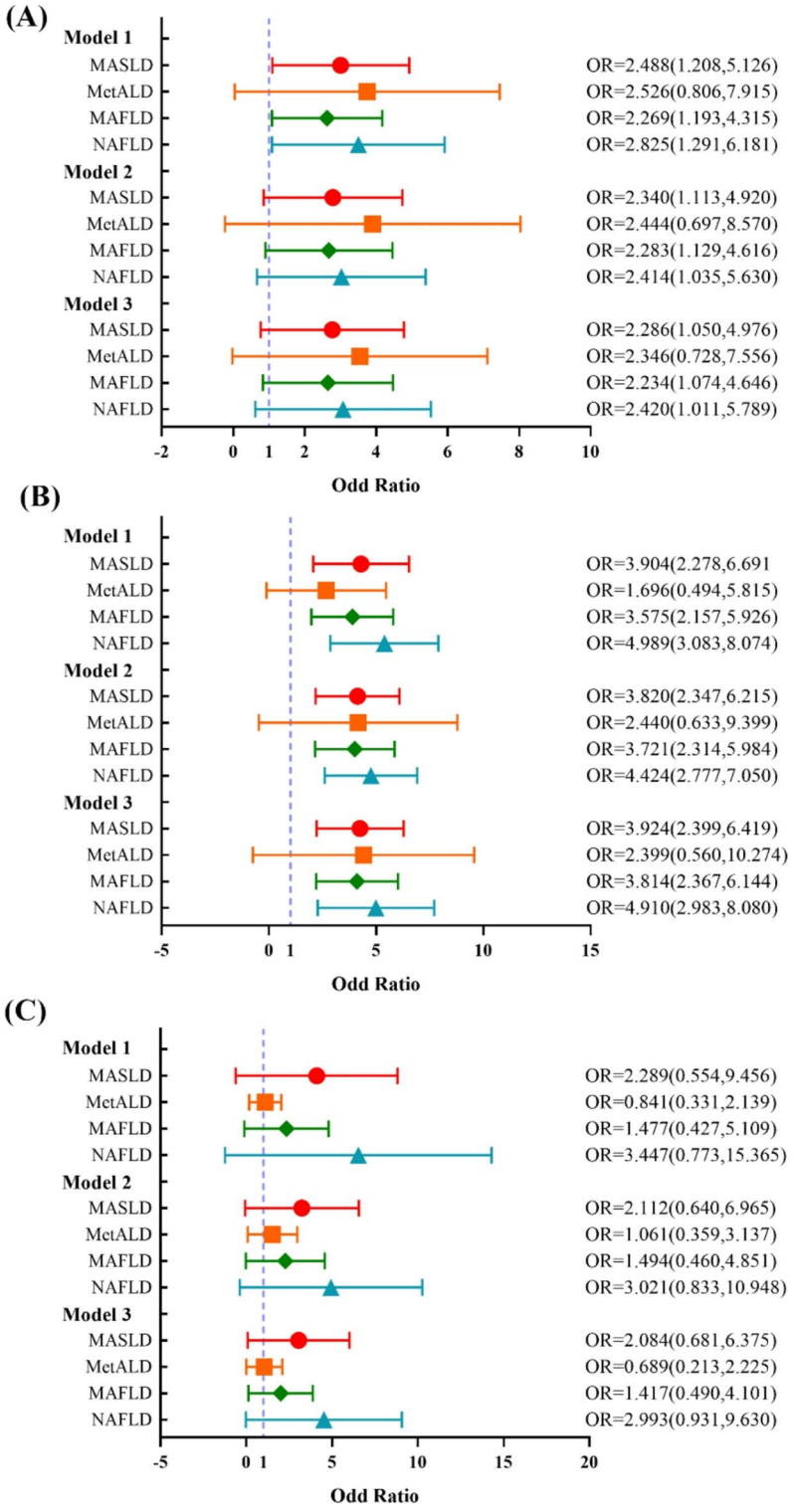

Fig. 3 Multi-variate adjusted odds ratio (95% CIs) for the relationship between steatosis grade (moderate to severe versus mild) and the risk of hypertension (**A**), T2DM (**B**), and hyperlipidemia (**C**) among participants in NHANES 2017–2018. Model 1 contains only independent variables; Model 2 was additionally adjusted for gender, age, ethnicity, FIPR, and education level; and Model 3 was further adjusted for smoking and physical activity. Reference category: mild steatosis

liver disease deaths in patients with MAFLD. YOUNOSSI et al. [21] further found that metabolic syndrome and excessive alcohol consumption had a supercumulative effect on all-cause mortality, but excessive alcohol consumption was linked to outcome only when metabolic syndrome was present. This suggests that the risk of poor prognosis in patients with steatotic liver is greatly increased when alcohol consumption and metabolic risk factors coexist. These results indicate that the group with coexisting metabolic and alcohol risks possesses specificity, which deserves further in-depth study. The proposed definition of MetALD provides an important basis for early screening of this population and subsequent targeted clinical and basic research. Kim et al. further found that, compared to MAFLD, MetALD patients had a higher risk of all-cause and cancer-related mortality [22].

Additionally, we found that MetALD is associated with an increased risk of hypertension (OR = 1.802, 95% CI = 1.355–2.398) and hyperlipidemia (OR = 2.399, 95%CI = 0.560–10.274). Biddinger and colleagues indicated that an increase of one standard deviation in genetically predicted alcohol consumption was linked to a 1.3 times higher risk of developing hypertension and that a reduction in alcohol intake could lower blood pressure in a dose-dependent manner [23]. However, we found no association between MetALD and T2DM risk. This may be related to the fact that chronic consumption of alcohol may increase insulin sensitivity by increasing intrahepatic glutathione synthesis and thus insulin sensitivity [24–27], as well as the small sample size of patients with MetALD in this study.

Facilitating early intervention and drug development

Our results indicate that, compared to NAFLD, participants with MASLD appear to have a higher risk of developing T2DM, hypertension, and hyperlipidemia. We provide evidence to support the renaming and change in diagnosis based on real-world data. The new name and diagnosis are worthy of attention. It is well known that the primary interventions for fatty liver disease are lifestyle modifications, such as weight loss and alcohol abstinence, which have led to a general lack of awareness and attention about these diseases. By redefining and adjusting the diagnostic criteria for fatty liver diseases to more strongly emphasize the roles of metabolic dysregulation and alcohol, it's hoped that more individuals may receive timely interventions. As our understanding of these diseases deepens, the initiation of clinical studies related to MetALD could pave the way for the development of new pharmacological treatments, thereby filling a crucial gap in current therapeutic options.

Aiding in prognosis improvement

In addition, we compared the differences in clinical characteristics among the three groups: MASLD, MAFLD, and NAFLD. We found that participants with MASLD/MAFLD/NAFLD had higher BMI/WC/FBG/Hb1Ac/TG/HOMA-IR levels than those without. This suggests that this group consistently possessed higher levels of obesity, glucose, and lipids than the control group, no matter what the definition of diagnostic criteria, which means that metabolic dysfunction is an important driver of fatty liver disease. Early intervention in populations with metabolic disorders, including managing blood sugar, reducing cholesterol, and controlling blood pressure, may help delay the onset and progression of the disease.

Moreover, it's worth noting that the risk of T2DM was strongly and independently correlated with the severity of hepatic steatosis for the participants with MASLD/MAFLD/NAFLD. This is consistent with previous studies. Steatosis is one of the main pathologic features of fatty liver disease, and NASR et al. [28] found that steatosis grading was strongly associated with mortality and the risk of T2DM in participants with NAFLD. A study with a mean follow-up of 18.4 years reported a 34% increase in the risk of T2DM for every 1 grade increase in steatosis grading in patients with stage 0–2 fibrosis [29]. Here are some possible reasons: When excess fat is deposited in the liver, the intrinsic immune cells of the liver (Kupffer cells, hepatic stellate cells, etc.) are activated, releasing cytokines such as MCP1, IL-1β, and IL-6. These cytokines, on the one hand, promote T2DM by exacerbating the inflammatory response [30–32]; on the other hand, they obstruct insulin signaling via serine phosphorylation on IRS1/2 or reduce β-Cell insulin sensitivity through nitric oxide mediation [33, 34]. Patients who have both NAFLD and T2DM face an increased risk of developing NASH, experiencing liver fibrosis, and encountering cardiovascular diseases [35]. Therefore, early intervention in patients with moderate-to-severe fatty liver disease is important to delay the risk of T2DM, reduce the risk of intrahepatic and extrahepatic complications, and improve the prognosis.

MAFLD identifies High-Risk metabolic disorder patients

In our study, we found that MAFLD has higher odds ratios with hypertension, T2DM, and hyperlipidemia respectively compared to MASLD. This may be due to the definitions of MASLD and MAFLD themselves. MASLD requires the presence of at least one metabolic risk, whereas MAFLD requires the fulfillment of two or more. Our findings indicate that MAFLD is more effective in identifying individuals likely to develop metabolic diseases. Patients with MAFLD should undergo a comprehensive metabolic disease-related assessment, including monitoring of risk factors such as hypertension,

diabetes mellitus, and hyperlipidemia, in order to facilitate early identification and intervention to reduce the risk of complications.

Comparison with the previous study

Chen et al. [36] compared the differences in clinical and histological characteristics of NAFLD, MAFLD, MASLD, and MetALD. The difference between them was that our study was based on a larger sample population, and the subjects were more representative. In addition, we further compared the associations of these four populations with metabolic diseases. In the study by Lee et al. [37]., based on data from 9,775,066 participants in South Korea, the prevalence of MASLD and MetALD was 27.5% and 4.4%, respectively. This finding is significantly lower than ours, a difference that may be related to population, ethnicity, and lifestyle habits. In contrast, Ciardullo et al. [38], based on NHANES data from 2017 to 2020, found no significant difference in the prevalence of MAFLD and MASLD, with a high degree of consistency between the two definitions. This aligns with our research. However, our study further investigated the differences in clinical characteristics between patients with MASLD, MAFLD, MetALD, and NAFLD, as well as the relationship between the degree of steatosis and the risk of metabolic diseases (hypertension, T2DM, and hyperlipidemia) in these four groups. To achieve more objective and accurate results, we accounted for various potential confounders including gender, age, smoking history, and physical activity, and established three regression models. To our limited knowledge, we first tried to explore the relationship between the degree of steatosis in MASLD/MetALD and the risk of metabolic diseases based on a large national sample and found that patients with MASLD may face a higher risk of metabolic diseases compared to NAFLD.

Strengths and limitations

Our study has certain strengths. To our limit knowledge, this is an initial study to explore the relationship between clinical characteristics of MASLD and MetALD, as well as the degree of steatosis and the risk of metabolic disease. Second, we adjusted for several important covariates, including age, sex, race, physical activity, and so on. Further, we included subjects from the NHANES database, which has a wide sample coverage and representativeness. However, this study has some limitations. First, the diagnosis of steatosis was identified by ultrasound rather than biopsy, which may lead to some bias, and second, this is based on data from U.S. adults, and it's uncertain whether these findings are applicable to different racial and age groups, which needs to be confirmed by a large-scale clinical study. Finally, due to the retrospective cross-sectional design of the study, definitive causal inferences cannot be established. Future prospective, multi-center, large-scale studies are needed to further validate these findings.

Conclusion

In conclusion, using NHANES data from 2017 to 2018, we compared the characteristics and risk of T2DM/HTN/HLP participants with MASLD, MetALD, MAFLD, and NAFLD. We investigate the relationship between the steatosis grade and the risk of T2DM, HTN, and HLP further. We found that participants with MASLD or MetALD have a higher BMI and metabolic level. As the degree of steatosis increases, patients with MASLD are at progressively higher risk of developing T2DM. The proposed definitions of MASLD and MetALD are valuable and deserve further exploration. Our findings suggest that MAFLD is a more effective indicator for identifying patients at increased risk for metabolic disorders.

Abbreviations

BMI	Body mass index
CI	Confidence intervals
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
FIPR	Family income-poverty ratio
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
MAFLD	Metabolic Associated Fatty Liver Disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetALD	Metabolic alcohol-related liver disease
MET	Metabolic equivalent of task
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Surveys
OR	Odds ratio
PA	Physical activity
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03912-0.

Supplementary Material 1: **Table S1** The diagnostic criteria for NAFLD, MAFLD, MASLD and MetALD. **Figure S1** The flow chart of case selection.

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Author contributions

Study concept and design: Hong-ye Peng, Chun-li Lu, and Mo Zhao. Acquisition, clearning of data: Hong-ye Peng, Chun-li Lu, and Mo Zhao. Drafting of the manuscript: Hong-ye Peng and Chun-li Lu. Critical revision: Xiao-qiang Huang, and Shu-xia Huang. Statistical analysis: Hong-ye Peng, Zi-wen Zhuo and Jing Liu. Study supervision: Yan-ping Lu and Wen-liang Lv.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The protocol of NHANES was reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics. Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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