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Original Article

Metabolic Risk Factors and Clinical Presentations of Metabolic Dysfunction-associated Steatotic Liver Disease Using Data from the *All of Us* Research Program

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Abstract

Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 32% of the US adult population. The present study aimed to utilize the All of Us electronic health record-linked large cohort to assess seven metabolic risk factors (MRFs) simultaneously, the impact by ethnicity and age, and clinical presentations of MASLD. ***Methods:*** This study included a MASLD group (n = 15,060) and a frequency-matched control group (n = 75,300). Multivariable analyses were performed to compare the frequencies of MRFs and clinical outcomes between the two groups. Type 1 diabetes was not included in the multivariable analysis. Subgroup analyses were conducted according to race and ethnicity, as well as age. ***Results:*** The overall frequency of MASLD was 6.0%. Compared with the control group, individuals with MASLD had significantly higher independent frequencies of obesity (66.1% vs. 41.3%), type 2 diabetes (39.5% vs. 16.9%), hypertension (64.3% vs. 38.6%), hyperlipidemia (59.8% vs. 37.3%), obstructive sleep apnea (28.9% vs. 13.4%), and hypothyroidism (21.2% vs. 13.4%). Obesity was identified as the strongest independent MRF among Asians, Whites, and Hispanics, particularly in individuals younger than 50 years, whereas hypertension was the strongest independent MRF in Blacks. MASLD was also associated with significantly higher frequencies of cardiac events, including coronary artery disease (17.1% vs. 9.4%) and myocardial infarction (7.1% vs. 4.2%); hepatic events, including cirrhosis (7.5% vs. 1.1%) and hepatocellular carcinoma (0.5% vs. 0.1%); and elevated liver enzymes, including alanine aminotransferase (27.7% vs. 10.1%), aspartate aminotransferase (18.0% vs. 6.4%), and alkaline phosphatase (19.8% vs. 13.1%), compared with the control group. ***Conclusions:*** Our study demonstrated that obesity, hypertension, hyperlipidemia, type 2 diabetes, obstructive sleep apnea, and hypothyroidism were independent MRFs for MASLD overall, but the ranking of these MRFs by odds ratios could vary by ethnicity and age. MASLD presents with significantly higher rates of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase elevation, as well as cardiac and hepatic events.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease, has emerged as a significant public health concern, as it is the most common etiology of chronic liver disease, with most current literature estimating the global prevalence to be approximately 32–38% in adult populations.[1–7] MASLD can cause cirrhosis, is a rising etiology for hepatocellular carcinoma (HCC), and is now the most common indication for liver transplantation in those > 65 years old, particularly in women.[8–11] This alarming trend parallels the global trends of obesity, insulin resistance, dyslipidemia, hypertension (HTN), and cardiovascular disease.[12,13]

Although most patients with MASLD are asymptomatic, 7–30% of them may develop metabolic dysfunction-associated steatohepatitis (MASH), previously termed nonalcoholic steatohepatitis.[14,15] MASH, a more severe form of MASLD, is associated with varying ethnic disparities and carries a higher risk for developing cirrhosis, HCC, cardiac-related mortality, and all-cause mortality.[14–19]

Despite active clinical trials aimed at addressing this global epidemic, currently there are only two treatments approved by the U.S. Food and Drug Administration, i.e., resmetirom and semaglutide, for MASH.[20–22] Early diagnosis and identifying and correcting the metabolic risk factors (MRFs) remain the mainstay in managing MASLD. While studies have explored the association of MRFs with the clinical presen-

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; Metabolic risk factor; MRF; All of Us program; Type 1 diabetes; Type 2 diabetes; Hypertension; Hyperlipidemia; Hypothyroidism; Obesity; Obstructive sleep apnea.

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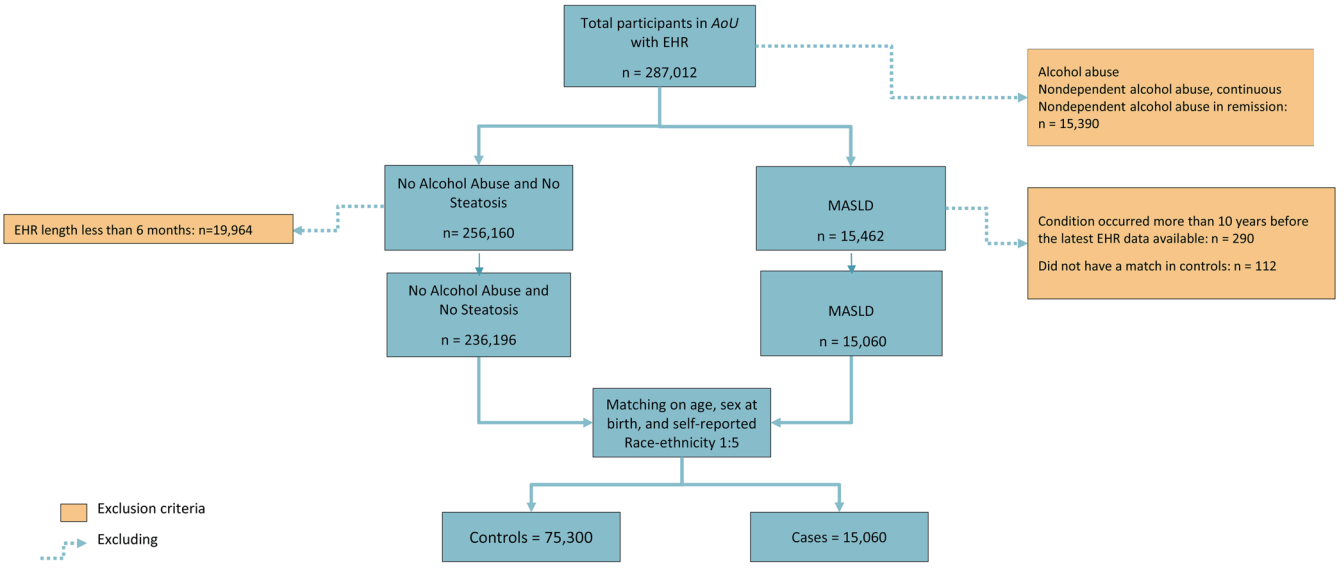

Fig. 1. Overview of the study inclusion/exclusion criteria for the present frequency-matched case-control study. EHR, electronic health record; MASLD, Metabolic dysfunction-associated steatotic liver disease.

tations, natural course, and long-term outcomes of MASLD, many have been limited by study design, often single-center, retrospective, and involving small sample sizes. Although type 2 diabetes mellitus (T2DM), obesity, hyperlipidemia (HLD), and HTN are considered the most common MRFs for MASLD,[9,14,15,23,24] the rank or importance of these MRFs in MASLD remains undetermined. Some studies indicate that ethnicity and age may also impact MASLD-related MRFs.[25–27] Using the 2017–2018 National Health and Nutrition Examination Survey (NHANES) database, a recent cross-sectional study assessed 2,346 cases with MASLD and found that individuals aged 40–64 and ≥ 65 years, higher body mass index (BMI), diabetes, HTN, and hypertriglyceridemia were independently associated with a higher risk.[28] These findings remain to be confirmed by larger cohort studies using different data sources. Additionally, understanding ethnicity-related differences in MRFs will help in developing individualized approaches for the early diagnosis of MASLD. The roles of other MRFs, such as obstructive sleep apnea (OSA),[27–29] hypothyroidism (HT),[28–30] and type 1 diabetes mellitus (T1DM),[29–31] remain unknown or even controversial. To the best of our knowledge, no study has assessed all seven possible MRFs simultaneously in a large cohort. Therefore, additional studies utilizing large, multi-center designs are needed to address these issues.

Likewise, some studies indicated that MASLD is clinically associated with increased cardiac events, such as coronary artery disease (CAD) and myocardial infarction (MI), and hepatic events, such as cirrhosis and HCC.[8,10,13,14,23] However, high-quality studies using large cohorts with direct comparisons to control groups remain lacking. It is known that some MASLD patients present with elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST),[16,32,33] but the exact rates of such elevations have not been assessed in large cohorts with appropriate comparisons. Additionally, the rates of alkaline phosphatase (ALP) elevation in MASLD patients remain to be determined.

The "All of Us (AoU) Research Program" is sponsored by the National Institute of Health to advance precision diagnosis, prevention, and treatment.[34] AoU represents a unique opportunity, as it provides a large cohort of diverse participants[34] to address the above issues for MASLD. The present study aimed to utilize the AoU electronic health record (EHR)-linked large cohort to assess MASLD comprehensively in a real-world setting. By comparing the MASLD group with a control group, we investigated crucial aspects of MASLD-related MRFs and the clinical presentation of MASLD that may impact the prevention, early diagnosis, and management of this disease.

Methods

Study population

This work was performed on data from the NIH AoU Research Program, a diverse nationwide cohort of over 800,000 participants. Data were accessed via the AoU Researcher Workbench, the program's online data repository and research environment. We first created a research cohort consisting of participants whose EHR was linked to the rest of their AoU data. Then we identified participants (cases) with MASLD and from the available non-case participants we randomly selected controls in ratio of 1:5 frequency matched on age, sex, race and ethnicity. Since May 2018, AoU has enrolled participants aged 18 or older from various recruitment sites across the U.S., with a special focus on recruiting individuals from historically underrepresented communities in biomedical research. After a participant consented, their de-identified EHR data were submitted to AoU, and the data were made available to researchers through the program's Researcher Workbench. In addition to EHR data, health questionnaires, physical measurements, the use of digital health technology, and the collection and analysis of biospecimens were also available. Data standardization in the AoU database was based on the Observational Medical Outcomes Partnership Common Data Model using the Systematized Nomenclature of Medicine Clinical Terms (SNOMED) vocabulary. More related information is available at https://allofus.nih.gov.

Case selection for MASLD and control groups

The initial cohort of AoU with available EHR data consisted of 287,012 participants (AoU Controlled Tier Dataset v7).

As shown in Figure 1, 15,390 participants were excluded due to diagnoses of "alcohol abuse", "nondependent alcohol abuse, continuous", and "nondependent alcohol abuse in remission" (SNOMED codes: 15167005, 191882002, 191884001) in their EHR history. Among 271,622 eligible participants, MASLD was diagnosed in 15,462 by "steatosis of liver" (SNOMED code: 197321007), and the other 256,160 without a diagnosis of MASLD were considered eligible study controls. We further excluded 19,964 eligible controls whose EHR length was less than six months, resulting in 236,196 eligible controls. Among the 15,462 participants with a diagnosis of MASLD, we further excluded 290 who had an initial diagnosis more than 10 years before their latest available EHR data. We created the race and ethnicity characteristic based on the two separately recorded data columns in the AoU database, following this rule: if a participant reported their ethnicity as Hispanic or Latino, their race and ethnicity were considered Hispanic in our study; otherwise, it was their race (i.e., White, Black or African American [Black], Asian). We created a case-control study of participants with a diagnosis of MASLD (MASLD group) and those without a diagnosis of MASLD (control group). We chose the control group by frequency-matching with a ratio of 1:5 on age (for the MASLD group: age at diagnosis; for the control group: age at the latest available EHR date), assigned sex at birth, and race and ethnicity. Consequently, 112 cases were further excluded because they did not have an exact match on age, sex at birth, and self-reported race and ethnicity among the control group. As a result, our case-control study included 15,060 cases, which we refer to as MASLD group, and 75,300 cases as controls, i.e., the control group. Figure 1 illustrates the inclusion/exclusion criteria for this frequency-matched case-control study.

Characteristics of interest

The characteristics of interest in this study were age (i.e., age at initial diagnosis of MASLD for cases and age at the latest EHR data available for the controls), assigned sex at birth (i.e., female, male, other/unknown), self-reported race and ethnicity (i.e., White, Black, Hispanic or Latino, Asian, and other/unknown), country of birth (i.e., USA vs. non-USA), MRFs (i.e., obesity by average BMI with a threshold of 25 for Asians and a threshold of 30 for non-Asians[35–37]), T2DM (SNOMED code: 44054006), HLD (SNOMED code: 55822004), HTN (SNOMED code: 38341003), OSA (SNOMED code: 78275009), HT (SNOMED code: 40930008), T1DM (SNOMED code: 46635009), cardiac events [i.e., CAD (SNOMED code: 53741008) and MI (SNOMED code: 22298006)], and hepatic events [i.e., cirrhosis (SNOMED code: 19943007) and HCC (SNOMED code: 109841003)]. Additionally, liver injury-related laboratory data, including ALT, AST, and ALP, were also available and collected in a small portion (as detailed in the RESULTS section) in both groups. All the above-mentioned variables were considered if their diagnosis occurred before, at the same time, or up to a maximum of three months after the diagnosis of MASLD. For BMI, due to data availability, we used the average value of data points in the participants' EHR data.

Statistical analysis

Comparisons of characteristics of interest between MASLD and control groups were performed using Fisher's exact test or the contingency χ^2 test. We performed multivariable logistic regression analysis with the dependent binary variable of presence or absence of MASLD diagnosis. All seven models were adjusted for the characteristics on which the MASLD and control groups were matched, including age, assigned sex at birth, race and ethnicity, and length of EHR. For each multivariable model, in addition to age, race and ethnicity, assigned sex at birth, and length of EHR, we included obesity, T2DM, HTN, HLD, OSA, and HT. Considering the variability observed in the results, we created additional multivariable logistic regression models on subgroups based on race and ethnicity (i.e., White, Black or African American, Hispanic or Latino, and Asian), age (< 50 vs. ≥ 50 years), and the combination of both. This study was implemented in the AoU Researcher Workbench Cloud environment using Python. All *p*-values associated with reported results in this analysis were considered statistically significant at *p*-value < 0.001 unless otherwise noted.

Results

Race- and ethnicity- and age-related distribution of MASLD in our study

As shown in Table 1, out of the 251,256 total eligible participants, 6.0% (n = 15,060) met the diagnostic criteria for MASLD. Within the MASLD group, the mean age was 54.3 ± 14.1 [median (IQR), 56 (44–65)], the male-to-female ratio was 1.95:1 (33.3% and 65.0%, respectively), and the race- and ethnicity distribution was 54.9%, 26.0%, 10.8%, and 2.5% for White, Hispanic, Black, and Asian participants, respectively. In addition, among the MASLD group, the distribution of age was as follows: age > 65 (26.3%), 50–59 (25.4%), 60–64 (13.4%), 40–49 (17.2%), and < 40 (17.7%) subgroups.

Comparison of overall MRFs in MASLD vs. control group

As shown in Table 2 and Figure 2, we compared the differences in frequencies of the four most common or major MRFs (i.e., obesity, T2DM, HLD, and HTN) and three less-studied or minor MRFs (i.e., OSA, HT, and T1DM) in the MASLD vs. control group. Among the four major MRFs, obesity showed the highest frequency (66.1% vs. 41.3%) in the MASLD vs. control group. This included BMI ≥ 25 for Asians (71.1% vs. 43.2%) and BMI ≥ 30 for non-Asians (65.9% vs. 41.2%). The next most frequent major MRF was HTN (64.3% vs. 38.6%), followed by HLD (59.8% vs. 37.3%) and T2DM (39.5% vs. 16.9%) in the MASLD vs. control group. Among the three minor MRFs, OSA (28.9% vs. 13.4%) represented the highest frequency, followed by HT (21.2% vs. 13.4%) and T1DM (4.3% vs. 1.9%) in MASLD vs. control group. All *p*-values were < 0.0001.

We then further assessed whether these MRFs were independently associated with the diagnosis of MASLD. T1DM was excluded from the analysis because of its smaller sample size. As shown in Table 3 and Figure 3A, A, multivariable logistic regression analysis showed that obesity, T2DM, HTN, HLD, OSA, and HT were all independently and significantly associated with MASLD. For MASLD overall, the odds ratios (ORs) were as follows: obesity (OR = 2.2) was the strongest independent MRF, followed by T2DM (OR = 1.8), HTN (OR = 1.7), HLD (OR = 1.6), OSA (OR = 1.4), and HT (OR = 1.3). Table 3 summarizes ORs in different categories of analysis. All *p*-values were < 0.0001.

Comparison of self-reported race- and ethnicity- and age-related MRFs distribution in MASLD vs. control group

Self-reported race- and ethnicity-related MRFs: Table 3 and Figures 3A, B–E summarize the ORs and 95% confidence intervals (CIs) of these six MRFs in different self-

Table 1. Baseline demographics in MASLD and frequency-matched control groups

Characteristic	MASLD cases (n = 15,060)		Frequency-matched controls (n = 75,300)	
Age				
Mean (STDEV)	54.3 (±14.1)		54.3 (±14.1)	
Median (IQR)	56 (44–65)		56 (44–65)	
Age categories	n	%	n	%
<40	2,659	17.7%	13,295	17.7%
40–49	2,585	17.2%	12,925	17.2%
50–59	3,832	25.4%	19,160	25.4%
60–64	2,020	13.4%	10,100	13.4%
65+	3,964	26.3%	19,820	26.3%
Sex at birth				
Female	9,785	65.0%	48,925	65.0%
Male	5,017	33.3%	25,085	33.3%
Other/Unknown	258	1.7%	1,290	1.7%
Self-reported race-ethnicity				
White	8,265	54.9%	41,325	54.9%
Hispanic or Latino	3,911	26.0%	19,555	26.0%
Black or African American	1,623	10.8%	8,115	10.8%
Asian	377	2.5%	1,885	2.5%
Other/Unknown	884	5.9%	4,420	5.9%
Country born				
USA	11,909	79.1%	59,210	78.6%
Not USA	2,883	19.1%	14,744	19.6%
Unknown	268	1.8%	1,345	1.8%

MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease.

reported race and ethnicity subgroups. Obesity showed the strongest association with MASLD in Asian, White, and Hispanic subgroups (ORs: 2.8, 2.4, 2.1), whereas HTN showed the strongest association with MASLD in the Black subgroup (OR: 2.0). Additionally, the rank of ORs for these MRFs varied across race and ethnicity subgroups, as shown in Table 3. For instance, OSA was the third MRF in the Black subgroup but was less common MRF in the other subgroups.

Age-related MRFs: Table 3 and Figure 3B, A1 and Figure 3C, A2 summarizes the ORs and 95% CIs of these six MRFs in participants younger than 50 years old (Figure 3B, A1) and in those aged 50 years or older (Figure 3C, A2), respectively. Although obesity and T2DM showed the strongest association with MASLD in both subgroups, the ORs were higher in the younger age subgroup (ORs in younger participants: 3.2 and 2.0; ORs in older participants: 1.9 and 1.8, respectively).

Age- and self-reported race- and ethnicity-related MRFs: Table 3 and Figures 3B, B1–E1 and Figures 3C, B2–E2 summarizes the ORs and 95% CIs of these six MRFs in participants younger than 50 years old (Figures 3B, B1–E1) and in those aged 50 years or older (Figures 3C, B2–E2), stratified by self-reported race and ethnicity. In younger participants, across all self-reported race and ethnicity subgroups, obesity showed the strongest association with MASLD (ORs: Asian 5.3, White 4.0, Hispanic 2.7, Black 2.1). However, in older participants, HLD (OR = 2.0) in the Asian subgroup and T2DM (OR = 1.9) in the Black subgroup showed the strongest association with MASLD.

MASLD clinical presentation

We then assessed MASLD clinical presentation by the frequencies of cardiac and hepatic events and liver enzyme elevations. As shown in Table 2 and Figure 4A, compared to the control group, the MASLD group had significantly higher frequencies of CAD (17.1% vs. 9.4%) and MI (7.1% vs. 4.2%). As shown in Figure 4B, the frequencies of both cirrhosis (7.5% vs. 1.1%) and HCC (0.5% vs. 0.1%) were significantly higher in the MASLD group than in the control group. All *p*-values were <0.001.

In our data, 1,017 participants in the MASLD group and 989 participants in the control group also had laboratory data available. Using these data, we compared the frequencies of ALT (≥ 40 U/L), AST (≥ 40 U/L), and ALP (≥ 110 U/L) elevations in both groups. As shown in Figure 4C, the MASLD group had not only significantly higher rates of ALT (27.7% vs. 10.1%) but also AST (18.0% vs. 6.4%) and ALP (19.8% vs. 13.1%) elevations compared to the control group. All *p*-values were < 0.001.

Discussion

MASLD has emerged as a significant public health concern, with estimated global prevalence of approximately 32%–

Table 2. Comparison of metabolic risk factors, cardiac and hepatic events in MASLD and control groups

Types of variables	Variables	Cases (n = 15,060)		Frequency-matched controls (n = 75,300)		*p*-value
		n	%	n	%	
Metabolic risk factors	Obesity	9,949	66.1%	31,091	41.3%	<0.0001
	Asian	268	71.1%	815	43.2%	<0.0001
	Non-Asian	9,681	65.9%	30,276	41.2%	<0.0001
	Type 2 diabetes	5,951	39.5%	12,732	16.9%	<0.0001
	Hyperlipidemia	9,007	59.8%	28,107	37.3%	<0.0001
	Hypertension	9,682	64.3%	29,074	38.6%	<0.0001
	Obstructive sleep apnea	4,346	28.9%	10,059	13.4%	<0.0001
	Hypothyroidism	3,193	21.2%	10,105	13.4%	<0.0001
	Type 1 diabetes	651	4.3%	1,406	1.9%	<0.0001
Cardiac and hepatic events	Coronary artery disease (CAD)	2,570	17.1%	7,066	9.4%	<0.0001
	Myocardial infarction	1,073	7.1%	3,138	4.2%	<0.0001
	Cirrhosis	1,126	7.5%	799	1.1%	<0.0001
	Hepatocellular Carcinoma	81	0.5%	90	0.1%	<0.0001

MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease.

38% in adult populations.[1–7] In the present study, we used the large cross-sectional AoU dataset, identified 15,060 participants with MASLD, and assessed its association with all seven reported MRFs simultaneously by comparing them with a matched control group containing 75,300 participants, creating a large and thorough case-control study. In a previous study that included a large primary care cohort of 17,669,973 subjects, the frequency of MASLD was 1.9%.[38] In our cohort, the rate of MASLD was 6.0%, and the distribution by race and ethnicity showed that the frequency of MASLD was higher among Hispanics (7.8%), followed by Whites (5.8%), Asians (5.0%), and Blacks (3.1%). Such differences may be derived from participant selection. AoU data are collected from multicenter, nationwide, highly diversified sites and may be more representative of the general population. Previous studies indicated that prevalence could be age-related. For instance, Cheng *et al*. reported the highest prevalence at 34.6% in the 50–59 age group, followed by 33.1% in the 20–49 age group.[26] Based on the AoU data, the highest frequency was in participants aged > 65 (26.3%) and 50–59 years (25.4%), followed by < 40 (17.7%), 40–49 (17.2%), and 60–64 (13.4%) subgroups. Our results reconfirmed the findings by Díaz *et al*., showing a higher frequency of MASLD in individuals aged ≥ 65 years using the NHANES database.[28]

Huang *et al*. reported that based on the third NHANES, the Hispanic population had a higher prevalence of MASLD at 37.0%, followed by Whites at 29.3%, whereas the non-Hispanic Black population had a lower prevalence at 24.7%.[39]

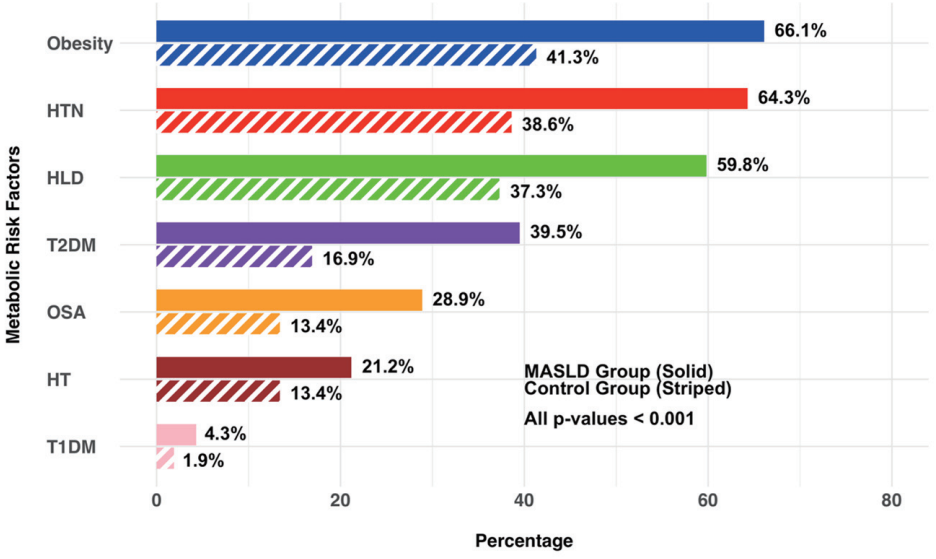

Fig. 2. Univariable analysis of overall frequencies of seven MRFs in cases vs. controls. MRFs, metabolic risk factors; HTN, hypertension; HLD, hyperlipidemia; T2DM, type 2 diabetes mellitus; OSA, obstructive sleep apnea; HT, hypothyroidism; T1DM, type 1 diabetes mellitus.

Table 3. Odds ratios (ORs) for various MRFs in the full MASLD group, and age- and race-ethnicity subgroups

Variables	All	<50	≥50	White	Hispanic	Black	Asian	<50-year-old				≥ 50-year-old			
								White	Hispanic	Black	Asian	White	Hispanic	Black	Asian
Obesity	2.2[a]	3.2[a]	1.9[a]	2.4[a]	2.1[a]	1.6[a]	2.8[a]	4.0[a]	2.7[a]	2.1[a]	5.3[a]	2.1[a]	1.7[a]	1.5[b]	1.8[c]
T2DM	1.8[a]	2.0[a]	1.8[a]	1.9[a]	1.6[a]	1.9[a]	1.7[a]	2.4[a]	1.8[a]	2.1[a]	2.1[c]	1.9[a]	1.5[b]	1.9[a]	1.5[c]
HTN	1.7[a]	1.6[a]	1.7[a]	1.9[a]	1.4[b]	2.0[a]	1.7[a]	1.6[a]	1.4[b]	2.0[a]	1.7[c]	1.9[a]	1.4[b]	1.8[a]	1.5[c]
HLD	1.6[a]	1.7[a]	1.4[b]	1.6[a]	1.6[a]	1.6[a]	2.3[a]	1.5[a]	1.8[a]	1.7[a]	2.3[a]	1.5[b]	1.4[b]	1.5[b]	2.0[a]
OSA	1.4[b]	1.6[a]	1.4[b]	1.3[b]	1.4[b]	1.8[a]	1.2[d]	1.6[a]	1.4[b]	1.8[a]	0.9[d]	1.3[b]	1.4[b]	1.7[a]	1.5[d]
HT	1.3[b]	1.4[b]	1.2[b]	1.2[b]	1.5[b]	1.3[c]	0.9[d]	1.3[b]	1.8[a]	1.7[c]	1.3[d]	1.2[b]	1.3[b]	1.1[c]	0.6[d]

[a]OR > 1.5 and *p*-value <0.0001. [b]OR ≤ 1.5 and *p*-value <0.0001. [c]*p*-value 0.0001-0.05. [d]NS. HTN, hypertension; HLD, hyperlipidemia; T2DM, type 2 diabetes mellitus; OSA, obstructive sleep apnea; HT, hypothyroidism.

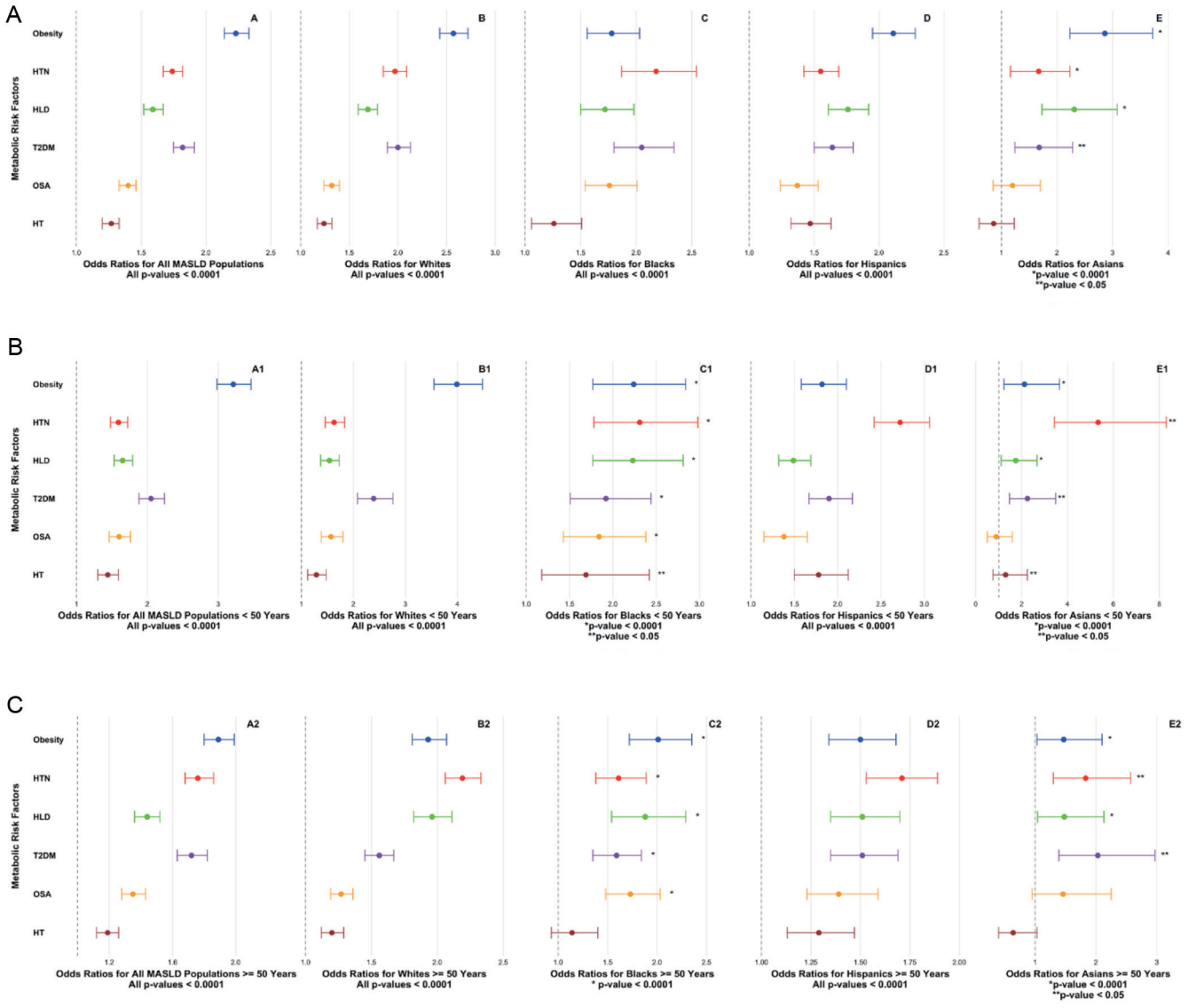

Fig. 3. Multivariable analysis of overall and race- and ethnicity-related frequencies of Metabolic Risk Factors (MRFs). Fig. 3A: Comparison of OR distribution for variable MRFs overall (A) and in various race- and ethnicity-related MASLD subgroups (B–E). Fig 3B and 3C: Comparison of OR distribution for variable MRFs in participants aged <50 years (A1–E1) vs. ≥50 years (A2–E2) overall (A1 vs. A2) and in various ethnicity-related MASLD subgroups (B1–E1 vs. B2–E2). MRFs, metabolic risk factors; HTN, hypertension; HLD, hyperlipidemia; T2DM, type 2 diabetes mellitus; OSA, obstructive sleep apnea; HT, hypothyroidism.

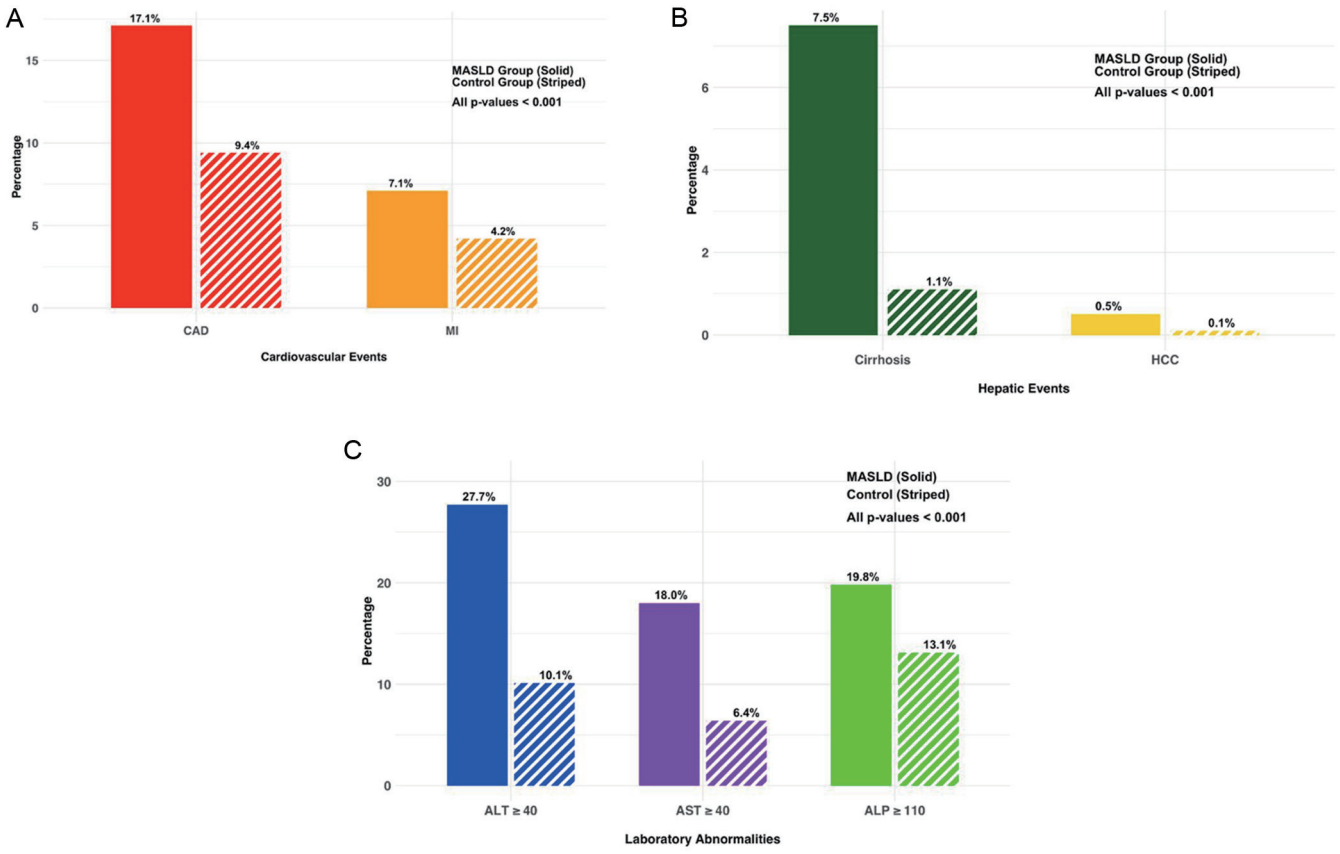

Fig. 4. Clinical presentation of MASLD. Comparison of the frequencies for: (A) CAD and MI; (B) Cirrhosis and HCC; (C) ALT, AST, and ALP elevations in MASLD vs. control group. MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; CAD, Coronary Artery Disease; M, Myocardial Infarction; HCC, Hepatocellular Carcinoma; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase

Using the same NHANES database, Díaz *et al*. also reported that the Hispanic group carried the highest prevalence of MASLD, i.e., 47.0%.[28] In population-based studies performed in the U.S., the prevalence of MASLD was higher in Hispanics (22.9%), followed by Whites (14.4%) and Blacks (13.0%).[40] In our cohort, the distribution of race and ethnicity among the MASLD group was 54.9%, 26.0%, 10.8%, and 2.5% for Whites, Hispanics, Blacks, and Asians, respectively, consistent with the previous reports.[28,39,40]

Previous studies have shown that the primary MRFs for MASLD include obesity, T2DM, HLD, and HTN, with obesity and T2DM found to be the most significant MRFs.[9,14,15,22,23,28] Indeed, around 90% of individuals with MASLD have at least one MRF. Based on our large and diversified dataset, we reconfirmed that the frequencies of these four major MRFs were independently and significantly associated with MASLD in our MASLD group. Although the criteria may not be identical, our results confirmed Díaz *et al*.'s findings that overweight/obesity is the most common MRF for MASLD.[28]

Although OSA and HT have been reported as other MRFs for MASLD,[29,30] such associations remain controversial. In the present study, we assessed OSA, HT, and T1DM in parallel with the four major MRFs, representing the first study to assess all seven MRFs simultaneously. Multivariable analysis confirmed that OSA and HT were independently and significantly associated with MASLD, although their ORs were lower than those of the four major MRFs. Thus, both OSA and HT should be considered as additional MRFs for MASLD. The frequency of T1DM in MASLD patients is almost unknown; one previous study with a very small sample size reported that 4.7% (6/128) of individuals with T1DM had MASLD.[31] The present study demonstrated that the frequency of T1DM was low (4.3%) in the MASLD group, making it a relatively less common, but significant MRF for MASLD.

Studies have indicated different distributions of MRFs by ethnicity and age.[25–27] However, no study had used a large and diversified dataset to address these issues. In this study, we stratified our data by self-reported race and ethnicity and found that the distribution of the six MRFs (excluding T1DM) varied among subgroups. For instance, obesity was the most common MRF in Asian, White, and Hispanic MASLD subgroups. Previous studies have reported a lower incidence of MASLD in Black populations, with cardiometabolic factors, such as HLD and HTN playing a more prominent role in hepatic steatosis.[32] Consistent with this, our findings showed that the MRFs for MASLD in the Black subgroup differed significantly from those in other ethnic groups, with HTN being the strongest independent MRF. Consistent with prior reports,[41,42] using the AoU dataset, we demonstrated that both OSA and HT were weaker or minor MRFs for MASLD in general and across all race and ethnicity subgroups, except that OSA was the third most common MRF for MASLD in the Black subgroup.

We further conducted age-stratified analyses of MRF distributions and found that among participants younger than 50 years, obesity was the strongest MRF for MASLD, followed by T2DM, HLD, OSA, HTN, and HT. However, in participants aged 50 years or older, the ORs for these MRFs were in the order of obesity, T2DM, HTN, HLD, OSA, and HT. Thus, com-

pared with HLD, HTN had a stronger association with MASLD in older participants. Additionally, the strength of all these MRFs in association with MASLD, as measured by ORs, was generally weaker in the older age group compared with the younger group.

The variability in MRFs across race, ethnicity, and age subgroups may indicate the potential pathogenic roles of genetic susceptibility and other environmental factors. Prior studies have documented racial differences in key genetic polymorphisms associated with hepatic fat storage, such as PNPLA3, which occurs at higher frequency in Hispanics and Asians, especially those of Southeast Asian descent.[43,44] Clinically, understanding these ethnicity- and age-related variations in MRF distribution for MASLD will help not only in age- and ethnicity-focused early diagnosis, but also in understanding MASLD-related pathogenesis and, likely, future individualized management.

Studies have reported increased cardiac and hepatic events in MASLD patients.[8,10,13,14,23] Using the AoU dataset, we demonstrated that the frequencies of CAD and MI were significantly higher in the MASLD group than in the control group. Additionally, the frequencies of cirrhosis and HCC were also significantly higher in the MASLD group. These findings, derived from the large AoU dataset, reconfirmed previous studies showing the association of MASLD with the development of cardiac and hepatic comorbidities.[8,10,14–16] Thus, assessing cardiac and hepatic comorbidities should be an essential part of MASLD management.

The most common abnormal laboratory test results in MASLD are elevated ALT and AST, although ALP may also be elevated.[14,32,33] In our MASLD group with available data on ALT and AST, the frequencies of ALT and AST elevations were significantly higher than those in the control group. The relatively low frequencies of ALT/AST elevation in our MASLD group support the recommendation that the normal values of ALT/AST for MASLD should be lower than the current cutoff values of most laboratory references,[45] and normal ALT/AST values by current laboratory references cannot rule out MASLD. Furthermore, in the MASLD group, the frequency of ALP elevation was slightly higher than that of AST elevation and was also significantly higher than in the control group. Thus, MASLD should be considered in individuals with ALP elevation after other possible causes are ruled out.

It should be noted that the present study has several limitations. First, the diagnosis of MASLD was based on EHR and ICD codes, which cannot fully rule out other coexisting liver diseases, such as viral hepatitis B and C, autoimmune hepatitis, and primary biliary cholangitis. Second, using alcohol-related codes alone may not exclude all patients with alcohol misuse. We also recognize that this study may have selection bias, as participants were selected based on the availability of existing records, which may not represent the general population. To mitigate potential recruitment variability in the AoU Research Program, we designed and performed a frequency-matched case-control study. Additionally, data accuracy depends on the quality of existing records entered by individual providers and ancillary medical staff into the EHR, so the data may be incomplete. We acknowledge that the reported results pertaining to ALT, AST, and ALP elevation are limited due to incomplete laboratory recordings in AoU.

Conclusions

The present study provides a unique opportunity to assess a large cohort of MASLD with diversified participants, and our results expand knowledge on the association of MASLD with the seven MRFs and the clinical presentation of MASLD.

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Conflict of interest

KQH is on the Madrigal Pharmaceuticals speaker bureau. The other authors have no conflict of interests related to this publication.

Author contributions

Study initiation (KQH, HAC), study design (KQH), study coordination (KQH, SH, JF, HAC), data collection (KQH, SNP, AZ, SH, JF), data analysis (KQH, SNP, AZ), data interpretation (KQH, SNP, AZ, HAC), and manuscript preparation (KQH, SNP, AZ, KS, TL, HAC). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study used data from the National Institutes of Health (NIH) All of Us Research Program, a nationwide research cohort designed to advance precision medicine. All participants in the All of Us Research Program provided written informed consent for participation and for the use of their data for research purposes. The data used in this study were accessed through the All of Us Researcher Workbench in accordance with program policies and data use agreements. This study involved analysis of de-identified data and did not involve direct contact with participants. In accordance with federal regulations and institutional policy, the study was determined to be exempt from human subjects research oversight or not human subjects research, as applicable, by the investigators' Institutional Review Board (IRB). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

Individual-level data cannot be provided as per AoU's data dissemination policy. The code used for analyses is available at the workbench environment of the All of Us research program.

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