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Metabolic outcomes in non-alcoholic and alcoholic steatotic liver disease among Korean and American adults

Yeongmin Kim[1], Tae Sic Lee[2*] and Chang-Myung Oh[1*]

Abstract

Background This study investigated the prevalence and causal relationships of chronic metabolic diseases (diabetes, hypertension, and dyslipidemia) with steatotic liver disease (SLD), specifically metabolically associated alcoholic liver disease (MetALD).

Methods We conducted a comprehensive analysis using cross-sectional data from the KNHANES from 2011 to 2021 and the NHANES from 1999 to 2020. Longitudinal data from 2001 to 2014 from the KoGES were used. Participants were categorized into the metabolic dysfunction-associated SLD(MASLD), MetALD, and ALD groups based on their hepatic steatosis index (HSI), including liver profiles, body composition, and diabetes, and alcohol consumption. Multivariable, including age and smoking status, logistic and Cox regression analyses were performed to assess the prevalence and incidence of chronic diseases.

Results In both the KNHANES and NHANES cohorts, an increased HSI was significantly associated with a higher prevalence of chronic metabolic diseases. Longitudinal data from the KoGES cohort showed that MASLD and MetALD were significant predictors of chronic metabolic disease in both men and women. MetALD showed a higher hazard ratio for the development of chronic metabolic diseases than MASLD in Cox regression analysis.

Conclusions This study highlighted the intertwined nature of SLD and metabolic health, with an emphasis on the role of MetALD. The significant association between MetALD and chronic metabolic diseases underscores the need for integrated management strategies that address both liver health and metabolic risk factors.

Keywords Steatotic liver disease, Diabetes, Hypertension, Dyslipidemia, Cohort study

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Background

Steatotic liver disease (SLD) comprises a spectrum of liver disorders that are characterized by excessive accumulation of fat within hepatocytes. Non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis, affects approximately 25% of adults worldwide [1–3]. NAFLD has emerged as a major health concern owing to its increasing prevalence and detrimental impact on global health [4].

SLD is associated with various complications that significantly affect patient morbidity and mortality. Cardiovascular disease (CVD) is the leading cause of death in patients with SLD, reflecting the profound systemic effects of the disease [1, 4]. Additionally, patients with SLD are at an increased risk of developing extrahepatic malignancies, liver-related complications, chronic kidney disease, and type 2 diabetes mellitus [1]. These comorbidities illustrate the complex and multifaceted pathophysiology of SLD and underscore the need for a holistic and multidisciplinary approach to management and therapeutic interventions to mitigate the extensive burden of the associated comorbidities.

Recently, the scientific community revised the terminology from SLD to steatotic liver disease (SLD) and proposed a new classification of SLD to reflect a more nuanced understanding of its multifactorial etiology and complex pathophysiology. The newly proposed categories include metabolically associated SLD (MASLD), metabolically associated alcoholic liver disease (MetALD), and ALD [5–8]. MetALD includes patients with SLD due to mild alcohol consumption [5]. A recent health checkup-based cross-sectional study in the Japanese population highlighted the prevalence of SLD based on the new nomenclature [9]. The study reported that MASLD accounted for the majority of SLD cases, with a prevalence of approximately 24–30%. In addition, MetALD made up about 5–7% of individuals, while ALD 2–3%. This refined classification system aims to better capture multiple metabolic and lifestyle factors that contribute to liver pathology, thereby facilitating more precise diagnosis and management strategies [5, 10].

Herein, we examined the associations and causal relationships between SLD and chronic metabolic disorders using community-based cohort data [11, 12]. We also analyzed the metabolic risks associated with MASLD, MetALD, and ALD in the context of chronic metabolic diseases using data from a comprehensive Korean cohort. By examining the prevalence and interplay of hypertension, diabetes, and dyslipidemia in these different liver disease categories, we aimed to elucidate their unique metabolic profiles, particularly MetALD. Our goal was to form clinical strategies for the management of patients with SLD and provide a basis for tailored healthcare approaches. Additionally, this study underscores the importance of accurate disease classification to address the broader burden of chronic metabolic diseases, ultimately contributing to improved patient care and outcomes.

Methods

Study population

We conducted a comprehensive analysis using cross-sectional data from the 2011–2021 Korea National Health and Nutrition Examination Survey (KNHANES) and the 1999–2020 National Health and Nutrition Examination Survey (NHANES). The KNHANES datasets are publicly available on the KNHANES website (http://knhanes.cdc.go.kr) [13]. NHANES records are publicly available on the CDC website (www.cdc.gov/nchs/nhanes/index.htm) [14]. All participants consented to the use of their information for research purposes. Both the KNHANES and NHANES datasets contain extensive information on health, nutrition, medical history, physical measurements, and laboratory results (Supplementary Figs. 1 and 2). Additionally, we examined the longitudinal data from the Korean Genome and Epidemiology Study (KoGES) from 2001 to 2014 that included detailed records of health, diet, medical history, physical measurements, and laboratory results (Supplementary Fig. 3) [9, 11]. These datasets served as the basis for our investigation of the association between liver diseases, specifically variations related to alcohol consumption and chronic diseases such as diabetes, hypertension, and dyslipidemia.

The KNHANES and NHANES datasets were preprocessed and merged into a single file, regardless of the survey year, using R software version 4.1.2 (Fig. 1A) [15]. The KNHANES, NHANES, and KoGES datasets were initially heterogeneous. To analyze with the identical source code (R language), we standardized the dataset by making the names and number of columns consistent. When calculating the daily amount of alcohol consumption to distinguish MASLD, MetALD, and ALD, we quantified the following information: (1) the alcohol content in different beverage types, such as beer and wine. (2) the amount and frequency of consumption. Clinical biomarkers are influenced by a complex interplay of genetic and environmental factors and tend to exhibit independence among features, making imputation-based approaches particularly challenging. Therefore, participants with missing values for key baseline characteristics, biochemistry, alcohol consumption, smoking status, and medication information were excluded from further analysis. The KoGES dataset underwent similar pre-processing, resulting in a single consolidated file. For the KoGES dataset, which is longitudinal data distinct from KNHANES and NHANES, participants who did not have at least one follow-up were excluded from the analysis. To examine the causality of chronic diseases resulting from steatotic

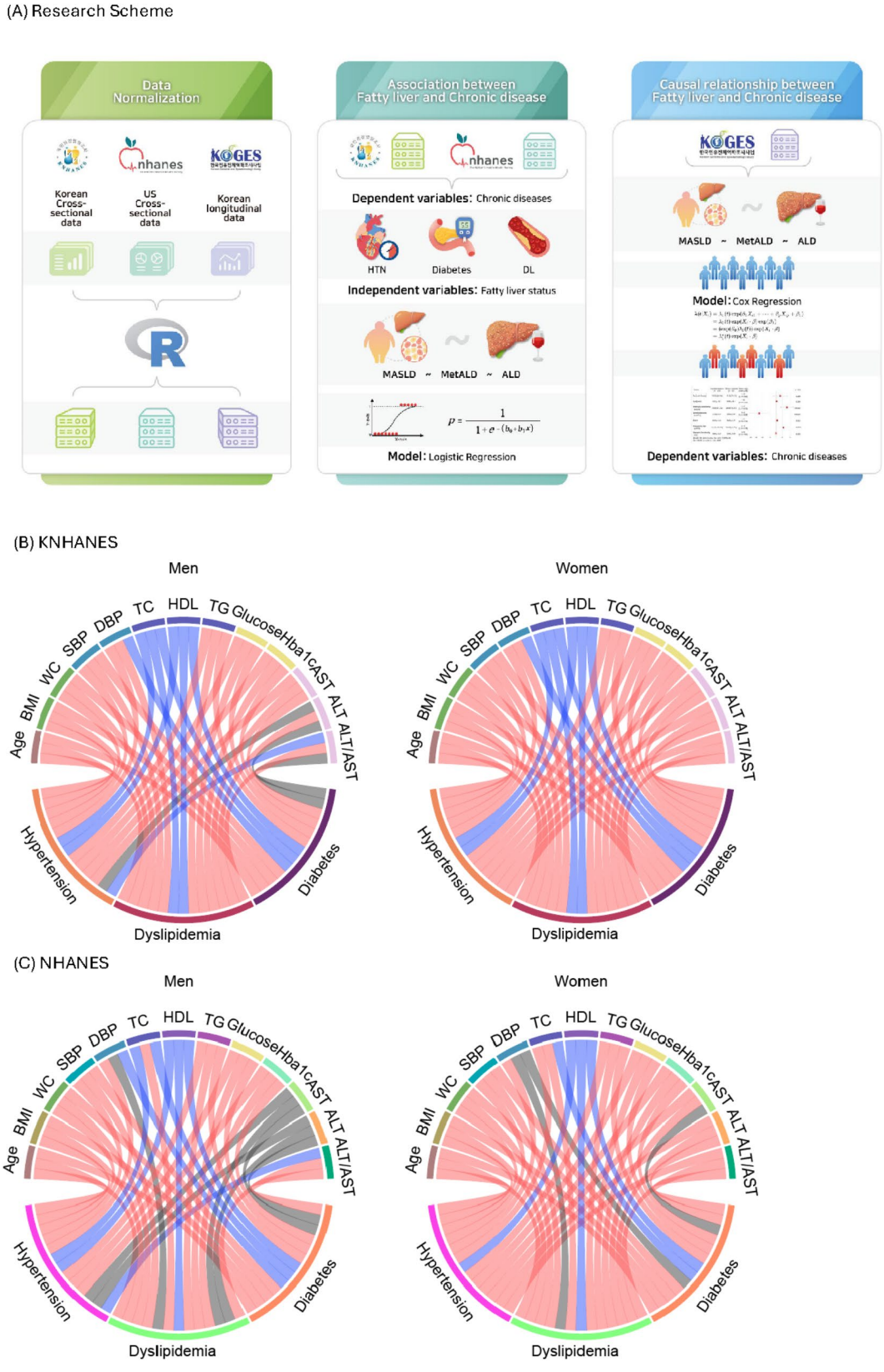

Fig. 1 Associations between chronic metabolic disease and metabolic parameters. **(A)** Research scheme for data normalization, association, and causality analysis for the three cohorts. **(B)** Circos plot of associations between chronic metabolic diseases and metabolic parameters in the KNHANES cohort. **(C)** Circos plot of associations between chronic metabolic diseases and metabolic parameters in the NHANES cohort

liver disease, we developed separate models for diabetes, hypertension, and dyslipidemia. Only participants with at least seven follow-up records (over 12 years) were included in the causality analysis to ensure robust longitudinal data for reliable inferences.

Definition of chronic diseases and MASLD, MetALD, ALD

The presence of chronic diseases, including diabetes and hypertension, and the classification of healthy participants were determined based on whether a physician had diagnosed the disease at least once. Dyslipidemia was identified by either a physician's diagnosis or the use of dyslipidemia medications.

A comprehensive score for SLD, incorporating liver profiles, body composition, and diabetes, provides an indirect assessment of MASLD. Most of the individual components, except for diabetes, are utilized to evaluate SLD, with their original value showing continuous distribution. Diabetes is used in the formula as a dichotomous value, present or absent. Steatotic liver status was assessed using the hepatic steatosis index (HSI), which was calculated using the following formula: HSI = 8 × ALT/AST + BMI + 2 (if diabetic) + 2 (if female) [16]. An HSI score of ≥ 36 was used to diagnose steatotic liver disease (SLD) in the Korean cohort, based on thresholds established in previous studies [16–20]. For the American cohort, an HSI score of ≥ 41 was used to diagnose SLD, based on two key considerations. First, we calibrated the prevalence of MASLD in the NHANES dataset, as defined by the HSI threshold, to match the prevalence observed in the KNHANES cohort (Supplementary Fig. 4). Second, we adjusted for the significant difference in BMI, which averaged about 5 units between the Korean and American cohorts. This adjustment is pivotal in ensuring that the threshold reflects population-specific characteristics, thereby enhancing the comparability and accuracy of our results across cohorts.

To classify MASLD, MetALD, and ALD among patients with SLD, daily alcohol consumption was utilized for further categorization. Men who consumed < 30 g and women who consumed < 20 g of alcohol per day were classified as having MASLD, whereas men who consumed between 30 g and 60 g and women who consumed between 20 g and 50 g of alcohol per day were classified as having MetALD. Finally, men who consumed > 60 g and women who consumed > 50 g of alcohol per day were classified as having ALD [5].

Collection of data and covariates

Demographics of participants with and without liver disease across were obtained from KNHANES, NHANES, and KoGES. Participants were stratified based on the presence or absence of liver disease. Demographic data are presented as mean ± standard deviation for continuous variables and as frequency and percentage (%) for categorical variables. To select the covariates, we conducted a comprehensive review of eight peer-reviewed studies [18, 21–27] that used logistic regression or Cox regression models with covariates. These studies were selected based on their relevance to the analysis of covariates in the context of steatotic liver disease and chronic diseases. The number of covariates used in these studies was 24 variables (Supplementary Table 2). A review of eight relevant studies revealed that six consistently included age and smoking status as covariates in multivariable analyses. The repeated selection of these variables across studies indicates their recognition as potential confounders. Accordingly, age and smoking status were incorporated as covariates in this study to improve comparability and ensure adequate adjustment for confounding. The table also shows the covariates included in the multivariate analyses of each study. To ensure a systematic approach to confounder selection, we used a directed acyclic graph (DAG) to identify variables for adjustment. The DAG helped to clarify relationships between variables and guided the inclusion of covariates in our analysis [28]. The final DAG is shown in Supplementary Fig. 5. The multivariable logistic regression model employed in this study includes two covariates. In the KNHANES dataset, there are 5584 cases of diabetes, 10,150 cases of dyslipidemia, and 14,190 cases of hypertension. Similarly, in the NHANES dataset, there are 1212 cases of diabetes, 4261 cases of dyslipidemia, and 4106 cases of hypertension. Given the considerable number of events observed in each dataset, the inclusion of two covariates is unlikely to result in model overfitting relative to the number of events.

To investigate the association between SLD and chronic diseases, we included variables related to liver damage, specifically AST and ALT levels, ALT/AST ratio, HSI, and alcohol consumption. Each of these variables was treated as continuous, and values were categorized into eight groups to examine the proportion of chronic diseases in each group. The KoGES dataset included precise information on daily alcohol intake in grams per day, enabling classification of participants into MASLD, MetALD, and ALD groups based on thresholds. In contrast, the KNHANES dataset did not directly provide daily alcohol intake but included data on annual drinking frequency and the average number of glasses consumed per occasion. To estimate daily alcohol consumption, we referred to the alcohol content of commonly consumed Korean beverages, calculating an average of 10 g of alcohol per glass (6.5 g for soju and 18.5 g for beer). Daily alcohol intake was then estimated by multiplying the annual drinking frequency by the average alcohol intake per occasion. Similarly, the NHANES dataset provided information on annual drinking frequency and

the average number of glasses consumed per occasion. Unlike the Korean standard, the U.S. standard defines one drink as containing 14 g of alcohol, which was applied to estimate daily intake in NHANE [29]. For alcohol consumption, different grouping criteria were applied based on sex in accordance with MASLD guidelines and as follows: men were grouped into 0–30, 30–60, and > 60 g per day, while women were grouped into 0–20, 20–50, and > 50 g per day.

Statistical analysis

To assess the statistical significance of the differences in the characteristics between groups with and without chronic diseases, one-way analysis of variance was employed, and p-values were reported. Logistic and Cox regression analyses were performed to determine the prevalence and incidence of chronic diseases related to SLD. Multivariate logistic regression was used to calculate the odds ratios (ORs) for chronic disease prevalence, whereas Cox regression was used to calculate the hazard ratios (HRs) for chronic disease incidence after adjusting for selected covariates. All statistical analyses were conducted using R software version 4.1.2, and significance was set at $p < 0.05$.

Ethical considerations

The Institutional Review Board of Gwangju Institute of Science and Technology (South Korea) approved the study protocol (IRB No. 20221201-BR-69-02-02). All research procedures were conducted in accordance with the relevant guidelines and regulations. All participants volunteered and provided written informed consent before enrollment, and their records were anonymized before being accessed by the authors.

Results

Baseline characteristics of the participants

The general characteristics of the participants in the KNHANES, NHANES, and KoGES cohorts according to steatotic liver status are summarized in Tables 1 and 2, and Supplementary Table 1. The KNHANES cohort included 22,597 healthy men and 7,017 men with steatotic liver. Among men with steatotic liver, most were categorized under MASLD ($n = 3,494$), followed by ALD ($n = 2,980$) and MetALD ($n = 543$) (Table 1). Meanwhile, there were 29,493 healthy women and 7,042 women with steatotic liver, primarily with MASLD ($n = 5,733$) (Table 1). Healthy Korean men were generally older, whereas those with steatotic liver were younger; no substantial age differences were observed among the MASLD, MetALD, and ALD groups. For women, no differences were observed among healthy subjects and those with MetALD and ADL. Women with MASLD were generally older than men with MASLD.

There are no established HSI thresholds for determining the presence of steatotic liver in ethnic groups outside Korea. The HSI was analyzed using the threshold of 36, identical to the Korean data, in the NHANES dataset to confirm the prevalence. The prevalence rates were 79%, 14%, 6%, and 2% for KNHANES; 74%, 23%, 1%, and 1% for KoGES; and 25%, 39%, 25%, and 12% for NHANES. Despite the globally reported SLD prevalence of 20–30%, NHANES demonstrated a striking prevalence of 75%, when HSI cutoff value was set at 36 [3]. When comparing the variables used in the HSI calculation between Korea and America, a notable difference was observed in BMI. Therefore, we adopted an HSI threshold of 41 for subsequent analyses for two reasons. First, we approximated the prevalence in the Korean population (Supplementary Fig. 4). Second, we adjusted for the BMI difference, which was approximately 5, between the KNHANES and NHANES cohorts. The NHANES cohort included 3,478 healthy men and 2,863 men with steatotic liver. Among men with steatotic liver, most were categorized under MASLD ($n = 1,537$), followed by MetALD ($n = 707$) and ALD ($n = 619$) (Table 2). Meanwhile, there were 2,794 healthy women and 2,798 women with steatotic liver, primarily with MASLD ($n = 1,259$) (Table 2). Men with MetALD and ALD were generally younger, similar to those in the KNHANES cohort. Women with MASLD and ALD were generally older and younger, respectively, similar to those in the KNHANES cohort.

The KoGES cohort included 3,235 healthy men, 744 men with MASLD, 98 with MetALD, and 72 with ALD. Meanwhile, there were 3,273 healthy women, 1,291 women with MASLD, 26 with MetALD, and 5 with ALD. In the KNHANES, NHANES, and KoGES cohorts, men with MetALD and ALD were generally younger, whereas those with MASLD varied. Women with MASLD were generally older and had younger ALD patterns.

Across all cohorts, participants with steatotic liver had significantly higher BMI, WC, and TC levels than healthy subjects regardless of sex. Markers of liver injury, such as AST and ALT levels, were elevated in patients in the MASLD, MetALD, and ALD groups compared to healthy participants. The ALT/AST ratio was also consistently increased in patients in the MASLD, MetALD, and ALD groups compared with healthy participants. Blood parameters associated with hypertension, such as SBP and diastolic BP (DBP), were raised in subjects with steatotic liver compared with healthy subjects in all cohorts and regardless of sex. Dyslipidemia parameters, including TC levels, were higher in participants with steatotic liver than in healthy individuals regardless of sex. Conversely, high-density lipoprotein (HDL) levels were lower in participants with steatotic liver than in healthy participants in all cohorts and regardless of sex sexes. Additionally, diabetes parameters, including fasting glucose and

Table 1 General characteristics of the participants in the KNHANES cohort according to steatotic liver status

	Healthy	Steatotic Liver Disease		
		MASLD	MetALD	ALD
Male, *N*	22,597	3494	543	2980
Age, years	47.18 ± 20.824	43.74 ± 18.147	43.42 ± 14.546	44.24 ± 13.415
BMI	22.8 ± 2.731	27.93 ± 3.127	27.86 ± 3.331	28.21 ± 2.871
Waist circumference	81.6 ± 9.093	94.4 ± 8.357	94.15 ± 8.85	95.42 ± 7.677
Systolic blood pressure, mm Hg	119.04 ± 15.394	121.49 ± 13.183	121.91 ± 13.157	124.18 ± 13.477
Diastolic blood pressure, mm Hg	74.84 ± 10.724	78.68 ± 10.352	80.34 ± 10.424	82.68 ± 10.569
Total cholesterol, mg/dL	182.02 ± 36.447	189.38 ± 39.178	195.06 ± 40.681	197.72 ± 39.084
HDL cholesterol, mg/dL	49.19 ± 11.534	42.07 ± 8.56	42.76 ± 8.174	45.11 ± 9.862
Triglyceride, mg/dL	133.35 ± 114.166	171.65 ± 120.11	191.9 ± 142.22	220.84 ± 165.85
Fasting plasma glucose, mg/dL	99.96 ± 21.363	108.16 ± 30.403	105.82 ± 24.338	110.41 ± 30.367
HbA1C, %	5.69 ± 0.746	6.03 ± 1.078	5.9 ± 0.873	5.97 ± 1
AST, IU/L	23.9 ± 15.745	28.54 ± 16.338	28.84 ± 20.829	29.55 ± 16.02
ALT, IU/L	20.43 ± 12.199	45.18 ± 34.874	45.3 ± 38.737	43.89 ± 31.044
ALT/AST	0.86 ± 0.251	1.53 ± 0.41	1.54 ± 0.413	1.45 ± 0.389
HSI	29.87 ± 3.778	40.49 ± 4.149	40.4 ± 4.372	40.09 ± 3.771
Alcohol Intake, g/day	100.37 ± 159.501	6.04 ± 8.416	40.87 ± 2.787	248.69 ± 182.875
Female, *N*	29,493	5733	650	659
Age, years	46.62 ± 19.29	55.67 ± 15.976	47.87 ± 14.192	44.81 ± 13.945
BMI	22.06 ± 2.646	28.21 ± 3.214	28.6 ± 3.201	28.85 ± 3.472
Waist circumference	75.44 ± 8.442	90.89 ± 8.332	90.95 ± 8.3	91.94 ± 8.725
Systolic blood pressure, mm Hg	114.32 ± 17.064	124.19 ± 16.912	120.69 ± 15.933	121.43 ± 16.226
Diastolic blood pressure, mm Hg	71.96 ± 9.507	76.1 ± 9.663	77.71 ± 9.699	78.47 ± 9.929
Total cholesterol, mg/dL	188.75 ± 36.134	193.94 ± 40.556	197.3 ± 42.156	199.38 ± 40.422
HDL cholesterol, mg/dL	55.4 ± 12.53	48.48 ± 10.732	50.21 ± 11.096	53.15 ± 12.519
Triglyceride, mg/dL	103.57 ± 69.52	149.06 ± 91.456	148.85 ± 100.813	165.37 ± 137.577
Fasting plasma glucose, mg/dL	94.7 ± 16.392	111.18 ± 32.65	107.16 ± 26.98	108.42 ± 28.447
HbA1C, %	5.59 ± 0.59	6.24 ± 1.109	5.99 ± 0.962	5.87 ± 0.944
AST, IU/L	20.39 ± 9.815	25.25 ± 13.301	24.83 ± 15.091	26.4 ± 17.383
ALT, IU/L	15.16 ± 8.607	29.45 ± 21.934	30.42 ± 29.446	31.4 ± 29.653
ALT/AST	0.74 ± 0.196	1.13 ± 0.32	1.15 ± 0.335	1.15 ± 0.5
HSI	30.05 ± 3.313	39.7 ± 3.503	40.09 ± 3.55	40.21 ± 4.561
Alcohol Intake, g/day	25.03 ± 72.955	2.12 ± 3.498	33.04 ± 8.483	202 ± 166.539

Data are presented as mean ± standard deviation

HDL, high-density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; HSI, hepatic steatosis index

HbA1c levels, were elevated in participants with steatotic liver compared to healthy participants in all cohorts and regardless of sex.

Associations between chronic metabolic disease and disease parameters

The prevalence of chronic diseases, such as diabetes, hypertension, and dyslipidemia, increase annually [30–32]. Tracking annual prevalence trends using preprocessed cross-sectional data from the NHANES and KNHANES databases revealed an increasing prevalence of diabetes, hypertension, and dyslipidemia over time (Supplementary Fig. 6).

Sex-specific association patterns between chronic metabolic diseases and clinical parameters were compared between the two cross-sectional cohorts. In the KNHANES cohort (Fig. 1B), hypertension in both sexes showed positive correlations with age, BMI, WC, SBP, DBP, and TG, fasting glucose, HbA1c, and AST levels and negative linear trends with TC and HDL levels. When comparing the sex-specific hypertension-related signatures in the KNHANES and NHANES cohorts, the following variables exhibited correlations independent of sex and ethnicity: age, BMI, WC, SBP, DBP, TG, fasting glucose, and HbA1c levels. In Korea, the pattern of association between liver profile and hypertension risk differed between men and women but was consistently positive in men and women in the United States. TC and HDL levels were negatively related to the prevalence of hypertension in most cases, except for women in the United States.

Dyslipidemia-related signatures largely coincide with those linked to hypertension risk, including TG, fasting glucose, and ALT levels, as well as the ALT/AST ratio,

Table 2 General characteristics of the participants in the NHANES cohort according to steatotic liver status

	Healthy	Steatotic Liver Disease		
		MASLD	MetALD	ALD
Male, *N*	3478	1537	707	619
Age, years	50.75 ± 18.685	51.17 ± 15.566	45.21 ± 14.338	42.81 ± 13.756
BMI	24.93 ± 2.958	33.19 ± 5.153	32.99 ± 4.985	33 ± 5.432
Waist circumference	92.25 ± 10.267	112.89 ± 13.272	111.04 ± 12.94	111.18 ± 13.68
Systolic blood pressure, mm Hg	124.96 ± 17.558	126.09 ± 16.444	126.38 ± 15.04	126.32 ± 14.742
Diastolic blood pressure, mm Hg	70.13 ± 12.677	74.31 ± 12.659	74.88 ± 12.639	74.58 ± 12.833
Total cholesterol, mg/dL	188.01 ± 41.373	193.15 ± 41.917	199.73 ± 42.95	200.59 ± 43.499
HDL cholesterol, mg/dL	53.39 ± 14.899	44.17 ± 10.846	45.45 ± 11.359	44.76 ± 11.795
Triglyceride, mg/dL	116.71 ± 95.866	160.02 ± 119.658	162.14 ± 144.901	189.23 ± 235.343
Fasting plasma glucose, mg/dL	106.99 ± 32.64	115.34 ± 36.337	113.25 ± 36.957	115.57 ± 42.383
HbA1C, %	5.62 ± 1.013	5.87 ± 1.14	5.76 ± 1.116	5.84 ± 1.286
AST, IU/L	27.79 ± 40.16	26.43 ± 11.759	27.97 ± 15.45	29.43 ± 14.932
ALT, IU/L	24.71 ± 40.152	33.25 ± 18.572	37.22 ± 24.567	40.59 ± 27.415
ALT/AST	0.9 ± 0.223	1.25 ± 0.343	1.31 ± 0.35	1.35 ± 0.374
HSI	35.92 ± 3.371	46.86 ± 5.253	47.23 ± 5.363	47.51 ± 5.57
Alcohol Intake, g/day	47.26 ± 336.239	21.1 ± 7.002	47.19 ± 6.766	195.5 ± 1113.971
Female, N	2794	1259	1186	353
Age, years	47.57 ± 18.363	52.5 ± 16.03	45.21 ± 14.328	39.21 ± 12.978
BMI	23.63 ± 2.907	34.17 ± 6.233	34.45 ± 6.365	35.44 ± 6.704
Waist circumference	84.26 ± 9.063	107.32 ± 13.529	107.93 ± 13.904	109.79 ± 14.951
Systolic blood pressure, mm Hg	118.52 ± 19.541	124.71 ± 18.531	120.68 ± 17.251	118.21 ± 17.215
Diastolic blood pressure, mm Hg	67.53 ± 12.169	70.54 ± 12.23	71.6 ± 11.61	71.53 ± 11.769
Total cholesterol, mg/dL	196.88 ± 42.255	199.14 ± 42.172	198.92 ± 41.918	191.54 ± 38.667
HDL cholesterol, mg/dL	65.92 ± 17.902	54.83 ± 14.153	55.26 ± 14.34	53.53 ± 15.44
Triglyceride, mg/dL	100.97 ± 81.22	132.91 ± 79.699	128.2 ± 87.909	131.64 ± 83.643
Fasting plasma glucose, mg/dL	97.14 ± 21.129	111.01 ± 39.491	106.93 ± 32.508	107.69 ± 39.074
HbA1C, %	5.39 ± 0.656	5.89 ± 1.191	5.67 ± 0.993	5.71 ± 1.36
AST, IU/L	22.69 ± 13.637	22.51 ± 10.143	22.65 ± 13.642	22.67 ± 15.538
ALT, IU/L	17.87 ± 9.573	23.07 ± 13.992	23.87 ± 18.274	23.83 ± 19.5
ALT/AST	0.79 ± 0.177	1.01 ± 0.276	1.02 ± 0.28	1.04 ± 0.33
HSI	35.89 ± 3.11	48 ± 6.162	48.45 ± 6.529	49.57 ± 6.993
Alcohol Intake, g/day	32.17 ± 264.867	14 ± 0	32.01 ± 6.334	224.75 ± 1399.73

Data are presented as mean ± standard deviation

HDL, high-density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; HSI, hepatic steatosis index

with the exception of DBP and TC. The ALT/AST ratio, which is a predictor of MASLD and IR [16, 33] exhibited a positive relationship with the ratio of dyslipidemia regardless of sex and ethnicity. Furthermore, TC levels showed a positive association with the risk of dyslipidemia in the US dataset and a negative association in the Korean cohort.

Diabetes-related signatures mostly converged with those associated with the risk of diabetes, except for DBP and the ALT/AST ratio, which exhibited a positive relationship with the hypertension ratio depending on sex.

Associations between chronic metabolic disease and hepatic steatosis in the KNHANES cohort

HSI of patients in the KNHANES cohort were transformed into octile percentiles to identify linear trends in hepatic steatosis status with the prevalence of chronic diseases. As HSI increased, all diseases exhibited monotonic escalation patterns (Fig. 2A and B).

After an extensive review of existing literature, age and smoking status were identified as important confounding factors that could significantly affect the relationship between steatotic liver status and chronic diseases (Supplementary Table 2). The association between steatotic liver status and chronic diseases was further assessed using a multivariable logistic regression model that adjusted for confounders such as age and smoking status. The Hosmer-Lemeshow test was performed to assess the calibration of the multivariable logistic regression model (Supplement Fig. 7A A). The observed value, represented by the blue bars, indicates the actual number of events, while the expected value, depicted by the red dots, represents the number of events predicted by the logistic regression model. Therefore, the Hosmer-Lemeshow

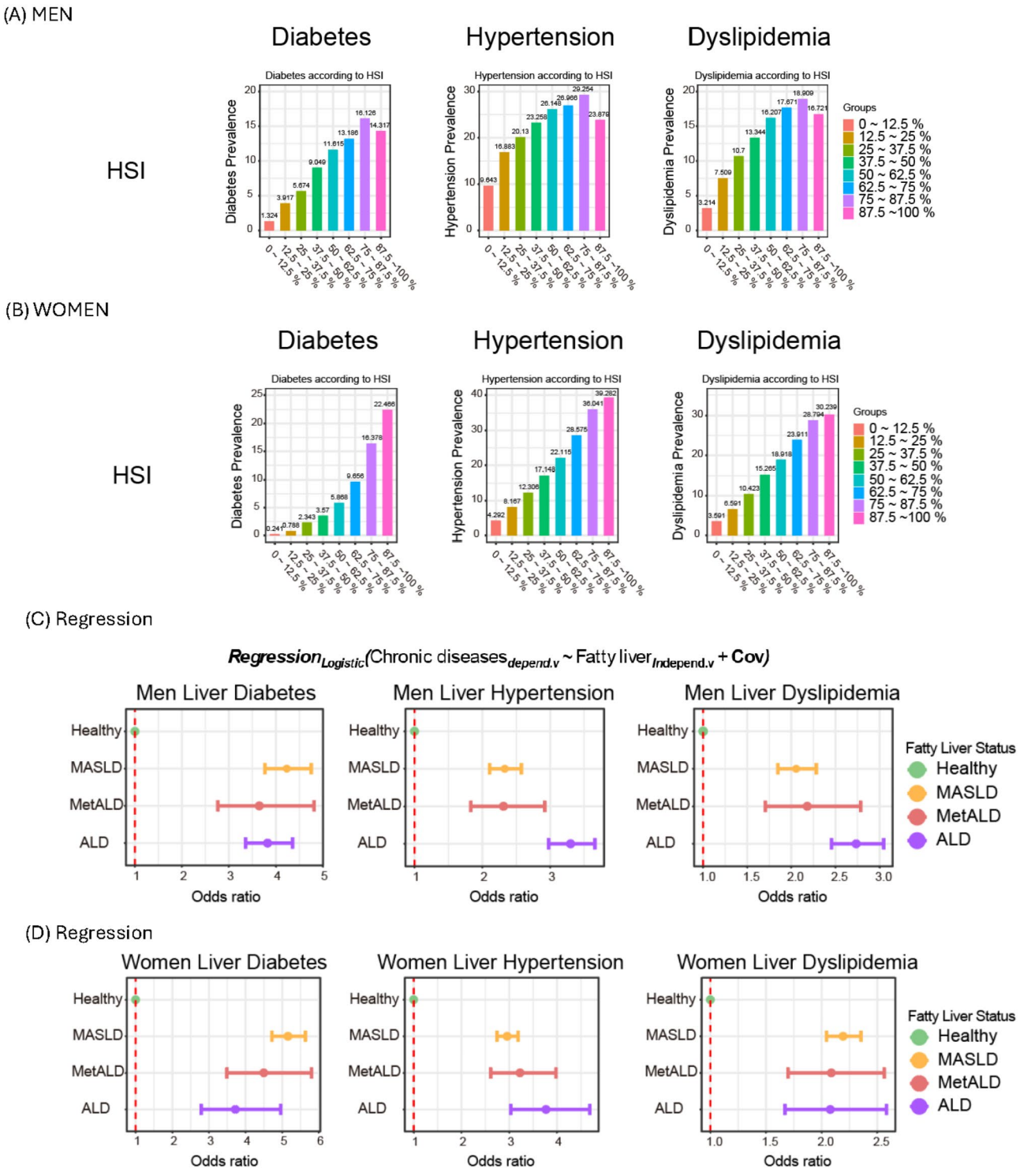

Fig. 2 Disease prevalence according to hepatic steatosis in the KNHANES cohort. (**A**, **B**) Chronic metabolic disease prevalence according to the hepatic steatosis index (HSI) in men **(A)** and women **(B)**. (**C**, **D**) Hazard ratio of chronic metabolic disease according to steatotic liver status in multiple logistic regression analysis in men **(C)** and women **(D)**. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolically associated alcoholic liver disease; ALD, alcoholic liver disease

test indicated a close correlation between observed and expected values, validating the robustness calibration of the multivariable logistic regression model in KNHANES. Among men in the KNHANES cohort, the ORs for MASLD, MetALD, and ALD were 4.232 (95% CI, 3.767–4.755), 3.647 (95% CI, 2.764–4.813), and 3.824 (95% CI, 3.356–4.357) for diabetes (Fig. 2C and D), 2.330 (95% CI, 2.108–2.576), 2.312 (95% CI, 1.829–2.921), and 3.301 (95% CI, 2.977–3.660) for hypertension, and 2.055 (95% CI, 1.848–2.285), 2.180 (95% CI, 1.706–2.787), and 2.735 (95% CI, 2.456–3.046) for dyslipidemia, respectively. Among women in the KNHANES cohort, the ORs for diabetes (MASLD > MetALD > ALD), hypertension (ALD > MetALD > MASLD), and dyslipidemia (MASLD > MeALD > ALD) were similar to those in men.

Associations between chronic metabolic disease and hepatic steatosis in the NHANES cohort

HSI in NHANES data were transformed into octile percentiles to identify linear trends in hepatic steatosis status with the prevalence of chronic diseases. The results showed that as HSI increased, all diseases exhibited monotonic escalation patterns (Fig. 3A and B).

The association between steatotic liver and chronic diseases was assessed using a multivariate logistic regression model. The Hosmer-Lemeshow test indicated a close correlation between observed and expected values, validating the robustness calibration of the multivariable logistic regression model in NHANES(Supplement Figs. 7B and 8B). Among men in the NHANES cohort, the ORs for MASLD, MetALD, and ALD were 1.524 (95% CI: 1.269–1.830), 1.328 (95% CI: 1.009–1.748), and 1.893 (95% CI: 1.438–2.492) for diabetes (Fig. 3C and D), 1.960 (95% CI, 1.713–2.242), 2.215 (95% CI, 1.848–2.656), and 2.166 (95% CI, 1.783–2.631) for hypertension, and 1.621 (95% CI, 1.423–1.846), 1.770 (95% CI, 1.484–2.111), and 1.778 (95% CI, 1.472–2.147) for dyslipidemia, respectively. Among women in the NHANES cohort, the ORs for diabetes, hypertension (ALD > MASLD > MetALD), and dyslipidemia (MetALD > MASLD > ALD) were similar to those in men.

We also analyzed the association between alcohol consumption and the prevalence of chronic metabolic diseases and found no significant increase in the KNHANES or NHANES cohorts. However, in the KNHANES cohort, an inverse relationship was observed among women, wherein higher alcohol consumption was associated with a lower prevalence of chronic metabolic diseases (Supplementary Fig. 8).

Risks of chronic metabolic diseases in SLD

To examine the causal relationship between chronic diseases and steatotic liver status, we used longitudinal data from the KoGES cohort and performed Cox regression analysis. The Schoenfeld analysis was utilized to verify the proportional hazards assumption, the basic tenet of the Cox proportional hazards model. A Schoenfeld p-value exceeding 0.05 confirms that the variable's effect does not vary with time, thereby satisfying the proportional hazards assumption(Supplementary Fig. 10). Figure 4 shows the causal effects of the steatotic liver status on the development of chronic metabolic diseases. To predict the development of chronic metabolic diseases in patients with steatotic liver disease, we used data from 2 years.

Based on the 2-year data, we calculated the risk of early development of chronic metabolic diseases. Both MASLD and MetALD were significant predictors of diabetes in men (HR, 4.076; 95% CI, 2.172–7.647 and HR, 8.012; 95% CI, 2.365–27.139, respectively) and women (HR, 6.450; 95% CI, 5.072–8.202 and HR, 10.218; 95% CI, 4.130–25.285, respectively). For hypertension, MetALD was a significant predictor in men (HR, 3.637; 95% CI, 1.111–11.900), whereas MASLD was a significant predictor in women (HR, 2.662; 95% CI, 1.803–3.930). For dyslipidemia, the 2-year data showed no significant predictive value based on steatotic liver status in either sex (Fig. 4A and B). Regarding overall causality, among men (Fig. 4A), the HRs for MASLD, MetALD, and ALD were 4.354 (95% CI, 3.371–5.624), 6.037 (95% CI, 3.654–9.975), and 5.831 (95% CI, 3.343–10.171) for diabetes, 1.517 (95% CI, 1.257–1.830), 2.069 (95% CI, 1.319–3.245), and 2.050 (95% CI, 1.242–3.383) for hypertension, and 1.398 (95% CI, 1.120–1.743), 2.109 (95% CI, 1.338–3.325), and 2.867 (95% CI, 1.818–4.522) for dyslipidemia, respectively. Meanwhile, the number of women with ALD was insufficient to provide reliable HR estimates; however, their HRs for diabetes and dyslipidemia were similar to those in men.

Discussion

In this study, we comprehensively examined the prevalence and causality of chronic metabolic diseases, such as diabetes, hypertension, and dyslipidemia, in relation to steatotic liver status. We used cross-sectional data from KNHANES and NHANES and longitudinal data from KoGES. The prevalence of chronic metabolic diseases (diabetes, dyslipidaemia and hypertension) has increased over the decade in KNHANES and over the two decades in NHANES (Supplementary Fig. 11). Among men, the association between chronic metabolic diseases and liver injury markers was inconsistently significant. However, in women, positive correlations were observed between these conditions and AST and ALT levels, suggesting a stronger association between liver injury and chronic conditions (Fig. 1B and C). The prevalence of chronic diseases also significantly increased with HSI in both men and women in the KNHANES and NHANES cohorts

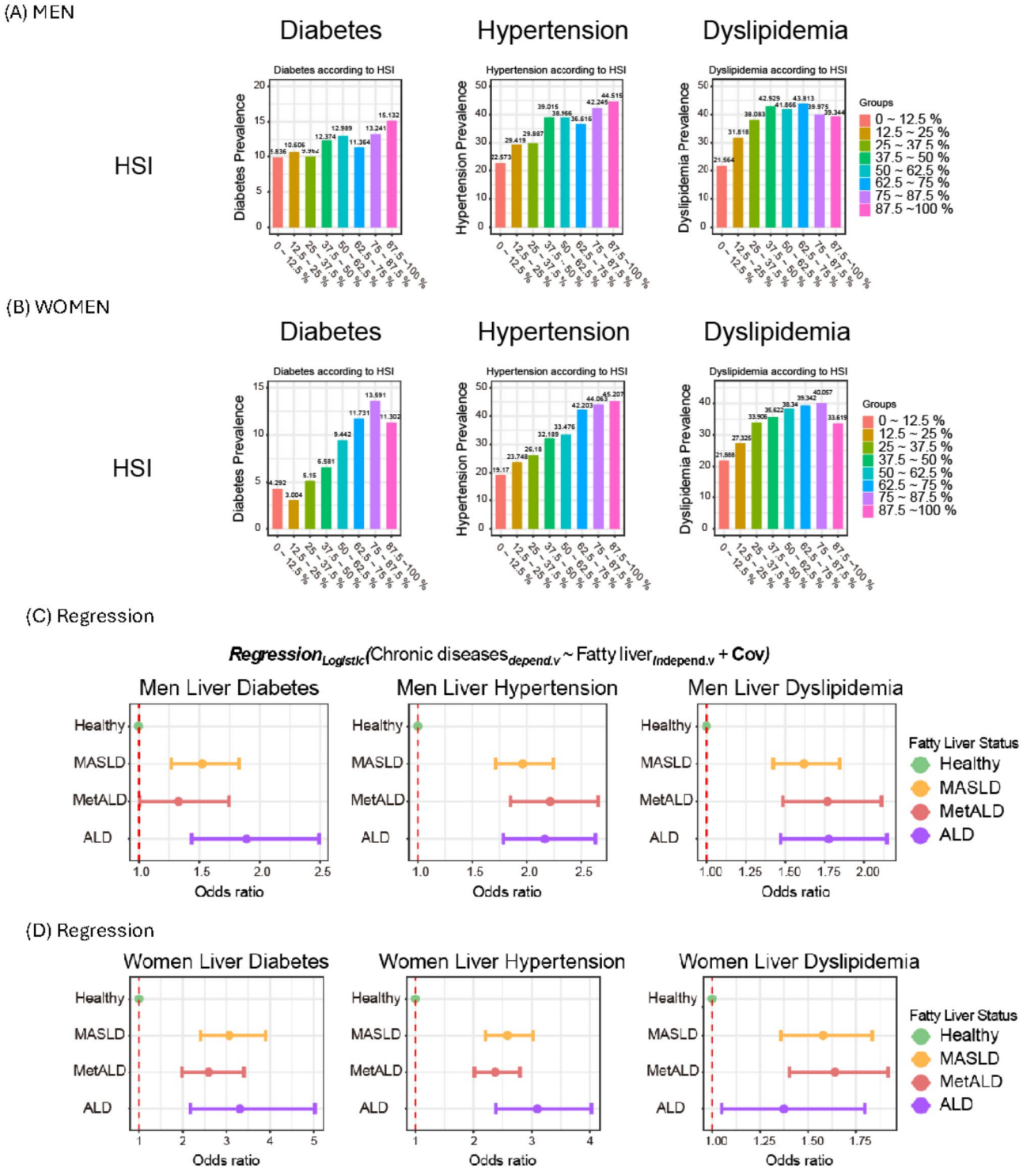

Fig. 3 Disease prevalence according to hepatic steatosis in the NHANES cohort. (**A**, **B**) Chronic metabolic disease prevalence according to the hepatic steatosis index (HSI) in men **(A)** and women **(B)**. (**C**, **D**) Hazard ratio of chronic metabolic disease according to steatotic liver status in multiple logistic regression analysis in men **(C)** and women **(D)**. MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolically associated alcoholic liver disease; ALD, alcoholic liver disease

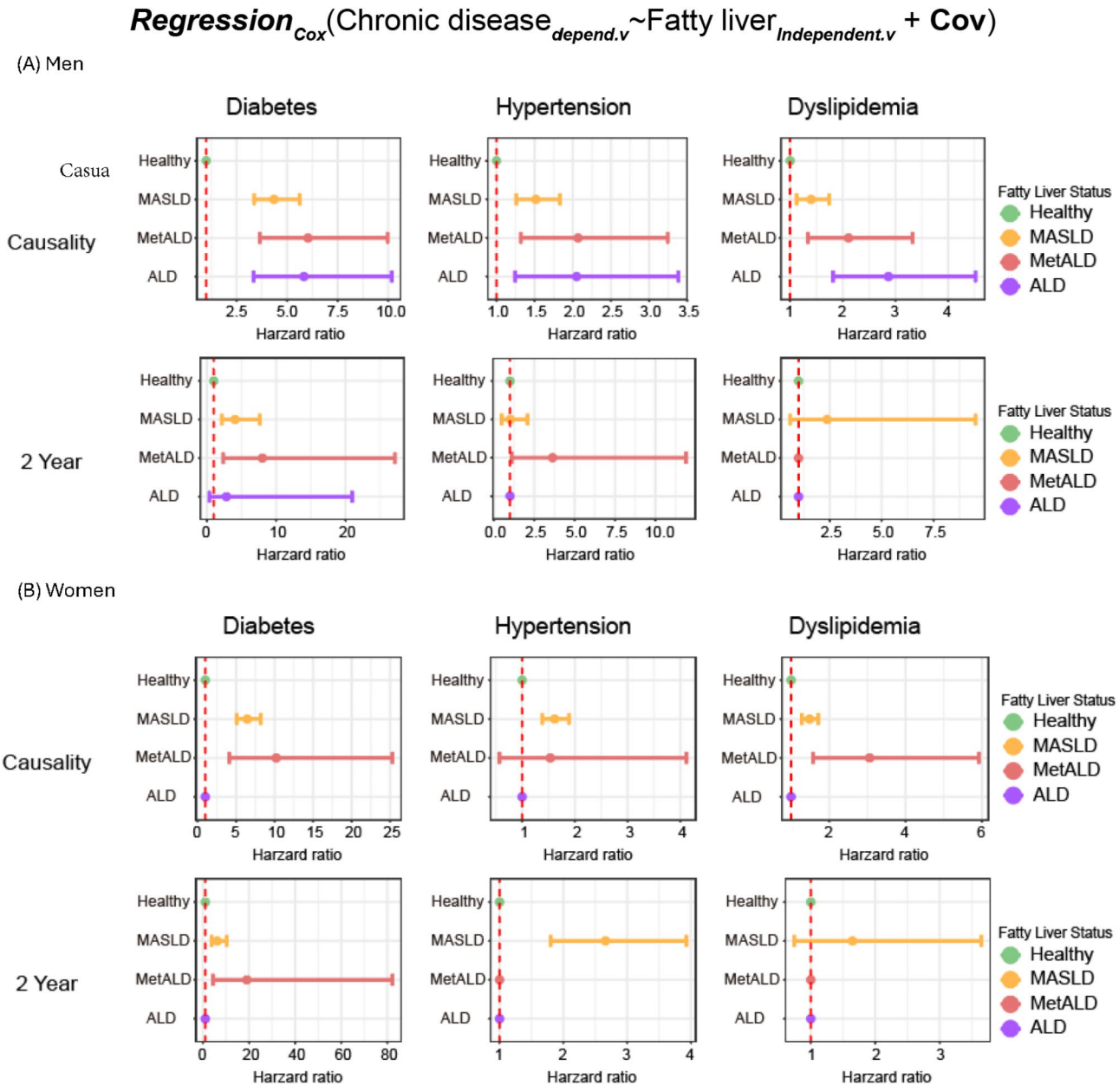

Fig. 4 Causal relationship between chronic metabolic disease and steatotic liver status in the KoGES cohort. **(A)** Hazard ratio of chronic metabolic disease according to steatotic liver status in Cox regression analysis in men. **(B)** Hazard ratio of chronic metabolic disease according to steatotic liver status in Cox regression analysis in women. Causality: Cox regression analysis was performed to assess the relationship between baseline steatotic liver status and the incidence of chronic metabolic diseases over the 2-year follow-up period

(Figs. 2A and B and 3A, and 3B), highlighting the critical role of liver health in the management of metabolic diseases. Logistic regression analysis confirmed these associations, with higher HSI correlating with an increased risk of chronic metabolic disease (Figs. 2C and D and 3C, and 3D). MetALD emerged as a significant predictor, underscoring the need for further attention to this newly defined category.

A subsequent analysis of the data, focusing on short-term (2-year) causality, revealed that metabolic disease has distinct sex-specific influences on hypertension. Among men, MetALD was significantly associated with hypertension, whereas MASLD showed no such relationship. Conversely, in women, MASLD exhibited a significant association with hypertension. These findings underscore the potential sex-specific interplay between SLD subtypes and hypertension risk. This observation is further corroborated by earlier studies conducted in Japanese cohorts, which have also demonstrated differences in steatotic liver disease status between men and

women [34, 35]. Further research is warranted to elucidate the underlying biological mechanisms driving these sex-specific associations and to inform the development of targeted strategies for the prevention and management of hypertension in patients with different SLD subtypes.

The identification of MetALD as a significant predictor of diabetes, hypertension, and dyslipidemia suggests the necessity of integrating liver health assessments into routine metabolic disease management. Current clinical guidelines predominantly focus on non-alcoholic steatotic liver disease (MASLD), often overlooking the impact of moderate alcohol consumption on liver pathology. Our findings indicate that clinicians should adopt a more nuanced approach to liver disease diagnosis, recognizing MetALD as a distinct entity that requires tailored intervention strategies [36]. Recently, Gratacós-Ginès, Jordi et al. reported the clinical implications of MetALD, estimating its prevalence to be between 1.7% and 17%, emphasizing the need for early screening and detection. In addition, emerging evidence suggests that many drugs studied for MASLD, including glucagon-like peptide-1 receptor agonists and fibroblast growth factor 21 analogues [37]. For instance, patients presenting with metabolic syndrome and moderate alcohol consumption may benefit from earlier screening for liver fibrosis and hepatocellular injury markers, even in the absence of elevated transaminases [38]. This approach may facilitate earlier identification and management of liver-related complications, ultimately reducing the progression to cirrhosis or hepatocellular carcinoma.

Furthermore, the strong association between MetALD and chronic metabolic diseases may be attributed to the dual influence of alcohol consumption and metabolic dysfunction. Alcohol, even at moderate levels, can exacerbate hepatic fat accumulation by altering lipid metabolism and impairing mitochondrial β-oxidation [39]. This synergistic effect, when combined with underlying metabolic risk factors such as obesity, insulin resistance, and dyslipidemia, accelerates hepatic inflammation and fibrosis [40]. Additionally, alcohol can upregulate pro-inflammatory cytokines and oxidative stress pathways, further contributing to liver injury and systemic metabolic disturbances [41]. The interplay between these mechanisms highlights why MetALD may present a more aggressive clinical course compared to MASLD or ALD alone.

A comparison of the two cohorts revealed some notable differences. In the KNHANES cohort, the prevalence of chronic metabolic diseases did not increase with alcohol consumption. Interestingly, higher alcohol consumption was associated with a lower prevalence of these diseases among women, suggesting a possible protective effect of moderate alcohol consumption. However, this was not observed in the NHANES cohort (Supplementary Fig. 7), suggesting possible differences in the population characteristics or lifestyle factors between Korean and American adults.

Using longitudinal data from the KoGES cohort, we performed Cox regression analyses to explore causal relationships (Fig. 4). MetALD was a significant predictor of diabetes in both men and women, with the HRs indicating a strong association. MetALD is a significant predictor of hypertension in men, highlighting its role in the progression of cardiovascular diseases. Predictions for dyslipidemia varied, with MetALD showing significant associations in both men and women, although the magnitudes were different. These findings are consistent with the notion that alcohol-related hepatic inflammation, coupled with insulin resistance, contributes to endothelial dysfunction and hypertension progression [42]. The unique metabolic profile of MetALD underscores the importance of its recent categorization. This group, which is characterized by specific alcohol consumption patterns coupled with metabolic risk factors, highlights the complex interplay between lifestyle factors and liver health. Our findings suggest that MetALD is not just an intermediate category but a distinct entity with specific clinical implications.

From a public health perspective, the recognition of MetALD as a significant contributor to chronic metabolic diseases underscores the need for updated screening protocols and preventive strategies. Public health policies aimed at reducing the prevalence of steatotic liver disease should not only target high-risk MASLD populations but also include individuals with moderate alcohol consumption [43]. Incorporating MetALD screening into national health programs could lead to earlier detection of at-risk populations and facilitate timely intervention. Additionally, educational campaigns highlighting the risks of alcohol-related liver disease in the context of metabolic dysfunction could enhance public awareness and promote healthier lifestyle choices, ultimately reducing the burden of MetALD and its associated comorbidities.

Given the limited therapeutic options currently available for steatotic liver disease, it is important to deal with closely related chronic metabolic diseases, such as hypertension, dyslipidemia, and diabetes to alleviate steatosis. Public health strategies should prioritize policies that promote healthier lifestyle choices, such as reducing the consumption of high-sugar foods and restricting access to hepatotoxic substances, including alcohol, for the management of MASLD [44, 45]. Recent meta-analysis reported that exercise training showed significant improvement in liver function markers in MASLD patients [46]. These interventions not only have the potential to reduce steatosis but also to lessen the broader socioeconomic costs of managing chronic diseases associated with metabolic dysfunction. Recently, Liwei et al. proposed a novel risk prediction model for

the 2-year risk of MASLD in a non-obese population using a Chinese cohort [10], highlighting the need for further research to develop comprehensive risk stratification models for MASLD, MetALD and ALD.

This study had several limitations. First, the cross-sectional nature of the KNHANES and NHANES data limits their ability to establish causality. Although longitudinal data from the KoGES cohort provided insights into causal relationships, the length of follow-up may not fully capture the long-term progression of liver disease and chronic metabolic conditions. Second, the reliance on self-reported data on alcohol consumption and other lifestyle factors may introduce recall bias, potentially affecting the accuracy of categorization into MASLD, MetALD, and ALD. Thirdly, our study used the HSI to diagnose fatty liver, but this tool does not have clear cut-off values to measure the severity of the disease. Also, because relatively low numbers of women in our study consumed alcohol, we did not do further subgroup analyses based on disease severity or sex. Future studies should aim to address these limitations by incorporating more robust methodologies and exploring tailored clinical interventions based on MetALD. In addition, further research into the molecular mechanisms underlying MetALD progression and the identification of specific biomarkers could facilitate the development of novel therapeutic strategies and the development of risk prediction models for MetALD.

Conclusions

In conclusion, this study underscores the intertwined nature of liver and metabolic health, with a particular emphasis on the role of MetALD. The significant association between MetALD and chronic metabolic diseases highlights the need for integrated management strategies that address both liver health and metabolic risk factors. In addition, the high prevalence of SLD in the US cohort compared to Korea suggests the necessity for population-specific diagnostic criteria and reinforces the need for standardized but adaptable screening thresholds.

Abbreviations

SLD	Steatotic liver disease
MetALD	Metabolically associated alcoholic liver disease
KNHANES	Korea National Healthy and Nutrition Examination Survey
NHANES	National Healthy and Nutrition Examination Survey
KoGES	Korean Genome and Epidemiology study
MASLD	Metabolic dysfunction–associated SLD
HSI	Hepatic steatosis index
ALD	Alcoholic related liver disease
SLD	Steatotic liver disease
NAFLD	Non–alcoholic fatty liver disease
CVD	Cardiovascular disease
WC	Waist circumference
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TG	Triglyceride
TC	Total cholesterol
HbA1c	HemoglbinA1c
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ORs	Odds ratios
HRs	Hazard ratios
HDL	High–density lipoprotein

Supplementary Information

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Supplementary Material 1

Author contributions

Chang-Myung Oh (Writing– original draft: Supporting; Writing– review and editing: lead).Tae Sic Lee (Data curation: Lead; Writing– review and editing: support)Yeongmin Kim (Data curation: Supporting; Writing: original draft: Lead; Writing: review and editing: Supporting).

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Data availability

All data used in the paper are publicly available.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Gwangju Institute of Science and Technology (20221201-BR-69-02-02).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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