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ORIGINAL ARTICLE
Ischemic Heart Disease

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Is an Independent Risk Factor for the Development of Ischemic Heart Disease

— A 10-Year Cohort Study —

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Background: The association of each of the recently classified steatotic liver diseases (SLDs), including metabolic dysfunction-associated SLD (MASLD), MASLD and increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD), with new development of ischemic heart disease (IHD) remains unclear.

Methods and Results: We investigated the associations of various SLDs with the development of IHD during a 10-year follow-up period in 13,815 Japanese individuals without a history of IHD (men/women 8,933/4,882; mean age 48 years) who underwent annual health checkups including an abdominal ultrasound examination. Among the participants, 4,639 (33.6%) subjects were diagnosed as having SLDs, and the proportions of subjects with MASLD, MetALD and ALD were 25.4%, 4.7% and 1.9%, respectively. During the follow-up period, 1,963 (16.2%; men/women 1,374 [17.2%]/589 [14.2%]) subjects had new development of IHD. Multivariable Cox proportional hazard model analysis after adjustment of age, sex, estimated glomerular filtration rate (eGFR), current smoking habit, diabetes, hypertension and dyslipidemia showed that the adjusted risk for new onset of IHD was significantly higher in subjects with MASLD (hazard ratio 1.20 [95% confidence interval 1.01–1.55]; P=0.042) than in those without SLD. Other SLDs were not selected as independent risk factors for the development of IHD.

Conclusions: The presence of MASLD, but not other SLDs, is an independent risk factor for new onset of IHD during a 10-year follow-up period.

Key Words: Alcohol-associated liver disease (ALD); Cardiovascular-kidney-metabolic (CKM) syndrome; Ischemic heart disease (IHD); MASLD and increased alcohol intake (MetALD); Metabolic dysfunction-associated steatotic liver disease (MASLD)

Steatotic liver disease (SLD) is a comprehensive term that encompass various causes of hepatic steatosis.[1] Although SLD is asymptomatic unless it progresses to liver cirrhosis, the presence of SLD has recently been recognized as a significant risk factor for not only hepatic diseases including liver cirrhosis and hepatocellular carcinoma but also for cardiovascular, kidney and metabolic diseases via interorgan communications.[2,3] Given its increasing global prevalence and the current lack of established therapeutic strategies, SLD represents a pressing public health challenge worldwide.[4] Classically, the condition of hepatic steatosis had been categorized as either alcoholic fatty liver disease or non-alcoholic fatty liver disease (NAFLD).[5] However, due to concerns regarding the stigmatizing

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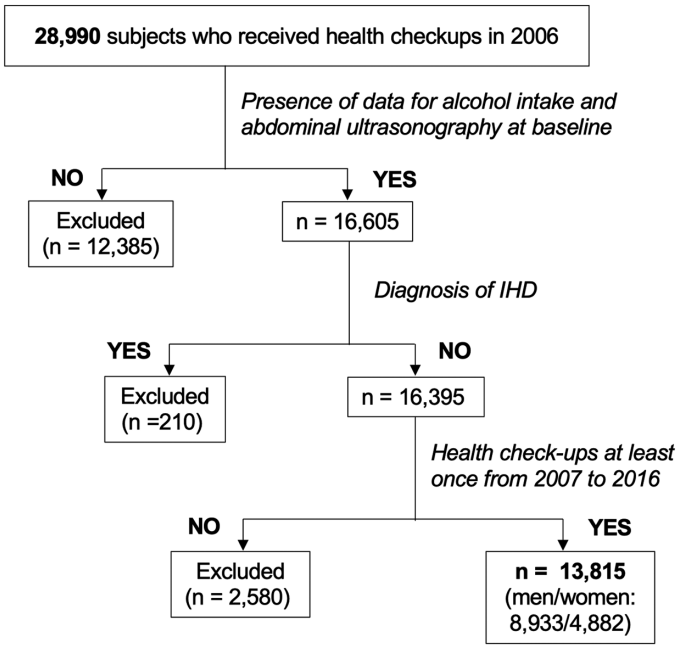

Figure 1. Flow chart of the selected study participants. Among 28,990 subjects enrolled in 2006, a total of 13,815 individuals (men/women 8,933/4,882) were recruited for analyses in the present study. IHD, ischemic heart disease.

implications of terms such as 'fatty' and 'alcoholic', the condition has recently been re-classified under the term of 'SLD'.[6,7]

The pathophysiology of SLDs largely depends on the presence and absence of concurrent metabolic abnormalities.[8,9] A previous disease concept of metabolic dysfunction-associated fatty liver disease (MAFLD) regardless of alcohol consumption has emerged as an evolution of the former NAFLD terminology, highlighting that MAFLD constitutes a prominent risk factor for cardiovascular and renal complications compared with NAFLD.[10] However, there was concern that the effects of alcohol consumption, as another factor for causing liver diseases, as well as atherosclerotic cardiovascular diseases,[11,12] were hidden within the framework of MAFLD. To address the limitation, a new classification for SLDs has recently been proposed by 3 large pan-national liver associations including the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Latin American Association for the Study of the Liver.[6,7] The new classification is characterized by the inclusion of both metabolic dysfunction and alcohol intake for the definitions of SLD categories. The categories include metabolic dysfunction-associated SLD (MASLD), MASLD and increased alcohol intake (MetALD), alcohol-associated liver disease (ALD), SLD with other specific etiology and cryptogenic SLD.[6,7]

Several previous studies have shown that hepatic steatosis or biomarkers for SLDs including the fatty liver index (FLI)[9,10] can be potent risk factors for cardiovascular, kidney and metabolic diseases.[13–21] However, the association between the newly proposed SLD classification, which accounts for metabolic dysfunction and alcohol consumption, and risk for the development of ischemic heart disease (IHD), a representative life-threatening atherosclerotic disease, remains unclear. Given that hepatic steatosis is strongly influenced by factors such as glucose and lipid metabolism, lifestyle and genetic predispositions,[22] it is essential to evaluate these relationships within specific regions or populations.

Therefore, in the present study, we investigated whether the risk for new onset of IHD in Japanese subjects with various SLDs is different depending on the co-existence of metabolic diseases and/or the amount of alcohol consumption by using the newly classified disease concept of SLDs.

Methods

Study Subjects

Among individuals who received annual health examinations at Keijinkai Maruyama Clinic, Sapporo, Japan in 2006, subjects who agreed with our project addressing studies on health checkup data and the development of several diseases were initially enrolled in this registry (n=28,990). The study conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval of the institutional ethics committee of Sapporo Medical University (no. 30-2-32). All of the enrolled subjects agreed with participating in the present study by providing written informed consent.

A flow chart for the selection of study subjects is shown in **Figure 1**. Prespecified exclusion criteria were: (1) absence of data for abdominal ultrasonography at baseline; (2) presence of IHD at baseline; and (3) subjects who had not received any health examinations during a follow-up period from 2007 to 2016. Subjects with IHD was defined as individuals who had angina pectoris, myocardial infarction or treatment with percutaneous coronary intervention and/or coronary artery bypass grafting, which were determined by a self-reported questionnaire survey. After exclusion, a total of 13,815 subjects (men/women 8,933/4,882; mean age 48 years) was recruited in the present study. The clinical endpoint was the development of IHD during the 10-year follow-up period.

Table 1. Characteristics of the Recruited Subjects at Baseline

	All (n=13,815)	Men (n=8,933)	Women (n=4,882)	P value
Age (years)	48±9	49±9	47±9	<0.001
Body mass index	23.2±3.4	24.0±3.2	21.6±3.3	<0.001
Waist circumference (cm)	83.6±9.3	86.2±8.4	78.9±9.1	<0.001
Systolic BP (mmHg)	116±17	120±16	110±16	<0.001
Diastolic BP (mmHg)	75±11	77±11	70±10	<0.001
Current smoking habit	4,759 (35.3)	3,900 (44.8)	859 (18.0)	<0.001
Alcohol drinking habit (g/week)	60 [0–140]	120 [20–200]	0 [0–60]	<0.001
Comorbidity				
SLDs	4,639 (33.6)	3,959 (44.3)	680 (13.9)	<0.001
SLD-MD[–]	217 (1.6)	185 (2.1)	32 (0.7)	<0.001
MASLD	3,507 (25.4)	2,926 (32.8)	581 (11.9)	<0.001
MetALD	649 (4.7)	592 (6.6)	57 (1.2)	<0.001
ALD	266 (1.9)	256 (2.9)	10 (0.2)	<0.001
Hypertension	2,383 (17.2)	1,897 (21.2)	486 (10.0)	<0.001
Diabetes	797 (5.8)	702 (7.9)	95 (1.9)	<0.001
Dyslipidemia	6,192 (44.8)	4,730 (52.9)	1,462 (29.9)	<0.001
Medication				
Anti-hypertensive drugs	1,414 (10.2)	1,099 (12.3)	315 (6.5)	<0.001
Anti-diabetic drugs	442 (3.2)	391 (4.4)	51 (1.0)	<0.001
Anti-dyslipidemic drugs	643 (4.7)	449 (5.0)	194 (4.0)	0.005
Family history				
IHD	1,316 (9.5)	808 (9.0)	508 (10.4)	0.010
Biochemistry				
Hemoglobin (g/dL)	14.3±1.5	15.1±1.1	12.9±1.2	<0.001
Platelet ($10^4/\mu L$)	23.8±5.2	23.4±5.0	24.6±5.5	<0.001
Albumin (g/dL)	4.4±0.2	4.4±0.2	4.3±0.2	<0.001
AST (IU/L)	21 [18–26]	22 [19–28]	19 [16–22]	<0.001
ALT (IU/L)	21 [15–31]	25 [18–36]	15 [12–20]	<0.001
GGT (IU/L)	31 [19–57]	42 [27–74]	18 [14–27]	<0.001
FLI	22.5 [7.9–48.7]	35.1 [17.1–59.0]	7.0 [3.4–17.4]	<0.001
FIB-4	0.94 [0.73–1.22]	0.95 [0.73–1.24]	0.93 [0.72–1.18]	0.001
Creatinine (mg/dL)	0.73±0.25	0.81±0.24	0.60±0.19	<0.001
eGFR (mL/min/1.73 m^2)	84.6±14.6	83.3±14.2	86.9±15.2	<0.001
Uric acid (mg/dL)	5.5±1.4	6.1±1.2	4.4±1.0	<0.001
Total cholesterol (mg/dL)	205±33	206±34	204±34	0.001
LDL cholesterol (mg/dL)	122±31	124±31	119±31	<0.001
HDL cholesterol (mg/dL)	61±16	56±14	69±15	<0.001
Triglycerides (mg/dL)	92 [64–137]	111 [78–160]	67 [49–92]	<0.001
Fasting glucose (mg/dL)	93±19	96±21	87±14	<0.001
HbA1c (%)	5.3±0.7	5.4±0.8	5.2±0.5	<0.001

Variables are expressed as n (%), mean±SD, or median [interquartile range]. ALD, alcohol-associated liver disease; ALT, alanine transaminase; AST, aspartate transaminase; BP, blood pressure; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; FLI, fatty liver index; GGT, γ-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD and increased alcohol intake; SLD, steatotic liver disease; SLD-MD[–], SLD without metabolic dysfunction.

Measurements

Medical examinations including samplings of urine and blood and ultrasonography were performed after overnight fasting. Blood pressure was measured by a nurse twice consecutively on the upper arm in a sitting position using a sphygmomanometer (#601, Kenzmedico, Saitama, Japan), and the average level of blood pressure measurements was used for analysis. Waist circumference (WC) was measured, and body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were measured using enzymatic assays. The low-density lipoprotein (LDL) cholesterol level was measured directly. Estimated glomerular filtration rate (eGFR) was calculated using the following formula for Japanese people:[23]

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{serum creatinine}^{(-1.094)} \times$$

Table 2. Characteristics of the Recruited Subjects Grouped by SLD Category at Baseline

	Non-SLD (n=9,176)	SLDs (n=4,639)				P value
		SLD-MD[−] (n=217)	MASLD (n=3,507)	MetALD (n=649)	ALD (n=266)	
Age (years)	47±9	47±8	50±9	51±8	51±7	<0.001
Sex, Men	4,974 (54.2)	185 (85.3)	2,926 (83.4)	592 (91.2)	256 (96.2)	<0.001
Body mass index	21.8±2.6	21.7±1.1	26.2±3.2	25.4±2.8	24.9±3.1	<0.001
Waist circumference (cm)	79.9±7.7	80.4±4.4	91.3±7.9	90.7±7.4	90.3±8.3	<0.001
Systolic BP (mmHg)	114±16	111±10	122±16	125±15	129±17	<0.001
Diastolic BP (mmHg)	72±11	72±7	79±11	81±9	83±11	<0.001
Current smoking habit	2,967 (33.5)	92 (42.4)	1,236 (35.4)	309 (47.8)	155 (58.3)	<0.001
Alcohol drinking habit (g/week)	60 [0–140]	60 [0–140]	40 [0–120]	280 [280–280]	420 [103–220]	<0.001
Comorbidity						
Hypertension	1,105 (12.0)	0 (0)	946 (27.0)	220 (33.9)	112 (42.1)	<0.001
Diabetes	242 (2.6)	0 (0)	438 (12.5)	75 (11.6)	42 (15.8)	<0.001
Dyslipidemia	3,140 (34.2)	75 (34.6)	2,392 (68.2)	410 (63.2)	175 (65.8)	<0.001
Medication						
Anti-hypertensive drugs	627 (6.8)	0 (0)	570 (16.3)	149 (23.0)	68 (25.6)	<0.001
Anti-diabetic drugs	163 (1.8)	0 (0)	233 (6.6)	26 (4.0)	20 (7.5)	<0.001
Anti-dyslipidemic drugs	288 (3.1)	0 (0)	286 (8.2)	46 (7.1)	23 (8.6)	<0.001
Family history						
Ischemic heart disease	856 (9.3)	17 (7.8)	356 (10.2)	61 (9.4)	26 (9.8)	0.599
Biochemistry						
Hemoglobin (g/dL)	14.0±1.5	14.8±1.0	15.0±1.3	15.2±1.2	15.3±1.3	<0.001
Platelet ($10^4/\mu L$)	23.8±5.1	23.9±5.1	24.2±5.3	23.0±5.4	23.3±5.4	<0.001
Albumin (g/dL)	4.4±0.2	4.5±0.2	4.4±0.2	4.4±0.2	4.4±0.2	<0.001
AST (IU/L)	20 [17–23]	22 [18–26]	24 [20–30]	26 [21–33]	29 [23–39]	<0.001
ALT (IU/L)	17 [13–24]	24 [18–32]	32 [22–47]	32 [23–43]	36 [25–50]	<0.001
GGT (IU/L)	25 [17–42]	32 [22–48]	45 [29–73]	77 [52–125]	103 [67–171]	<0.001
FLI	12.2 [5.1–27.6]	16.5 [9.9–25.4]	52.4 [33.9–71.0]	61.5 [42.5–76.6]	64.0 [47.4–81.2]	<0.001
FIB-4	0.94 [0.74–1.22]	0.86 [0.69–1.11]	0.90 [0.69–1.16]	1.06 [0.83–1.38]	1.16 [0.90–1.47]	<0.001
Creatinine (mg/dL)	0.71±0.28	0.76±0.12	0.78±0.15	0.77±0.13	0.76±0.15	<0.001
eGFR (mL/min/1.73 m^2)	85.3±14.6	85.3±13.1	82.8±14.6	84.0±14.1	86.8±16.1	<0.001
Uric acid (mg/dL)	5.2±1.3	5.8±1.2	6.1±1.3	6.3±1.4	6.3±1.5	<0.001
Total cholesterol (mg/dL)	201±33	208±30	213±34	212±36	216±42	<0.001
LDL cholesterol (mg/dL)	119±30	130±31	132±31	122±31	122±33	<0.001
HDL cholesterol (mg/dL)	64±16	59±13	51±11	57±14	59±16	<0.001
Triglycerides (mg/dL)	78 [56–110]	94 [72–119]	131 [95–184]	144 [100–206]	146 [103–220]	<0.001
Fasting glucose (mg/dL)	89±15	88±6	100±24	103±26	105±28	<0.001
HbA1c (%)	5.2±0.5	5.1±0.3	5.6±0.9	5.6±0.9	5.6±0.9	<0.001

Variables are expressed as n (%), mean±SD or median [interquartile range]. Abbreviations as in Table 1.

$age^{(-0.287)} \times 0.739$ (if female). The FLI was calculated using the following formula:[24,25]

$$FLI = [e^{(0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745)}]/[1+e^{(0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745)}]\times 100.$$

The Fibrosis-4 index (FIB-4) was calculated using the following formula:[26] age (years)×AST (IU/L)/(platelet count [10^9/L]×ALT (IU/L)$^{1/2}$). Plasma glucose was measured using the glucose oxidase method. Hemoglobin A1c (HbA1c) was expressed on the National Glycohemoglobin Standardization Program (NGSP) scale.

A self-administered questionnaire survey was conducted to obtain information on habits of current smoking and alcohol drinking, family history of IHD, and medical histories including treatment for hypertension, diabetes and dyslipidemia. Information about the types of agents and the amount of each therapeutic drug was not obtained in the present study.

Hypertension was diagnosed in accordance with the guidelines of the Japanese Society of Hypertension:[27] systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of anti-hypertensive drugs. Diabetes was diagnosed in accordance with the guidelines of the American Diabetes Association:[28] fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, or use of anti-diabetic drugs. Dyslipidemia was diagnosed according to the guidelines of the Japan Atherosclerosis Society:[29] LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, TG ≥150 mg/dL, or use of anti-dyslipidemic drugs.

Abdominal Ultrasonography

Abdominal ultrasonography was performed as an option available to all participants who received annual health checkups using SSA-250A or SSA-340A (Toshiba Medical,

Table 3. Information on Newly Developed IHD During the Follow-up Period in Subjects With Various SLDs

	All	Non-SLD	SLDs			
			SLD-MD[−]	MASLD	MetALD	ALD
Number						
All	13,815	9,176	217	3,507	649	266
Men	8,933	4,974	185	2,926	592	256
Women	4,882	4,202	32	581	57	10
New onset of IHD, n (%)						
All	458 (3.3)	243 (2.6)	5 (2.3)	166 (4.7)	32 (4.9)	12 (4.5)
Men	379 (4.2)	185 (3.7)	5 (2.7)	149 (5.1)	28 (4.7)	12 (4.7)
Women	79 (1.6)	58 (1.4)	0 (0)	17 (2.9)	4 (7.0)	0 (0)
Observed person-years						
All	95,081	63,606	1,534	24,132	4,130	1,679
Men	61,342	34,252	1,363	20,333	3,768	1,626
Women	33,739	29,354	171	3,799	362	53
Incidence rate, value per 1,000 person-years						
All	4.8	3.8	3.3	6.9	7.7	7.1
Men	6.2	5.4	3.7	7.3	7.4	7.4
Women	2.3	2.0	0	4.5	11.0	0

Abbreviations as in Table 1.

Otawara, Japan) by well-experienced echographers with at least 5 years of experience who were trained by gastroenterologists. Hepatic steatosis was identified by any findings of high-intensity bright liver, hepato-renal contrast, vascular obscuration, and deep attenuation in the liver.[30] The images and the presence of hepatic steatosis were independently reviewed by certified gastroenterologists who were blinded to clinical data.

Definitions of Various SLDs

The presence of SLDs was defined by findings of hepatic steatosis assessed using abdominal ultrasonography. MASLD was diagnosed by the absence of other discernible causes for hepatic steatosis and the presence of SLD with at least one of 5 cardiometabolic risk factors.[6] The 5 cardiometabolic criteria include: (1) BMI ≥23 or WC >90/80 cm in Asian men and women; (2) fasting glucose ≥100 mg/dL, 2-h post-load glucose levels ≥140 mg/dL (no measurement in the present study), HbA1c ≥5.7%, type 2 diabetes or treatment for type 2 diabetes; (3) blood pressure ≥130/85 mmHg or specific antihypertensive drug treatment; (4) plasma TG ≥150 mg/dL or lipid-lowering treatment; and (5) plasma HDL cholesterol ≤40 mg/dL for men and ≤50 mg/dL for women or lipid-lowering treatment. MetALD was diagnosed by the presence of MASLD and average alcohol intake of 140–350 g/week (20–50 g/day) for women and 210–420 g/week (30–60 g/day) for men. ALD was diagnosed by the presence of SLD with alcohol consumption >350 g/week (>50 g/day) for women and >420 g/week (>60 g/day) for men irrespective of metabolic dysfunction.[31] In the present study, subjects with SLD who did not meet any of the 5 cardiometabolic criteria and were not diagnosed with ALD were defined as subjects with SLD without metabolic dysfunction (SLD-MD[−]).

Statistical Analysis

Numeric variables are presented as means±standard deviation (SD) for parameters with normal distributions and as medians (interquartile ranges) for parameters with skewed distributions. Categorical variables are presented as counts with percentages. Intergroup differences in percentages of demographic parameters were examined using the chi-square test. One-way analysis of variance was used to detect significant differences between data in multiple groups. The distribution of each parameter was tested for its normality using the Shapiro-Wilk W test. Comparisons between 2 groups for parametric and nonparametric factors were performed by using Student's t-test and the Mann-Whitney U test, respectively. The associations of new onset of IHD with the categories of SLDs were investigated using the log-rank test of Kaplan-Meier curves. Hazard ratios (HRs), 95% confidence intervals (CIs), and Akaike's information criterion (AIC) for the development of IHD in subjects with each category of SLDs were calculated by using Cox proportional hazard models with adjustment for confounders including age, sex, family history of IHD, current smoking habit, eGFR, diabetes, hypertension, and dyslipidemia. Statistical tests were 2-sided and a P value <0.05 was considered statistically significant. All data were analyzed using EZR[32] and R version 4.2.2 (2020; R Core Team, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Results

Characteristics of the Study Subjects at Baseline

Characteristics of the recruited and excluded subjects at baseline are shown in **Supplementary Table 1**. The excluded subjects were significantly younger than the enrolled subjects and included a significantly lower proportion of men than did the enrolled subjects. Characteristics of recruited subjects grouped by sex at baseline are shown in **Table 1**. Men were significantly older than women, and also had a significantly higher alcohol intake and higher prevalences of hypertension, diabetes and dyslipidemia than women. The prevalences of SLDs, including SLD-MD[−], MASLD, MetALD and ALD, were significantly higher in men than in women.

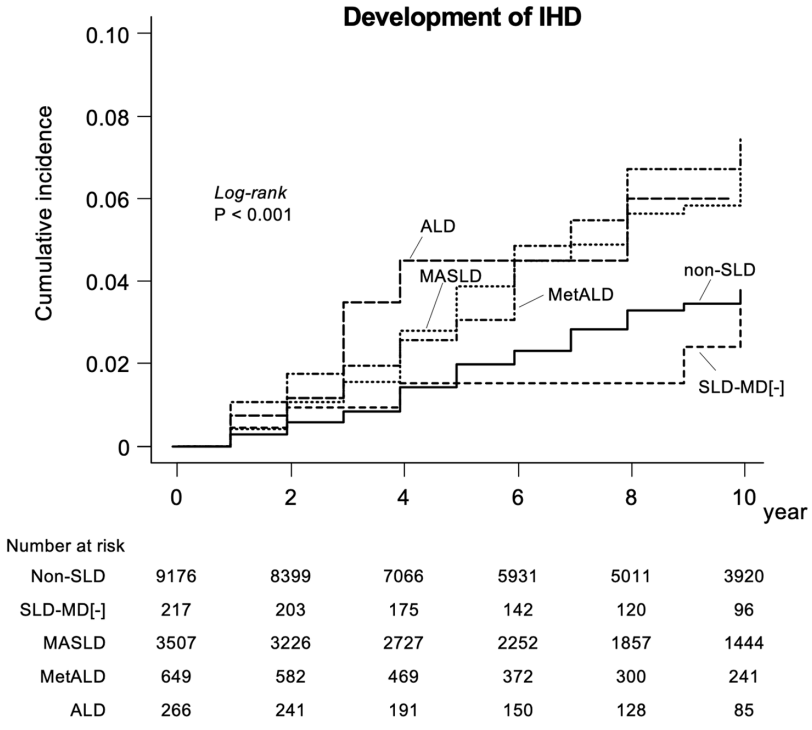

Figure 2. Impact of steatotic liver disease (SLD) categories for cumulative incidence of new development of ischemic heart disease (IHD). Kaplan-Meier survival curve analysis for cumulative incidence of IHD in subjects with an absence of SLD (non-SLD) and subjects with various SLDs, including SLD without metabolic dysfunction (SLD-MD[−]), metabolic dysfunction-associated SLD (MASLD), MASLD and increased alcohol intake (MetALD) and alcohol-associated liver disease (ALD).

Table 4. Multivariable Cox Proportional Hazard Model Analyses for the Development of IHD

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Non-SLD	1.00 (Ref.)	–	1.00 (Ref.)	–	1.00 (Ref.)	–
SLD-MD[−]	0.73 (0.30–1.77)	0.488	0.75 (0.31–1.82)	0.524	0.84 (0.34–2.04)	0.694
MASLD	1.36 (1.11–1.66)	0.002	1.41 (1.15–1.73)	<0.001	1.25 (1.01–1.55)	0.042
MetALD	1.37 (0.94–1.99)	0.099	1.37 (0.94–1.99)	0.099	1.20 (0.82–1.76)	0.344
ALD	1.22 (0.68–2.20)	0.494	1.10 (0.60–2.03)	0.756	0.92 (0.50–1.72)	0.813
Age	1.07 (1.06–1.08)	<0.001	1.07 (1.06–1.08)	<0.001	1.06 (1.05–1.07)	<0.001
Sex, male	2.23 (0.68–2.20)	<0.001	2.14 (1.64–2.78)	<0.001	2.00 (1.53–2.60)	<0.001
Family history of IHD	–	–	1.72 (1.34–2.21)	<0.001	1.69 (1.31–2.18)	<0.001
Current smoking	–	–	1.21 (0.99–1.49)	0.053	1.24 (1.02–1.52)	<0.001
eGFR	–	–	1.00 (0.99–1.01)	0.584	1.00 (0.99–1.01)	0.888
Diabetes	–	–	–	–	1.70 (1.28–2.26)	<0.001
Hypertension	–	–	–	–	1.45 (1.17–1.80)	<0.001
Dyslipidemia	–	–	–	–	1.09 (0.89–1.32)	0.383
	AIC (8,195)		AIC (7,877)		AIC (7,856)	
Interaction (Sex×SLD classification)	–	0.052	–	0.100	–	0.168

AIC, Akaike's information criterion; CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

The characteristics of recruited subjects with an absence of SLD (non-SLD) and with various SLDs at baseline are shown in **Table 2**. Subjects with non-SLD and those with SLD-MD[−] were younger than subjects with MASLD, those with MetALD, and those with ALD. Subjects with non-SLD and those with ALD included the lowest proportion and highest proportion of men, respectively. Subjects with SLD-MD[−] did not have hypertension or diabetes, being consistent with the category definition. Subjects with ALD had the highest prevalences of hypertension and diabetes among the SLD categories.

Incidence of Newly Developed IHD During the Follow-up Period

The median follow-up period was 8 years (range 1–10 years), and the follow-up summation was 95,081 person-years (men/women 61,342/33,739; **Table 3**). Among the 13,815 recruited subjects, 458 individuals (men/women 379/79)

had new development of IHD during the follow-up period. The incidence rate of IHD overall was 4.8 (men/women 6.2/2.3) per 1,000 person-years. The incidence rates of IHD in subjects with non-SLD, SLD-MD[−], MASLD, MetALD and ALD were 3.8, 3.3, 6.9, 7.7 and 7.1 per 1,000 person-years, respectively. Kaplan-Meier survival curves showed that there was a significant difference in rates of cumulative incidence of newly developed IHD among the non-SLD, SLD-MD[−], MASLD, MetALD, and ALD groups (log-rank test P<0.001; **Figure 2**).

Impact of Each Category of SLD on New Onset of IHD During the Follow-up Period

Multivariable Cox proportional hazard model analysis after adjustment of age and sex (Model 1) showed that the adjusted risk for new onset of IHD in subjects with MASLD (HR [95% CI] 1.36 [1.11–1.66]; P=0.002) was significantly higher than that in subjects with non-SLD as the reference (**Table 4**). After additional adjustment of family history of IHD, current smoking habit and eGFR in Model 1 (Model 2), the adjusted HR in subjects with MASLD (HR [95% CI] 1.41 [1.15–1.73]; P<0.001) was significantly higher than that in subjects with non-SLD. After further additional adjustment of diabetes, hypertension and dyslipidemia into Model 2 (Model 3), the adjusted HR in subjects with MASLD (HR [95% CI] 1.25 [1.01–1.55]; P=0.042) was significantly higher than that in subjects with non-SLD. There were no significant differences in any of the adjusted HRs for new onset of IHD (Models 1–3) in subjects with SLD-MD[–], MetALD and ALD compared with subjects with non-SLD as the reference (**Table 4**). Since there were no significant interactions between sex and SLD categories for the development of IHD in Models 1–3, sex-specific analyses were not conducted.

Multivariable Cox proportional hazard model analysis after adjustment of age and sex (Model 1) using only subjects with MASLD (n=3,507) and subjects without hepatosteatosis who have cardiometabolic criteria (n=5,459) showed that the adjusted risk for new onset of IHD in subjects with MASLD (HR [95% CI] 1.22 [0.99–1.51]; P=0.069) was higher, but not significantly, than that in subjects without hepatosteatosis who have cardiometabolic criteria as the reference (**Supplementary Table 2**). After additional adjustment of family history of IHD, current smoking habit and eGFR in Model 1 (Model 2), the adjusted HR in subjects with MASLD (HR [95% CI] 1.28 [1.03–1.58]; P=0.027) was significantly higher than that in subjects without hepatosteatosis who have cardiometabolic criteria.

Discussion

The present study showed that MASLD, a new classification of SLD that is associated with metabolic dysfunction but not excessive alcohol intake, was independently associated with the development of IHD during a 10-year follow-up period after adjustment of conventional risk factors for IHD in a Japanese general population. It has been reported that more than 95% of patients with NAFLD, a conventional and comprehensive classification of liver diseases, meet the diagnostic criteria for MASLD.[9,33] Since NAFLD has been reported to be a risk factor for the development of IHD in various races and populations,[34–36] the results of the present study can be rationally derived. The present study also showed that MASLD itself, rather than cardiometabolic impairments required for its criteria, could be an independent risk factor for the development of IHD (**Supplementary Table 2**). Interestingly, it has been reported that the risks for cardiovascular disease were comparable in subjects who had no hepatosteatosis and those who had hepatosteatosis without metabolic abnormalities.[37] Taken together, it is important to recognize that the presence of MASLD is not only fat deposition in the liver accompanied by metabolic abnormalities, but also a distinct risk factor for cardiovascular diseases, especially IHD.

In the present study, Kaplan-Meier curves for the cumulative incidence of IHD in subjects with MetALD and those with ALD showed a similar trend to a curve in subjects with MASLD, although the curves were not adjusted for confounding factors (**Figure 2**). However, MetALD and ALD in addition to SLD-MD[−] were not selected as independent risk factors for the development of IHD after adjustment of confounding risk factors for IHD (**Table 4**). The exact mechanisms of the differences in SLD categories remain unknown. However, since relatively small numbers of subjects were classified into SLD categories other than MASLD, a possible reason would be heterogeneity of the prevalence of SLD categories, which was suggested in other studies,[38,39] potentially leading to a statistical β error. It is well known that there is a J-curve phenomenon in the relationship between alcohol consumption and cardiovascular events.[40] In contrast, the categories of MetALD and ALD were considered by only the amount of alcohol consumed and not the types of alcoholic drinks.[6,7] Although there is still debate whether moderate alcohol consumption is really beneficial for the cardiovascular system,[12] it is undeniable that some types of alcoholic drinks, such as red wine containing polyphenols, might have had a positive effect on the cardiovascular system. Nevertheless, further studies using a large number of subjects are needed to determine whether SLD categories other than MASLD can be risk factors for the development of IHD.

The present study did not address the molecular mechanisms underlying why MASLD, rather than other SLDs, was a significant risk factor for the development of IHD. However, in the present study, subjects with MASLD did not have the highest values for liver injury-associated indicators including levels of transaminases and FIB-4, a marker for liver fibrosis, compared with other SLD categories (**Table 2**), suggesting that the risk for new onset of IHD in MASLD is related less to the degree of liver damage and fibrosis at baseline. Recently, the American Heart Association has proposed a concept of cardiovascular-kidney-metabolic (CKM) syndrome.[41] The concept includes the aim of enlightening people about the inter-organ relationships among cardiovascular, kidney, and metabolism-related organ abnormalities with a focus on obesity and/or MASLD and the importance of lifestyle and weight management for the maintenance of health.[42,43] As the underlying pathology of CKM syndrome, various mechanisms including chronic inflammation,[44] redox imbalance[45] and abnormalities in sex hormone signals[46] have been proposed. SLD, especially MASLD, can be one of the most upstream pathophysiological factors, and the establishment of specific therapeutic strategies for preventing MASLD is urgently required.

We recently showed that the presence of MASLD is independently associated with the development of chronic kidney disease (CKD),[21] which is not only associated with

end-stage renal dysfunction but is also a significant risk factor for cardiovascular events.[47,48] In addition, it has been shown that the coexistence of MAFLD and CKD is independently associated with the risk for development of IHD and is a better predictor than MAFLD or CKD alone.[19] From the perspective of metabolic abnormalities, it is important to clarify the relationships between each category of SLDs and metabolic abnormalities including fatty acid metabolism and amino acid metabolism as well as glucose metabolism in the whole body, which are related to the development of various atherosclerotic diseases[49,50] and renal diseases.[51,52] There have been some studies showing a link of MASLD with heart diseases including heart failure[53] and arrhythmias.[54] However, it is still unclear whether MASLD is also linked to cerebrovascular diseases, which are other life-threatening problems. Therefore, elucidation of the precise risks for the development of various cerebro-cardiovascular, renal and metabolic diseases, and their pathophysiology depending on each SLD category, would provide useful information for the establishment of strategies for their prevention and novel treatment. Future longitudinal studies to determine the incidences of various diseases for each SLD category are warranted.

The validity of the new SLD classification is still being debated, and more detailed classifications based on pathophysiology have also been proposed.[55] Pathophysiological classifications might make risk stratification for cardiovascular diseases clearer. In addition to clinical research, further basic research is necessary to not only clarify the validity of the new category classification of SLDs but also the perspective of risk stratification of cardiovascular disease and the development of new therapeutic targets.

Study Limitations

The present study has several limitations. First, since the study subjects consisted only of participants who received annual health checkups including abdominal ultrasonography at a single facility, the possibility of selection bias cannot be ruled out. Second, although sensitivity for assessing the development of IHD using a self-administered questionnaire is sufficiently high, the positive predictive value is relatively low.[56] Therefore, there is a possibility that the self-reported incidence of IHD during the follow-up period is overestimated. Last, the presence of hepatic steatosis was determined by the findings of abdominal ultrasound alone and was not confirmed by liver biopsy, a gold standard for the diagnosis of SLD.

Conclusions

The risk for new onset of IHD is different in each SLD category, and the presence of MASLD, but not other SLDs, is an independent risk factor for the development of IHD in the general Japanese population, suggesting that prevention and early detection of the development of MASLD are important strategies for maintenance of healthy life expectancy.

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IRB Information

The Ethics Committee of Sapporo Medical University (no. 30-2-32).

Disclosures

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Supplementary Files

Please find supplementary file(s);
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