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Steatotic Liver Disease: A Key Related Risk Factor in the Emergence of Metabolic Syndrome-Related Disorders

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ABSTRACT

Background: Steatotic liver disease (SLD) is a hepatic phenotype of metabolic syndrome (MetS). However, little is known about the relationship between SLD and the onset of each MetS-related disease (type 2 diabetes [T2D], hypertension, and dyslipidemia). In this study, we examined the relationship between the onset of MetS-related diseases and SLD using health checkup data at baseline and 7 years later.

Methods: A total of 2167 individuals who underwent a health examination were initially recruited to the study. After excluding cases with a history of hepatic disease, a total of 714 subjects were selected and received an abdominal ultrasound test at baseline and again 7 years later. New-onset cases were defined as subjects who were free of each disease at baseline but developed one by the 7-year follow-up. Logistic regression analysis was used to estimate odds ratios and quantify the impact of SLD on the development of MetS-related diseases.

Results: We found the following results: (1) SLD at baseline is an independent risk factor for the incidence of MetS-related disease 7 years later. (2) T2D and hypertension are not independent risk factors for the incidence of SLD 7 years later. Dyslipidemia and obesity are independent risk factors for the incidence of SLD. Obesity is the only independent risk factor for the new development of SLD within 7 years. (3) No individual MetS-related disease is an independent risk factor for the development of SLD.

Conclusion: The presence of SLD is more associated with the incidence of MetS-related diseases than obesity.

1 | Introduction

Steatotic liver disease (SLD) is the most common chronic liver disease, affecting one in four adults in Japan [1, 2]. Approximately 60%–70% of patients SLD are obese. In 2023, the diagnostic criteria for SLD were revised, and the previous names of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis were changed to metabolic dysfunction–associated steatotic liver

Abbreviations: A/G ratio, albumin/globulin ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMY, amylase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHE, choline esterase; CRP, C-reactive protein; FBG, fasting blood glucose; GGT, gamma glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDH, lactate dehydrogenase; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MetS, metabolic syndrome; n.s., not significant; RBC, red blood cells; SBP, systolic blood pressure; SLD, steatotic liver disease; T-Bil, total bilirubin; T-Chol, total cholesterol; T2D, type 2 diabetes mellitus; TG, triglyceride; TP, total protein; UA, uric acid.

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disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH) [3]. In addition, SLD with high alcohol intake is now called alcohol-related liver disease, and SLD with intermediate alcohol intake is now called metabolic and alcohol-related liver disease. Some cases of MASLD/MASH may progress to cirrhosis or hepatocellular carcinoma [4].

According to the recently established diagnostic criteria, MASLD is defined as SLD diagnosed by imaging or liver biopsy in addition to at least one of the cardiometabolic criteria (body mass index [BMI], blood glucose, blood pressure, triglyceride level, and high-density lipoprotein cholesterol [HDL-C] level) and an alcohol intake of ≤ 30 g/day for men or ≤ 20 g/day for women [5]. In our recent study of a health checkup cohort, NAFLD and MASLD were 99% consistent. This fact implies that most NAFLD cases have metabolic risk factors. It can be seen that SLD and metabolic syndrome (MetS) are very closely related.

MetS is an obesity-related multiple-risk factor syndrome that includes type 2 diabetes (T2D), hypertension, and dyslipidemia. Patients with SLD often suffer from MetS. SLD complicated with MetS is prone to progression of the disease [6]. Individuals with T2D-associated SLD are a particularly high-risk group, and it has been reported that 38% of such patients have advanced liver fibrosis [7].

Although SLD is said to be a hepatic phenotype of MetS, little is known about the relationship between SLD and the onset of each MetS-related disease (T2D, hypertension, and dyslipidemia). We hypothesized that the presence of SLD may be an upstream risk factor for the development of each MetS-related disease. To verify this hypothesis, this study examined the relationship between the onset of MetS-related diseases and SLD using health checkup data at baseline and 7 years later.

2 | Subjects and Methods

2.1 | Ethical Committee Approval

Our research and informed consent protocols were approved for use in this multicenter study by the institutional review boards at Osaka University Hospital and aMs New Otani Clinic (IRB No. 13563). Written informed consent was obtained from each subject at the time of enrollment at each institute. The study was conducted in accordance with the Declaration of Helsinki.

2.2 | Subjects in Medical Health Checkups

A total of 2167 individuals who underwent a health examination at aMs New Otani Clinic (Osaka, Japan) in 2009–2011 (baseline) were initially recruited to the study, and 806 of these subjects received a follow-up health examination 7 years later. No specific inclusion criteria were applied. The following exclusion criteria were applied: history of hepatic disease, such as chronic hepatitis C or concurrent active hepatitis B (seropositive for hepatitis B surface antigen), autoimmune hepatitis, primary biliary cholangitis, sclerosing cholangitis, hemochromatosis, α1-antitrypsin deficiency, Wilson's disease, or hepatic injury caused by substance abuse. A total of 714 subjects received an abdominal ultrasound test during the health checkup. The diagnosis of SLD was based on the results of the abdominal ultrasound examination carried out by trained technicians. A steatotic liver was defined as a liver parenchyma with an echogenicity greater than that of the kidney cortex, the presence of vascular blurring, and deep attenuation of the ultrasound signal [8, 9]. This study did not take into account the presence or absence of so-called cardiometabolic risk factors.

2.3 | Anthropometric and Laboratory Evaluation

Anthropometric variables (height and weight) were measured while each subject was in the standing position. BMI was calculated as weight in kilograms divided by the square of height in meters (m^2). Systolic and diastolic blood pressure values were measured (to the nearest mm Hg) while each subject was in the sitting position. Serum biochemical variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], γ-glutamyltransferase, total bilirubin, creatinine, choline esterase, total cholesterol, triglycerides [TG], HDL-C, low density lipoprotein cholesterol [LDL-C], uric acid, iron, fasting blood sugar, albumin, and platelet counts) were measured using a conventional automated blood analyzer. The interviews were conducted at both visits to obtain information on lifestyle habits (food intake, meal frequency, alcohol consumption, and other recreational items), including smoking status, number of cigarettes smoked per day, and smoking duration. Alcohol consumption was calculated from interview data as previously reported [2]. Briefly, daily alcohol consumption was calculated in grams using our modified template [10]. We classified the frequency of alcohol intake into three categories: 1 day/week, 3 days/week, or daily. We also classified each participant's average alcohol consumption into four categories: 10 g, 30 g, 50 g, or 70 g. Daily alcohol consumption (g/day) was calculated as follows: [(frequency of alcohol intake) × (average alcohol consumption in g)]/7. Based on answers to the interviews, we calculated the Brinkman index (number of cigarettes consumed per day multiplied by years of smoking) for each participant.

2.4 | Diagnostic Criteria for MetS-Related Diseases

The diagnostic criteria for MetS-related diseases were as follows. T2D was defined as fasting blood sugar ≥ 126 mg/dL, hemoglobin A1c ≥ 6.5%, or ongoing treatment for T2D [11]. Similarly, systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or ongoing treatment for hypertension was defined as hypertension [12]. Serum HDL-C < 40 mg/dL, TG ≥ 150 mg/dL, or ongoing treatment for dyslipidemia was defined as dyslipidemia [13]. Obesity was defined as BMI ≥ 25 kg/m^2 [14].

2.5 | Statistical Analysis

Statistical analyses were carried out using JMP Pro 17.2 software (SAS Institute Inc., Cary, NC). Results were expressed as

mean ± standard deviation. The statistical analysis included descriptive statistics, t-tests, and the Wilcoxon test. Chi-squared tests were used for categorical factors. The variables were categorically divided into two groups based on whether they had the disease or not, and whether their test values were within the normal range or outside. Multivariate logistic regression analyses were carried out to identify significant determinants. Differences were considered statistically significant at $p < 0.05$.

3 | Results

3.1 | Characteristics of the Study Participants

The results of the clinical and biochemical analyses of individuals in the study population are presented in Table 1. Among the 714 study subjects (521 men and 193 women), 435 (60.9%) were diagnosed with SLD at baseline using abdominal ultrasound and 422 (59.1%) subjects were diagnosed with SLD at the 7-year follow-up. Among the 435 SLD subjects diagnosed at baseline, 376 subjects (86.4%) were still diagnosed with SLD at follow-up. The ratio of subjects with SLD at follow-up was lower than that at baseline. The ratio of men in the group with SLD [SLD (+)] was greater than the ratio of men in groups without SLD [SLD (−)] at both baseline and follow-up. BMI was greater in subjects with SLD. The serum levels of AST, ALT, γ-glutamyltransferase, albumin, choline esterase, TG, LDL-C, uric acid, and FBG were significantly higher in SLD (+) subjects than in SLD (−) subjects at both baseline and follow-up. Serum HDL-C levels were lower in SLD (+) subjects.

3.2 | Number of Patients With Obesity, T2D, Hypertension, and Dyslipidemia With or Without SLD, and Number of New-Onset Cases of Each Disease After 7 Years

The SLD group had significantly higher rates of obesity, T2D, hypertension, and dyslipidemia (high TG and low HDL-C) both at 1 year and 7 years later (Table 2). New-onset cases were defined as subjects who were free of each disease (obesity, T2D, hypertension, dyslipidemia, and SLD) at 1 year but developed a disease by the 7-year follow-up. By this definition, there were 25 new cases of obesity, 67 new cases of T2D, 81 new-onset cases of hypertension, 120 new cases of dyslipidemia, and 46 new cases of SLD.

3.3 | The Presence of SLD at Baseline Was an Independent Risk Factor for the Incidence of MetS-Related Diseases 7 Years Later

Multiple logistic regression analysis was used to examine factors at baseline associated with the 7-year incidence of each MetS-related disease (T2D, hypertension, and dyslipidemia) (Table 3). For T2D, sex (male) and the presence of SLD, low AST, low uric acid, hypertension, and dyslipidemia at baseline were independent risk factors. For hypertension, age (older age) and the presence of SLD, T2D, and dyslipidemia at baseline were independent risk factors. For dyslipidemia, the presence of SLD, low AST, high uric acid, T2D, and dyslipidemia at baseline were independent risk factors. Surprisingly, obesity was not an independent risk factor for developing any disease.

3.4 | The Presence of SLD at Baseline Was an Independent Risk Factor for the Development of MetS-Related Diseases 7 Years Later

Multiple logistic regression analysis was used to examine which factors at baseline were associated with the development of each MetS-related disease (T2D, hypertension, and dyslipidemia) 7 years later (Table 4). The independent risk factors for the onset of T2D 7 years later were SLD, low uric acid levels, and dyslipidemia at baseline. The only independent risk factor for the onset of hypertension 7 years later was SLD at baseline. The only independent risk factor for the onset of dyslipidemia 7 years later was female sex at baseline. Obesity was not a risk factor for the development of any MetS-related disease 7 years later. We created a Sankey diagram to visualize the extent to which the presence or absence of SLD in the first year contributes to the development of each MetS-related disease 7 years later (Figure 1). The Sankey diagram shows that SLD incidence in the first year is significantly associated with the onset of each MetS-related disease.

3.5 | The Presence of Obesity and Dyslipidemia at Baseline Were Independent Predictors of SLD Incidence 7 Years Later

Conversely, multiple logistic regression analysis was used to examine which factors during the baseline were associated with the incidence of SLD 7 years later (Table 5).

T2D and hypertension were not independent risk factors for the development of SLD 7 years later, whereas obesity and dyslipidemia were independent risk factors for the development of SLD. Other independent risk factors for the incidence of SLD 7 years later were younger age, male sex, high CRP levels, and a high Brinkman's index.

3.6 | The Presence of Obesity at Baseline Was the Only Independent Predictor of SLD Development 7 Years Later

Multiple logistic regression analysis was used to examine which factors during the baseline were associated with new-onset SLD 7 years later (Table 6). Interestingly, none of the MetS-related diseases (T2D, hypertension, and dyslipidemia) were independent risk factors, and obesity was the only independent risk factor for the development of SLD.

3.7 | Changes in the Type of SLD and Incidence of MetS-Related Diseases

Finally, we examined the change in SLD incidence at baseline and 7 years later, and the incidence of each MetS-related disease

TABLE 1 | Clinical and biochemical parameters of the study subjects.

	Baseline parameters			Follow-up parameters after 7 years		
Variable	**SLD (−)**	**SLD (+)**	***p* value**	**SLD (−)**	**SLD (+)**	***p* value**
Number of study subjects	279	435		292	422	
Sex (F/M)	120/159	73/362	< 0.0001	117/175	76/346	< 0.0001
Age (years)	53.5 ± 8.1	53.5 ± 6.8	n.s.	61.4 ± 8.7	59.8 ± 6.3	< 0.05
BMI (kg/m^2)	22.0 ± 2.8	26.3 ± 3.8	< 0.0001	21.9 ± 2.8	26.0 ± 3.8	< 0.0001
SBP (mm Hg)	110.2 ± 13.9	119.7 ± 15.4	< 0.0001	106.8 ± 15.8	114.2 ± 14.2	< 0.0001
TP (g/dL)	7.00 ± 0.44	7.28 ± 0.42	< 0.0001	7.05 ± 0.40	7.28 ± 0.42	< 0.0001
Albumin (g/dL)	4.23 ± 0.24	4.40 ± 0.22	< 0.0001	4.33 ± 0.23	4.46 ± 0.23	< 0.0001
A/G ratio	1.55 ± 0.20	1.56 ± 0.20	n.s.	1.62 ± 0.22	1.61 ± 0.23	n.s.
T-bil (mg/dL)	0.79 ± 0.32	0.80 ± 0.30	n.s.	0.8 ± 0.30	0.86 ± 0.34	< 0.05
AST (U/L)	24.4 ± 13.0	32.1 ± 15.4	< 0.0001	23.2 ± 10.2	30.4 ± 18.3	< 0.0001
ALT (U/L)	23.6 ± 17.5	43.8 ± 24.8	< 0.0001	19.5 ± 10.0	35.7 ± 23.4	< 0.0001
ALP (U/L)	198.1 ± 66.9	210.0 ± 57.6	< 0.0005	206.1 ± 62.5	206.1 ± 61.1	n.s.
GGT (U/L)	51.0 ± 84.2	74.0 ± 78.7	< 0.0001	42.3 ± 62.3	62.9 ± 66.5	< 0.0001
LDH (U/L)	169.5 ± 30.8	176.9 ± 30.9	< 0.005	178.5 ± 33.7	181.0 ± 32.9	n.s.
CHE (U/L)	315.5 ± 63.8	378.7 ± 67.5	< 0.0001	315.1 ± 63.9	359.0 ± 65.5	< 0.0001
AMY (U/L)	74.4 ± 27.3	63.3 ± 19.4	< 0.0001	80.3 ± 27.8	69.6 ± 25.3	< 0.0001
BUN (mg/dL)	14.3 ± 3.5	13.8 ± 3.1	n.s.	14.6 ± 4.0	14.7 ± 4.5	n.s.
Creatinine (mg/dL)	0.78 ± 0.16	0.83 ± 0.16	< 0.0001	0.80 ± 0.18	0.87 ± 0.30	< 0.0001
T-chol (mg/dL)	199.4 ± 35.0	208.4 ± 34.1	< 0.0001	202.1 ± 35.6	197.7 ± 33.2	n.s.
TG (mg/dL)	92.9 ± 82.6	157.7 ± 108.3	< 0.0001	89.6 ± 50.4	143.5 ± 115.3	< 0.0001
HDL-C (mg/dL)	65.6 ± 14.0	53.8 ± 10.7	< 0.0001	67.9 ± 15.3	56.5 ± 12.3	< 0.0001
UA (mg/dL)	5.31 ± 1.36	6.13 ± 1.32	< 0.0001	5.27 ± 1.32	5.89 ± 1.26	< 0.0001
FBS (mg/dL)	107.3 ± 27.3	120.4 ± 32.6	< 0.0001	107.9 ± 22.7	120.8 ± 26.8	< 0.0001
HbA1c (%)	6.07 ± 0.97	6.49 ± 1.08	< 0.0001	6.14 ± 0.82	6.52 ± 0.98	< 0.0001
RBC ($10^4/\mu L$)	441.2 ± 39.9	474.1 ± 40.7	< 0.0001	441.1 ± 41.4	472.0 ± 42.2	< 0.0001
Hb (g/dL)	13.6 ± 1.30	14.6 ± 1.3	< 0.0001	13.7 ± 1.2	14.7 ± 1.2	< 0.0001
Platelets ($10^4/\mu L$)	21.5 ± 4.8	21.8 ± 5.0	n.s.	21.3 ± 5.3	21.0 ± 4.9	n.s.
CRP (mg/dL)	0.10 ± 0.32	0.18 ± 0.54	< 0.0001	0.11 ± 0.30	0.16 ± 0.63	< 0.0001
Brinkman index	82.8 ± 210.7	141.1 ± 293.3	< 0.05	94.0 ± 248.9	170.4 ± 342.2	< 0.005
Alcohol consumption (g/day)	13.9 ± 19.1	17.3 ± 22.1	n.s.	14.8 ± 21.4	18.5 ± 23.2	< 0.05

Note: Values represent mean ± SD. *p* values correspond to the comparison between groups without and with SLD; Wilcoxon's test for continuous factors and Pearson's chi-squared test for categorical factors were used. Pearson's chi-squared test between data at baseline and follow-up.
Abbreviations: A/G ratio, albumin/globulin ratio; AMY, amylase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHE, choline esterase; CRP, C-reactive protein; FBG, fasting blood glucose; GGT, gamma glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; n.s., not significant; RBC, red blood cells; SBP, systolic blood pressure; SLD, steatotic liver disease; T-Bil, total bilirubin; T-Chol, total cholesterol; TG, triglycerides; TP, total protein; UA, uric acid.

(Table 7). There were 376 subjects who had SLD at baseline and still had SLD 7 years later, and 59 subjects who had SLD at baseline but no longer had SLD after 7 years. Compared with the former group, the latter had a lower incidence of each MetS-related disease after 7 years (T2D, 54% vs. 50.8%; hypertension, 46.3% vs. 37.3%; and dyslipidemia, 68.6% vs. 64.4%). This result suggests that improving SLD improves the incidence of each MetS-related disease.

In addition to this analysis, we investigated we also investigated which factors are involved in the regression of each MetS-related disease. Interestingly, SLD regression was a significant independent factor for the regression of all MetS-related disorders (Supporting Information S1: Table 1). Conversely, the only significant factor associated with SLD regression was age but not any of the MetS-related diseases (Supporting Information S1: Table 2).

4 | Discussion

In carrying out this study, we hypothesized that the presence of SLD may be an upstream risk factor for the development of each MetS-related disease. The hypothesis was tested using health

TABLE 2 | The number of subjects with obesity, T2D, hypertension, dyslipidemia (hypertriglyceridemia and low HDL-C), and SLD.

	Baseline			7-Year follow-up			
Variable	**SLD (−) (*n*)**	**SLD (+) (*n*)**	***p* value**	**SLD (−) (*n*)**	**SLD (+) (*n*)**	***p* value**	**New onset (*n*)**
Obesity (y/n)	43/236	267/168	< 0.0001	36/256	239/183	< 0.0001	25
T2D (y/n)	80/199	193/242	< 0.0001	96/196	220/202	< 0.0001	67
Hypertension (y/n)	38/241	152/283	< 0.0001	65/227	183/239	< 0.0001	81
Dyslipidemia (y/n)	88/191	277/158	< 0.0001	148/144	284/138	< 0.0001	120
Hypertriglyceridemia (y/n)	40/252	147/275	< 0.0001	24/268	136/286	< 0.0001	59
Low HDL-C (y/n)	7/285	24/398	< 0.05	5/287	21/401	< 0.05	11
SLD	279	435	n.s.	292	422	n.s.	46

Abbreviations: HDL-C, high-density lipoprotein cholesterol; n.s., not significant; SLD, steatotic liver disease; T2D, type 2 diabetes.

checkup data from the same subjects at baseline and 7 years later. SLD at baseline was an independent risk factor for the incidence of T2D, hypertension, and dyslipidemia 7 years later. SLD at baseline was also an independent risk factor for the development of T2D and hypertension within 7 years. Interestingly, obesity at baseline was not an independent risk factor for the incidence or development of any MetS-related disease by the 7-year follow-up. Conversely, T2D and hypertension at baseline were not related to the incidence of SLD 7 years later, but obesity and dyslipidemia at baseline were related to this incidence. In this study, only obesity at baseline was an independent risk factor for the new onset of SLD by the 7-year follow-up. Finally, the results suggest that improving SLD contributes to a reduction in the incidence of each MetS-related disease. We believe these are important data showing that improving SLD upstream of each MetS-related disease contributes to preventing and ameliorating the onset of each subsequent MetS-related disease. From the results of this study, it can be inferred that SLD is upstream of the onset of each MetS-related disease and that obesity is upstream of the onset of SLD.

SLD may precede and promote the development of components of MetS, such as T2D, hypertension, dyslipidemia, and cardiovascular disease, whereas MetS itself predicts the onset and progression of SLD—a "chicken-and-egg" relationship that has sparked debate among researchers [15]. It has been reported that NAFLD increases the risk of developing T2D by approximately 2-fold through insulin resistance in the liver [16]. It has also been reported that many cases of MASLD are accompanied by T2D [7]. This study found that SLD is upstream of the onset of T2D and, conversely, that T2D contributes little to the onset of SLD. It is extremely important to have been able to elucidate the factors that cause the onset of these two conditions. The liver is an important organ for the body's metabolism. In glucose metabolism, excess glucose is stored as glycogen, and when needed, glucose is produced from glycogen through gluconeogenesis and released into the blood. In SLD, the metabolic function of the liver is impaired; these glucose metabolic functions are no exception. Therefore, it is believed that the onset of new T2D is more frequent in SLD due to the decline in glucose metabolic function. Moreover, although T2D has a large impact on the progression of SLD pathology (such as steatohepatitis, progression of liver fibrosis, and onset of liver cancer) [7], it has been suggested that T2D is not directly involved in the onset of SLD. Considering the results of this study, it is expected that controlling SLD will contribute to reducing the onset of T2D. The development of T2D should be anticipated and managed in individuals with SLD.

There have been many reports on the causal relationship between SLD and hypertension [15]. Approximately 50% of hypertensive patients have NAFLD [17–19]. It has been shown that hypertension, even within the normal range, contributes to the onset and progression of NAFLD, and the presence and severity of NAFLD are associated with an increased risk of developing hypertension [20–23]. In addition, a meta-analysis reported that NAFLD increases the risk of developing hypertension by approximately 1.7-fold and that obesity is the most important confounding factor that can partially explain this association [24]. These reports also suggest a two-way relationship in which the higher the blood pressure, the higher the risk of NAFLD, and vice versa. The results of our current study demonstrate that SLD at baseline was an independent risk factor for the development of hypertension by the 7-year follow-up. Conversely, hypertension at baseline was not related to the incidence of SLD 7 years later. Based on the results in our study, it can be inferred that SLD is upstream of the onset of hypertension. However, since there are reports that SLD and hypertension influence each other, we must be careful when deciding which is upstream. It can be inferred that SLD is upstream of the onset of hypertension. Because patients with NAFLD are at risk of developing new-onset hypertension, regular cardiovascular evaluation, including blood pressure monitoring, is recommended. Based on these findings, we believe that controlling SLD is reasonable to prevent the onset of T2D and hypertension. In addition, because dyslipidemia and SLD can each be the cause and effect of the other, there are compounding benefits of controlling both conditions as controlling each one may also improve the pathology of the other.

Our study had some limitations. First, this study was based on an analysis comparing only two timepoints, the baseline and 7 years later, so it does not accurately capture the point at which each disease developed. Next, because this was a comparative study of two timepoints, we were able to clarify the progression from obesity to fatty liver and from fatty liver to various MetS-related diseases, but we were unable to grasp the overall progression from obesity to fatty liver and then to MetS-related

TABLE 3 | Multiple logistic regression analysis of factors associated with disease incidence at the 7-year follow-up using baseline variables.

Variable	Target category	Odds ratio	95% CI		*p* value
			Lower	Upper	
T2D					
Age	≥ 65 years	1.62	0.86	3.05	n.s.
Sex	Female	0.63	0.41	0.99	< 0.05
SLD	Presence	1.83	1.22	2.73	< 0.005
AST	≥ 40 U/L	0.34	0.21	0.54	< 0.0001
Creatinine	≥ 1.0 mg/dL	0.82	0.49	1.37	n.s.
Uric acid	> 7.0 mg/dL	0.37	0.24	0.59	< 0.0001
CRP	> 0.06 mg/dL	1.25	0.88	1.78	n.s.
Brinkman index	≥ 400	1.27	0.79	2.06	n.s.
Ethanol intake	≥ 30 g/day	0.99	0.67	1.46	n.s.
Hypertension	Presence	2.48	1.66	3.70	< 0.0001
Dyslipidemia	Presence	2.20	1.54	3.14	< 0.0001
Obesity	BMI ≥ 25 kg/m^2	1.35	0.92	1.98	n.s.
Hypertension					
Age	≥ 65 years	2.67	1.43	5.00	< 0.005
Sex	Female	0.81	0.50	1.32	n.s.
SLD	Presence	2.36	1.54	3.63	< 0.0001
AST	≥ 40 U/L	1.23	0.79	1.91	n.s.
Creatinine	≥ 1.0 mg/dL	1.36	0.82	2.24	n.s.
Uric acid	> 7.0 mg/dL	1.27	0.82	1.98	n.s.
CRP	> 0.06 mg/dL	1.25	0.88	1.79	n.s.
Brinkman index	≥ 400	1.18	0.74	1.89	n.s.
Ethanol intake	≥ 30 g/day	1.39	0.95	2.06	n.s.
T2D	Presence	2.27	1.57	3.29	< 0.0001
Dyslipidemia	Presence	1.56	1.08	2.25	< 0.05
Obesity	BMI ≥ 25 kg/m^2	1.28	0.87	1.87	n.s.
Dyslipidemia					
Age	≥ 65 years	0.55	0.30	1.01	n.s.
Sex	Female	1.48	0.97	2.27	n.s.
SLD	Presence	1.97	1.34	2.88	< 0.001
AST	≥ 40 U/L	1.25	0.81	1.93	n.s.
Creatinine	≥ 1.0 mg/dL	1.29	0.78	2.16	n.s.
Uric acid	> 7.0 mg/dL	1.76	1.11	2.78	< 0.05
CRP	> 0.06 mg/dL	1.05	0.75	1.48	n.s.
Brinkman index	≥ 400	0.88	0.56	1.41	n.s.
Ethanol intake	≥ 30 g/day	0.97	0.66	1.41	n.s.
T2D	Presence	1.48	1.03	2.13	< 0.05
Hypertension	Presence	1.98	1.30	3.00	< 0.005
Obesity	BMI ≥ 25 kg/m^2	0.90	0.62	1.32	n.s.

Note: Multivariate analysis was carried out using 12 items from the first year to assess the incidence of each MetS-related disease 7 years later.
Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; n.s., not significant; SLD, steatotic liver disease; T2D, type 2 diabetes.

TABLE 4 | Multiple logistic regression analysis of factors associated with disease development at 7-year follow-up using baseline variables.

Variable	Target category	Odds ratio	95% CI		*p* value
			Lower	Upper	
T2D					
Age	≥ 65 years	0.47	0.09	2.37	n.s.
Sex	Female	1.29	0.59	2.83	n.s.
SLD	Presence	2.13	1.02	4.44	< 0.05
AST	≥ 40 U/L	0.73	0.38	1.41	n.s.
Creatinine	≥ 1.0 mg/dL	1.34	0.61	2.96	n.s.
Uric acid	> 7.0 mg/dL	0.43	0.20	0.90	< 0.05
CRP	> 0.06 mg/dL	0.92	0.50	1.68	n.s.
Brinkman index	≥ 400	1.18	0.52	2.66	n.s.
Ethanol intake	≥ 30 g/day	1.12	0.57	2.18	n.s.
Hypertension	Presence	1.30	0.65	2.60	n.s.
Dyslipidemia	Presence	3.07	1.61	5.84	< 0.001
Obesity	BMI ≥ 25 kg/m^2	1.74	0.92	3.29	n.s.
Hypertension					
Age	≥ 65 years	0.88	0.27	2.83	n.s.
Sex	Female	0.78	0.39	1.59	n.s.
SLD	Presence	1.97	1.05	3.70	< 0.05
AST	≥ 40 U/L	1.31	0.69	2.50	n.s.
Creatinine	≥ 1.0 mg/dL	1.64	0.79	3.39	n.s.
Uric acid	> 7.0 mg/dL	0.90	0.45	1.77	n.s.
CRP	> 0.06 mg/dL	1.34	0.79	2.29	n.s.
Brinkman index	≥ 400	1.59	0.83	3.06	n.s.
Ethanol intake	≥ 30 g/day	0.98	0.55	1.75	n.s.
T2D	Presence	1.65	0.94	2.82	n.s.
Dyslipidemia	Presence	1.25	0.72	2.15	n.s.
Obesity	BMI ≥ 25 kg/m^2	0.97	0.55	1.72	n.s.
Dyslipidemia					
Age	≥ 65 years	0.55	0.19	1.61	n.s.
Sex	Female	1.81	1.01	3.26	< 0.05
SLD	Presence	1.53	0.87	2.68	n.s.
AST	≥ 40 U/L	1.04	0.52	2.08	n.s.
Creatinine	≥ 1.0 mg/dL	0.75	0.30	1.90	n.s.
Uric acid	> 7.0 mg/dL	1.27	0.62	2.57	n.s.
CRP	> 0.06 mg/dL	0.90	0.53	1.52	n.s.
Brinkman index	≥ 400	0.95	0.46	1.93	n.s.
Ethanol intake	≥ 30 g/day	1.12	0.64	1.97	n.s.
T2D	Presence	0.77	0.43	1.39	n.s.
Hypertension	Presence	1.79	0.90	3.57	n.s.
Obesity	BMI ≥ 25 kg/m$_2$	0.81	0.45	1.49	n.s.

Note: Multivariate analysis was carried out using 12 items from the first year to assess the development of each MetS-related disease 7 years later.
Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; n.s., not significant; SLD, steatotic liver disease; T2D, type 2 diabetes.

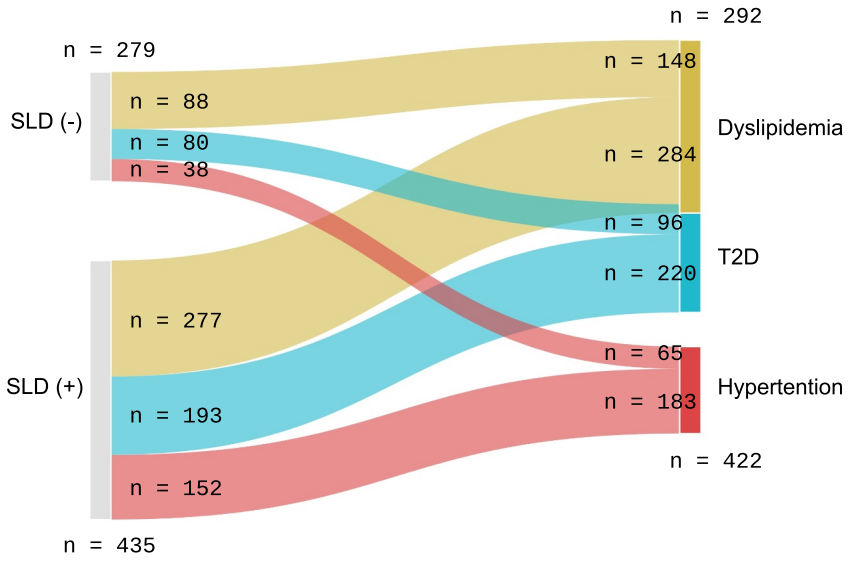

FIGURE 1 | Sankey diagram showing the 7-year incidence of each MetS-related diseases. Sankey diagram showing the 7-year incidence of type 2 diabetes (blue), hypertension (red), and dyslipidemia (yellow) among initially disease-free subjects with versus without baseline steatotic liver disease (SLD). Flows are proportional to incident case numbers and explicitly labeled. SLD presence at baseline is associated with a higher risk of developing metabolic diseases.

TABLE 5 | Multiple logistic regression analysis of factors associated with SLD incidence at 7-year follow-up using baseline variables.

Parameter	Target category	Odds ratio	95% CI		*p* value
			Lower	Upper	
Age	≥ 65 years	0.26	0.13	0.53	< 0.0005
Sex	Female	0.43	0.27	0.67	< 0.0005
AST	≥ 40 U/L	1.46	0.89	2.41	n.s.
Creatinine	≥ 1.0 mg/dL	1.08	0.61	1.92	n.s.
Uric acid	> 7.0 mg/dL	1.21	0.73	2.02	n.s.
CRP	> 0.06 mg/dL	1.75	1.20	2.56	< 0.005
Brinkman index	≥ 400	1.84	1.05	3.21	< 0.05
Ethanol intake	≥ 30 g/day	0.84	0.55	1.28	n.s.
T2D	Presence	0.96	0.64	1.44	n.s.
Hypertension	Presence	1.48	0.94	2/35	n.s.
Dyslipidemia	Presence	1.89	1.30	2.76	< 0.001
Obesity	Presence	4.45	3.00	6.59	< 0.0001

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; n.s., not significant; SLD, steatotic liver disease; T2D, type 2 diabetes.

diseases. Third, because validation was not carried out in a validation cohort, validation using a different cohort is necessary in the future. Over 60% (435/714) of the cohort used in this study suffered from SLD. Their characteristics are shown in the Supporting Information S1: Table 3. By gender, 73% (521/714) were male and the mean age was 53.5 years. In addition to the SLD prevalence, the cohort also had somewhat high rates of T2D (38.2%), hypertension (26.6%), and dyslipidemia (51.1%). Despite these limitations, this study revealed that SLD is upstream of the development of MetS-related diseases, independent of obesity. The fact that obesity did not remain an independent risk factor for MetS-related diseases suggests that obesity may lead to the development of MetS through SLD.

In conclusion, it is speculated that the onset of obesity-related diseases follows the sequence of obesity → SLD → MetS-related diseases (Figure 2). In this study, the contribution of SLD to each MetS-related disease was large for T2D and hypertension, and SLD contributed to the onset and new onset of the disease by the 7-year follow-up. Dyslipidemia and SLD were independent risk factors for the development of each other's disease.

TABLE 6 | Multiple logistic regression analysis of factors associated with SLD development at 7-year follow-up using baseline variables.

Parameter	Target category	Odds ratio	95% CI		*p* value
			Lower	Upper	
Age	≥ 65 years	0.19	0.02	1.75	n.s.
Sex	Female	0.44	0.18	1.07	n.s.
AST	≥ 40 U/L	0.96	0.30	2.99	n.s.
Creatinine	≥ 1.0 mg/dL	0.63	0.18	2.23	n.s.
Uric acid	> 7.0 mg/dL	1.04	0.33	3.31	n.s.
CRP	> 0.06 mg/dL	0.83	0.36	1.91	n.s.
Brinkman index	≥ 400	1.42	0.45	4.52	n.s.
Ethanol intake	≥ 30 g/day	0.71	0.27	1.84	n.s.
T2D	Presence	0.63	0.26	1.52	n.s.
Hypertension	Presence	1.08	0.34	3.46	n.s.
Dyslipidemia	Presence	1.58	0.71	3.50	n.s.
Obesity	Presence	6.79	2.97	15.52	< 0.0001

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; n.s., not significant; SLD, steatotic liver disease; T2D, type 2 diabetes.

TABLE 7 | Changes in the type of SLD and incidence of metabolic syndrome-related diseases.

SLD type	Number	T2D, *n* (%)	Hypertension, *n* (%)	Dyslipidemia, *n* (%)
SLD (+)→SLD (+)	376	203 (54)	174 (46.3)	258 (68.6)
SLD (+)→SLD (−)	59	30 (50.8)	22 (37.3)	38 (64.4)

Abbreviations: SLD, steatotic liver disease; T2D, type 2 diabetes.

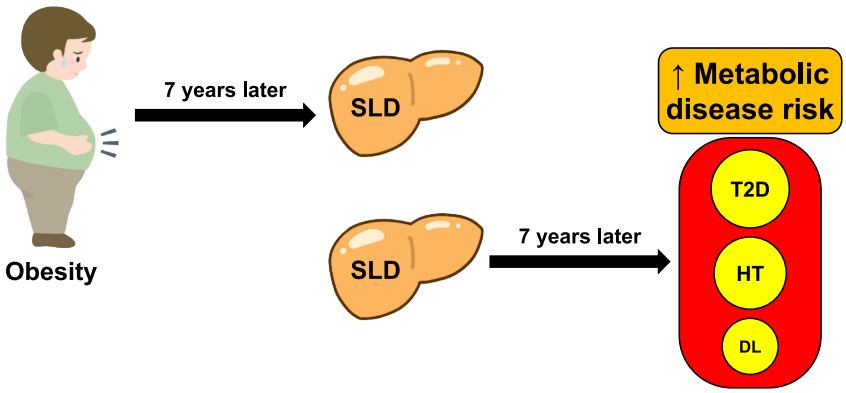

FIGURE 2 | Steatotic liver disease is an independent upstream risk factor in the development of metabolic syndrome-related diseases. Our research results suggest that the onset of obesity-related diseases may follow the order of obesity → SLD → MetS-related diseases. The contribution of SLD to each MetS-related disease was large for T2D and hypertension, and SLD contributed to the onset and new onset of the disease 7 years later. Dyslipidemia and SLD were mutually risk factors for onset. MetS, metabolic syndrome; SLD, steatotic liver disease; T2D, type 2 diabetes mellitus.

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Conflicts of Interest

Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to Boehringer Ingelheim substances as well as intellectual property considerations.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: hepr70088-sup-0001-suppl-data.docx.