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ORIGINAL ARTICLE

Hepatology Research

Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2014 to 2018 in Japan: A large-scale multicenter retrospective study

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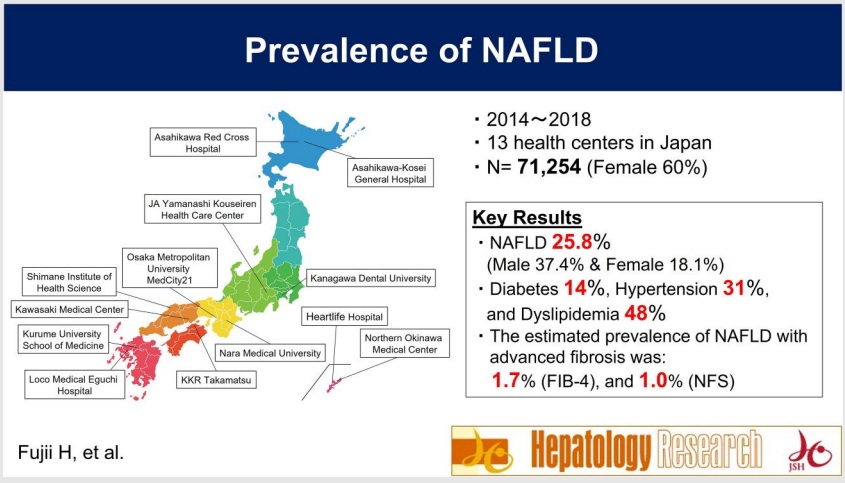
Graphical Abstract



A total of 71 254 participants from 13 health centers in Japan were analyzed, with an overall prevalence of NAFLD of 25.8%. A total of 14% of NAFLD patients had diabetes, 31% had hypertension, and 48% had dyslipidemia. The estimated prevalence of NAFLD with advanced fibrosis was 1%–2%.

Abbreviations: AAR, aspartate aminotransferase/alkaline phosphatase ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; DL, dyslipidemia; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Abstract

Aim: The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide. The aim of this study was to determine the recent prevalence and clinical characteristics of NAFLD in Japan.

Methods: This study initially included 410 061 retrospectively enrolled adults from the medical health checkup registry for metabolic syndrome, chronic kidney disease, and fatty liver in Japan (MIRACLE-J; UMIN-CTR no. UMIN000049419), who were evaluated between 2014 and 2018 at 13 health centers in Japan. Individuals consuming >20 g of alcohol/day or with chronic liver disease were excluded. Fatty liver was diagnosed by ultrasonography. The probability of NAFLD with advanced fibrosis was estimated based on the fibrosis-4 index and NAFLD fibrosis score.

Results: A total of 71 254 participants were included in the final analysis. The overall prevalence of NAFLD was 25.8%. There was a significant, twofold difference in NAFLD prevalence between men (37.4%) and women (18.1%). Nonalcoholic fatty liver disease prevalence increased linearly with body mass index, triglycerides, and low-density lipoprotein cholesterol regardless of threshold values, even in the absence of obesity. Among patients with NAFLD, 14% had diabetes mellitus, 31% had hypertension, and 48% had dyslipidemia. The estimated prevalence of NAFLD with advanced fibrosis was 1.7% and 1.0% according to the fibrosis-4 index and NAFLD fibrosis score, respectively.

Conclusions: The prevalence of NAFLD was approximately one-quarter of the general population in Japan. There was a linear relationship between NAFLD prevalence and various metabolic parameters, even in nonobese participants. The prevalence of NAFLD with advanced fibrosis was estimated to be 1%–2%.

KEYWORDS
abdominal obesity, central obesity, metabolic syndrome

INTRODUCTION

The prevalence rates of obesity and obesity-related lifestyle-related diseases are rapidly increasing, not only in Western countries, but also in Japan and worldwide.[1] Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome and is one of the largest health threats of the 21st century.[2] NAFLD is a clinical consequence of obesity and can progress to nonalcoholic steatohepatitis (NASH). NASH is characterized by histological evidence of steatosis and inflammation, with or without fibrosis, which ultimately leads to cirrhosis, hepatocellular carcinoma, or end-stage liver disease.[3–5]

Nonalcoholic fatty liver disease is rapidly becoming the most common liver disorder worldwide.[6,7] The prevalence of NAFLD globally was previously estimated to be 25%, although this increased to >30% in 2019.[6] A recent meta-analysis revealed a 27.37% (95% confidence interval [CI] 23.29–31.88) estimated pooled overall prevalence of NAFLD in Asia, diagnosed by imaging studies.[8] Furthermore, the estimated pooled overall NASH prevalence was 59% among patients with NAFLD who underwent liver biopsy,[9,10] and the global prevalence of NASH has been estimated to range from 3% to 5%.[7,9]

Recent analyses (which included adjustments for confounding factors) revealed that patients with histologically proven NASH, especially those with fibrosis, have an increased risk of adverse outcomes, such as cirrhosis and liver-related mortality.[11–15] Currently, liver biopsy remains the gold standard for assessing liver fibrosis in NAFLD. However, the need for liver biopsy when diagnosing NAFLD in the clinical setting has been gradually declining in the past decade, partly because of substantial advances in the noninvasive diagnosis of liver fibrosis and risk stratification of NAFLD.[16–19] Noninvasive approaches include primarily biological assessments (e.g. serum biomarker algorithms) or structural assessments (e.g. imaging evaluation of liver tissue stiffness),[16–18,20] and the diagnostic performance of some serum biomarkers for hepatic fibrosis has already been established. In particular, a recent meta-analysis revealed that the summary area under the receiver operating characteristics curve value for diagnosing advanced fibrosis in patients with NAFLD was 0.84 when using either the fibrosis-4 index (FIB-4) or the NAFLD fibrosis

score (NFS).[21] FIB-4 and NFS were also the most accurate predictors, with high negative predictive values (>90%) for ruling out advanced fibrosis. Additionally, both the American Association for the Study of Liver Disease and the European Association for the Study of the Liver recommend using FIB-4 and NFS clinically to rule in or rule out a high risk of advanced fibrosis in patients with NAFLD.[4,22] It may, therefore, be possible to estimate the approximate prevalence of NAFLD with advanced liver fibrosis in the general population using these predictive formulas.[2,9,23]

As more individuals in a country's population become obese, a larger proportion of the total annual national healthcare expenditure is spent on obesity and obesity-related health problems.[24,25] In 2019, the Ministry of Health, Labor, and Welfare of Japan reported that 33.0% of men and 22.3% of women were obese, with no significant change in prevalence in women over the past decade, but a significant increase in men.[26] To help control increasing national healthcare costs, it is important to accurately determine the frequency of obesity and NAFLD in the Japanese general population.

It is well known that age and sex differences exist for both the prevalence and severity of NAFLD. In 2012, Eguchi et al. used data from annual health checkups to describe in detail the prevalence of NAFLD in Japan.[27] They found a significant threefold difference in the overall prevalence of NAFLD between men (41.0%) and women (17.7%). The prevalence of NAFLD in men was >30% at all ages above the 30–39 years age group. Men had a higher prevalence than women at all ages. In women, the prevalence of NAFLD gradually increased from only 3.3% in the 20–29 years age group to 31.3% at age 70 years or older. However, this information was based on data obtained at the end of 2009–2010 from just three health checkup centers in West Japan, and included a total of approximately 5000 participants.

Therefore, the present study aimed to investigate the recent prevalence of NAFLD using real-world data from the general population in Japan, and to estimate the prevalence of NAFLD with advanced liver fibrosis using established scoring systems (FIB-4 and NFS).

METHODS

The present registry-based, multicenter, historical cohort study was approved by the institutional review board of Osaka Metropolitan University in a batch review (approval no. 2022-031, September 14, 2022), and registered in the UMIN Clinical Trials Registry (UMIN-CTR no. UMIN000049419). The requirement for informed consent was waived, because it was a retrospective observational study using only existing information. Instead, we provided an opt-out option, which was explained in the instructions posted on each hospital's website. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Data sources

We used a database from the Japan Study Group of NAFLD, called the medical health checkup registry for metabolic syndrome, chronic kidney disease, and fatty liver in Japan (MIRACLE-J) database, to obtain information regarding participants who underwent a health checkup. This database includes data from 13 health checkup centers in Japan: JA Yamanashi Koseiren Health Care Center, MedCity21, Asahikawa-Kosei General Hospital, KKR Takamatsu Hospital, Heart Life Hospital, Shimane Institute of Health Science, Saga Health and Clinical Examination Center, Nara Medical University, Japanese Red Cross Asahikawa Hospital, Kawasaki Medical Center, Kanagawa Dental University Yokohama Clinic, Loco Medical Eguchi Hospital, and Northern OKINAWA Medical Center (Appendix Figure 1). All study data were collected and managed using REDCap electronic data capture tools, hosted at Osaka Metropolitan University.[28,29]

Study cohort

For the present multicenter cross-sectional study, we retrospectively enrolled participants who underwent a health checkup between April 1, 2014 and March 31, 2018. This study initially included 410 061 participants who underwent a medical examination. We reviewed the records of all participants for missing age or health checkup date data. The exclusion criteria were as follows: (1) health checkup outside the study time period (n = 50,899), (2) age <20 years (n = 38), (3) positive serology for hepatitis B virus (HBV; n = 2196), (4) positive serology for HCV (n = 2111), (5) positive serology for both HBV and HCV (n = 26), (6) lack of serology data for HBV and/or HCV (n = 129,226), (7) lack of abdominal ultrasonography data (n = 5891), (8) second or subsequent visit (n = 117,450), (9) lack of data regarding daily alcohol intake (n = 825), and (10) daily alcohol intake >20 g (n = 30,145). After the exclusion criteria were applied, a total of 71 254 participants were analyzed (Appendix Figure 2). We excluded diseases affecting platelet counts (e.g. idiopathic thrombocytopenic purpura and essential thrombocythemia) from this study whenever possible. Before statistical analysis, the medical records were reviewed for data inconsistencies regarding the use of medications for diabetes mellitus (DM), hypertension, and dyslipidemia, as well as inconsistencies regarding smoking status (between the history and the number of cigarettes/day). Cases with missing values were excluded from the analysis.

Physical examination and serum biochemistry

Bodyweight and height were obtained, and body mass index (BMI) was calculated. Waist circumference was measured at the umbilical level. Venous blood samples were obtained from all participants following a >12-h overnight fast, and the following were measured using standard techniques: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl

transpeptidase, cholinesterase, albumin, platelet count, fasting plasma glucose (FPG), hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Diabetes mellitus was defined as an FPG ≥126 mg/dL, a hemoglobin A1c ≥ 6.5%, or ongoing treatment for DM.[30] Similarly, a systolic blood pressure ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or ongoing treatment for hypertension was defined as hypertension.[31] A serum total cholesterol level ≥220 mg/dL, a HDL-C level <40 mg/dL, a TG level ≥150 mg/dL, or ongoing treatment for dyslipidemia was defined as dyslipidemia.[32]

Alcohol intake screening

Daily alcohol consumption was calculated in grams using our modified template.[33] 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.

Abdominal ultrasonography and assessment of liver disease severity

Fatty liver was diagnosed via abdominal ultrasonography, which was performed at each health checkup center by experienced medical sonographers. Hepatic steatosis was semiquantified according to the criteria described by Hamaguchi, based on the presence of hepatorenal contrast, bright hepatic echoes, deep attenuation, and vessel blurring.[34]

The severity of liver fibrosis was assessed using two noninvasive scoring systems in participants with fatty liver: NFS and FIB-4. The NFS was calculated using the following formula based on Angulo's report: −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired glucose tolerance or DM (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/L) − 0.66 × serum albumin (g/dL).[35] In Angulo's original NFS article, diabetes was defined as a fasting blood glucose level of ≥126 mg/dL or taking antidiabetic medication. In the present study, we added to this definition the condition of hemoglobin A1c ≥6.5%. FIB-4 was calculated as follows: [age (years) × AST (U/L)] / [platelet count (×10^9/L) × ALT (U/L)$^{1/2}$].[36] The probability of advanced fibrosis was classified as low (FIB-4 ≤1.3 or NFS < −1.455), intermediate (FIB-4 >1.3 but <2.67 or NFS ≥ −1.455 but ≤0.676), or high (FIB-4 ≥2.67 or NFS >0.676).[35,37]

Statistical analysis

Descriptive statistics (mean [SD] or number [%]) were calculated for all variables. Differences between the two groups were compared using the Mann–Whitney *U*-test or χ^2-test. Logistic regression models adjusting for confounding factors (participant characteristics) were used for multivariate analysis, with NAFLD as the outcome. We selected the same explanatory variables as those used by Eguchi et al.[27] *p*-values < 0.05 were considered indicative of statistical significance. Statistical analyses were conducted using JMP 16.1.0 (SAS Institute, Cary, NC, USA).

RESULTS

Participant characteristics and the prevalence of nonalcoholic fatty liver disease

The clinical and biochemical characteristics of the 71 254 study participants are summarized in Tables 1 and 2. Four health checkup centers (*n* = 37,943) were located in east Japan, and nine (*n* = 33,311) were located in west Japan (Appendix Figure 1). The participants were predominantly middle-aged, with a mean (SD) age of 53.5 (12.3) years (range 20–94 years), and 60.1% were women. The mean BMI (SD) of the entire cohort was 22.8 (3.6) kg/m^2, with 22.6% of participants meeting the criteria for obesity (BMI ≥25 kg/m^2).

A total of 18 391 participants (25.8%) had evidence of NAFLD on ultrasonography. The mean age was significantly higher in participants with NAFLD than in those without NAFLD (54.6 [11.1] years vs. 53.1 [12.7] years, $p < 0.001$). The prevalence of NAFLD was approximately twofold higher in men (37.4%) than in women (18.1%) ($p < 0.001$). The prevalence of NAFLD in men was >20% in all age groups, and was greater than the prevalence in women of all ages. In women, the prevalence of NAFLD gradually increased from only 6.3% in the 20–29 years age group to 24.8% in the 60–69 years age group (Figure 1). The frequency of NAFLD was 23.1% in east Japan and 28.9% in west Japan ($p < 0.001$; Appendix Figure 1). Among the patients with NAFLD, 14% had DM, 31% had hypertension, and 48% had dyslipidemia (Table 1).

All clinical factors differed significantly between men and women with NAFLD, except the presence of dyslipidemia (Table 2). Multivariate logistic regression revealed several factors independently associated with the development of NAFLD in both men and women, although an elevated gamma-glutamyl transpeptidase was not a significant factor in women (Table 3).

Relationship between anthropometric and biochemical features and the presence of NAFLD

Body mass index was significantly higher in participants with NAFLD than in those without NAFLD ($p < 0.001$; Table 1). The prevalence of NAFLD increased linearly with increasing BMI (BMI <23 kg/m^2, 8.9%; BMI ≥23 kg/m^2 but <25 kg/m^2, 34.0%; BMI ≥25 kg/m^2 but <28 kg/m^2, 55.3%; and BMI ≥28 kg/m^2, 76.7%). The prevalence of NAFLD was 15.0% in nonobese participants (BMI <25 kg/m^2), 59.0% in obese

TABLE 1 Characteristics of all participants.

Variables	All *N* = 71 254	Non-NAFLD *n* = 52 863	NAFLD *n* = 18 391	*p*-value
Sex (male/female)	28,463/42,791	17,831/35,032	10,632/7759	<0.001
Age (years)	53.5 (12.3)	53.1 (12.7)	54.6 (11.1)	<0.001
Height (m)	1.61 (0.09)	1.61 (0.09)	1.63 (0.09)	<0.001
Bodyweight (kg)	59.6 (12.3)	56.2 (9.9)	69.5 (12.9)	<0.001
BMI (kg/m^2)	22.8 (3.6)	21.6 (2.9)	25.9 (3.7)	<0.001
WC (cm)	81.3 (9.8)	78.4 (8.3)	89.6 (9.1)	<0.001
DM (%)†	4932 (7)	2319 (5)	2613 (14)	<0.001
HT (%)†	13,832 (20)	8142 (16)	5690 (31)	<0.001
DL (%)†	21,156 (31)	12,562 (25)	8594 (48)	<0.001
AST (U/L)	21.6 (9.0)	20.4 (7.6)	25.1 (11.5)	<0.001
ALT (U/L)	21.3 (15.7)	17.7 (10.8)	31.8 (21.7)	<0.001
AAR	1.18 (0.41)	1.28 (0.40)	0.91 (0.03)	<0.001
ALP (U/L)	205 (63.7)	199.9 (62.9)	220 (63.5)	<0.001
GGT (U/L)	28.2 (31.2)	24.1 (27.2)	40.1 (38.1)	<0.001
ChE (U/L)	333.4 (73.4)	319.4 (70.8)	373.1 (65.8)	<0.001
Albumin (g/dL)	4.4 (0.3)	4.3 (0.3)	4.4 (0.3)	<0.001
Platelet count ($\times 10^9$/L)	232 (55.2)	229 (54.7)	239 (55.9)	<0.001
FPG (mg/dL)	98.1 (16.7)	95.5 (13.4)	105.5 (22.2)	<0.001
HbA1c (%)	5.7 (0.6)	5.6 (0.4)	5.9 (0.8)	<0.001
TC (mg/dL)	203.2 (33.7)	201.9 (33.3)	206.9 (34.6)	<0.001
TG (mg/dL)	97.7 (64.4)	83.7 (46.0)	137.9 (88.3)	<0.001
HDL-C (mg/dL)	61.6 (15.5)	64.6 (15.3)	52.9 (12.6)	<0.001
LDL-C (mg/dL)	122.2 (29.9)	119.3 (29.0)	130.6 (30.9)	<0.001

Note: Values are expressed as mean (standard deviation) or †number (%). Statistical analysis was conducted using the Mann–Whitney *U*-test or χ^2-test.
Abbreviations: AAR, aspartate aminotransferase/alanine aminotransferase ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; DL, dyslipidemia; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

participants (BMI ≥25 kg/m^2 but <30 kg/m^2), and 81.3% in morbidly obese participants (BMI ≥30 kg/m^2). A linear increase in NAFLD with increasing BMI was seen in both men and women (Figure 2).

In men, the prevalence of obesity was >20% in all age groups (Appendix Figure 3), and was higher than the prevalence in women at all ages. In women, the prevalence of obesity gradually increased from 8.5% in the 20–29 years age group to 20.0% in the 70 years and older age group (Appendix Figure 3).

Serum LDL-C, TG, FPG, and all liver function tests and enzymes (including AST and ALT) were significantly higher in participants with NAFLD than in those without NAFLD ($p < 0.001$; Tables 1 and 2). Conversely, serum HDL-C was significantly lower in participants with NAFLD than in those without NAFLD ($p < 0.001$; Tables 1 and 2). Nonalcoholic fatty liver disease prevalence increased linearly with increasing serum TG, total cholesterol, and LDL-C (Figure 3a, b, d), and decreased linearly with increasing serum HDL-C (Figure 3c). The prevalence of NAFLD was 20.5% in participants with a normal TG (<150 mg/dL), and 60.8% in those with hypertriglyceridemia (TG ≥150 mg/dL). The prevalence of NAFLD was 23.5% in participants with a normal HDL-C (≥40 mg/dL), and 59.1% in those with a low HDL-C (<40 mg/dL). The prevalence of NAFLD was 22.3% in participants with a normal LDL-C (<140 mg/dL), and 35.7% in those with an elevated LDL-C (≥140 mg/dL). Nonalcoholic fatty liver disease prevalence increased linearly as FPG increased up to an FPG of 140 mg/dL, after which the prevalence plateaued, especially in men (Figure 3e). The prevalence of NAFLD was 22.3% in participants with a normal FPG, 50.3% in participants with impaired glucose tolerance (FPG >110 mg/dL but <126 mg/dL), and 60.6% in participants with an elevated FPG (≥126 mg/dL). Nonalcoholic fatty liver disease prevalence gradually increased with increasing ALT. In men, the prevalence of NAFLD was 25.5% in those with a normal ALT (<30 U/L), and 69.4% in those with an elevated ALT (≥30 U/L). In women, the

TABLE 2 Characteristics of all participants according to sex.

Variables	Males			Females			
	Non-NAFLD $n = 17\,831$	NAFLD $n = 10\,632$	p-value[a]	Non-NAFLD $n = 35\,032$	NAFLD $n = 7759$	p-value[a]	p-value[b]
Age (years)	53.7 (13.4)	52.9 (11.2)	0.002	52.8 (12.3)	56.9 (10.5)	<0.001	<0.001
Ht (m)	1.69 (0.64)	1.69 (0.62)	<0.001	1.56 (0.59)	1.55 (0.58)	<0.001	<0.001
BW (kg)	64.5 (8.9)	74.8 (11.7)	<0.001	51.9 (7.5)	62.2 (10.7)	<0.001	<0.001
BMI (kg/m^2)	22.5 (2.7)	26.0 (3.5)	<0.001	21.2 (2.8)	25.8 (4.0)	<0.001	<0.001
WC (cm)	81.3 (7.8)	90.5 (8.9)	<0.001	77.0 (8.1)	88.5 (9.3)	<0.001	<0.001
DM (%)[†]	1324 (8)	1628 (16)	<0.001	995 (3)	985 (13)	<0.001	<0.001
HT (%)[†]	3366 (20)	3225 (31)	<0.001	4776 (14)	2465 (32)	<0.001	0.039
DL (%)[†]	4625 (27)	5011 (48)	<0.001	7937 (23)	3583 (47)	<0.001	0.178
AST (U/L)	21.5 (9.7)	26.1 (11.8)	<0.001	19.9 (6.2)	23.7 (10.9)	<0.001	<0.001
ALT (U/L)	21.1 (13.9)	36.1 (23.8)	<0.001	15.9 (8.4)	25.9 (16.7)	<0.001	<0.001
AAR	1.13 (0.41)	0.83 (0.27)	<0.001	1.35 (0.37)	1.03 (0.34)	<0.001	<0.001
ALP (U/L)	210.5 (61.7)	216 (60.0)	<0.001	194.5 (62.9)	225 (67.7)	<0.001	<0.001
GGT (U/L)	31.6 (37.0)	46.5 (41.3)	<0.001	20.2 (19.4)	31.4 (31.3)	<0.001	<0.001
ChE (U/L)	332.6 (66.4)	375.6 (65.9)	<0.001	312.6 (71.9)	369.6 (65.7)	<0.001	<0.001
Albumin (g/dL)	4.4 (0.3)	4.5 (0.3)	<0.001	4.3 (0.3)	4.3 (0.3)	<0.001	<0.001
Platelet count ($\times 10^9$/L)	220 (51.4)	230 (51.2)	<0.001	238 (55.6)	252 (59.7)	<0.001	<0.001
FPG (mg/dL)	99.2 (16.5)	106.9 (23.8)	<0.001	93.6 (11.0)	103.5 (19.6)	<0.001	<0.001
HbA1c (%)	5.6 (0.5)	5.9 (0.8)	<0.001	5.6 (0.4)	5.9 (0.7)	<0.001	<0.001
TC (mg/dL)	196.4 (31.5)	202.9 (34.2)	<0.001	204.8 (33.8)	212.5 (34.5)	<0.001	<0.001
TG (mg/dL)	98.5 (56.3)	149.5 (96.8)	<0.001	76.2 (37.7)	122.1 (72.1)	<0.001	<0.001
HDL-C (mg/dL)	57.0 (13.6)	48.9 (10.8)	<0.001	68.5 (14.6)	58.2 (12.9)	<0.001	<0.001
LDL-C (mg/dL)	120.8 (28.7)	129.8 (30.5)	<0.001	118.6 (29.2)	131.8 (31.5)	<0.001	<0.001

Note: Values are expressed as mean (standard deviation) or [†]number (%). Statistical analysis was conducted using the Mann–Whitney *U*-test or χ^2-test.

Abbreviations: AAR, aspartate aminotransferase/alanine aminotransferase ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; DL, dyslipidemia; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

[a]*p*-value for non-NAFLD versus NAFLD within each sex.

[b]*p*-value for males versus females with NAFLD.

prevalence of NAFLD was 10.6% in those with a normal ALT (<20 U/L), and 39.3% in those with an elevated ALT (≥20 U/L; Figure 3f).

Prevalence of advanced fibrosis in the general population and participants with NAFLD predicted by established scoring systems

We estimated the prevalence of advanced fibrosis using FIB-4 and NFS. The mean FIB-4 score was 1.23 (0.66) in the whole cohort, 1.26 (0.68) in participants without NAFLD, and 1.14 (0.56) in participants with NAFLD. The estimated prevalence of advanced fibrosis according to FIB-4 was 2.7% (FIB-4 cutoff value, ≥2.67) in the whole cohort, and 1.7% in participants with NAFLD. In contrast, the estimated prevalence of no advanced fibrosis was 69.5% (FIB-4 cutoff value, ≤1.30) in participants with NAFLD (Table 4).

The mean NFS was −2.19 (1.15) in the whole cohort, −2.20 (1.13) in participants without NAFLD, and −2.16 (1.18) in those with NAFLD. The estimated prevalence of advanced fibrosis according to NFS was 1.0% (NFS cutoff value, >0.676) in the whole cohort, and 1.0% in participants with NAFLD. In contrast, the estimated prevalence of no advanced fibrosis was 73.3% (NFS cutoff value, <−1.455) in participants with NAFLD (Table 4b). Furthermore, we examined the clinical characteristics of the advanced fibrosis group of NAFLD (Table 5). In both the high FIB-4 and high NFS groups, NAFLD had a significantly higher BMI, and a higher rate of hypertension and dyslipidemia compared with non-NAFLD. In addition, TG was significantly higher, whereas HDL-C was significantly lower in NAFLD than

non-NAFLD. Finally, we examined the role of HDL-C in the development of liver fibrosis in patients with NAFLD. When the cutoff was set at 40 mg/dL of HDL-C, the low HDL-C group had a significantly higher proportion of men, significantly lower albumin and platelet counts, and significantly higher NFS than the high HDL-C group (Table 6).

Discussion

This study provides updated information regarding the estimated prevalence and clinical characteristics of NAFLD in Japan using recent large-scale real-world data. Our findings revealed the following: (1) the overall prevalence of NAFLD was 25.8%; (2) there was a significant twofold difference in NAFLD prevalence between men (37.4%) and women (18.1%); (3) among individuals with NAFLD, 14% had DM, 31% had hypertension, and 48% had dyslipidemia; and (4) the prevalence of NAFLD with advanced fibrosis was 1.7% based on FIB-4 and 1.0% based on NFS.

FIGURE 1 Prevalence of nonalcoholic fatty liver disease according to age.

Our data showed a slightly lower prevalence of NAFLD overall and according to sex than the rates reported by Eguchi et al.[27] There are two possible reasons for these discrepancies. First, the male-to-female ratio of participants was 1:2.5 in our study, whereas it was approximately 1:1.4 in the study by Eguchi et al.[27] Because NAFLD is generally more frequent in men than in women,[38] the higher proportion of women in our cohort likely contributed to our lower overall frequency of NAFLD. Second, regional differences in the frequency of NAFLD may be responsible. In our study, 41.0% of men and 20.1% of women in west Japan had NAFLD, whereas the prevalence of NAFLD was significantly lower in east Japan for both men (33.8%) and women (16.5%). Ikeda et al. examined cross-sectional data of 233 988 men and 261 086 women aged 20–79 years from 44 annual National Health and Nutrition Surveys conducted between 1975 and 2018 in Japan.[39] They found variations in mean BMI across prefectures, as well as changes in the geographic distributions of BMI over time. The increase in mean BMI over time was most prominent among men in less-populated prefectures in the northeast and southwest rural regions.[39] A recent meta-analysis also reported that the overall prevalence of NAFLD in Japan was 25.5%, but exhibited significant regional variation.[40] Most recently, a large, long-term single-center examination of 416 066 participants in Japan revealed that the incidence of NAFLD increased significantly from the 1990s (21.3% in 1990–2000) to the 2000s (38.3% in 2000–2010), but did not change significantly during the 2010s (36.2% in 2011–2019).[41] Our data are consistent with the results of these previous studies.

TABLE 3 Clinical factors associated with nonalcoholic fatty liver disease in males and females on multivariate logistic regression analysis.

	Males			Females		
Factors	**Odds ratio**	**95% CI**	***p*-value**	**Odds ratio**	**95% CI**	***p*-value**
BMI >25 kg/m^2	4.21	3.96–4.48	<0.001	6.68	6.26–7.12	<0.001
Age >50 years	1.35	1.27–1.44	<0.001	1.78	1.66–1.90	<0.001
Elevated ALT[a]	2.50	2.31–2.70	<0.001	2.01	1.85–2.17	<0.001
AAR <1	2.60	2.43–2.78	<0.001	2.86	2.63–3.10	<0.001
FPG >110 mg/dL	1.79	1.65–1.93	<0.001	2.53	2.30–2.78	<0.001
TG >150 mg/dL	2.25	2.09–2.42	<0.001	3.55	3.24–3.89	<0.001
GGT >35 U/L	1.22	1.14–1.31	<0.001	1.01	0.92–1.10	0.91
HDL-C <40 mg/dL	1.55	1.41–1.70	<0.001	1.87	1.53–2.28	<0.001
LDL-C >140 mg/dL	1.31	1.22–1.39	<0.001	1.49	1.39–1.59	<0.001

Abbreviations: AAR, aspartate aminotransferase/alanine aminotransferase ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TG, triglycerides.

[a]ALT (males: >30 U/L; females: >20 U/L).

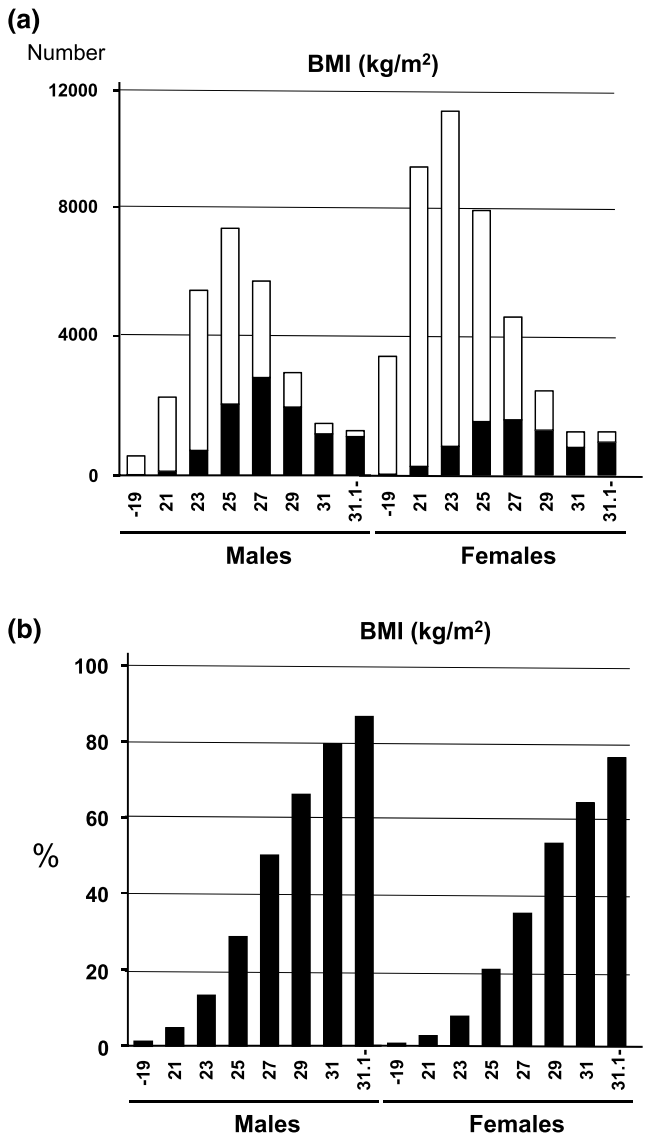


FIGURE 2 (a) Distribution of males and females with nonalcoholic fatty liver disease (black columns) and without nonalcoholic fatty liver disease (white columns) according to body mass index (BMI) (b) Relative percentage of nonalcoholic fatty liver disease in males and females according to BMI.

Currently, lean NAFLD (i.e. NAFLD in lean individuals) is defined as hepatic steatosis in patients with a BMI <25 kg/m^2 (<23 kg/m^2 in Asians) and no "significant" alcohol intake.[42] The definition of metabolic dysfunction-associated fatty liver disease proposed in 2020 also defines overweight or obesity as a BMI ≥25 kg/m^2 for white people and ≥23 kg/m^2 for Asians.[43] Our data showed that similar to the report by Eguchi et al.,[27] the prevalence of NAFLD increased linearly, even when BMI was within the normal range.

Similar to the study by Eguchi et al., we also confirmed previous findings that various traditional metabolic parameters and aminotransferases may be normal in an appreciable proportion of patients with NAFLD, and are thus not sensitive enough to diagnose NAFLD. The fatty liver index (FLI) is a steatosis score[44] consisting of four factors: BMI, waist circumference, serum TG, and serum gamma-glutamyl transpeptidase.[45] In a study of 618 patients with NAFLD, FLI exhibited good diagnostic performance, with an area under the receiver operating characteristics curve of 0.792 using a cutoff value of 27.[46] However, FLI and various other scoring systems for steatosis include anthropometric factors, such as BMI and waist circumference, and therefore cannot be calculated using only laboratory data.

Compared with FLI, FIB-4 may be more attractive to general practitioners, because it is based on widely available, simple parameters (age, transaminases, and platelet count).[17–19] In a study based on data from four European primary-care databases, the frequency of being high-risk for advanced liver fibrosis (i.e. FIB-4 >2.67) ranged from 2.9% to 10% in patients with NAFLD.[47] Similarly, Sugiyama et al. reported a 1.6% frequency of being at high risk for advanced liver fibrosis (according to FIB-4 values) in 17 968 patients with NAFLD.[48] Our percentage of 1.7% is consistent with this result. Of note, Sugiyama et al. found that a high FIB-4 was more common in the elderly, highlighting the need to consider age when using this scoring system in individuals undergoing ultrasound examinations during their health checkups.[48]

Although NFS can be used as a first-line tool in primary healthcare settings to identify patients without advanced fibrosis who require no further assessment,[16,18,19] some parameters (albumin and impaired glucose tolerance/DM) were not frequently measured in the health checkups. Reports based on NFS values among health checkup participants tend to be less frequent than reports based on FIB-4. Using NFS data, Kim et al. reported that of 11 154 participants, 34.0% had NAFLD and 3.2% of NAFLD patients fell into the high-risk group.[49] In the study of 43 166 generally healthy individuals in Korea, Chang et al. found that 438 (1.0%) had an intermediate or high risk of advanced fibrosis based on NFS.[50] Recently, Nagaoki et al. reported that liver stiffness measurement found cirrhosis in 1.0%, and severe fibrosis in 1.8%.[51] In our data, 1.0% of all participants had a high risk of advanced fibrosis according to NFS, with no difference in percentage between patients with or without NAFLD (Table 4).

We aimed to validate the study by Eguchi et al.[27] using data from a large number of health checkup participants, and as Eguchi et al. focused on lipids and blood glucose in particular, we also focused on these in the present analysis. We also determined the clinical importance of LDL-C, TG, and FPG in the diagnosis of NAFLD in a logistic regression analysis with NAFLD as the outcome in men and women. All of these factors were statistically independent risk factors for NAFLD, although there were sex differences (Table 3).

Eguchi et al. reported that the prevalence of NAFLD was 70.6% and 35.8% in participants with abnormal ALT levels in men (ALT ≥30 U/L) and women (ALT ≥20 U/L).[27] Also, in a study of biopsy-confirmed NAFLD, Yoneda et al. reported that ALT ≥40 U/L was found in 867 of 1102 patients (78.7%).[52] The proportion of ALT abnormalities in the different populations did not differ so much. Although the proportion of patients with severe NAFLD varies by population, the proportion of patients with abnormal ALT is not likely to change because: (1) the upper limit of normal liver function is low, and (2) AST and ALT decline with fibrosis progression, but the decline in ALT is mild compared with AST.

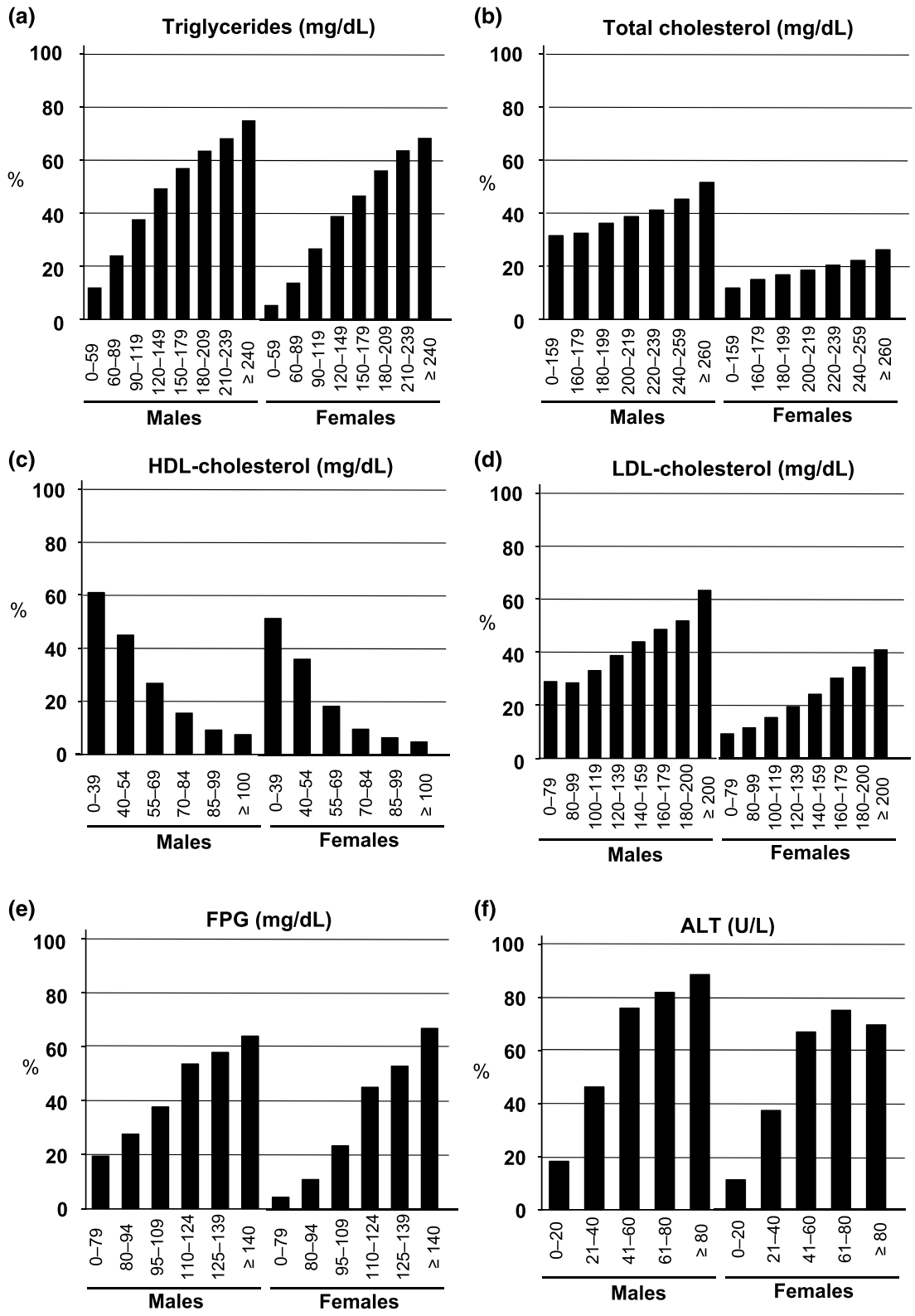


FIGURE 3 Prevalence of nonalcoholic fatty liver disease in males and females according to laboratory test parameters. (a) Triglycerides, (b) total cholesterol, (c) high-density lipoprotein (HDL) cholesterol, (d) low-density lipoprotein (LDL) cholesterol, (e) fasting plasma glucose (FPG), and (f) alanine aminotransferase (ALT).

Recently, we examined the role of HDL-C in liver fibrosis progression using a liver biopsy-confirmed NAFLD cohort (n = 1204).[53] Patients with an HDL-C level <40 mg/dL were significantly younger, men, and had higher BMI, with a greater occurrence of DM, advanced fibrosis, and NASH diagnoses than patients with an HDL-C level ≥40 mg/dL. Also, in univariate analysis, an HDL-C level <40 mg/dL

TABLE 4 Distribution of participants according to fibrosis-4 index and distribution of participants according to the nonalcoholic fatty liver disease fibrosis score.

	FIB-4			
	≤1.3	>1.3 but <2.67	≥2.67	Total
Non-NAFLD	32 506 (62.1)	18 233 (34.8)	1622 (3.1)	52 361 (100)
NAFLD	12 673 (69.5)	5252 (28.8)	307 (1.7)	18 232 (100)
Total	45 179 (64.0)	23 485 (33.3)	1919 (2.7)	70 593 (100)
	NAFLD fibrosis score			
	<−1.455	≥−1.455 but ≤0.676	>0.676	Total
Non-NAFLD	36 570 (75.7)	11 276 (23.4)	451 (0.9)	48 297 (100)
NAFLD	12 212 (73.3)	4284 (25.7)	175 (1.0)	16 671 (100)
Total	48 782 (75.1)	15 560 (23.9)	626 (1.0)	64 968 (100)

Note: Values are expressed as number (percentage).

Abbreviations: FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease.

TABLE 5 Differences in clinical characteristics with and without nonalcoholic fatty liver disease in the advanced fibrosis group.

FIB-4 ≥2.67	Non-NAFLD $n = 1622$	NAFLD $n = 307$	p-value	NFS >0.676	Non-NAFLD $n = 451$	NAFLD $n = 175$	p-value
Sex (male, %)	815 (50)	168 (55)	0.153	Sex (male, %)	273 (61)	102 (58)	0.64
Age (years)	71.1 (9.5)	68.6 (8.3)	<0.001	Age (years)	73.9 (8.7)	68.9 (8.8)	<0.001
BMI (kg/m^2)	21.6 (3.1)	26.1 (3.6)	<0.001	BMI (kg/m^2)	23.9 (4.1)	29.2 (6.1)	<0.001
WC (cm)	79.1 (9.0)	90.6 (9.6)	<0.001	WC (cm)	85.6 (10.4)	97.8 (13.6)	<0.001
DM (%)†	203 (13)	103 (34)	<0.001	DM (%)	292 (65)	155 (89)	<0.001
HT (%)†	622 (40)	157 (51)	<0.001	HT (%)	255 (57)	108 (62)	0.28
DL (%)†	518 (34)	159 (52)	<0.001	DL (%)	186 (41)	104 (59)	<0.001
AST (U/L)	30.1 (26.4)	48.1 (31.8)	<0.001	AST (U/L)	25.2 (12.1)	28.2 (14.1)	0.008
ALT (U/L)	21.5 (32.5)	46.5 (40.3)	<0.001	ALT (U/L)	16.2 (10.9)	25.7 (16.8)	<0.001
Albumin (g/dL)	4.19 (0.29)	4.31 (0.28)	<0.001	Albumin (g/dL)	4.05 (0.34)	4.13 (0.26)	0.013
Platelet count (×10^9/L)	144 (38.4)	151 (40.6)	0.004	Platelet count (×10^9/L)	154 (41.7)	157 (40.0)	0.33
FPG (mg/dL)	99.4 (16.7)	115 (30.1)	<0.001	FPG (mg/dL)	114 (25.4)	133 (34.9)	<0.001
HbA1c (%)	5.79 (0.52)	6.40 (1.11)	<0.001	HbA1c (%)	6.27 (0.73)	7.15 (1.39)	<0.001
TC (mg/dL)	195 (33.4)	191 (32.7)	0.04	TC (mg/dL)	184 (32.7)	186 (33.8)	0.46
TG (mg/dL)	82.1 (41.5)	125 (70.1)	<0.001	TG (mg/dL)	89.5 (51.1)	115 (60.4)	<0.001
HDL-C (mg/dL)	62.9 (16.4)	51.8 (12.4)	<0.001	HDL-C (mg/dL)	57.6 (15.3)	52.0 (12.8)	<0.001
LDL-C (mg/dL)	115 (28.5)	113 (29.4)	0.39	LDL-C (mg/dL)	108 (28.6)	111 (30.3)	0.30

Note: Values are expressed as mean (standard deviation) or †number (%). Statistical analysis was conducted using the Mann–Whitney *U*-test or χ^2-test.

Abbreviations: AAR, aspartate aminotransferase/alanine aminotransferase ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; DL, dyslipidemia; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

was significantly associated with advanced fibrosis (hazard ratio 1.69, 95% CI 1.20–2.38; $p < 0.003$).[53] In the health checkup cohort, we newly showed that HDL-C was significantly lower in the advanced fibrosis group than in the non-advanced fibrosis group, and that liver fibrosis progressed significantly in the group with low HDL-C in the patients with NAFLD.

Several limitations must be considered when interpreting our results. First, this was a retrospective cross-sectional study, so causal relationships are unknown. Future longitudinal, prospective studies are required to verify the accuracy of our conclusions. Second, selection bias is a major potential limitation. Most participants were healthy enough to be employed (in contrast to the

TABLE 6 Differences in clinical background of nonalcoholic fatty liver disease patients by high-density lipoprotein cholesterol.

	HDL-C (mg/dL)		
NAFLD	≥40 $n = 16\,071$	<40 $n = 2320$	*p*-value
Sex, male (%)	8665 (54)	1966 (85)	<0.001
Age (years)	54.9 (11.0)	52.8 (11.5)	<0.001
BMI (kg/m^2)	25.8 (3.7)	26.9 (3.8)	<0.001
WC (cm)	89.3 (9.1)	92.3 (9.3)	<0.001
DM (%)†	2182 (14)	431 (19)	<0.001
HT (%)†	4940 (31)	749 (33)	0.135
DL (%)†	7221 (46)	1373 (60)	<0.001
AST (U/L)	24.9 (11.2)	26.9 (12.9)	<0.001
ALT (U/L)	30.9 (20.8)	38.5 (25.9)	<0.001
Albumin (g/dL)	4.40 (0.27)	4.38 (0.27)	<0.001
Platelet count ($\times 10^9$/L)	240 (55.7)	233 (57.8)	<0.001
FPG (mg/dL)	105 (21.3)	109 (27.4)	<0.001
HbA1c (%)	5.96 (0.75)	6.10 (0.99)	<0.001
TC (mg/dL)	209 (33.9)	194 (37.4)	<0.001
TG (mg/dL)	127 (66.2)	212 (158)	<0.001
HDL-C (mg/dL)	55.3 (11.5)	35.8 (3.0)	<0.001
LDL-C (mg/dL)	128 (30.6)	116 (35.4)	<0.001
FIB-4	1.15 (0.55)	1.11 (0.61)	0.009
NFS	−2.17 (1.17)	−2.11 (1.25)	0.024

Note: Values are expressed as mean (standard deviation) or †number (%). Statistical analysis was conducted using the Mann–Whitney *U*-test or χ^2-test.

Abbreviations: AAR, aspartate aminotransferase/alanine aminotransferase ratio; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; DL, dyslipidemia; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

general population), and were also sufficiently conscientious about their health to voluntarily undergo health checkups.[54] The results of this study may not apply to individuals who are not generally healthy. Third, details regarding the duration of alcohol intake were not available. Fourth, details regarding the preferred alcoholic beverages, such as wine, beer, or other kinds of liquor, were not available for analysis. Further studies in a heterogeneous population (with respect to factors such as age, sex, race, background, ethnicity, drinking habits, preferred alcoholic beverages, kidney disease, and gastrointestinal disease) are required to validate our findings. Fifth, we do not have data on how many of our participants are foreign races.

In conclusion, the prevalence of NAFLD was approximately one-quarter of the general population in Japan, and 14% of patients with NAFLD had DM. There was a linear relationship between the prevalence of NAFLD and various metabolic parameters, even in non-obese participants. The estimated prevalence of NAFLD with advanced fibrosis was 1%–2% in our cohort.

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CONFLICT OF INTEREST STATEMENT

Hideki Fujii received an analysis cost from the Japan Strategic Medical Administration Research Center (J-SMARC). Associate Editors Takumi Kawaguchi and Miwa Kawanaka are Editorial Board members of *Hepatology Research*, and co-authors of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. Hitoshi Yoshiji is Editor-in-Chief of the journal and a co-author of this article. They were excluded from the peer-review process, and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by the Editor-in-Chief, who is in charge of this manuscript, to minimize bias.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENTS

Approval of the research protocol by an Institutional Reviewer Board: N/A.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Research involving recombinant DNA: N/A.

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