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ORIGINAL ARTICLE

The epidemiology of NAFLD and lean NAFLD in Japan: a meta-analysis with individual and forecasting analysis, 1995–2040

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Abstract

Background NAFLD is increasing in Asia including Japan, despite its lower obesity rate than the West. However, NAFLD can occur in lean people, but data are limited. We aimed to investigate the epidemiology of NAFLD in Japan with a focus on lean NAFLD.

Methods We searched PubMed, Cochrane Library, EMBASE, Web of Science, and the Japan Medical Abstracts Society (inception to 5/15/2019) and included 73 eligible full-text original research studies ($n = 258{,}531$). We used random-effects model for pooled estimates, Bayesian modeling for trend and forecasting, contacted authors for individual patient data and analyzed 14,887 (7752 NAFLD; 7135 non-NAFLD—8 studies) patients.

Results The overall NAFLD prevalence was 25.5%, higher in males ($p < 0.001$), varied by regions ($p < 0.001$), and increased over time ($p = 0.015$), but not by per-person income or gross prefectural productivity, which increased by 0.64% per year (1983–2012) and is forecasted to reach 39.3% in 2030 and 44.8% in 2040. The incidence of NAFLD, HCC, and overall mortality were 23.5, 7.6 and 5.9 per 1000 person-years, respectively. Individual patient-level data showed a lean NAFLD prevalence of 20.7% among the NAFLD population, with lean NAFLD persons being older and with a higher all-cause mortality rate (8.3 vs. 5.6 per 1000 person-years for non-lean NAFLD, $p = 0.02$). Older age, male sex, diabetes, and FIB-4 were independent predictors of mortality, but not lean NAFLD.

Conclusion NAFLD prevalence has increased in Japan and may affect half of the population by 2040. Lean NAFLD individuals makeup 20% of the NAFLD population, were older, and had higher mortality.

Keywords Fatty liver · Nonalcoholic steatohepatitis · Fibrosis · Prognosis · Hepatocellular carcinoma · Systematic review · Body Mass Index · FIB-4 Index · Metabolic syndrome · Japanese

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
DM	Diabetes mellitus
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
CDS	Collaboration with a medical librarian
FLI	Fatty Liver Index
HIV	Human immunodeficiency virus
QA	Quality assessment
BMI	Body Mass Index
GPP	Gross prefecture product
CI	Confidence interval
OR	Odds ratios
HR	Hazard ratio
HCC	Hepatocellular carcinoma
US	Ultrasonography
FIB-4	Fibrosis-4
PNPLA3	Patatin-like phospholipase domain containing 3
SNPs	Single nucleotide polymorphisms
NAFL	Non-alcoholic fatty liver
NASH	Non-alcoholic steatohepatitis
FPG	Fasting plasma glucose
FBG	Fasting blood glucose

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FBS	Fasting blood sugar
HBA1C	Hemoglobin A1C
AST	Aspartate aminotransferase
ALT	Alanine transaminase
GGT	Gamma glutamyl transferase
HOMA-IR	Homeostatic model assessment of insulin resistance

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common liver disease [1], with increasing incidence as the prevalence of obesity and diabetes mellitus (DM) rises worldwide [2]. NAFLD can also occur in normal-weight people; and importantly, nonobese NAFLD may comprise approximately 40% of the NAFLD population according to a recent systematic review and meta-analysis, which also confirmed that data on characteristics and clinical outcomes of nonobese or lean NAFLD were very limited [3]. In another recent review of the epidemiology of NAFLD in Asia, the prevalence of NAFLD in most countries/regions of Asia were fairly similar to those of the West except for Japan which was unique in having a much lower prevalence [4]. The people of Japan are also known to enjoy some of the highest life expectancy in the world [5]; and despite having the third-largest economy in the world by single-country gross domestic product [6], the Japanese diet is generally lower in fat and animal protein than diets in most other high-income areas [7, 8]. A recent modeling study forecasts rising NAFLD prevalence to the year 2030 for Asia including Japan, but these models were based on obesity rather than reported NAFLD prevalence, potentially limiting their conclusion especially when nonobese NAFLD is so prevalent [4, 9].

Therefore, we aimed to characterize the epidemiology of NAFLD in Japan and particularly on lean NAFLD. With a systematic review and meta-analytic approach combining study level with individual patient-level data, we investigated the prevalence, incidence, and clinical outcomes of NAFLD in Japan. We focused particularly on the prevalence, characteristics including fibrosis distribution and outcomes of the lean NAFLD population. We also forecasted the overall NAFLD prevalence for Japan to year 2040 using Bayesian network modeling based on NAFLD prevalence data obtained from systematic literature review.

Patients and methods

Search strategy, selection criteria, data collection, and quality assessment

We conducted the current study according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Supplementary Information) with search strategy in collaboration with a medical librarian (CDS) using 5 search engines (Pubmed, Embase, Cochrane Library, Web of Science, and the Japan Medical Abstracts Society) from inception to May 15, 2019 and without language restriction (details in Supplementary Methods)**.** Briefly, we included keywords and related terms for NAFLD, NASH, fatty liver and Japan.

We included original full-text research articles if they: (1) Included only adult (≥ 18 years) patients from Japan; (2) provided data for NAFLD prevalence, NAFLD incidence, and/or clinical outcomes such as mortality rates or hepatocellular carcinoma (HCC) incidence; (3) defined NAFLD by imaging (ultrasonography, computed tomography, and magnetic resonance imaging), liver biopsy, and/or serum diagnostic markers (fatty liver index [FLI] or hepatic steatosis index); and (4) excluded significant alcohol use defined as > 30 g/day or 210 g/week for men and > 20 g/day or 140 g/week for women, and other chronic liver diseases such as viral hepatitis among the NAFLD population. We excluded studies published before 1980; studies focusing in special populations such as patients with human immunodeficiency virus (HIV), cancer, immunosuppressive therapies, or pregnant patients; and studies with mixed populations inclusive of participants from outside of Japan.

Two authors independently performed the literature search (Fig. 1) and data extraction. Discordances were resolved by consensus and/or by a discussion with a third and senior author. If there were overlapping studies from the same cohort, we selected the most recent, the largest, and/or the most comprehensive report.

We used a quality assessment (QA) scale (Supplementary Tables 1, 2) based on the Newcastle–Ottawa Scale to grade study quality, 7–9 as high, 4–6 as moderate and 1–3 as low quality [10].

Additionally, we contacted authors of relevant studies to obtain de-identified individual patient-level data for subgroup analysis and/or individual patient-level data analysis. In total, we included data from eight studies ($n = 14{,}887$: 7752 NAFLD; 7135 no NAFLD) (Supplementary Methods). The study was conducted according to the Helsinki Declaration of 1975, as revised in 2008.

We defined body mass index (BMI, kg/m^2) < 23 as lean, 23–27.5 as overweight, and > 27.5 as obese based on WHO criteria for Asians [11]. For more accurate trend assessment, we used the median year of the study period (instead of publication year). To assess for economic factors, we used both the gross prefecture product (GPP) and the prefecture income per person of the study year (inflation adjusted to 2019, Supplementary Methods). Sub-analysis by geography was based on the eight major Japan regions (Fig. 2, Supplementary Methods).

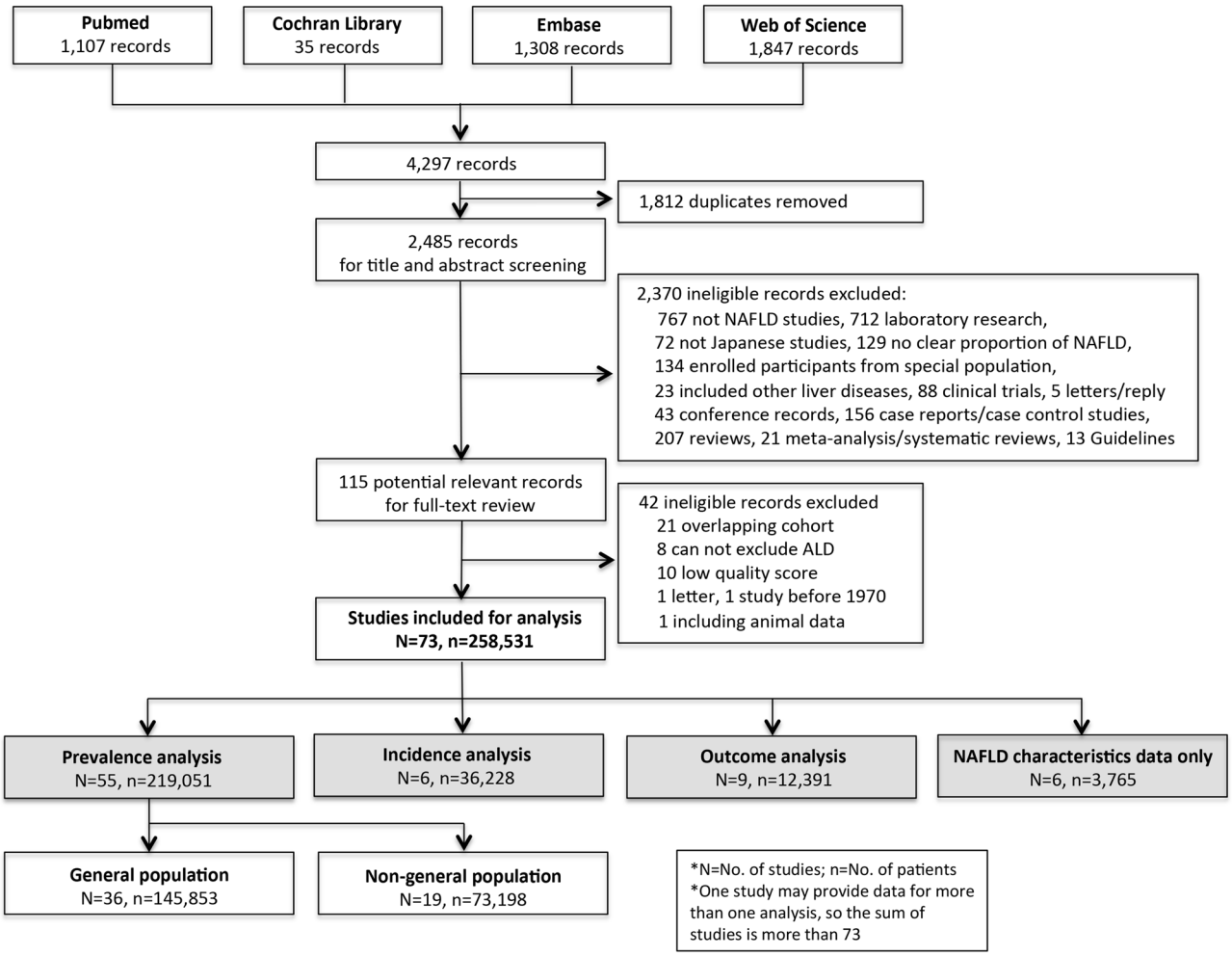

Fig. 1 Study selection. (Asterisk) Three papers were analyzed for both prevalence and incidence. NAFLD, non-alcoholic fatty liver disease; QA, quality assessment

Statistical analysis

Conventional meta-analysis

As heterogeneity is expected, we used a random-effects model to calculate pooled values and 95% confidence intervals (CIs) and Cochran's Q and I^2 statistic to assess heterogeneity. We performed subgroup analyses on age, sex, BMI, study period, the presence of DM, NAFLD diagnostic method, income levels, and study setting. We conducted meta-regression for several patient characteristics to identify factors related to NAFLD prevalence.

We used incident NAFLD case numbers among non-NAFLD individuals at baseline and the incident HCC or death numbers in NAFLD participants and follow-up period (person-years) to estimate the pooled NAFLD incidence, HCC incidence, and mortality, respectively.

We used funnel plot and Egger's test to assess publication bias. All meta-analytic analyses were performed with the meta-packages in R statistical software (version 3.5.2).

Trend analysis and forecast predicting model

We utilized a hierarchical Bayesian approach to best describe and fit the prevalence of age-related NAFLD. A random-effects parameter was used to address heterogeneity across the 33 prevalence studies with US-defined NAFLD (further details in Supplementary Methods). Trend and forecast analysis were performed using SAS (ver. 9.4, Cary NC).

Individual patient-level data analysis

We used the ANOVA test to compare the lean, overweight, and obese NAFLD groups for normally distributed continuous variables or Wilcoxon rank-sum test if not and chi-square test to compare categorical variables. We used the

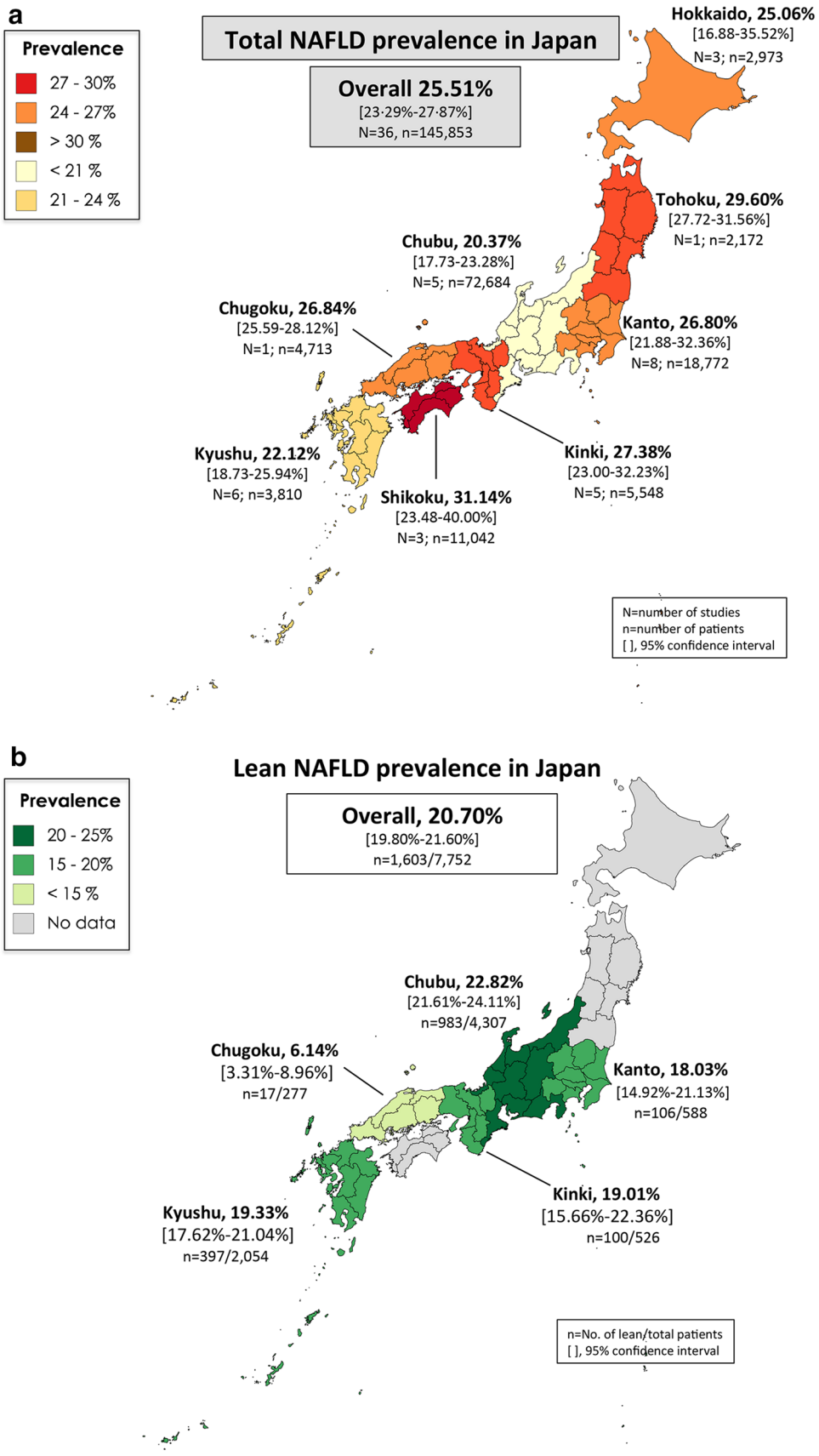

Fig. 2 The prevalence of NAFLD in Japan **a** overall and by region (study-level data), **b** the prevalence of lean (< 23 kg/m^2) NAFLD, overall and by region (individual patient-level data). (Asterisk) Data presented as prevalence (95% CI), *N* = number of studies, *n* = number of patients. Four papers were conducted in more than one region in **a**

Kaplan–Meier methods and log-rank test to assess cumulative mortality rates among the lean, overweight, and obese NAFLD populations. We performed logistic regression to estimate odds ratios (OR) for factors associated with fibrosis and Cox regression to estimate hazard ratio (HR) relating background risk including lean NAFLD to mortality. Statistical analyses were performed using STATA version 14 (Stata Corp., College Station, TX, USA).

Results

Study selection

From the initial 4297 records (Fig. 1), 2485 records remained for the title and abstract screening after duplicate removal, which yielded 115 records for full-text review. Finally, 73 eligible studies (258,531 participants) were selected for study inclusion. The QA scores and characteristics of included studies are described in Supplementary Tables 1–2 and 3–5. The median QA score was 8 (range 5–9). Ten studies had QA score ≤ 4 and were excluded from the meta-analysis.

NAFLD prevalence

Overall and subgroup analysis

The overall pooled NAFLD prevalence was 25.51% (95% CI 23.29–27.87) (36 studies, 145,853 participants) (Table 1). In most studies (33/36) and the vast majority of patients (138,203/145,863), NAFLD was diagnosed via ultrasonography (US).

Data were available for all eight regions of Japan (Fig. 2a, Table 1), which showed significant regional variation ($p < 0.001$), highest in Shikoku (31.14%, 95% CI 23.48–40.00) and lowest in Chubu (20.37%, 95% CI 17.73–23.28) (Fig. 2a, Table 1), though all three Shikoku studies were conducted in the same prefecture. The prevalence increased significantly over time: 22.22% in 1984–2005, 25.04% in 2006–2010, 29.61% in 2011–2016 ($p = 0.015$).

NAFLD prevalence was higher in men compared to women (34.11% *vs* 15.64%, $p < 0.001$) but not by age group > 50 *vs* ≤ 50 years or by study settings. Notably, the prevalence did not increase significantly by either increasing adjusted GPP ($p = 0.224$) or by prefecture income per person ($p = 0.990$) (Table 1).

There were differences in most metabolic markers such as BMI, blood pressure, liver enzymes, HBA1c, and lipid levels between the non-NAFLD and NAFLD groups (Supplementary Table 6). Among the NAFLD population, the mean BMI was 25.9 kg/m^2 (95% CI 25.5–26.2), and the mean ALT was 43.4 U/L (95% CI 39.6–47.1).

Meta-regression analysis revealed that median study year ($p < 0.001$) and waist circumference ($p = 0.004$) were factors significantly associated with NAFLD (Supplementary Table 7) but not the study region.

Incidence and outcome of NAFLD (Table 2)

Among the 36,228 participants without NAFLD at baseline from six studies, 5287 developed NAFLD, yielding an annual NAFLD incidence of 23.5 per 1000 person-years (95% CI 17.5–30.5).

Eight studies ($n = 8318$ NAFLD: 6508 via US and 1810 via histology; 114 incident HCC) provided data for HCC incidence analysis: 7.6 per 1000 person-years (95% CI 2.1–16.2) overall with the incidence being notably higher among the biopsy cohort (9.1 vs. 0.4 per 1000 person-years for US cohort, $p < 0.001$).

All-cause mortality rate was 5.9 (95% CI 3.5–8.9) per 1000 person-years overall but without significant difference between the US and biopsy cohorts (6.3 vs. 6.3 per 1000 person-years, $p = 0.85$).

Trend and forecasting of NAFLD prevalence

In trend analysis of data from 1984 to 2012 (Fig. 3a), the estimated rate of change in NAFLD prevalence was 0.64% per year (95% CI 0.28–0.98) overall, 0.91% per year (95% CI 0.21–1.60) in males, and 0.67% per year (95% CI 0.02–1.32) in females. The NAFLD prevalence were approximately 25% in 2004 and 30% in 2012. Subgroup data including region and income levels were described in Supplementary Fig. 1.

In forecasting analysis (Fig. 3b), the estimated prevalence for 2020, 2030, and 2040 were 33.7%, 39.3%, and 44.8% overall; 42.5%, 48.4%, and 54.2% for male; and 22.9%, 28.0%, and 33.0%% for female, respectively. By 2040, NAFLD may affect 29.87 million men and 19.19 million women in Japan (Fig. 3c).

Individual patient-level data analysis

Prevalence and characteristics of lean, overweight and obese NAFLD

We included individual patient data of 14,887 participants (7752 NAFLD, 7135 non-NAFLD) from eight cohorts in this analysis (Supplementary Method). NAFLD was also diagnosed via US in the vast majority of this cohort (88%).

Table 1 The prevalence of NAFLD in Japan, overall and subgroup

Population	Studies (*N*)	Participants (*n*)	NAFLD (*n*)	Prevalence (%, 95% CI)	I^2	*p* value
Total	55	219,051		–	–	–
Overall	36	145,853	32,929	25.51% (23.29–27.87)	98.8%	–
Subgroup						
By sex						< 0.001
Male	33	79,865	25,340	34.11% (31.20–37.14)	98.5%	
Female	30	71,520	9686	15.64% (13.44–18.12)	98.2%	
By age[a]						0.974
> 50.0	17	16,127	4281	25.85% (23.86–27.94)	87.3%	
≤ 50.0	9	97,037	20,663	25.94% (21.17–31.36)	99.6%	
By BMI in all participants						0.879
≥ 23.0	9	8917	2502	24.97% (21.97–28.23)	99.2%	
< 23.0	15	106,845	22,794	25.34% (22.01–28.99)	87.1%	
By BMI[a] in NAFLD participants						0.811
≥ 25.5	9	11,798	3290	25.79% (23.24–28.51)	87.7%	
< 25.5	7	15,903	4070	24.94% (19.14–31.82)	98.6%	
By presence of diabetes						0.081
DM	3	1129	330	29.99% (18.09–45.38)	95.5%	
Non-DM	5	45,209	8626	18.74% (15.67–22.25)	98.4%	
By median study year						0.015
1984–2005	8	68,859	12,917	22.22% (17.96–27.14)	98.8%	
2006–2010	19	59,198	14,896	25.04% (22.45–27.82)	98.1%	
2011–2016	9	17,796	5116	29.61% (26.71–32.68)	98.3%	
By region						< 0.001
Hokkaido	3	2973	861	25.06% (16.88–35.52)	96.2%	
Tohoku	1	2172	643	29.60% (27.72–31.56)	–	
Kanto	8	18,772	5361	26.80% (21.88–32.36)	98.4%	
Chubu	5	72,684	13,186	20.37% (17.73–23.28)	97.2%	
Kinki	5	5548	1494	27.38% (23.00–32.23)	91.2%	
Chugoku	1	4713	1265	26.84% (25.59–28.12)	–	
Shikoku	3	11,042	2852	31.14% (23.48–40.00)	98.4%	
Kyushu	6	3810	863	22.12% (18.73–25.94)	82.1%	
Tokyo vs· non-Tokyo in Kanto area						0.692
Tokyo	3	7173	2039	28.42% (27.35–29.51)	2.0%	
Non-Tokyo	5	11,599	3322	26.54% (18.55–36.45)	99.0%	
By study setting						
Population design						0.658
Population based	28	140,452	31,824	25.93% (23.47–28.56)	99.0%	
Non-population based	8	5401	1105	24.07% (17.26–32.52)	97.1%	
Clinical setting						0.831
Community health checkup	32	137,386	31,082	25.59% (23.19–28.14)	98.9%	
Clinical hospital	3	1180	346	26.64% (18.30–37.05)	88.0%	
Population setting						0.323
Urban	14	80,049	16,619	26.71% (22.33–31.59)	99.2%	
Rural	19	48,952	11,407	24.04% (21.42–26.87)	97.7%	
By diagnostic method						< 0.001
Ultrasonography	33	138,203	31,350	25.79% (23.41–28.33)	98.9%	
Fatty liver index	1	7287	1501	20.10% (19.69–21.54)	–	
Computed tomography	2	363	78	22.52% (16.47–29.99)	44.1%	
By income data (adjusted by study year)						
Gross prefecture product						0.224

Table 1 (continued)

Population	Studies (*N*)	Participants (*n*)	NAFLD (*n*)	Prevalence (%, 95% CI)	I^2	*p* value
< $ 70.95 billion	8	14,617	3685	26.58% (22.85–30.68)	95.3%	
$ 70.95–92.27 billion	7	28,972	6119	21.23% (17.18–25.93)	98.6%	
$ 92.27–183.50 billion	7	5250	1550	26.80% (22.58–31.50)	92.1%	
≥ $ 183.50 billion	8	71,414	14,802	28.07% (21.56–35.64)	99.5%	
Prefecture income per person						0.990
< $ 23,400	8	15,962	4074	25.52% (22.55–28.75)	93.8%	
$ 23,400–26,000	7	14,071	3812	25.64% (18.94–33.72)	98.9%	
$ 26,000–27,000	8	24,670	5578	26.47% (21.37–32.29)	98.6%	
≥ $ 27,700	7	65,550	12,692	25.26% (19.98–31.39)	98.9%	

CI, confidence interval; DM, diabetes mellitus; BMI, body mass index

[a]Median value among NAFLD participants

Table 2 The incidence and long-term outcome of NAFLD in Japan (study and individual patient level data)

Study level data					
Outcomes	Studies (*N*)	Participants (*n*)	Incident cases (*n*)	Incidence (95% CI) (per 1000 person-years)	I^2 (%)
Incidence of NAFLD	6	36,228	5287	23.5 (17.5–30.5)	98.7
Incidence of hepatocellular carcinoma	8	8318	114	7.6 (2.1–16.2)	96.8
Overall mortality	5	5242	210	5.9 (3.5–8.9)	68.3

Individual patient level data							
Mortality in NAFLD	Participants	Number of death (*n*)			Mortality rate (per 1000 person-years)		
		Total	Liver-related	Non liver-related	Overall	Liver-related	Non liver-related
All NAFLD	4307	187	15	172	6.2 (5.4–7.2)	0.5 (0.3–0.8)	5.7 (4.9–6.6)
Lean NAFLD	983	57	1	56	8.3 (6.3–10.7)	0.2 (0.0–0.8)	8.2 (6.2–10.6)
Non-lean NAFLD	3324	130	14	116	5.6 (4.7–6.7)	0.6 (0.3–1.0)	5.0 (4.1–6.0)

CI, confidence interval; *N*, number of studies; *n*, number of patients

Among the NAFLD population, 1603 (20.7%) were lean, 4137 (53.4%) were overweight, and 2012 (26.0%) were obese (Table 3). The prevalence of lean NAFLD was highest in Chubu (22.82%) and lowest in Chugoku area (6.14%) (Fig. 2b); however, the Chugoku cohort was small ($n = 277$), and there were no statistically significant differences among the regions ($p = 0.41$).

Lean NAFLD participants were notably older (median age 60 vs. 58 and 52 years for overweight and obese NAFLD, $p < 0.001$), had lower waist circumference (82.00 vs. 88.00 and 97.20 cm), lower proportions with diabetes (23.6% versus 28.0% and 38.5%), hypertension (38.0% vs. 51.2% and 53.8%), and metabolic syndrome (11.6% versus 36.9% and 53.8%) compared to overweight and obese NAFLD, respectively ($p < 0.001$ for all) (Table 3). Notably, lean NAFLD participants had lower ALT levels (22 vs. 28 and 39 U/L) ($p < 0.001$).

Fibrosis-4 (FIB-4) data were available for 7745 NAFLD participants from all eight cohorts (Supplementary Methods). The lean NAFLD group had a lower proportion of significant fibrosis compared to the overweight or obese NAFLD group ($p < 0.001$) (Table 3). Similar findings were observed among the 924 participants from 4 studies with histology data (Supplementary Methods). On multivariable logistic regression adjusting for age, sex, diabetes, and lean or overweight vs obese NAFLD ($n = 5591$), we found that older age (adjusted OR [aOR] 1.25 per 5 years, 95% CI 1.20–1.29) and DM (aOR 1.72 (95% CI 1.46–2.03) were independently associated with significant fibrosis (≥ F2 by FIB-4 or biopsy), while male sex (aOR 0.72, 95% CI 0.61–0.85) and lean (aOR 0.31, 95% CI 0.24–0.40) and overweight (aOR 0.52, 95% CI 0.44–0.63) NAFLD were independently associated with lower odds of having significant fibrosis (all $p < 0.001$). Similar findings were observed

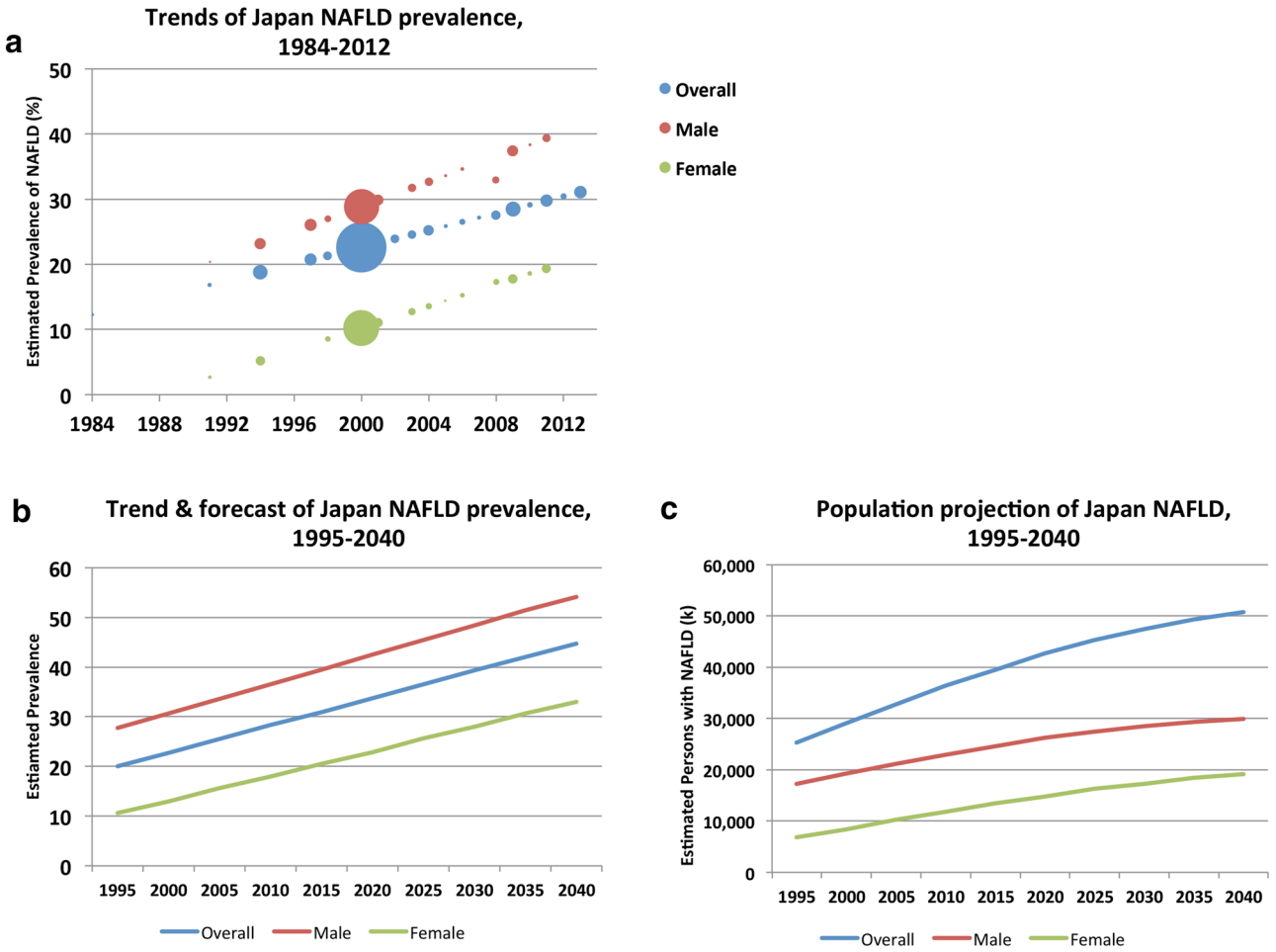

Fig. 3 **a** Trend analysis of overall NAFLD prevalence in Japan (1984–2012), **b** forecast analysis of NAFLD prevalence in Japan up to 2040, **c** projected number of people with NAFLD for up to 2040. (Asterisk) Size of each bubble indicates sample size for each study

in sensitivity analysis inclusive of only patients with liver biopsy and histologic data (n = 924) (aOR for age 1.25, $p < 0.001$; aOR for DM 1.48, $p = 0.007$; aOR for male 0.70, $p = 0.016$; aOR for lean NAFLD 0.29, $p < 0.001$; and aOR for overweight NAFLD 0.61, $p = 0.001$) (Supplementary Table 8).

Patatin-like phospholipase domain containing 3 (PNPLA3) rs738409 (encoding the I148M variant) data were available from 1808 participants from three cohorts (Supplementary Methods). Compared to obese NAFLD, we found higher CG allele frequencies among the lean and overweight NAFLD population (52.3%, 53.1% versus 39.5%) as well as higher GG frequency ($p < 0.001$). Overall, there was a higher non-CC allele frequency among the lean compared overweight and obese NAFLD (85.4% versus 79.2% and 70.6%, $p = 0.002$) (Table 3).

Mortality and factors associated with mortality in NAFLD by lean status

We included 4307 patients with NAFLD who had outcome data from 2 cohorts (Supplementary Methods) in this analysis (Table 2). Overall, mortality rates were 6.2, 0.5, and 5.7 per 1000 person-years for all-cause, liver-related mortality, and non-liver-related mortality, respectively. All-cause mortality rates differed significantly among the lean, overweight, and obese NAFLD subgroups, with lean NAFLD having the highest mortality followed by overweight then obese NAFLD ($p = 0.02$, Supplementary Fig. 2). The all-cause mortality was 8.3 versus 5.6 per 1000 person-years in the lean compared to the non-lean NAFLD group, and 6.8 versus 4.4 per 1000 person-years in the non-obese compared to the obese NAFLD group. The liver-related mortality rate was lower in the lean NAFLD group, but these data were limited as there was only one liver-related death in this group. On multivariable

Table 3 The prevalence and characteristics of lean, overweight, and obese NAFLD (individual patient level data)

Total	Non-NAFLD	NAFLD			p value[b]
$N=14,887$	$n=7135$	Lean	Overweight	Obese	–
		$n=1603$ (20.7%)[a]	$n=4137$ (53.4%)[a]	$n=2012$ (26.0%)[a]	
Age (years)	50 (42–58)	60 (50–69)	58 (49–66)	52 (42–62)	< 0.001
Sex, *n* (%)					< 0.001
Female	4107 (57.6)	716 (44.7)	1490 (36.0)	920 (45.7)	
Male	3028 (42.4)	887 (55.3)	2647 (64.0)	1092 (54.3)	
Diabetes, *n* (%)					< 0.001
Absent	–	935 (76.4)	2169 (72.0)	973 (61.5)	
Present	–	289 (23.6)	842 (28.0)	609 (38.5)	
Metabolic syndrome, *n* (%)					< 0.001
Absent	5609 (94.7)	404 (88.4)	845 (63.1)	215 (41.7)	
Present	316 (5.3)	53 (11.6)	495 (36.9)	301 (58.3)	
Hypertension, *n* (%)					< 0.001
Absent	1446 (67.5)	168 (62.0)	419 (48.8)	284 (46.2)	
Present	697 (32.5)	103 (38.0)	440 (51.2)	331 (53.8)	
Hyperlipidemia/dyslipidemia, *n* (%)					0.497
Absent	1210 (56.5)	112 (43.6)	321 (39.5)	216 (41.2)	
Present	933 (43.5)	145 (56.4)	491 (60.5)	308 (58.8)	
BMI (kg/m^2) ($n=14,887$)	21.5 (19.7–23.2)	21.9 (20.9–22.5)	25.1 (24.0–26.1)	29.6 (28.5–31.6)	< 0.001
Waist circumference (cm) ($n=8313$)	79.0 (73.4–84.0)	82.0 (79.0–84.6)	88.0 (85.0–91.5)	97.2 (93.8–102.1)	< 0.001
FPG, FBG, FBS (mg/dL) ($n=10,752$)	94 (89–101)	99 (93–108)	102 (95–112)	105 (97–120)	< 0.001
HBA1c (%) ($n=13,640$)	5.45 (5.20–5.70)	5.55 (5.20–6.10)	5.66 (5.30–6.20)	5.86 (5.40–6.76)	< 0.001
Creatinine (mg/dL) ($n=12,625$)	0.70 (0.60–0.85)	0.70 (0.60–0.82)	0.76 (0.61–0.90)	0.70 (0.60–0.87)	< 0.001
Albumin (g/dL) ($n=14,670$)	4.40 (4.30–4.60)	4.40 (4.20–4.60)	4.50 (4.30–4.60)	4.40 (4.20–4.60)	< 0.001
AST (IU/L) ($n=14,887$)	19 (17–23)	22 (18–29)	24 (19–32)	28 (21–44)	< 0.001
ALT (IU/L) ($n=14,887$)	16 (13–21)	22 (16–33)	28 (20–43)	39 (24–69)	< 0.001
GGT (IU/L) ($n=14,874$)	20 (14–30)	29 (20–49)	35 (23–58)	42.00 (27–69)	< 0.001
Platelet ($\times 10^9$/L) ($n=14,790$)	214 (185–246)	233 (198–275)	227 (192–269)	234 (197–281)	< 0.001
Uric acid (mg/dL) ($n=8335$)	4.8 (4.1–5.7)	5.7 (4.9–6.5)	6.1 (5.2–7.0)	6.2 (5.3–7.1)	< 0.001
HOMA-IR ($n=2425$)	1.2(0.80–1.8)	1.6 (1.1–2.5)	2.3 (1.6–3.6)	3.7 (2.7–5.3)	< 0.001
Fib-4 index, *n* (%) ($n=14,790$)					< 0.001
< 1.30	4572 (64.9)	939 (58.7)	2476 (59.9)	1306 (64.9)	
1.30–2.67	2318 (32.9)	569 (35.5)	1375 (33.3)	568 (28.2)	
≥ 2.67	155 (2.2)	93 (5.8)	282 (6.8)	137 (6.8)	
Diagnosis method, *n* (%)					< 0.001
Biopsy ($n=924$)	–	103 (6.4)	396 (9.6)	425 (21.1)	
Ultrasonography ($n=6828$)	–	1500 (93.6)	3741 (90.4)	1587 (78.9)	
Histology data ($n=924$)					
Pathological diagnosis, *n* (%)					< 0.001
NAFL		42 (40.8)	103 (26.0)	76 (17.9)	
NASH		61 (59.2)	293 (74.0)	349 (82.1)	
Individual fibrosis stage, *n* (%)					< 0.001
F0	–	32 (31.1)	85 (21.5)	66 (15.5)	
F1	–	38 (36.9)	133 (33.6)	143 (33.6)	
F2	–	15 (14.6)	93 (23.5)	79 (18.6)	
F3	–	13 (12.6)	62 (15.7)	105 (24.7)	
F4	–	5 (4.9)	23 (5.8)	32 (7.5)	
No versus significant fibrosis groups—F0–1 vs F2–4, *n* (%)					0.002

Table 3 (continued)

Total	Non-NAFLD	NAFLD			*p* value[b]
N = 14,887	*n* = 7135	Lean	Overweight	Obese	–
		n = 1603 (20.7%)[a]	*n* = 4137 (53.4%)[a]	*n* = 2012 (26.0%)[a]	
F0–F1	–	70 (68.0)	218 (55.1)	209 (49.2)	
F2–F4	–	33 (32.0)	178 (44.9)	216 (50.8)	
Low versus advanced fibrosis groups—F0–2 vs F3–4, n (%)					< 0.001
F0–F2	–	85 (82.5)	311 (78.5)	288 (67.8)	
F3–F4	–	18 (17.5)	85 (21.5)	137 (32.2)	
PNPLA3 data (*n* = 1808)					
PNPLA3, n (%)					< 0.001
CC	311 (30.5)	19 (14.6)	77 (20.8)	84 (29.4)	
CG	532 (52.1)	68 (52.3)	197 (53.1)	113 (39.5)	
GG	178 (17.4)	43 (33.1)	97 (26.1)	89 (31.1)	
Non-CC vs CC, n (%)					0.002
CC	311 (30.5)	19 (14.6)	77 (20.8)	84 (29.4)	
Non-CC	710 (69.5)	111 (85.4)	294 (79.2)	202 (70.6)	
Non-GG vs GG, n (%)					0.21
Non-GG	843 (82.6)	87 (66.9)	274 (73.9)	197 (68.9)	
GG	178 (17.4)	43 (33.1)	97 (26.1)	89 (31.1)	

All values are expressed as median (first-third interquartiles) and number (%)

BMI, body mass index; FPG, fasting plasma glucose; FBG, fasting blood glucose; FBS, fasting blood sugar; HBA1C, hemoglobin A1C; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma glutamyl transferase; HOMA-IR, homeostatic model assessment of insulin resistance; Fib-4, Fibrosis-4; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain containing 3

[a]Prevalence of lean, overweight, and obese NAFLD among NAFLD population

[b]*p* values are for comparison among lean, overweight, and obese NAFLD only

Cox regression analysis (Supplementary Table 9), independent factors associated with higher all-cause mortality were older age, male sex, DM, and higher FIB-4 but not lean (vs. non-lean) NAFLD (aHR 1.23, $p = 0.21$).

Heterogeneity and publication bias

There was significant heterogeneity among included studies (Table 1). Though Egger's test and funnel plot showed significant publication bias in the overall NAFLD prevalence analysis ($p = 0.013$), there was no longer significant bias after we removed four studies that were selected for younger participants ($p = 0.82$) (Supplementary Fig. 3).

Discussion

Our systematic review and meta-analysis confirmed the lower NAFLD prevalence in Japan (about 25%) compared to reported rates for the US, Europe, or Asia as a whole [4, 12]. However, despite having a lower NAFLD prevalence and incidence [4], the prevalence of NAFLD in Japan has increased significantly over the past few decades and is forecasted to reach nearly 50% affecting about 30 million men and 20 million women by 2040, highlighting a serious global public health threat involving both East and West, high-risk as well as low-risk regions. Our individual patient-level data analysis also found that only about one-quarter (26%) of the NAFLD population in Japan were obese, about one-fifth (21%) were lean, and over half (53%) were overweight. Moreover, lean NAFLD people were older and had the highest all-cause mortality followed by overweight then obese NAFLD, though lean NAFLD was not independently associated with higher mortality but older age, male sex, DM, and higher FIB-4 were.

The lower prevalence of NAFLD in Japan could be partly due to a dietary habit that is traditionally low in meat and fat [7, 8], and the rapid increase in the last few decades as shown in our meta-regression and trend analysis is also likely due to changes in diet and physical activity levels associated with rapid westernization following the post-war era [13]. However, according to the Organization for

Economic Co-operation and Development (OECD) Obesity Update 2017 for a sample of 36 countries from the Americas, Europe, and Asia Pacific, Japan still had the lowest obesity prevalence of 4.2%, followed by Korea (5.5%), then Italy (9.8%), etc.., while the United States had the highest prevalence of 40%. [19] Similarly, Japan still has one of the lowest age-adjusted diabetes prevalence among adults aged 20–79 years (5- < 7%) as compared to 9–< 12% for other areas such as China, India, Germany, and the United States or ≥ 12% for areas such as Mexico, Egypt, South Africa, etc… [20] Together, these factors can contribute to the lower prevalence of NAFLD in Japan. In addition, dietary factors can explain some of the observed regional differences with higher prevalence in the colder North such as Tohoku. These results can be due to differences in body size, including BMI and waist circumference in each region [14], intake of vegetables, fruits with rich fructose [15, 16], and higher sodium in cold areas [17, 18]. Indeed, though Japan covers a relatively small landmass, it is mostly mountainous and stretches from the Far North at a similar latitude as Siberia to the East China Sea to the South, giving rise to diverse regional agriculture, social, and dietary patterns that can affect NAFLD development. A recent study on Mainland China also found higher NAFLD prevalence in colder northern provinces [21]. However, in contrast to observations in the US and China [21, 22], there was no significant difference in NAFLD prevalence by income levels in Japan. The living standard in Mainland China moves along with changes in income levels, which has changed rapidly in the past two decades [23]. On the other hand, Japan is a fully industrialized country with a stable income and population for several decades. Japan is also a fairly homogenous nation with 98% of the population as Japanese ethnicity [5, 24], as opposed to the US, another industrialized country that is a "melting pot" of multiple races and ethnicities with its associated racial/ethnic disparities [24]. Taken together, the epidemiology of NAFLD is complex and affected by the presence and interaction of multiple demographic, social, and physical factors that should all be considered in disease control and prevention.

Our report broadened two recent Markov modeling studies which forecasted the NAFLD prevalence in 2030 for Hong Kong, Singapore, Taiwan, and South Korea, as well as for China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States [9, 25]. These studies found that NAFLD is expected to increase 0–30% by 2030 depending on country [25]. While these prior studies which relied on obesity and DM prevalence rather actual NAFLD prevalence for their model inputs reported a NAFLD prevalence of only 17.9% in 2016 and 18.8% in 2030 for Japan [9], our systematic review and trend analysis found that the NAFLD prevalence for Japan was already 25% by year 2004, 30% by 2012, and is projected to reach 45% by 2040. We suggest the differences in our prevalence rates were due to our methodology of using a systematic review of the literature which encompassed many more studies for Japan as well as the use of Bayesian network modeling which works on the conditional probability of an event occurring or not occurring rather than just being an independent event thus allowing the model to be more fluid and build upon each event [26]. Nonetheless, these findings are alarming and should inform stakeholders to increase preventive as well as therapeutic intervention efforts for this disease.

Another important finding in this study is the substantial proportion of people with non-obese NAFLD. Among those with NAFLD in our individual patient-level data analysis, three-quarters were not obese, and one-fifth of all NAFLD were neither overweight nor obese. Our lean NAFLD prevalence of 20% among the NAFLD population is consistent with a recent meta-analysis of global non-obese NAFLD epidemiology but notably higher than the 4% reported in a recent US study [3, 27]. In addition, while both our lean NAFLD and the US lean NAFLD populations were older and had a lower waist circumference, the US non-obese NAFLD population was more likely to have metabolic disease, higher liver enzymes, and significantly more liver fibrosis compared to obese NAFLD [27], but observations in our cohort were opposite. The reasons why both the prevalence and characteristics of lean NAFLD patients in our study differ from US data are unclear, but they might be related to environmental and host genetic factors. Previous reports showed that lean NAFLD patients had a different gut macrobiotic profile which could be influenced by regional diet and other environmental factors [28]. The genetic factor, non-synonymous single nucleotide polymorphisms (SNPs) of the PNPLA3 rs738409 that encodes the p.I148M (isoleucine-to-methionine substitution at residue 148) well known to associate with NAFLD can also play a role [29]. In our study, the lean NAFLD population had a significantly higher frequency of the GG phenotype, which has been shown to associate with a higher risk for NAFLD in normal-weight subjects [30]. In addition, prior studies have reported a higher G-allele rate of rs738409 in Japan compared with other countries [31], and this may partly explain the higher prevalence of lean NAFLD in Japan.

Despite these differences, consistent with prior data from the US [27], we observed higher all-cause mortality in our lean NAFLD as compared to non-lean NAFLD groups though lean NAFLD was not independently associated with mortality, but well-known drivers of mortality in NAFLD patients such as liver fibrosis were [32]. In regards to specific causes of death, we observed high rates of liver-related deaths in the non-lean group, while the majority of mortality among the lean NAFLD group were non-liver related. However, there was only one liver-related event in our lean NAFLD cohort, and thus we were not able to

perform cause-specific mortality analysis. Further studies on competing causes of death for lean NAFLD are warranted.

Our study has several strengths. To the best of our knowledge, this is the first and most comprehensive systematic review and meta-analysis of NAFLD for Japan including data from 73 studies and 258,531 participants as well as the largest study focusing on lean NAFLD with individual patient-level data. We also employed a meta-regression method to identify factors associated NAFLD and Bayesian modeling to estimate trend and provide projected prevalence and affected population data up to 2040 for Japan. In addition to study-level analysis, we obtained and analyzed individual patient data of 14,887 participants from eight studies representing five regions of Japan, enabling detailed analysis of the epidemiology and natural history of lean NAFLD that is still sparse in the current literature. We encourage a similar approach for other countries/regions, so comprehensive rigorously obtained data can be available to inform local practice and public health effort.

We also recognize several limitations. First, though our study included 73 studies representing all 8 regions of Japan, most are from central Japan, so further studies from other areas are needed. Second, there was high heterogeneity among included studies, which remained in sub-group analysis and was likely due to the complex nature of factors influencing NAFLD prevalence that subgroup analysis by one factor at a time was insufficient to resolve. Third, due to the lack of available data from included studies on demographic, anthropometric and clinical characteristics of NAFLD patients, we were not able to determine the prevalence, characteristics and outcomes of lean NAFLD using study-level data. However, we were able to obtain individual patient data from over 14,000 patients from eight studies to fill in these gaps, though there were still insufficient data to fully address the competing causes of mortality for lean NAFLD.

In conclusions, though Japan has a lower NAFLD prevalence compared to most industrialized areas, its prevalence has also increased significantly in the recent decades and is expected to affect almost half of the population in 2040. The majority of NAFLD people in Japan were not obese and about 20% had lean NAFLD. Lean NAFLD people were older and had higher all-cause mortality. Additional strategies are needed to curtail the NAFLD epidemic including the lean population.

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