Prevalence and Profile of Nonalcoholic Fatty Liver Disease in Lean Adults: Systematic Review and Meta-Analysis

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Data on prevalence and profile of nonalcoholic fatty liver disease (NAFLD) among individuals who are lean (normal body mass index) is unclear. Published data from studies comparing lean with obese NAFLD or with healthy subjects on prevalence, comorbidities, liver chemistry and histology, and metabolic/inflammatory markers were analyzed. Data were reported as odds ratio and 95% confidence interval for categorical variables and difference of means for continuous variables. Analysis of 53 studies on 65,029 subjects with NAFLD (38,084 lean) and 249,544 healthy subjects showed a prevalence of lean NAFLD at 11.2% in the general population. Among individuals with NAFLD, the prevalence of lean NAFLD was 25.3%. Lean NAFLD versus healthy subjects had higher odds for abnormalities on metabolic profile, including metabolic syndrome and its components, renal and liver function, and patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) G allele; and inflammatory profile, including uric acid and C-reactive protein. The abnormalities were less severe among lean versus obese NAFLD on metabolic syndrome with its components, renal and liver chemistry, liver stiffness measurement, *PNPLA3* and transmembrane 6 superfamily member 2 polymorphisms, and uric acid levels as markers of inflammation. Lean NAFLD had less severe histologic findings, including hepatocyte ballooning, lobular inflammation, NAFLD activity score, and fibrosis stage. Limited data also showed worse outcomes between obese versus lean NAFLD. *Conclusion:* Lean NAFLD is a distinct entity with metabolic, biochemical, and inflammatory abnormalities compared to healthy subjects and a more favorable profile, including liver histology of steatohepatitis and fibrosis stage, compared to obese NAFLD. We suggest that prospective multicenter studies examine long-term hepatic and extrahepatic outcomes in individuals with lean NAFLD. (*Hepatology Communications* 2020;4:953-972).

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in the world, with a global prevalence of approximately 25% and a prevalence of 24% in North America.[1,2] The incidence is increasing, especially in the Western world, due to the rising prevalence of obesity in the general population.[3] Approximately 15% to 20% of patients with NAFLD progress to the more advanced stage of nonalcoholic steatohepatitis (NASH), with a risk to progress to advanced liver

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model for insulin resistance; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PNPLA3, *patatin-like phospholipase domain-containing protein 3;* TM6SF2, *transmembrane 6 superfamily member 2.*

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disease, including cirrhosis and hepatocellular carcinoma.[1] Currently, NASH is the second most common indication for liver transplantation, surpassing hepatitis C virus infection and lagging behind alcohol-associated liver disease.[4,5]

Risk factors for NAFLD include insulin resistance and metabolic syndrome (≥3 of obesity, diabetes mellitus, hypertension, low high-density lipoprotein [HDL], and high triglyceride levels).[1] Of these, the most common and frequent risk factor is obesity.[1] However, NAFLD can occur among individuals who are not obese and have a normal body mass index (BMI). These individuals are labeled as "lean NAFLD" or "nonobese NAFLD."[1] Data on the prevalence of lean NAFLD among healthy adults in the general population vary from 7.8% to 74% across studies.[6-9] This is mainly due to the variation in the BMI cutoff used to define individuals who are lean: 25 in studies from the West,[10] 23 in studies from Asia,[6,11] and 30 in some studies given that obesity is defined as BMI >29.9.[12] Further, data remain unclear on the metabolic profile of lean NAFLD and whether this is an early manifestation of obese NAFLD or a separate entity.[9,13,14] Data are also scanty and controversial on the histology spectrum and outcomes among lean NAFLD compared to obese NAFLD. We performed this systematic review and meta-analysis of all studies to determine the prevalence of lean NAFLD. We further examined studies comparing lean and obese NAFLD on comorbidities and risk factors, metabolic and inflammatory markers, and liver histology findings.

Materials and Methods

LITERATURE SEARCH STRATEGY

We conducted a comprehensive search of the medical literature using the PubMed, Embase, and Cochrane databases. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to identify full-length articles in English reporting on lean NAFLD. All databases were searched from their inception through August 2019. Studies on lean NAFLD were identified using the following initial medical subject heading terms: "lean" "non-obese" "non-alcoholic fatty liver disease," "non-alcoholic fatty liver," "nonalcoholic fatty liver," "nafld," "nonalcoholic-steatohepatitis," and "non-alcoholic-steatohepatitis."

SELECTION OF STUDIES FOR ANALYSIS

From the searched literature, studies of adults were included in this pooled analysis that reported: a) the prevalence of lean NAFLD and/or b) the disease profile of lean NAFLD comparing with obese NAFLD or with healthy individuals who were lean. Prospective as well as retrospective studies were included. Studies were excluded if they reported data on the pediatric population; were mechanistic or animal studies; were reported as abstracts, case reports, editorials, reviews, meta-analyses, or clinical trials; and were published in a non-English language. In the case of multiple

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publications from the same cohort, data from the most recent and/or most appropriate report were included. Three authors (S.Y., A.K.S., and K.F.) independently reviewed the titles and abstracts of the studies identified in the primary search and excluded studies that did not address the research according to the inclusion and exclusion criteria. The full text of the remaining articles was reviewed for study selection. Any disagreement was resolved with a review of the article and discussion among the co-authors.

ASSESSMENT OF STUDY QUALITY

Each study was reviewed by two independent reviewers (S.Y. and J.P.) for quality using eight parameters on the Newcastle-Ottawa scale for the case-control or cohort studies. This scale measures each study on three domains: selection, comparability, and exposure (Supporting Table S1). In addition, studies were assessed on sample size (population-based study or sample size ≥500 for nonpopulation studies were adjudicated 1 point) and study design (prospective studies were adjudicated 1 point). Of the maximum score of 10, studies with ≥6 points were rated as good quality and the remaining as poor quality.

DATA EXTRACTION

Published data from all studies selected for the analysis were extracted independently by three authors (S.Y., K.F., and A.K.S.) based on seven criteria. Any disagreement between the investigators was resolved with consensus after review of the study data in question. The criteria were as follows:

1. Study characteristics: geographic location, study design, sample size, study population.
2. Demographics: age, sex, race, and BMI.
3. NAFLD prevalence: overall, lean NAFLD, and obese NAFLD.
4. Comorbidities and risk factors: metabolic syndrome, increased waist circumference, central obesity, hypertension, dyslipidemia, diabetes mellitus, impaired fasting glucose, low HDL, elevated triglycerides, insulin resistance, coronary artery disease, carotid plaque, smoking, hyperuricemia, and genetic polymorphisms for patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*) genes.
5. Metabolic and inflammatory markers: waist circumference; waist to hip ratio; blood pressure; blood lipid panel, including total cholesterol, HDL, low-density lipoprotein (LDL), and triglycerides; fasting glucose, 2-hour postprandial glucose, hemoglobin A1c, fasting insulin level, and homeostatic model assessment for insulin resistance (HOMA-IR); serum ferritin; serum C-reactive protein (CRP); serum uric acid; and carotid intima-media thickness.
6. Hematologic and biochemical assessment: hemoglobin, hematocrit, platelet count, blood urea nitrogen, serum creatinine, serum bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase, and serum albumin.
7. Liver histology: steatosis, lobular inflammation, ballooning, portal inflammation, fibrosis stage, NAFLD activity score (NAS), and NASH.

Patients with lean NAFLD were compared to healthy controls and patients with obese NAFLD. For comparison of obese versus lean NAFLD, subgroup analysis was also performed among nine studies, including individuals who were overweight. Data on continuous variables were reported as mean, with unit of variation as SD. If the studies reported continuous variables with median values, they were converted into mean using the standard approach. Similarly, if the unit of variation was reported as SEM, this was converted to SD to ensure uniformity of the data across studies. If the laboratory values were reported as molar concentration, conversion was made using the standard approach for respective values to mass concentration to ensure a homogeneous unit of measurement across studies.

DEFINITIONS

We used the following definitions:

1. NAFLD: hepatic steatosis in the absence of other causes of liver disease and alcohol use <30 g/day in men and <20 g/day in women.[1]
2. Lean: BMI <25 in Western studies and <23 in most studies from Asia.
3. Metabolic syndrome: presenting with ≥3 of the following: abdominal or central obesity (waist circumference >40 inches in men and >35 inches in

women), triglyceride level ≥150 mg/dL, HDL level <40 mg/dL in men and <50 mg/dL in women, blood pressure ≥130/85 mm Hg, and fasting glucose ≥110 mg/dL.[15]
4. HOMA-IR: fasting insulin level (μU/L) × blood glucose level (mg/dL).[1]
5. Steatosis grade: on liver histology with a percentage of hepatocytes showing fat as grade 1 (5%-33%), grade 2 (34%-66%), and grade 3 (≥66%).[16]
6. Lobular inflammation grade: graded by number of inflammatory foci per 200× field as grade 1 (<2 foci), grade 2 (2-4 foci), and grade 3 (>4 foci).[16]
7. Hepatocyte ballooning grade: graded by number of ballooned hepatocytes as grade 1 (few ballooned cells) and grade 2 (many ballooned cells).[16]
8. NAS: sum of the scores for steatosis, lobular inflammation, and ballooning.[16]
9. NASH: defined on liver histology with NAS ≥5.[16]
10. Fibrosis stage: graded as stage 1 with perisinusoidal or portal fibrosis, stage 2 with periportal fibrosis, stage 3 as bridging fibrosis, and stage 4 with cirrhosis.[16]

DATA ANALYSES

Comprehensive statistical analysis software was used to pool the published data on the analyses. Random effects model was used to analyze pooled data, and the pooled effect size was represented as forest plots. Effect size on categorical variables data is reported as proportions or odds ratio (OR) with 95% confidence interval (CI). OR not crossing 1 is considered significant. Effect size on continuous variables is reported as differences of means with 95% CI and considered significant if the 95% CI does not cross 0. $P < 0.05$ was considered significant for all analyses. Interstudy heterogeneity was examined using I^2 statistics and defined as $I^2 > 50\%$ or $P < 0.05$.[17] For heterogeneous data, subgroup or sensitivity analyses were performed to examine reasons for heterogeneity. Publication bias was assessed by visual inspection of funnel plots and with Egger's regression test, with $P < 0.05$ considered significant for the presence of publication bias.[18]

Results

BASELINE CHARACTERISTICS

Of the 424 studies identified in the initial literature search, 53 were included in the analysis (Supporting Fig. S1) on 65,029 subjects with NAFLD (38,084 lean) and 249,544 subjects who were healthy. Of these, 42 studies were reported from Asia, six from Europe, five from the Middle East, and two from North America (Table 1). There were 46 studies of good quality, and the remaining seven were adjudicated as poor quality with a study quality score of <6 (Supporting Table S1). Mean age was similar when comparing subjects with obese versus lean NAFLD, with a mean difference of 0.26 (95% CI, −0.35 to 0.86; $P = 0.40$). However, subjects with lean NAFLD compared to subjects who were healthy and lean were older, with a mean difference of 0.70 (95% CI, 0.44-0.96; $P < 0.001$). Data were heterogeneous with $I^2 = 99$, $P < 0.001$, but without publication bias on either analysis. There were no differences in the proportion of smokers comparing subjects with obese NAFLD versus lean NAFLD from seven studies and lean NAFLD versus subjects who were healthy from 10 studies (OR, 0.91; 95% CI, 0.51-1.61; $P = 0.74$ and OR, 1.23; 95% CI, 0.93-1.63; $P = 0.14$, respectively).

PREVALENCE OF LEAN NAFLD

Pooled data from 30 studies showed a prevalence of lean NAFLD in the general population of 11.2% (95% CI, 9.6-13.0) (Fig. 1A) and 9.2% (95% CI, 7.4-11.3) from 15 studies and a sample size ≥1,000 subjects (Fig. 1B). Based on geographic location, the prevalence of lean NAFLD was 12% (95% CI, 10.2-14.2) in Asia from 23 studies, 10.2% (95% CI, 6.3-16.0) in the Middle East from four studies, and 9.2% (95% CI, 8.4-10.2) on the Western continent from three studies (Supporting Fig. S2). Among five studies of adults who were lean, the pooled prevalence of NAFLD was 12.6% (95% CI, 9.0-17.4). Among 24 studies that included adults who were not lean, the pooled prevalence of NAFLD was 26.0% (95% CI, 21.6-30.9), 10.9% (95% CI, 9.1-12.8) in subjects who were overweight, and 46.0% (95% CI, 36.3-56.1) in subjects with obesity.

TABLE 1. BASELINE CHARACTERISTICS OF STUDIES INCLUDED IN THE META-ANALYSIS

References	Country of Origin	Study Type	Sample Size (n)			Mean Age (Years)			% Male			BMI	Quality Score
			O-NAFLD	L-NAFLD	Healthy	O-NAFLD	L-NAFLD	Healthy	O-NAFLD	L-NAFLD	Healthy		
Akyuz et al.[25]	Turkey	0	446	37	NA	45.5	41.2	NA	53.1	70.3	NA	25	7
Alam et al.[26]	Bangladesh	0	346	119	NA	40.5	41.7	NA	34.7	52.1	NA	25	6
Bhat et al.[27]	India	0	120	30	NA	42.8	39.9	NA	-	-	NA	23	7
Biswas et al.[28]	Bangladesh	1	NA	38	152	NA	44.18	50.5	NA	68.4	75.7	25	8
Chen et al.[29]	Taiwan	1	291	61	1,383	-	-	-	61.2	60.7	41.9	25	8
Chen et al.[21]	Australia	1	439	99	NA	47	46	NA	64.9	69.7	NA		7
Cho[30]	South Korea	1	347	213	1,498	43.5	44	43	96.5	89.7	78.9	25	7
Chon et al.[31]	South Korea	0	NA	107	1,054	NA	44.0	44.8	NA	100	100	25	7
Das et al.[9]	India	1	NA	90	134	NA	36	39	NA	70.0	60.4	25	8
Du et al.[6] (healthy)	China	1	1,847	332	3,625	50.4	48.8	44.8	-	-	-	23	6
Du et al.[6] (at risk)	China	1	1,936	203	437	53.6	56.4	56.2	-	-	-	23	6
Eguchi et al.[7]	Japan	1	1,184	325	1,175	-	-	-	-		-	25	8
Erkan et al.[32]	Turkey	1	NA	143	76	NA	49.2	36.4	NA	58.7	43.4	25	8
Feldman et al.[33]	Austria	0	61	55	71	63	61	56	47.5	47.3	35.2	25	7
Feng et al.[34]	China	1	764	134	597	46.9	48.2	43.2	72.3	54.5	28.5	24	8
Fracanzani et al.[35]	Italy	0	526	143	NA	49	46	NA	71.7	72.0	NA	25	8
Fukuda et al.[11]	Japan	1	591	139	2,850	42.2	42.6	41	87.1	85.6	47.6	23	8
Hagstrom et al.[23]	Sweden	1	188	123	NA	45.2	51.4	NA	55	58	NA		8
Hao et al.[36]	China	0	NA	76	438	NA	54.3	58.0	NA	-	-	25	8
Harrison et al.[37]	USA	1	618	26	NA	-	-	NA	-	-	NA		7
Hillenbrand et al.[38]	Germany	0	46	2	30	-	-	-	-	-	-	25	6
Honarvar et al.[39]	Iran	1	82	13	191	50	50	34	46.3	30.8	51.8	25	8
Honda et al.[40]	Japan	1	406	134	782	48.5	56.6	51.7	56.2	42.5	46.3	25	8
Kim et al.[12]	South Korea	0	106	74	386	54.3	51.6	51	56.6	64.9	42.2	25	8
Kim et al.[41]	South Korea	1	NA	98	661	NA	57.4	56.7	NA	65.3	49.2	25	7
Kim et al.[42]	South Korea	1	NA	40	1,127	NA	36.3	33.9	NA	0	0	25	8
Kumar et al.[43]	India	0	NA	27	131	NA	38	40.1	NA	70.4	67.9	23	7
Kurinna and Kolesnikova[44]	Ukraine	0	48	22	NA	-	-	NA	75	63.6	NA	25	7
Kwak et al.[45]	South Korea	0	65	23	62	38.9	43.8	41	-	-	-	25	8
Kwon et al.[46]	South Korea	1	3,025	3,014	20,994	47.7	49.4	44	67.3	52.8	24.3	25	8
Lee et al.[47]	Korea	0	25	22	NA	-	-	NA	-	-	NA		6
Leung et al.[23]	Hong Kong	0	235	72	NA	51	54	NA	58.7	45.8	NA	25	7
Liu et al.[48]	China	1	NA	121	407	NA	-	-	NA	0	0	25	7
Liu et al.[49]	China	1	1,331	288	1,648	45.2	46.9	37.9	76.0	65.6	47.1	25	8

TABLE 1. *Continued*

References	Country of Origin	Study Type	Sample Size (n)			Mean Age (Years)			% Male			BMI	Quality Score
			O-NAFLD	L-NAFLD	Healthy	O-NAFLD	L-NAFLD	Healthy	O-NAFLD	L-NAFLD	Healthy		
Lu et al.[50]	China	1	NA	639	5,223	NA	48	42.7	NA	63.2	36.5	23	8
Luo et al.[51]	China	1	6,308	1,161	23,599	48.0	48.8	40.7	70.0	63.7	40.1	25	8
Margariti et al.[52]	Greece	0	143	19	NA	47	44	NA	59.4	57.9	NA	25	7
Naderian et al.[53]	Iran	1	NA	55	259	NA	43.2	41.6	NA	43.6	44.4	25	7
Nakamuta et al.[54]	Japan	0	14	11	NA	-	-	NA	50.0	45.5	NA	25	6
Nishioji et al.[55]	Japan	1	212	60	331	-	-	-	-	-	-	23	8
Nishioji et al.[8] (M)	Japan	1	340	260	847	54.1	57.7	57.8	100	100	100	25	8
Nishioji et al.[8] (F)	Japan	1	235	151	1,438	58.9	62.2	55.6	0	0	0	25	8
Okur and Karacaer[56]	Turkey	0	NA	27	227	NA	31	27	NA	100	100	25	8
Oniki et al.[57]	Japan	1	NA	119	472	NA	61.9	65.2	NA	69.7	56.6	25	8
Park et al.[58]	South Korea	0	NA	120	240	NA	42.8	42.5	NA	100	100	25	6
Qi et al.[59]	China	0	NA	96	53	NA	52.9	53.6	NA	85.4	92.5	25	7
Sharma et al.[60]	India	0	20	20	20	37.4	33.7	34.1	-	-	-	25	7
Sun et al.[61]	China	1	NA	25,503	158,400	NA	46.8	40.0	NA	77.6	45.1	25	8
Vendhan et al.[62]	India	1	125	48	NA	46	46	NA	52.0	54.2	NA	23	8
Wang et al.[63]	China	1	NA	43	83	NA	47	40.5	NA	83.7	84.3	25	7
Wei et al.[64]	China	1	127	135	NA	51	51	NA	50.4	57.0	NA	25	7
Xu et al.[65]	China	1	NA	502	6,403	NA	47	43	NA	80.1	61.7	25	8
Yasutake et al.[66]	Japan	0	44	12	NA	53.5	47.2	NA	50.0	33.3	NA	25	6
Yoshitaka et al.[67]	Japan	1	243	69	915	48.8	50	47.2	80.7	78.3	48.6	23	8
Younossi et al.[10]	United States	1	2,061	431	4,026	49.1	41.9	39.6	54.8	43.6	42.3	25	7
Zhang et al.[68]	China	0	NA	1,630	5,179	NA	51.5	46	NA	71.2	56.0	25	8

Abbreviations: L-NAFLD, lean NAFLD; NA, not applicable; O-NAFLD, obese NAFLD..

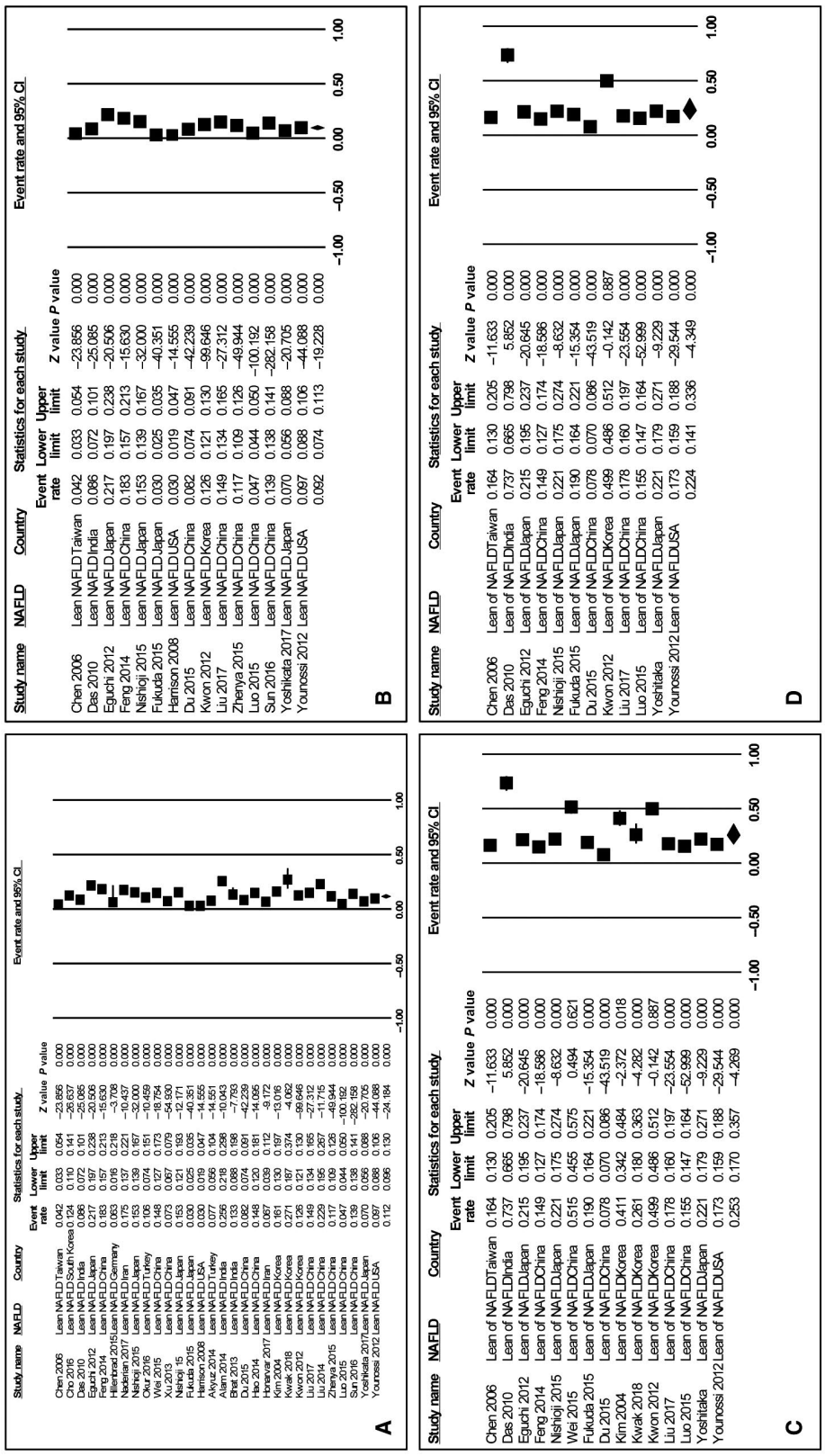


FIG. 1. Prevalence of lean NAFLD. (A) Pooled prevalence of lean NAFLD, (B) population prevalence of lean NAFLD among all NAFLD, and (D) population prevalence of lean NAFLD among all NAFLD. The graph represents effect size from each study and black square represents the pooled effect size.

Among subjects with NAFLD, the proportion of lean NAFLD analyzed from 15 studies was 25.3% (95% CI, 17.0-35.7) (Fig. 1C) and 22.4% (95% CI, 14.1-33.6) from 12 studies with a sample size ≥1,000 subjects (Fig. 1D). All analyses on pooled prevalence showed heterogeneous data with I^2 ≥ 75%. However, there was no publication bias (P > 0.05).

METABOLIC AND INFLAMMATORY MARKERS

Obese Versus Lean NAFLD

Of 34 studies included in the analysis, 28 on 21,860 subjects with obese NAFLD and 7,349 subjects with lean NAFLD reported data on some or all of the markers of interest.

For the metabolic markers, subjects with obese NAFLD compared to lean NAFLD had higher mean systolic and diastolic blood pressure, hemoglobin A1C, and HOMA-IR (Supporting Fig. S3A-D). Mean serum level was lower for HDL and higher for triglycerides among obese NAFLD versus lean NAFLD (Supporting Fig. S3E,F). However, the data were similar on pooled mean difference for fasting insulin from eight studies, 1.22 (95% CI, −0.10 to 2.55; P = 0.48); fasting glucose from 26 studies, −0.13 (95% CI, −0.78 to 0.51; P = 0.68); 2-hour postprandial glucose from four studies, −0.03 (95% CI, −0.19 to 0.40; P = 0.69); total cholesterol from 25 studies, 0.48 (95% CI, −0.04 to 0.99; P = 0.07); and LDL from 20 studies, 0.69 (95% CI, −0.03 to 1.41; P = 0.062). Data were heterogeneous on all the analyses except for hemoglobin A1C, and there was no publication bias on any of the analyses (Egger's regression test) (Supporting Table S2).

For biochemical and hematologic markers, subjects with obese NAFLD compared to those with lean NAFLD had higher mean serum ALT, albumin, and creatinine levels (Fig. 2A,B,D). Other biochemical data were similar for AST from 24 studies, 0.41 (95% CI, −0.009 to 0.81; P = 0.045); ALP from seven studies, −0.06 (95% CI, −0.15 to 0.03; P = 0.17); total bilirubin from four studies, −0.04 (95% CI, −0.14 to 0.07; P = 0.53); and blood urea nitrogen from four studies, −0.06 (95% CI, −0.14 to 0.02; P = 0.16). On hematologic evaluation, obese NAFLD compared to lean NAFLD had higher mean hemoglobin levels (Fig. 2C) but similar platelet counts from four studies, 0.76 (95% CI, −1.3 to 2.80; P = 0.47). Pooled data on all the analyses were heterogeneous except for hemoglobin and serum bilirubin. There was no publication bias for any of the analyses (Egger's regression test) (Supporting Table S2).

For the liver stiffness measurement, pooled values from two studies comparing 407 subjects with obese NAFLD and 207 subjects with lean NAFLD showed higher values in obese NAFLD (Fig. 2F). Data were homogeneous (I^2 = 0; P = 0.92), and publication bias could not be assessed with only two studies in the analysis.

For inflammatory markers, subjects with obese NAFLD compared to those with lean NAFLD had higher mean uric acid levels (Fig. 2E). Analyses for other inflammatory markers were similar on mean serum ferritin from four studies, 0.15 (95% CI, −0.04 to 0.35; P = 0.12); CRP from five studies, 0.13 (95% CI, −0.04 to 0.31; P = 0.13); and carotid intima-media thickness from two studies, 0.01 (95% CI, −0.93 to 0.95; P = 0.98). Data were heterogeneous for all the analyses but without any publication bias (Egger's regression test) (Supporting Table S2).

In a subgroup analysis after excluding nine studies that included patients who were overweight in the lean group, the results of all the analyses were similar (Supporting Table S3). We also performed subgroup analyses from seven studies comparing individuals with obesity without NAFLD and those who were lean without NAFLD to discern the effect of NAFLD itself (Supporting Table S4). Groups with obesity versus lean groups had worse metabolic and inflammatory profiles.

Lean NAFLD versus healthy lean

Data for markers comparing lean NAFLD versus subjects who were healthy were extracted from 33 studies on 36,029 subjects with lean NAFLD and 243,815 subjects who were healthy.

For metabolic markers, subjects with lean NAFLD compared to healthy subjects who were lean without NAFLD had higher mean BMI, diastolic blood pressure, hemoglobin A1C, and insulin resistance (Supporting Fig. S4A-D). The lipid profile showed lower mean levels for HDL and higher triglyceride

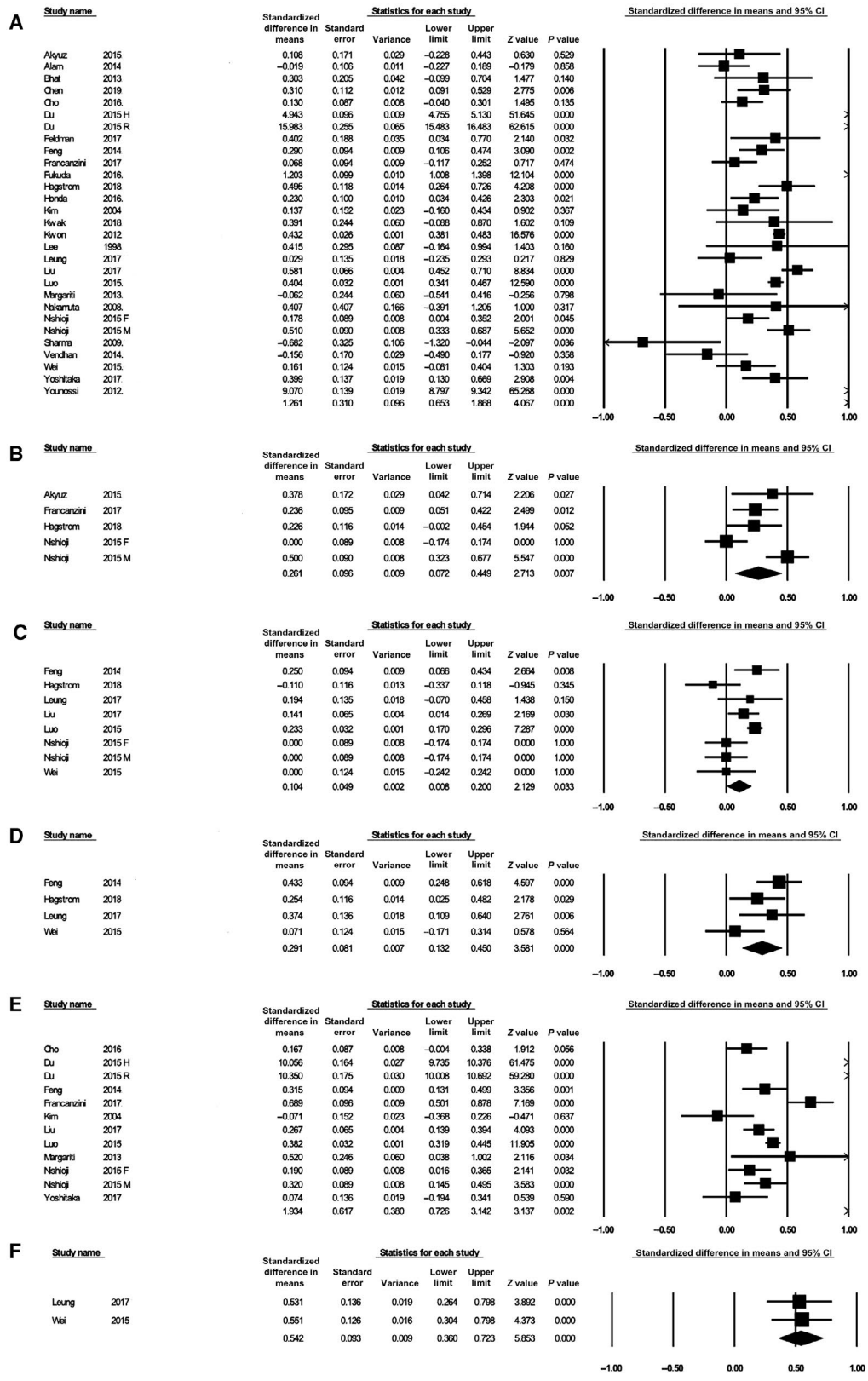


FIG. 2. Pooled data on liver biochemical markers of subjects with obese NAFLD versus those with lean NAFLD. (A) ALT, (B) albumin, (C) hemoglobin, (D) creatinine, (E) uric acid, and (F) liver stiffness measurement. The graph represents effect size from each study and black square represents the pooled effect size.

levels among subjects with lean NAFLD compared to healthy subjects without NAFLD (Supporting Fig. S4E,F). Lean NAFLD also had higher mean waist circumference from 22 studies, 0.81 (95% CI, 0.71-0.91); waist to hip ratio from five studies, 0.67 (95% CI, 0.43-0.92); systolic blood pressure from 25 studies, 0.36 (95% CI, 0.27-0.45); fasting glucose from 31 studies, 1.51 (95% CI, 1.21-1.80); and 2-hour postprandial glucose from four studies, 0.45 (95% CI, 0.28-0.62; $P < 0.001$ for all analyses). Data were heterogeneous on all the analyses except for 2-hour postprandial glucose ($I^2 = 0$; $P = 0.54$). There was publication bias on analysis for waist circumference (Egger's $P = 0.03$) but not for any other analysis (Supporting Table S5).

For biochemical and hematologic markers, subjects with lean NAFLD compared to healthy subjects without NAFLD had higher mean serum ALT, ALP, and total bilirubin levels (Fig. 3A-C). Subjects with lean NAFLD also had higher mean serum AST from 27 studies, 0.91 (95% CI, 0.63-1.19; $P < 0.001$); and similar serum albumin levels from three studies, 0.005 (95% CI, −0.48 to 0.49; $P = 0.98$). Subjects with lean NAFLD had higher mean serum creatinine compared to healthy subjects without NAFLD (Fig. 3D). On hematologic assessment, there were no differences comparing subjects with lean NAFLD and healthy subjects on blood hemoglobin from four studies, 0.76 (95% CI, −0.06 to 1.57; $P = 0.09$); and platelet count from six studies, −0.70 (95% CI, −2.06 to 0.66; $P = 0.31$). Data were heterogeneous for all the analyses except total bilirubin ($I^2 = 33$; $P = 0.2$). There was no publication bias on any of the analyses except for serum creatinine analysis (Egger's $P = 0.03$) (Supporting Table S5).

For inflammatory markers, subjects with lean NAFLD compared to healthy subjects had higher mean serum CRP and uric acid levels (Fig. 3E,F). However, there were no differences on mean serum apolipoprotein A from two studies, −2.29 (95% CI, −7.18 to 2.61; $P = 0.36$). Data were heterogeneous with publication bias by Egger's regression test for CRP (Egger's $P = 0.04$) but not for analyses of uric acid (Egger's $P = 0.36$) (Supporting Table S5). Publication bias could not be assessed for apolipoprotein A comparison because there were only two studies in this analysis.

RISK FACTORS AND COMORBIDITIES

Obese NAFLD Versus Lean NAFLD

Of 34 studies included in the analysis, 17 on 9,321 subjects with obese NAFLD and 4,832 subjects with lean NAFLD reported data on risk factors or comorbidities.

Odds of central obesity, hypertension, type 2 diabetes mellitus, impaired fasting glucose, low HDL, and metabolic syndrome were significantly higher among subjects with obese NAFLD compared to subjects with lean NAFLD (Fig. 4A-F). Subjects with obese NAFLD compared to those with lean NAFLD also had approximately a 4-fold risk for increased waist circumference (OR, 3.76; 95% CI, 2.51-5.63; $P < 0.001$). However, there were no differences on elevated triglycerides from four studies (OR, 1.28; 95% CI, 0.82-2.0; $P = 0.28$), dyslipidemia from eight studies (OR, 1.42; 95% CI, 0.83-2.42; $P = 0.20$), and smoking status from eight studies (OR, 0.96; 95% CI, 0.61-1.54; $P = 0.88$).

Odds of coronary artery disease assessed in one study did not find any difference comparing subjects with obese NAFLD versus those with lean NAFLD (OR, 1.84; 95% CI, 0.10-34.02; $P = 0.68$). However, carotid plaques assessed in another study showed higher odds among subjects with obese versus lean NAFLD (OR, 2.24; 95% CI, 1.41-3.56; $P < 0.001$). None of these studies examined clinical outcomes or development of cardiac events. There was no difference in prevalence between subjects with obese NAFLD and those with lean NAFLD with respect to genetic polymorphisms for *PNPLA3* (reported in six studies) and *TM6SF2* genes (reported in three studies) (OR, 0.75; 95% CI, 0.53-1.07; $P = 0.11$ and OR, 0.49; 95% CI, 0.18-1.3; $P = 0.15$, respectively). Data were homogeneous for analyses on central obesity, low HDL, and impaired fasting glucose. Remaining analyses showed heterogeneous data with $I^2 > 50$ or $P < 0.05$. There was no publication bias for any of the analyses (Supporting Table S6) except for dyslipidemia analysis.

Lean NAFLD Versus Healthy Lean

A total of 20 studies on 5,515 subjects with lean NAFLD and 54,652 healthy controls reported data on some or all of the markers of interest.

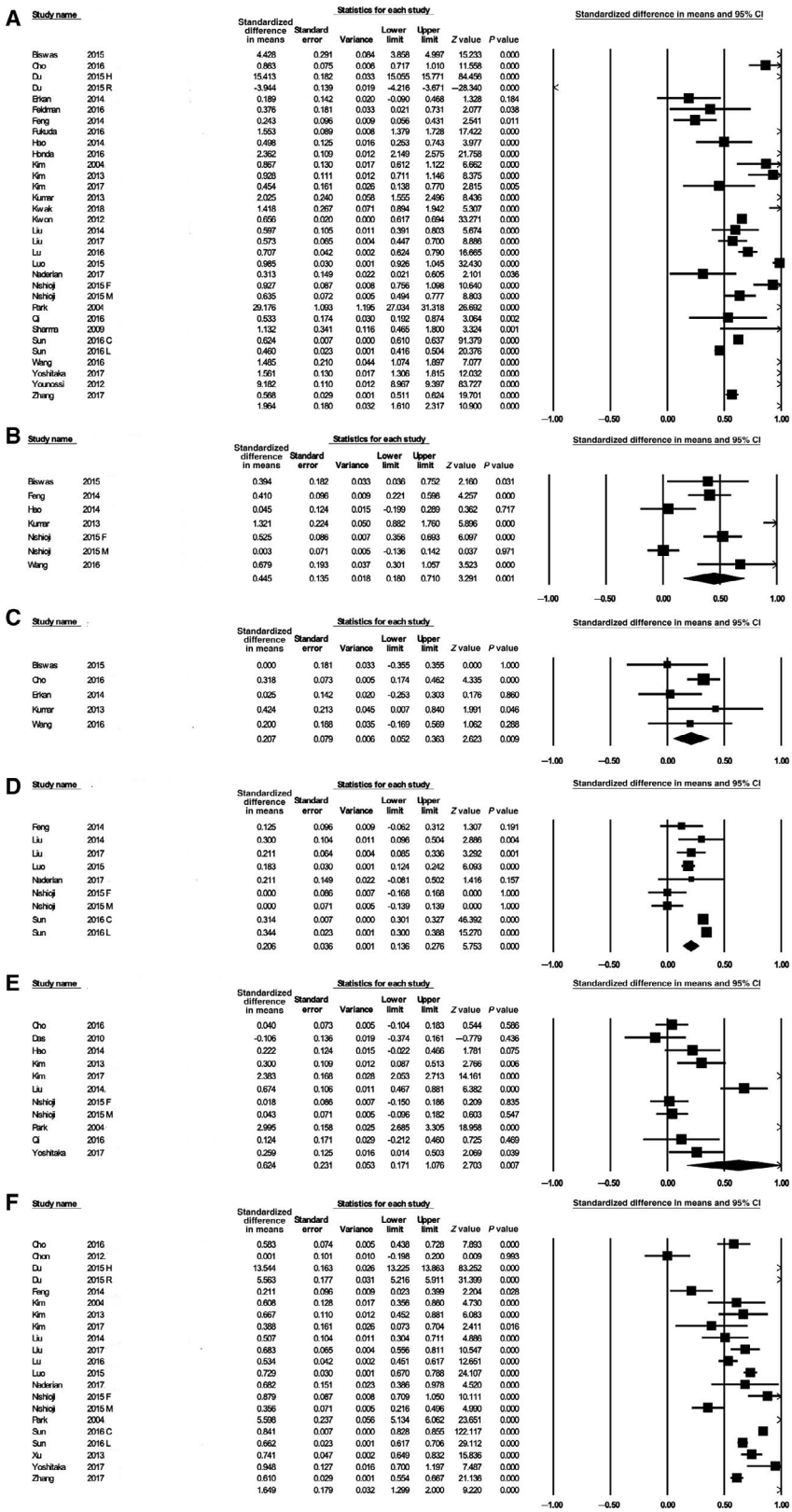


FIG. 3. Pooled data on liver chemistry and biochemical markers of subjects with lean NAFLD versus healthy subjects. (A) ALT, (B) ALP, (C) total bilirubin, (D) creatinine, (E) CRP, and (F) uric acid. The graph represents effect size from each study and black square represents the pooled effect size.

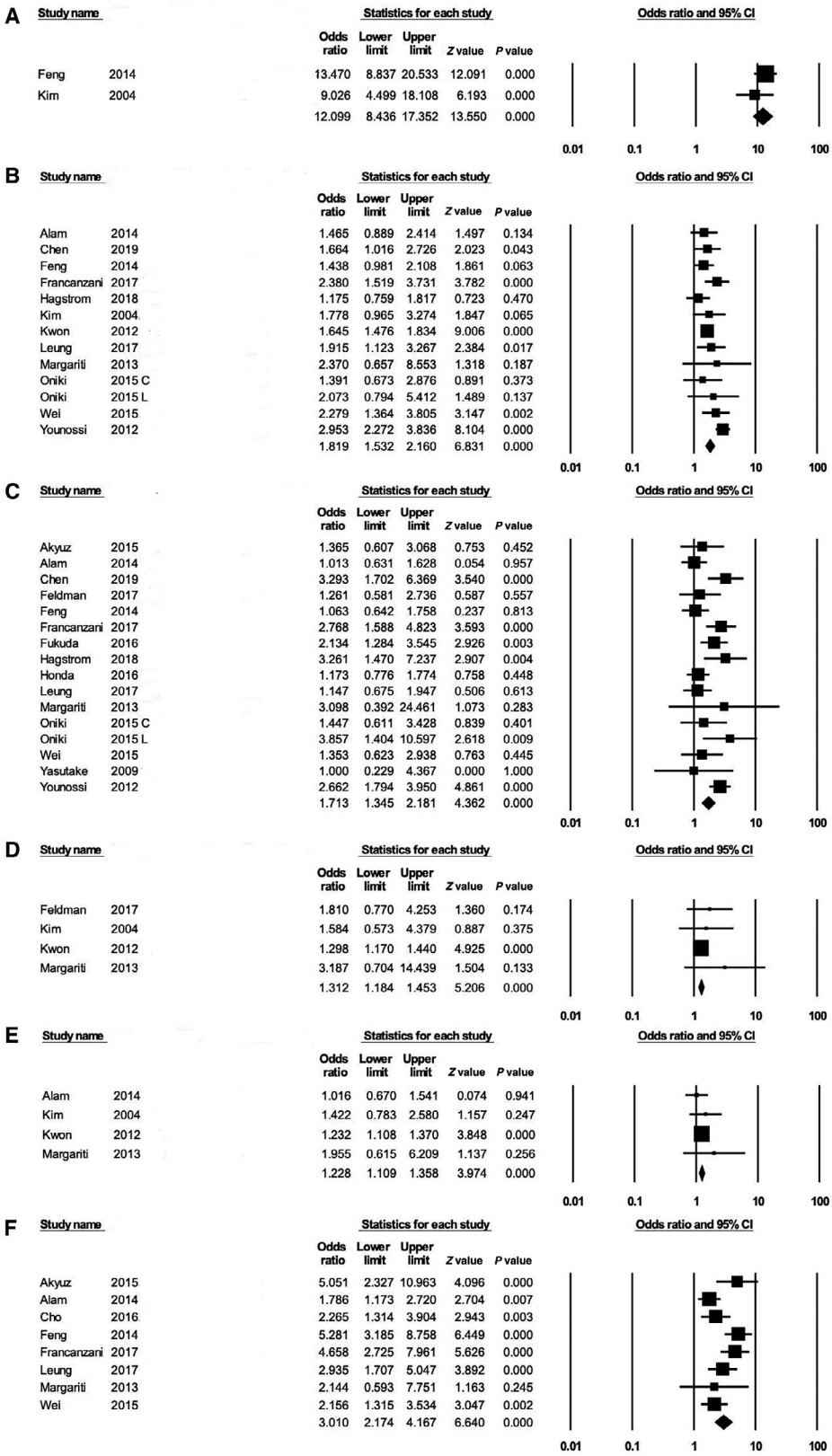


FIG. 4. Pooled data on metabolic syndrome and its components in subjects with obese versus lean NAFLD. (A) Central obesity, (B) hypertension, (C) type 2 diabetes mellitus, (D) impaired fasting glucose, (E) low HDL, and (F) metabolic syndrome. The graph represents effect size from each study and black square represents the pooled effect size.

Subjects with lean NAFLD compared to healthy subjects without NAFLD had increased odds for central obesity, hypertension, type 2 diabetes mellitus, low HDL, and metabolic syndrome (Fig. 5A-E). Subjects with lean NAFLD also had higher odds for impaired fasting glucose and insulin resistance from four studies on each analysis (OR, 3.06; 95% CI, 2.82-3.32 and OR, 3.99; 95% CI, 2.40-6.61, respectively; $P < 0.001$ for all analyses). Data were homogeneous for central obesity ($I^2 = 0$; $P = 0.48$), metabolic syndrome ($I^2 = 45$; $P = 0.08$), and impaired fasting glucose ($I^2 = 0$; $P = 0.46$). Remaining analyses showed heterogeneous data. There was publication bias for analysis on insulin resistance (Egger's $P = 0.03$), but the other analyses did not show any publication bias (Supporting Table S7). Odds for presence of *PNPLA3* genetic polymorphisms evaluated in three studies comparing subjects with lean NAFLD with healthy subjects were 2.69-fold ($P = 0.005$) (Fig. 5F). Data were heterogeneous ($I^2 = 79\%$; $P = 0.008$) without any publication bias (Egger's regression test, $P = 0.98$).

LIVER HISTOLOGY

Because liver biopsies were not performed on healthy subjects without NAFLD, analysis was only done to compare 1,388 subjects with obese NAFLD versus 563 subjects with lean NAFLD from six studies. Odds of hepatocyte ballooning and lobular inflammation on pooled data from four studies were 2.4-fold and 1.9-fold higher, respectively, in subjects with obese NAFLD versus lean NAFLD (Fig. 6A,B). However, odds of severe steatosis (≥66% hepatocytes with steatosis) were similar (OR, 0.85; 95% CI, 0.28-2.57; $P = 0.77$). The presence of NASH on liver biopsy on data pooled from five studies was more than 2-fold more likely with obese NAFLD (Fig. 6C). Data were homogeneous for ballooning (I^2, 43; $P = 0.15$), lobular inflammation (I^2, 52; $P = 0.08$), and NASH (I^2, 51; $P = 0.08$). However, there was significant heterogeneity on steatosis analysis with I^2 ($P = 89$; $P < 0.001$). All analyses were devoid of any publication bias (Supporting Table S8).

The severity of NASH and its components were assessed comparing two groups on the score of the respective variable. Obese NAFLD compared to lean NAFLD had a higher mean score for ballooning (0.29), steatosis grade (0.20), and NAS (0.31) (Supporting Fig. S5A-C). The severity assessment did not show any difference on mean score for lobular inflammation comparing subjects with obese versus lean NAFLD, with a mean difference in score of 0.40 (95% CI, −0.11 to 0.90; $P = 0.12$). Data were homogeneous for ballooning (I^2, 27; $P = 0.25$), but significant heterogeneity was observed for analysis on lobular inflammation ($I^2 = 92$; $P < 0.001$) and NASH (I^2, 69; $P = 0.04$). All analyses were devoid of any publication bias (Supporting Table S8).

Pooled data on liver fibrosis from four studies showed that 890 subjects with obese NAFLD compared to 397 subjects with lean NAFLD were more than 2.5-fold more likely to have fibrosis (Fig. 6D). The data were heterogeneous ($I^2 = 69$; $P = 0.03$) without any publication bias (Supporting Table S6). Severity of fibrosis and its stage reported from two studies showed that mean fibrosis stage tended to be higher by 0.17 among 641 subjects with obese NAFLD compared to 206 subjects with lean NAFLD ($P = 0.06$) (Supporting Fig. S5D). The data were homogeneous ($I^2 = 16$; $P = 0.28$), and publication bias could not be assessed because there were only two studies in this analysis.

OUTCOMES

Two studies[23,24] compared patients with obese NAFLD versus lean NAFLD for overall survival, hepatic decompensation, and cause of death, whether liver related or from a cardiovascular cause. The analyses (Fig. 7) demonstrated that lean had better outcomes, with 28% lower odds of mortality compared to patients with obese NAFLD. The data were homogeneous ($I^2 = 0$), without publication bias (Egger's $P = 0.46$). Although the odds for hepatic decompensation were no different, the odds of liver-related mortality in one study was 78% lower among patients with lean NAFLD versus those with obese NAFLD.[24] The analysis of cardiovascular causes of death was similar in pooled data from both studies. Data were homogeneous on all analyses without publication bias, except for the analysis of liver-related decompensation (Fig. 7).

Discussion

The prevalence of lean NAFLD in this pooled data and meta-analysis is 11.2% in the general population and 25.2% among individuals with NAFLD,

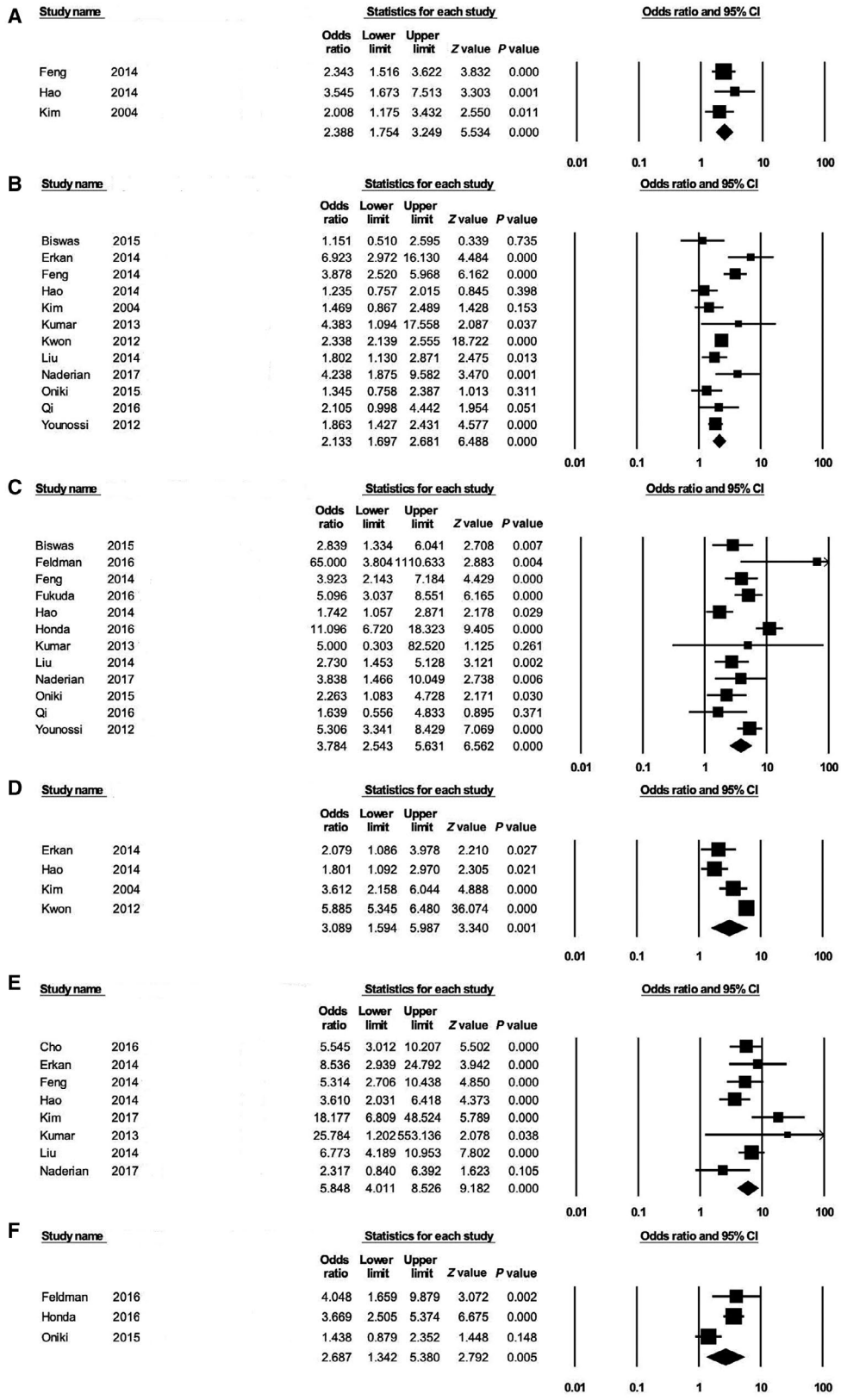


FIG. 5. Pooled data on metabolic syndrome components and genetics in subjects with lean NAFLD versus healthy subjects. (A) Central obesity, (B) hypertension, (C) type 2 diabetes mellitus, (D) low HDL, (E) metabolic syndrome, and (F) *PNPLA3*. The graph represents effect size from each study and black square represents the pooled effect size.

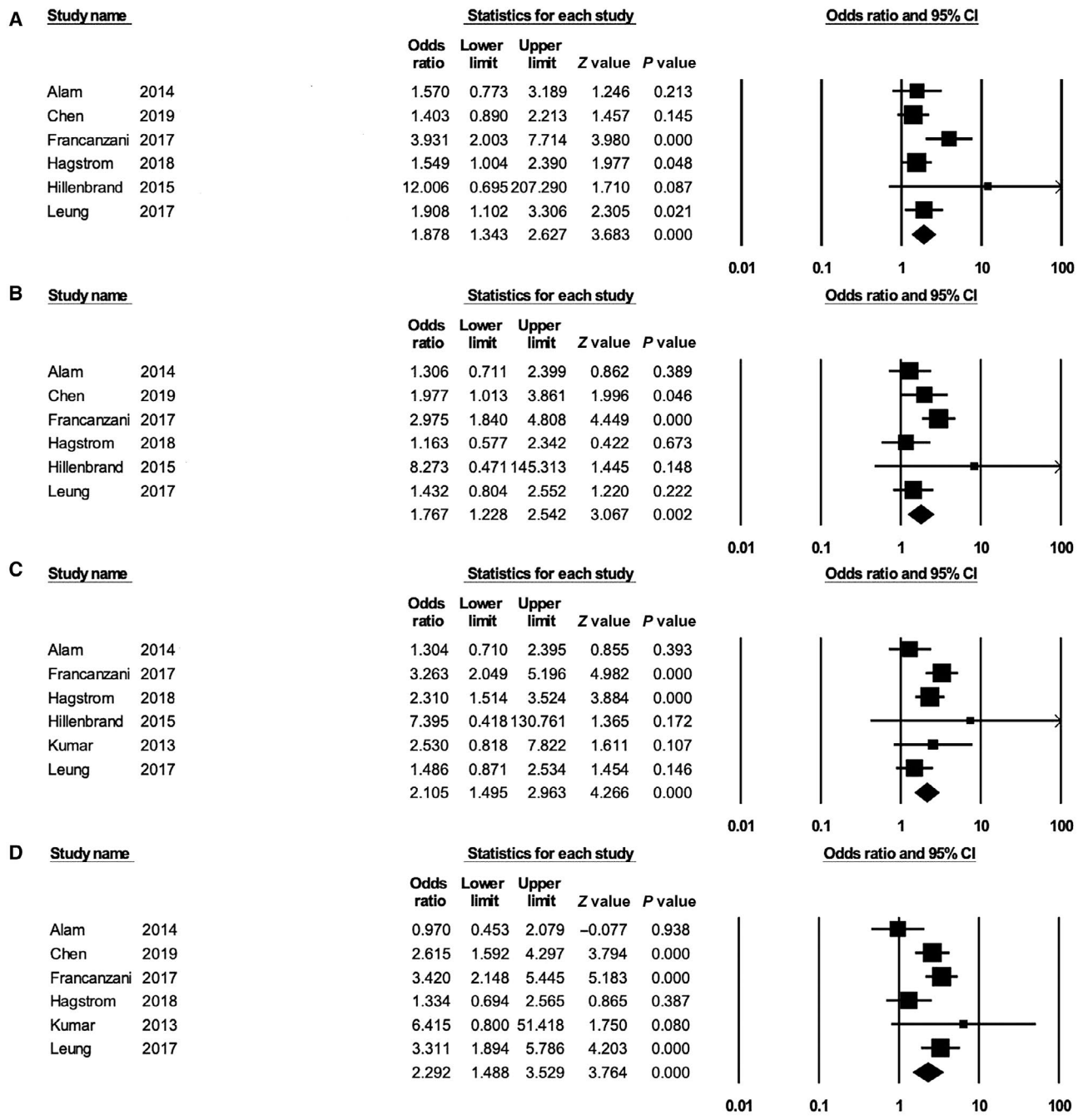
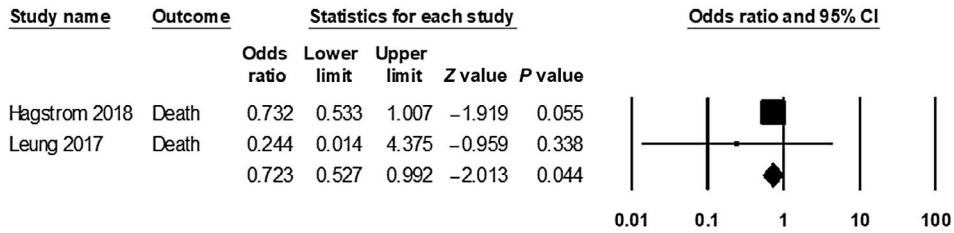


FIG. 6. Pooled data on liver histology comparing obese NAFLD versus lean NAFLD. Odds for (A) hepatocyte ballooning, (B) lobular inflammation, (C) NASH, and (D) fibrosis stage ≥3. The graph represents effect size from each study and black square represents the pooled effect size.

with the highest prevalence in Asia. Patients with lean NAFLD versus healthy adults have an abnormal metabolic and inflammatory profile, with higher prevalence of metabolic syndrome and risk factors for NAFLD. Further, the metabolic and inflammatory profile is less severe and more favorable among lean compared to obese NAFLD. These findings are associated with less severe liver histology in lean NAFLD, including NASH with its inflammatory components and fibrosis stage (Table 2).

The prevalence of lean NAFLD across different studies varies from 5% to 26% in the general population and



	No. of studies	OR (95% CI), *P*	I^2, *P*
CV death	2	0.71 (0.41–1.22), 0.21	29, 0.23
Liver-related death	1	0.22 (0.11–0.47), <0.001	NA
Decompensation	2	0.29 (0.04–2.08), 0.22	83, 0.016

FIG. 7. Pooled data on clinical outcomes comparing lean versus obese NAFLD. The forest plot compares patient survival. The table shows other outcomes for liver-related mortality, cardiovascular-related mortality, and liver decompensation. The graph represents effect size from each study and black square represents the pooled effect size. Abbreviations: CV, cardiovascular; NA, not applicable.

TABLE 2. SUMMARY OF FINDINGS OF SYSTEMATIC REVIEW AND META-ANALYSIS

	Lean NAFLD Versus Healthy Controls	Obese Versus Lean NAFLD
Demographics	Older with higher BMI; no sex difference	Higher BMI; no difference in age and sex
Comorbidities	Higher odds for metabolic syndrome with all its components	Higher odds for metabolic syndrome with all its components
PNPLA3 and *TM6SF2* polymorphisms	Increased odds for *PNPLA3* polymorphisms	No difference
Metabolic markers	Increased measurements on insulin resistance and all components of metabolic syndrome	Increased measurements on insulin resistance and all components of metabolic syndrome
Biochemical and hematologic	Higher ALT, AST, ALP, serum bilirubin, and serum creatinine levels	Higher ALT, serum creatinine, and hemoglobin levels
Inflammatory markers	Higher serum uric acid levels	Higher serum CRP and uric acid levels
Liver histology	Not available	Higher odds for NASH with its components and fibrosis Higher mean score for steatosis grade, ballooning, and NAS Higher mean fibrosis stage
Liver stiffness measurement	Not available	Higher mean liver stiffness measurement

from 20% to 50% among individuals with NAFLD.[14] The reasons for this variation across studies are differences in the study population, the method to detect steatosis, and the cutoff to define lean (Table 1). Disease modifiers, especially genetic predisposition, may also explain this variation, as observed in this study with subjects with lean NAFLD having higher odds of *PNPLA3* polymorphisms compared to healthy individuals.

The presence of NAFLD among individuals with normal BMI and absence of other known causes of steatosis raises a question as to whether lean NAFLD is a unique syndrome or falls within the spectrum of metabolic disease and phenotype of typical NAFLD in individuals who are overweight or obese. BMI is not a measure of body fat content or a surrogate of increased waist circumference and abdominal/visceral obesity, which actually predisposes an individual to steatosis.[19,20] Individuals with lean NAFLD compared to healthy individuals were more likely to have central obesity with increased waist circumference, other

components of metabolic syndrome, insulin resistance, and higher levels of inflammatory markers. Hence, these individuals have an unhealthy metabolism with a worse inflammatory profile compared to healthy individuals. It is suggested that individuals with lean NAFLD have a gut-dominant pathology with higher primary and secondary bile acid levels, with changes in gut microbiota predisposing them to NAFLD and NASH.[21] It can be speculated that individuals with lean NAFLD have a body composition that favors development of visceral obesity, insulin resistance, and NAFLD.[22]

Furthermore, metabolic and inflammatory abnormalities were less severe and more favorable among patients with lean NAFLD compared to those with obese NAFLD. Data comparing NAFLD versus without NAFLD in subjects with obesity is not available, with limited evaluation of the specific effect of NAFLD. These differences between the profiles of obese versus lean NAFLD may also suggest that lean NAFLD is in the spectrum of the typical phenotype of obese NAFLD. Worse metabolic and inflammatory profiles in obese versus lean NAFLD translated into more advanced liver disease in individuals with obesity, with higher liver stiffness measurements and worse histologic findings of severe steatosis, NASH along with its components, and fibrosis stage. Similarly, clinical outcomes were worse in individuals with obese versus individuals with lean NAFLD. Limited prospective data have not reported a transition of lean NAFLD to the obese phenotype to confirm the hypothesis that lean NAFLD is an earlier stage in the spectrum of NAFLD.[22,23]

A recent elegant study from Australia comparing lean to obese NAFLD confirmed a more favorable metabolic, inflammatory, and metabolic profile. However, patients with lean NAFLD had higher bile acid levels, with increased farnesoid X receptor activity, as reflected in levels of fibroblast growth factor (FGF). This may explain the phenotype of these lean patients as bile acids and FGF activity are known to improve metabolism of glucose and lipids as well as regulate energy expenditure.[24] Further, the gut microbiome profile was distinctly different in lean compared to obese NAFLD.[21] These gut-mediated adaptation mechanisms distinct in lean NAFLD in this study suggest that lean NAFLD is a distinct phenotype of metabolically obese with normal weight.

Prospective studies will address long-term patient outcomes of overall and transplant-free survival. In the only available prospective study on 307 subjects with NAFLD, 72 (23.5%) patients with lean NAFLD had less advanced histologic findings, and this translated into improved survival and outcomes among lean versus obese NAFLD over a median follow-up of 49 months.[23] In this study, negative outcomes developed in 9 patients, with 6 patients dying, 2 patients developing hepatocellular carcinoma, and 1 patient developing liver failure.[23] In contrast, another study on a larger cohort of biopsy-proven 646 patients with NAFLD, lean NAFLD (19% of the cohort) had a favorable histologic profile, as seen in our study. However, over a mean follow-up of approximately 20 years, patients with lean NAFLD compared to those with obese NAFLD had a 2.7-fold increased risk of liver-related mortality without increased risk for overall mortality.[22] Pooling these two studies, lean versus obese NAFLD had better outcomes in terms of patient survival and liver-related mortality. More prospective studies with a large sample and long-term follow-up are needed to examine long-term outcomes and also fibrosis progression rate among patients with lean versus obese NAFLD.

A strength of this study is the large sample size analyzed with inclusion of multiple studies, and it is the first systematic review and meta-analysis focusing on lean NAFLD. However, our study suffers from limitations, especially heterogeneous data on most of the analyses (Supporting Tables S2-S6). The heterogeneity is likely due to variations on study population, especially a different cutoff to define leanness (25 in most studies and 23 in some studies; Table 1), and the observational nature of studies with some poor quality studies as assessed using the Newcastle-Ottawa scale. However, after excluding studies that included individuals who were overweight, the data that remained unchanged comparing obese versus lean NAFLD overcame the limitation of BMI cutoff for defining individuals who are lean. Further, the data are overrepresented with studies from Asia, limiting generalizability and impact on results. In spite of these limitations, we feel that the study findings are relevant for physicians in clinical practice to be diligent in individuals with normal BMI but with other risk factors, especially central obesity, diabetes, and metabolic syndrome, and to screen them for the presence of NAFLD. Early identification to address their metabolic abnormalities with counseling for weight loss will help in preventing progression to a more

advanced NAFLD spectrum of NASH and/or fibrosis. It has been shown that weight loss of 7% to 10%, even in individuals with NAFLD and normal BMI, helps in the regression of NAFLD, with improvement of metabolic abnormalities.[24]

In summary, lean NAFLD is a recognized distinct entity with an abnormal metabolic and inflammatory profile compared to healthy individuals and a more favorable metabolic, inflammatory, and histologic profile compared to obese NAFLD. Although limited data suggest better clinical outcomes and natural history for lean versus obese NAFLD, larger multicenter prospective studies with long-term follow-up are needed.

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