Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis

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Summary

Background Although non-alcoholic fatty liver disease (NAFLD) is commonly associated with obesity, it is increasingly being identified in non-obese individuals. We aimed to characterise the prevalence, incidence, and long-term outcomes of non-obese or lean NAFLD at a global level.

Methods For this systematic review and meta-analysis, we searched PubMed, Embase, Scopus, and the Cochrane Library from inception to May 1, 2019, for relevant original research articles without any language restrictions. The literature search and data extraction were done independently by two investigators. Primary outcomes were the prevalence of non-obese or lean people within the NAFLD group and the prevalence of non-obese or lean NAFLD in the general, non-obese, and lean populations; the incidence of NAFLD among non-obese and lean populations; and long-term outcomes of non-obese people with NAFLD. We also aimed to characterise the demographic, clinical, and histological characteristics of individuals with non-obese NAFLD.

Findings We identified 93 studies (n=10 576 383) from 24 countries or areas: 84 studies (n=10 530 308) were used for the prevalence analysis, five (n=9121) were used for the incidence analysis, and eight (n=36 954) were used for the outcomes analysis. Within the NAFLD population, 19·2% (95% CI 15·9–23·0) of people were lean and 40·8% (36·6–45·1) were non-obese. The prevalence of non-obese NAFLD in the general population varied from 25% or lower in some countries (eg, Malaysia and Pakistan) to higher than 50% in others (eg, Austria, Mexico, and Sweden). In the general population (comprising individuals with and without NAFLD), 12·1% (95% CI 9·3–15·6) of people had non-obese NAFLD and 5·1% (3·7–7·0) had lean NAFLD. The incidence of NAFLD in the non-obese population (without NAFLD at baseline) was 24·6 (95% CI 13·4–39·2) per 1000 person-years. Among people with non-obese or lean NALFD, 39·0% (95% CI 24·1–56·3) had non-alcoholic steatohepatitis, 29·2% (21·9–37·9) had significant fibrosis (stage ≥2), and 3·2% (1·5–5·7) had cirrhosis. Among the non-obese or lean NAFLD population, the incidence of all-cause mortality was 12·1 (95% CI 0·5–38·8) per 1000 person-years, that for liver-related mortality was 4·1 (1·9–7·1) per 1000 person-years, cardiovascular-related mortality was 4·0 (0·1–14·9) per 1000 person-years, new-onset diabetes was 12·6 (8·0–18·3) per 1000 person-years, new-onset cardiovascular disease was 18·7 (9·2–31·2) per 1000 person-years, and new-onset hypertension was 56·1 (38·5–77·0) per 1000 person-years. Most analyses were characterised by high heterogeneity.

Interpretation Overall, around 40% of the global NAFLD population was classified as non-obese and almost a fifth was lean. Both non-obese and lean groups had substantial long-term liver and non-liver comorbidities. These findings suggest that obesity should not be the sole criterion for NAFLD screening. Moreover, clinical trials of treatments for NAFLD should include participants across all body-mass index ranges.

Funding None.

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects about 25% of the global population and is associated with metabolic derangements such as diabetes, obesity, hyperlipidaemia, and hypertension.[1] NAFLD can progress from simple steatosis (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, hepatocellular carcinoma, and death.[1] NAFLD has surpassed viral hepatitis as the leading cause of morbidity due to chronic liver disease in western countries, given the recent therapeutic advances for both chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV). The prevalence of NAFLD has also increased in the other parts of the world, such as Asia.[2] Additionally, NAFLD is increasingly being recognised in non-obese individuals, who might even have worse outcomes than obese individuals with NAFLD, with more rapid development of cirrhosis.[3–6]

Therefore, we aimed to characterise the prevalence of, and factors associated with, non-obese or lean NAFLD at

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Research in context

Evidence before this study

Non-alcoholic fatty liver disease (NAFLD) affects about 25% of the global population. Although commonly associated with obesity, NAFLD is increasingly being identified in non-obese individuals. However, data on the global prevalence of non-obese NAFLD and its associated outcomes are scarce. Before undertaking this study, we searched four databases (PubMed, Embase, Scopus, and the Cochrane Library) using the search terms "NAFLD" AND "Non-obese" without any language restrictions, for articles published from database inception to May 1, 2019. No meta-analysis of such a study has been published.

Added value of this study

In this systematic review and meta-analysis, we estimated that the overall prevalence of non-obese NAFLD was 40·8% among the NAFLD population and 12·1% in the general population. The prevalence of lean NAFLD was 19·2% among the NAFLD population and 5·1% in the general population. The incidence of NAFLD among non-obese people was 24·6 per 1000 person-years. Among people with non-obese or lean NALFD, about 39·0% had non-alcoholic steatohepatitis (NASH) and 29·2% had significant fibrosis; incidence of all-cause mortality was 12·1 per 1000 person-years, of liver-related mortality was 4·1 per 1000 person-years, of cardiovascular-related mortality was 4·0 per 1000 person-years, incidence of new-onset hypertension was 56·1 per 1000 person-years, new-onset diabetes was 12·6 per 1000 person-years, and new-onset cardiovascular disease was 18·7 per 1000 person-years.

Implications of all the available evidence

Around 40% of people with NAFLD are not obese but they have high mortality and are just as metabolically unhealthy as obese people with NAFLD; almost 40% of non-obese people with NAFLD have NASH and almost 30% have significant fibrosis. Therefore, screening for NAFLD should consider other metabolic risks besides bodyweight, and clinical trials of treatments for NAFLD should include participants across all body-mass index ranges.

a global level, the incidence of NAFLD in non-obese individuals, and the long-term clinical sequelae of NAFLD in this population. Such data could help health-care systems develop appropriate guidance and interventions to treat this liver disease.

Methods

Search strategy and selection criteria

See Online for appendix

This systematic review and meta-analysis was done in accordance with PRISMA guidelines (appendix pp 2–3).[7] We searched for published studies in PubMed (including MEDLINE), Embase, Scopus, and the Cochrane Library from inception to May 1, 2019, using search terms that were chosen in collaboration with an experienced medical librarian (CDS) so that as many relevant articles for each hypothesis could be retrieved.[8]

Our search term for PubMed (from inception to May 1, 2019) was as follows: ("nonalcoholic fatty liver" [tw] OR "non-alcoholic fatty liver" [tw] OR ("non-alcoholic" [ti] AND fatty [ti]) OR "non-alcoholic fatty liver disease" [mesh] OR (nonalcoholic [ti] AND fatty [ti]) OR ((non-alcoholic [ti] OR nonalcoholic [ti]) AND "fatty liver" [mesh]) OR "nonalcoholic steatohepatitis" [tw] OR NAFLD [tw]) AND ("thinness" [mesh] OR thin [tw] OR thinness [tw] OR lean [tw] OR "non obese" [tw] OR nonobese [tw] OR "normal weight" [tw] OR "non overweight" [tw] OR nonoverweight [tw] OR "non obesity" [tw] OR nonobesity [tw] OR underweight [tw]) NOT ("animals" [mesh] NOT "humans" [mesh]). Further details of our search strategy and data collection, including terms for other databases, are described in the appendix (pp 4–5).

We included original research articles that defined their population as non-obese or lean individuals aged 18 years or older and defined NAFLD with stratification according to weight status (non-obese or lean). We included studies in which data about the prevalence, incidence, and clinical outcomes of NAFLD in the non-obese or lean population were either available or allowed for such calculations. We applied no language restrictions.

We excluded articles if we were unable to ascertain how NAFLD was diagnosed; if patients with HBV, HCV, or those with other causes of liver disease or excess alcohol consumption were not excluded; if they were duplicate research articles on the same cohort from the same time period (we only included the articles with the most data available); if the study population comprised individuals with another chronic disease such as HBV, HIV, obstructive sleep apnoea, or polycystic ovary syndrome; if the number of study participants was lower than 50; or if the study excluded certain populations known to be at risk of NAFLD (eg, individuals with diabetes).

To enhance the sensitivity of the search, we included synonyms for "non-alcoholic fatty liver disease" and "non-obese", without further limiting the search with terms related to epidemiology (eg, prevalence, incidence, and so on).[8] We also searched the bibliographies of selected studies for additional articles. The literature search, data review, and data extraction were done with a case report form to provide consistency throughout the data collection process. Data were extracted independently by two investigators (any two of QY, JL, DQH, YW, HY, CL, LYK, XXET, NC, ST, or TH). The κ coefficient was 0·83. Discordance and disagreements were resolved by consensus between the two investigators or by consultation with a third and senior investigator (MHN).

NAFLD was diagnosed by ultrasound, CT, MRI or magnetic resonance spectroscopy, controlled attenuation

parameter, fatty liver index, hepatic steatosis index, liver-spleen attenuation index, or liver biopsy,[9] in the absence of excessive alcohol consumption, viral hepatitis, autoimmune hepatitis, haemochromatosis, Wilson's disease, and other secondary causes of fatty liver (eg, drugs or hereditary disorders).

The NAFLD population was derived from patients diagnosed with NAFLD as mentioned above; the general population was defined in each study included in our analysis, and included patients from health-care centres and clinics (health-care check-up clinics and regular medical clinics) and from epidemiological surveys (group surveys of patients from a defined geographical region based on reasonably generalisable methods when sampling the population) that included both individuals with and without NAFLD and both obese and non-obese individuals.

Generally, non-Asians were considered to be lean if they had a body-mass index (BMI) lower than 25 kg/m² and overweight if they had a BMI of 25·0–29·9 kg/m², whereas Asians were considered to be lean if they had a BMI lower than 23 kg/m² and overweight if they had a BMI of 23·0–27·5 kg/m², as defined in the studies included in our analysis.[10,11] Since our study was not designed to capture obese NAFLD, we were not able to compare all study outcomes to those of obese individuals with NAFLD; however, for studies that provided data on obese NAFLD, we have included these data in our analyses.

The non-obese population comprised individuals who were considered lean and overweight in the original study. The lean population comprised only those individuals who were considered lean by the original studies. Studies reporting data for the lean population were included in the analysis for lean NAFLD but not for non-obese NAFLD. Global regions were defined according to the UN classification.[12]

To study the prevalence of NASH among the non-obese and lean NAFLD populations, we only used research articles that had liver biopsy data. NASH was defined as the presence of steatosis (>5% of the parenchyma), lobular inflammation, and ballooning.[13]

We estimated the incidence of non-obese or lean NAFLD among non-obese or lean populations using studies that provided data on incidence and follow-up years for study populations with no NAFLD at baseline. We also provided pooled estimates for all-cause, cardiovascular, and liver-related mortality as well as the incidence of diabetes, cardiovascular disease, and hypertension for individuals with NAFLD.

We used a quality assessment scale based on the Newcastle-Ottawa scale for this study, ranging from 0 to 9, with 7–9 representing high quality scores, 4–6 representing medium scores, and 1–3 representing low scores.[14]

Data analysis

Primary outcomes were the prevalence of non-obese or lean people within the NAFLD group and the prevalence of non-obese or lean NAFLD in the general, non-obese, or lean populations (including those with and without NAFLD); the incidence of NAFLD among non-obese and lean populations; and long-term outcomes for non-obese individuals with NAFLD.[10,11] In our secondary outcome analysis we aimed to characterise the demographic,

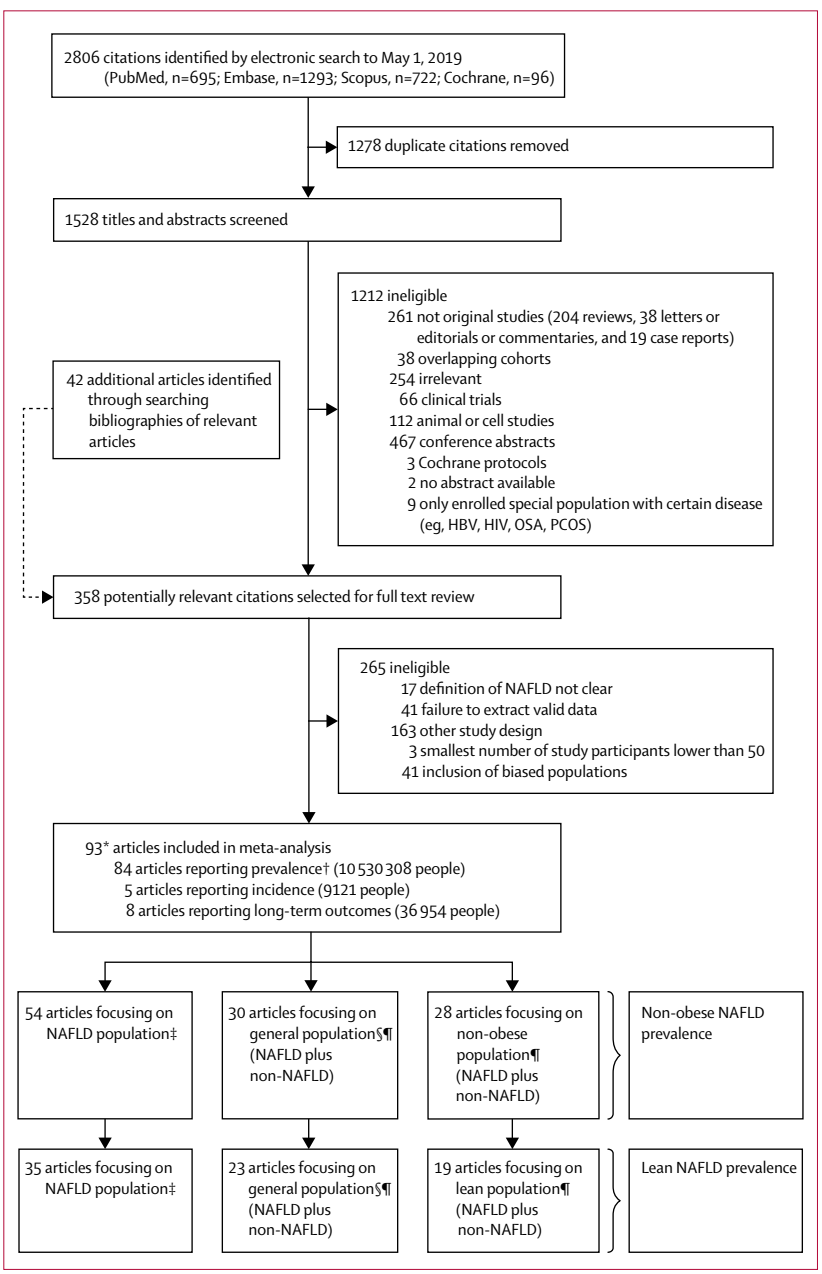

Figure 1: **Study selection**

NAFLD=non-alcoholic fatty liver disease. HBV=hepatitis B virus. OSA=obstructive sleep apnoea. PCOS=polycystic ovary syndrome. *Some articles were used for more than one of the analyses of prevalence, incidence, and long-term outcomes. †Some articles provided data for more than one of the following six analyses: non-obese NAFLD prevalence in the NAFLD population, general population, and non-obese population, and lean NAFLD prevalence in the NAFLD population, general population, and non-obese population. ‡For prevalence of non-obese or lean NAFLD among NAFLD population. §Including obese and non-obese people. ¶For prevalence of non-obese or lean NAFLD among the population with NAFLD and those without NAFLD.

clinical, and histological characteristics of non-obese individuals with NAFLD.

We assessed heterogeneity using the Cochran Q-statistic and I^2 statistic. Estimates with a p value lower than 0·05 for the Q-statistic and I^2 of 50% or greater were considered to have moderate heterogeneity. As global data were expected to be heterogeneous, we used a random-effects model to pool the prevalence of non-obese individuals with NAFLD. For prevalence, we used the number of participants in each study as the denominator. For incidence, the denominator was person-years of follow-up. Additionally, in the overall analyses, we did not include data from studies that included only men (n=2)[15,16] or only women (n=1).[17] Additional references can be found in the appendix (pp 5–9). However, these studies were included in our subgroup analyses as described below.

The following subgroup analyses were done to determine the source of heterogeneity: age, sex, BMI

	Studies (n)	NAFLD (n)	Non-obese NAFLD (n)	Prevalence (95% CI)	p value	I^2*
Overall NAFLD population	54	63 017	24 890	40·8% (36·6–45·1)	..	99·0%
By sex†						
Male	24	2 016 819	330 850	39·2% (30·7–48·3)	0·64	99·6%
Female	23	12 532	4813	41·8% (35·5–48·4)	..	98·3%
By age						
<45 years	17	15 999	6960	35·9% (27·1–45·8)	0·32	99·0%
≥45 years	35	45 981	17 348	41·4% (36·5–46·6)	..	99·0%
By median year of study						
Before 2006	13	27 849	11 696	39·1% (32·6–46·0)	0·96	99·0%
2006–12	19	15 372	6212	40·3% (35·3–45·5)	..	96·5%
After 2012	18	18 305	6327	40·4% (29·1–52·7)	..	99·5%
By BMI cutoff‡						
Normal bodyweight	11	23 105	2740	15·8% (10·1–23·8)	<0·0001	99·0%
Overweight	20	27 191	9176	32·2% (27·4–37·4)	..	98·3%
By country or area						
Mainland China	10	22 861	8599	44·3% (30·2–59·3)	<0·0001	99·7%
South Korea	10	9794	3466	37·4% (30·6–44·7)	..	97·8%
India	8	1691	734	47·7% (35·8–60·0)	..	94·9%
Taiwan	5	12 168	5493	36·3% (22·8–52·4)	..	99·2%
Japan	4	2379	931	39·1% (37·2–41·1)	..	97·2%
Spain	2	1130	379	38·7% (25·8–53·4)	..	84·1%
Hong Kong	2	569	207	36·4% (14·4–65·9)	..	97·8%
Netherlands	1	8259	3288	39·8% (38·8–40·9)	..	..
Sri Lanka	1	974	305	31·3% (28·5–34·3)	..	..
Sweden	1	646	458	70·9% (67·3–74·3)	..	..
Romania	1	604	282	46·7% (42·7–50·7)	..	..
Austria	1	466	316	67·8% (63·4–71·9)	..	..
Bangladesh	1	465	119	25·6% (21·8–29·8)	..	..
Italy	1	428	232	54·2% (49·5–58·9)	..	..
Pakistan	1	142	32	22·5% (16·4–30·1)	..	..
USA	1	125	54	43·2% (34·8–52·0)	..	..
Malaysia	1	101	13	12·9% (7·6–20·9)	..	..
Finland	1	82	41	50·0% (39·3–60·7)	..	..
Turkey	1	70	37	52·9% (41·2–64·2)	..	..
Mexico	1	63	44	69·8% (57·5–79·9)	..	..
By world region§						
Eastern Asia	31	47 771	18 556	37·8% (32·0–43·9)	<0·0001	99·3%
Southern Asia	11	3272	1190	40·9% (32·5–49·9)	..	95·1%
Southeast Asia	1	101	13	12·9% (7·6–20·9)	..	..
Western Asia	1	70	37	52·9% (41·2–64·2)	..	..
Europe	8	11 615	4996	51·3% (41·6–61·0)	..	98·2%
America	2	188	98	56·6% (30·4–79·5)	..	91·3%

(Table 1 continues on next page)

	Studies (n)	NAFLD (n)	Non-obese NAFLD (n)	Prevalence (95% CI)	p value	I^2*
(Continued from previous page)						
By study setting						
Population based	9	19 239	7859	39·9% (33·9–46·2)	0·60	97·9%
Health-care centres (check-up clinics)	20	34 470	13 450	44·1% (35·3–53·3)	..	99·5%
Health-care centres (medical clinics)	25	9308	3581	38·4% (32·0–45·2)	..	97·3%
By diagnostic method						
Ultrasound	33	46 951	18 493	42·0% (36·3–47·9)	<0·0001	99·2%
CT	1	271	188	69·4% (63·6–74·6)	..	..
MRS	2	344	176	51·2% (45·9–56·4)	..	..
FLI	1	8259	3288	39·8% (38·8–40·9)	..	..
HSI	1	409	52	12·7% (9·8–16·3)	..	..
Liver biopsy	14	5168	1910	35·7% (25·2–47·9)	..	98·4%
CAP	2	1615	783	50·1% (42·5–57·6)	..	86·9%
By sample size						
>500	21	56 280	22 087	39·5% (33·2–46·2)	0·65	99·5%
50–500	33	6737	2803	41·7% (35·2–48·4)	..	96·2%
By study quality assessment score						
≥7	45	49 689	19 436	40·8% (35·8–46·1)	0·54	99·1%
<7	9	13 328	5454	43·5% (36·9–50·3)	..	96·1%

NAFLD=non-alcoholic fatty liver disease. BMI=body-mass index. MRS=magnetic resonance spectroscopy. FLI=fatty liver index. HSI=hepatic steatosis index. CAP=controlled attenuation parameter. *All p values for I^2 are less than 0·05. †Three articles included only either men or women and were included only in subgroup analysis by sex (appendix p 25). ‡One article included only overweight participants and were included only in subgroup analysis by BMI cutoff (appendix p 25). §Eastern Asia comprised data from mainland China, Japan, South Korea, Taiwan, and Hong Kong; southeast Asia comprised data from Malaysia; southern Asia comprised data from India, Bangladesh, Pakistan, and Sri Lanka; western Asia was comprised Turkey and Iran; Europe comprised data from Italy, the Netherlands, Romania, Finland, Spain, Sweden, Greece, Germany, Belgium, and Austria; and the Americas comprised data from the USA and Mexico.

Table 1: **Non-obese NAFLD prevalence among the NAFLD population**

cutoff, study period, study setting, and country or area. Pooled mean values were reported for the anthropometric measurements of lipid profiles, blood sugar results, blood pressure, renal function tests, and liver function tests in the overall NAFLD population, and in non-obese NAFLD and obese NAFLD populations. Additionally, we did a subgroup analysis of the prevalence of non-obese NAFLD for different diagnostic modalities, age, study sample size, and study quality assessment score. We also did a subgroup analysis of the prevalence of non-obese NAFLD for studies with ultrasound diagnosis only and with liver biopsy diagnosis only. We used a random-effects model to pool the incidence of non-obese NAFLD among non-obese individuals without NAFLD at baseline and to estimate the pooled incidence of mortality, new-onset diabetes, cardiovascular disease, and hypertension among non-obese individuals with NAFLD. Additionally, we used Egger's test to assess for publication bias. All statistical analyses were done with the meta packages in R statistical software (version 3.5.2).

Role of the funding source

There was no external funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We retrieved 2806 articles using our search method. After removing duplicates, 1528 records were retained (figure 1). We excluded 1212 ineligible titles and abstracts using the aforementioned exclusion criteria. Consequently, we retained and evaluated the full text of 316 published articles. After adding 42 studies from the bibliographies of relevant articles and excluding 265 ineligible citations, 93 reports were included in the study analysis. These 93 reports covered 24 countries and areas: 18 from mainland China,[16–33] 16 from South Korea,[15,34–48] 11 from India,[49–59] ten from Japan[60–69] six from Taiwan,[70–75] four from Hong Kong,[76–79] four from the USA,[80–83] three from Italy,[84–86] three from Turkey,[87–89] two from Iran,[90,91] two from Spain,[92,93] two from Sri Lanka,[94,95] and one from each of the following countries: Austria,[96] Bangladesh,[97] Belgium,[98] Finland,[99] Germany,[100] Greece,[101] Malaysia,[102] Mexico,[103] Netherlands,[104] Pakistan,[105] Romania,[106] and Sweden.[6] 84 studies[6,15–32,34–46,49–66,70–78,80–82,84–97,99–106] including 10 530 308 people were used for the prevalence analysis; five studies[27,33,47,79,95] including 9121 people were used for the incidence analysis; and eight studies[6,48,67–69,76,83,95] including 36 954 people were used for long-term NAFLD outcomes (mortality, new-onset diabetes, cardiovascular disease, and hypertension). Some articles contained data for more than one of our aims, so the numbers do not add up directly.

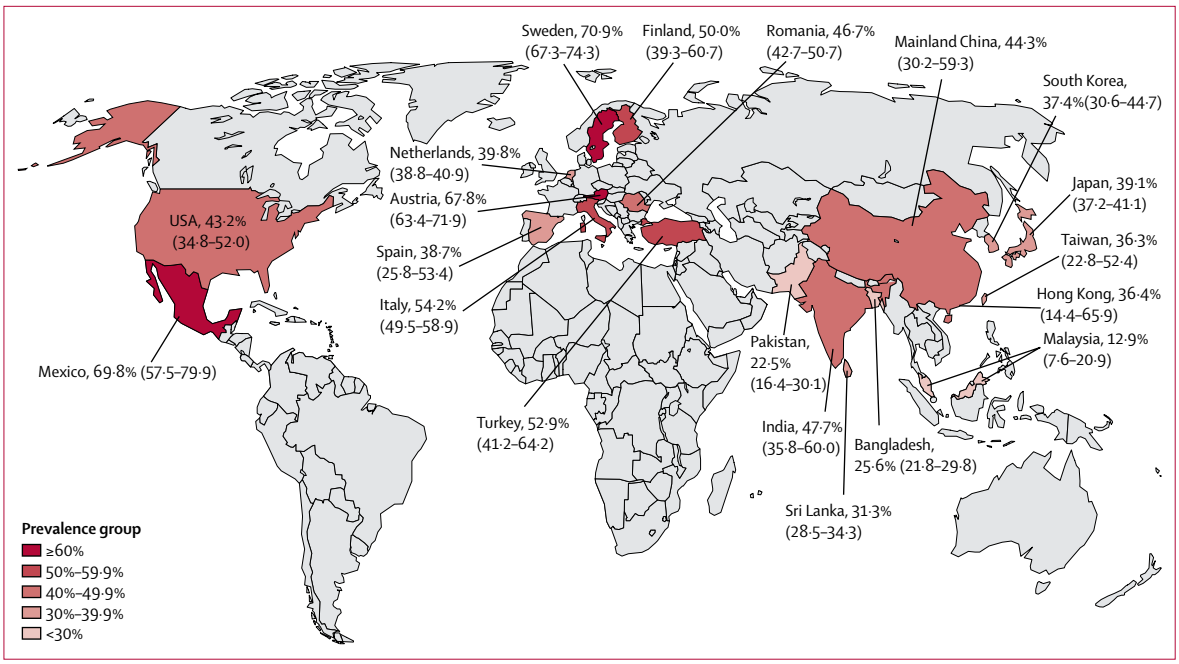

Figure 2: **The global prevalence of non-obese NAFLD in the NAFLD population**
Data are percentages with 95% CI. NAFLD=non-alcoholic fatty liver disease.

The quality assessment of each paper included in the study is shown in the appendix (pp 10–21). The average score in the quality assessment was 7·4, indicating that most studies were of a high quality. Egger's test did not show significant publication bias in the overall and major subgroup analyses (p=0·81 for non-obese NAFLD prevalence analysis for the general population, p=0·58 for the non-obese general population, and p=0·80 for the NAFLD population; appendix pp 56–58).

Because the majority of studies (54 studies, n=63 017; appendix pp 22–25)[6,18–27,34–43,49–56,60–63,70–74,76,77,80,84,87,92–94,96,97,99,102–106] were done within the NAFLD population, we chose this population for our main analysis. There was high heterogeneity among the results. The overall prevalence of non-obese NAFLD within the NAFLD population was 40·8% (95% CI 36·6–45·1). Prevalence varied by country (p<0·0001), as noted in table 1 and the appendix (pp 26–29).

Figure 2 shows the prevalence of non-obese NAFLD among individuals with NAFLD for all countries with at least one study. Significant differences were observed among the countries. Among countries that had at least four studies, India had the highest prevalence of non-obese NAFLD, at 47·7% (95% CI 35·8–60·0) and Taiwan had the lowest, at 36·3% (22·8–52·4). However, one study from Taiwan[72] had a potentially biased sample (patients were selected for biopsy), and when this study was excluded the pooled estimate for non-obese NAFLD in Taiwan increased to 41·4% (25·6–59·2). Among the regions that had at least four studies, Europe had the highest prevalence of non-obese NAFLD, at 51·3% (95% CI 41·6–61·0) and eastern Asia had the lowest, at 37·8% (95% CI 32·0–43·9). Ultrasound was the most common method used to diagnose NAFLD and the prevalence of non-obese NAFLD detected with ultrasound was 42·0% (95% CI 36·3–47·9; table 1).

The overall and subgroup prevalence for non-obese NAFLD in the general population is shown in table 2 and the appendix (pp 33–35). There was high heterogeneity among the results. The overall non-obese NAFLD prevalence (30 studies, n=218 106; appendix pp 30–32)[21,24–27,34–37,39–44,49,52,56,61,62,70,71,73,74,77,84,94,103–105] in the general population was 12·1% (95% CI 9·3–15·6), which did not differ significantly compared with the general population when including those with (10·4% [95% CI 6·0–17·3]) and without (12·2% [9·2–16·0]) other liver diseases (p=0·59). Prevalence varied by BMI, with the highest prevalence among those who were overweight (8·6% [95% CI 6·7–11·0]) compared to those with a normal weight (4·9% [3·1–7·7]; p<0·0001).

Among countries that had at least four studies on which to draw, Taiwan had the highest prevalence of non-obese NAFLD (12·9%; 95% CI 7·2–22·2) and mainland China the lowest, at 9·0% (95% CI 4·4–17·5; p<0·0001). The most common diagnostic method used, reported in 23 studies (n=171 361)[21,24–27,34,35,39–41,43,49,52,56,61,62,70,71,73,74,94,103,105] was ultrasound, which provided a non-obese NAFLD prevalence of 11·1% (95% CI 8·1–15·1). Prevalence was 12·8% (95% CI 9·1–17·6) among those diagnosed in check-up clinics compared to 8·4% (6·7–10·6) for population-based cohorts (p<0·0001).

The prevalence of non-obese NAFLD among the non-obese subgroup of the general population, and study

	Studies (n)	Participants (n)	Non-obese NAFLD (n)	Prevalence (95% CI)	p value	I^2*
Overall general population	30	218 106	22 160	12·1% (9·3–15·6)	..	99·7%
With or without other liver disease† in denominator population						
With other liver disease	3	10 636	893	10·4% (6·0–17·3)	0·59	98·5%
Without other liver disease	27	207 470	21 267	12·2% (9·2–16·0)	..	99·8%
By sex‡						
Male	13	10 565 552	330 578	9·9% (5·7–16·7)	0·22	99·9%
Female	13	79 784	4993	6·5% (4·5–9·5)	..	99·3%
By age						
<45 years	9	89 581	7886	9·8% (5·4–17·3)	0·54	99·8%
≥45 years	19	127 403	14 061	12·1% (8·8–16·5)	..	99·7%
By median year of study						
Before 2006	9	104 730	11 073	9·2% (5·2–15·6)	0·57	99·9%
2006–12	11	56 355	6137	12·7% (8·8–17·9)	..	99·4%
After 2012	9	56 861	4906	13·3% (6·9–24·0)	..	99·8%
By BMI cutoff§						
Normal weight	14	77 731	3482	4·9% (3·1–7·7)	<0·0001	99·3%
Overweight	12	72 795	7813	8·6% (6·7–11·0)	..	98·9%
By country or area						
South Korea	10	36 546	4174	11·7% (7·3–18·3)	<0·0001	99·6%
Mainland China	5	107 583	7683	9·0% (4·4–17·5)	..	99·9%
Taiwan	4	24 502	5469	12·9% (7·2–22·2)	..	99·6%
India	3	2173	257	13·2% (4·9–30·7)	..	98·0%
Japan	2	4095	541	14·0% (11·1–17·4)	..	83·0%
Hong Kong	1	911	135	14·8% (12·7–17·3)	..	98·0%
Sri Lanka	1	2985	305	10·2% (9·2–11·4)	..	..
Pakistan	1	806	32	4·0% (2·8–5·6)	..	..
Netherlands	1	37 496	3288	8·8% (8·5–9·1)	..	..
Italy	1	890	232	26·1% (23·3–29·1)	..	..
Mexico	1	119	44	37·0% (28·8–46·0)	..	..
By world region¶						
Eastern Asia	22	173 637	18 002	11·7% (8·4–16·1)	<0·0001	99·8%
Southern Asia	5	5964	594	10·0% (5·7–16·9)	..	97·4%
Europe	2	38 386	3520	15·5% (4·9–39·6)	..	99·6%
America	1	119	44	37·0% (28·8–46·0)	..	..
By study setting						
Population based	9	104 232	7859	8·4% (6·7–10·6)	<0·0001	98·7%
Health-care centres (check-up clinics)	19	111 460	13 417	12·8% (9·1–17·6)	..	99·7%
Health-care centres (medical clinics)	2	2414	884	32·9% (24·1–43·1)	..	83·5%
By diagnostic method						
Ultrasound	23	171 361	16 874	11·1% (8·1–15·1)	<0·0001	99·7%
CT	1	1184	188	15·9% (13·9–18·1)	..	..
MRS	1	911	135	14·8% (12·7–17·3)	..	..
FLI	1	37 496	3288	8·8% (8·5–9·1)	..	..
HSI	1	1812	52	2·9% (2·2–3·8)	..	..
Liver biopsy	1	2254	840	37·3% (35·3–39·3)	..	..
CAP	2	3088	783	25·4% (23·9–26·9)	..	..

NAFLD=non-alcoholic fatty liver disease. BMI=body-mass index. MRS=magnetic resonance spectroscopy. FLI=fatty liver index. HSI=hepatic steatosis index. CAP=controlled attenuation parameter. NAFLD=non-alcoholic fatty liver disease. *All p values for I^2 are lower than 0·05. †Other liver diseases, especially viral hepatitis, alcoholic liver diseases, autoimmune hepatitis, Wilson's disease, cirrhosis or liver cancer, or other secondary causes of fatty liver (eg, drugs or hereditary disorders). ‡Two articles included either men or women and were included only in subgroup analysis by sex (appendix p 32). §Six articles included overweight or normal weight participants' data and were included when in subgroup analysis by BMI cutoff. One article included only overweight participants and was included only when in subgroup analysis by BMI cutoff (appendix pp 31–32). ¶Eastern Asia comprised data from mainland China, Japan, South Korea, Taiwan, and Hong Kong; southern Asia comprised data from India, Pakistan, and Sri Lanka; Europe comprised data from Italy and the Netherlands, whereas the Americas comprised data from Mexico.

Table 2: **Non-obese NAFLD prevalence among the general population**

	Studies (n)	Participants (n)	Lean NAFLD (n)	Prevalence (95% CI)	I^2**
NAFLD population	35	36 529	5387	19·2% (15·9–23·0)	98·0%
General population	23	113 394	4575	5·1% (3·7–7·0)	99·0%
Lean population	19	49 503	4211	10·6% (7·8–14·1)	99·0%

NAFLD=non-alcoholic fatty liver disease. *All p values for I^2 are lower than 0·05.

Table 3: **Lean NAFLD prevalence among the NAFLD, general, and lean populations**

characteristics are summarised in the appendix (pp 36–40). There was high heterogeneity among the results. The overall prevalence of non-obese NAFLD among the non-obese general population was 18·3% (95% CI 14·0–23·7, 28 studies, n=160 879).[21,24–26,28,34–37,39–42,44,45,49,61,62,70,71,73,74,77,84,88,103–105] Notably, those diagnosed from 2006 to 2012 had a higher prevalence of NAFLD (22·7%, 95% CI 14·5–33·9) than did those diagnosed before 2006 (10·9%, 7·6–15·4) or after 2012 (19·3%, 12·0–29·7; p=0·022).

The prevalence of non-obese NAFLD in the NAFLD population with diabetes was 27·0% (95% CI 7·0–64·7, two studies, n=173; appendix p 24)[57,64] and among the general population with diabetes it was 2·4% (0·5–11·9, two studies, n=2301; appendix p 31).[57,64] The prevalence of non-obese NAFLD among the non-obese general population with diabetes was 36·1% (95% CI 1·9–94·4), but this analysis only included two studies and 189 individuals (appendix p 40).[64,85] There was high heterogeneity among the results.

The prevalence of lean NAFLD is shown in table 3 and the appendix (p 45). Among the NAFLD population (35 studies, n=36 529),[6,19,23,24,27,29–31,35,50,51,52,54-56,58,59,62,65,66,71,75,78,82,86,87,89,90,95,96,101,103–106] 19·2% (95% CI 15·9–23·0) of individuals were considered to have lean NAFLD. Among the general population (23 studies, n=113 394),[24,27,30,31,35,46,52,56,58,62,65,66,71,75,78,82,90,91,95,100,103–105] the prevalence of lean NAFLD was 5·1% (95% CI 3·7–7·0); whereas among the lean population (19 studies, n=49 503),[24,29–32,35,45,58,62,65,66,75,78,82,90,91,103–105] the prevalence of lean NAFLD was 10·6% (95% CI 7·8–14·1). There was high heterogeneity among the results. The characteristics of the studies included in these analyses are summarised in the appendix (pp 41–44).

The incidence of NAFLD among the non-obese, lean, and obese populations is shown in table 4, and individual study characteristics are summarised in the appendix (p 46). There was high heterogeneity among the results. The incidence of non-obese NAFLD among the non-obese population at baseline was 24·6 (95% CI 13·4–39·2) per 1000 person-years (four studies, n=8827)[27,33,47,79] and was similar to the incidence of lean NAFLD among the lean population (23·2 [95% CI 7·3–48·0] per 1000 person-years, four studies, n=3925;[24,33,79,95] p=0·92). The incidence of NAFLD among the obese population was 77·5 (95% CI 28·3–150·6) per 1000 person-years (four studies, n=1969).[27,33,47,79] Due to the large confidence interval, we did a subgroup analysis excluding the study by Wong and colleagues[79] and the one by Yu,[27] because of the small sample sizes of these studies. This analysis provided a pooled incidence of 50·2 (95% CI 6·6–134·3) per 1000 person-years.

The general clinical characteristics of non-obese individuals with NAFLD are summarised in the appendix (pp 48–49), along with those of obese individuals with NAFLD and the total NAFLD population. Non-obese patients with NAFLD had abnormalities in several physical and metabolic measurements: systolic blood pressure (mean 126·3 mm Hg [95% CI 124·1–128·5]), diastolic blood pressure (mean 79·1 mm Hg [77·0–81·3]); fasting blood glucose (mean 104·1 mg/dL [101·3–107·0]; 5·8 mmol/L [5·6–5·9]); Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; mean 2·8 [2·1–3·4]), and cholesterol (mean 202·2 mg/dL [197·1–207·2]; 5·2 mmol/L [5·1–5·4]). Except for blood pressure and HOMA-IR (p=0·035 for systolic blood pressure; p=0·026 for diastolic blood pressure, and p=0·048 for HOMA-IR), the other measurements did not differ significantly to those of obese individuals with NAFLD.

The prevalence of diabetes was 24·1% (95% CI 15·8–35·1) among non-obese individuals with NAFLD (12 studies, n=2248; appendix pp 50–51),[6,36,38,39,60,62,63,72,76,77,96,97] and 13·6% (8·6–21·0) among lean individuals with NAFLD (11 studies, n=1153).[6,30,62,66,75,83,86,89,95,96,101]

The prevalence of NASH among non-obese or lean individuals with NAFLD (appendix pp 52–53) who had a liver biopsy (eight studies, n=1441)[6,38,63,76,86,96,97,101] was 39·0% (95% CI 24·1–56·3), whereas in obese individuals with NAFLD (eight studies, n=2227), NASH prevalence was 52·9% (38·3–67·0). The prevalence of significant lobular inflammation (five studies, n=820)[6,38,86,97,98] was 25·1% (95% CI 14·3–40·1) for non-obese or lean individuals with NAFLD, whereas in obese individuals with NAFLD (five studies, n=1336) it was 35·5% (22·7–50·8). The prevalence of significant fibrosis (six studies, n=1076) in non-obese or lean individuals with NAFLD[6,38,63,86,97,98] was 29·2% (95% CI 21·9–37·9), whereas in obese individuals with NAFLD (six studies, n=1842) it was 38·3% (30·6–46·6). Cirrhosis prevalence (one study, n=316)[96] was 3·2% (95% CI 1·5–5·7; ten of 316 non-obese individuals with NAFLD had cirrhosis) but was 2·0% (0·4–5·7) for obese individuals with NAFLD (one study, n=150). Heterogeneity was high across all analyses.

Long-term NAFLD-related outcomes among the non-obese or lean NAFLD population and, where applicable, the obese NAFLD population, are shown in table 5 (individual study characteristics are provided in the appendix [pp 54–55]). Among the non-obese or lean NAFLD population, the incidence was 12·1 (95% CI 0·5–38·8) per 1000 person-years (three studies, n=35 707) for all-cause mortality,[6,48,83] 4·0 (0·1–14·9) per 1000 person-years for cardiovascular-related mortality (three studies, n=35 707),[6,48,83] and 4·1 (1·9–7·1) per 1000 person-years for liver-related mortality (one study, n=123).[6] The incidence of diabetes (three studies, n=771)[67,68,95] was 12·6 (95% CI 8·0–18·3) per 1000 person-years, incidence of new-onset

	Studies (n)	Non-NAFLD participants at baseline (n)	Incident patients with NAFLD (n)	Follow up (person-years)	Incidence per 1000 person-years (95% CI)	I^2*
Non-obese population	4	8827	678	50 234·9	24·6 (13·4–39·2)	97·7%
Lean population	4	3925	187	10 423·5	23·2 (7·3–48·0)	97·5%
Obese population	4	1969	433	10 033·8	77·5 (28·3–150·6)	98·6%

NAFLD=non-alcoholic fatty liver disease. *All p values for I^2 are lower than 0·05.

Table 4: **NAFLD incidence among non-obese, lean, and obese populations**

	Studies (n)	Non-obese or lean and obese NAFLD (n)	Incident cases (n)	Follow up (person-years)	Incidence per 1000 person-years (95% CI)	I^2*
All-cause mortality (non-obese or lean NAFLD group)	3	35 707	590	194 805·8	12·1 (0·5–38·8)	99·6%
All-cause mortality (obese NAFLD group)	2	56 577	495	296 566·0	7·5 (0·0–33·6)	99·2%
Cardiovascular-related mortality† (non-obese or lean NAFLD group)	3	35 707	156	194 805·8	4·0 (0·1–14·9)	99·2%
Cardiovascular-related mortality† (obese NAFLD group)	2	56 577	105	296 566·0	2·4 (0·0–13·3)	98·3%
Liver-related mortality (non-obese or lean NAFLD group)	1	123	10	2447·7	4·1 (1·9–7·1)	..
Liver-related mortality (obese NAFLD group)	1	168	8	3343·2	2·4 (1·0–4·4)	..
New-onset diabetes (non-obese or lean NAFLD group)	3	771	67	5655·2	12·6 (8·0–18·3)	58·6%
New-onset diabetes (obese NAFLD group)	..	..	..	..	..	..
New-onset cardiovascular disease† (non-obese or lean NAFLD group)	2	141	12	640·2	18·7 (9·2–31·2)	..
New-onset cardiovascular disease† (obese NAFLD group)	1	235	32	959·6	33·3 (22·7–46·0)	..
New-onset hypertension (non-obese or lean NAFLD group)	1	84	33	588	56·1 (38·5–77·0)	..
New-onset hypertension (obese NAFLD group)	..	..	..	..	..	..

NAFLD=non-alcoholic fatty liver disease. *All p values for I^2 are lower than 0·05. †Death from cardiovascular disease included coronary heart disease, stroke, and cerebral haemorrhage.

Table 5: **Long-term outcomes of non-obese, lean, and obese NAFLD**

cardiovascular disease was 18·7 (9·2–31·2) per 1000 person-years (two studies, n=141),[69,76] and incidence of new-onset hypertension was 56·1 (38·5–77·0) per 1000 person-years (one study, n=84).[95]

Among the obese NAFLD population, the incidence was 7·5 (95% CI 0·0–33·6) per 1000 person-years (two studies, n=56 557) for all-cause mortality,[6,48] 2·4 (0·0–13·3) per 1000 person-years for cardiovascular-related mortality (two studies, n=56 557)[6,48] and 2·4 (1·0–4·4) per 1000 person-years for liver-related mortality (one study, n=168).[6] The incidence of new-onset cardiovascular disease (one study, n=235)[76] was 33·3 (95% CI 22·7–46·0) per 1000 person-years. Heterogeneity was high across all incidence data except for new-onset diabetes for the non-obese or lean population with NAFLD.

Discussion

We found that the global prevalence of non-obese NAFLD among the NAFLD population was just over 40% and the prevalence of non-obese NAFLD in non-obese population was almost 20%, suggesting that non-obese NAFLD contributes to a large share of the burden of this chronic liver disease. Additionally, contrary to the common belief that non-obese NAFLD is more prevalent among Asian countries, we found that Europe had the highest (about 50%) and eastern Asia had the lowest prevalence of non-obese NAFLD among the NAFLD population, although it was still high at 38%.

The reason for the observed difference in non-obese NAFLD prevalence between Europe and east Asia is unclear but one potential explanation might be due to differences in gut microbiota of different ethnic populations; a previous microbiome study has also indicated a substantial difference in faecal and blood microbiota profiles between obese and lean individuals with NAFLD.[107]

NAFLD is a disease with complex traits. Therefore, the interaction between environmental factors and host genetic background has a substantial role in the pathogenesis of NAFLD.[108–111] Previous studies showed a pivotal

role of interferon lambda 4 rs368234815 TT>δG and rs12979860CC variants in mediating the inflammation and fibrosis associated with NAFLD, and development of the disease.[112,113] There are also ethnic variations and genetic variations, especially within Asia, that can contribute to the development of NAFLD. When compared with obese NAFLD, non-obese NAFLD showed a more favourable metabolic and histological profile.[114] Based on a previous survey on food intake, non-obese individuals with NAFLD had substantially higher cholesterol and lower polyunsaturated fatty acid intake than did obese individuals with NAFLD.[115] Gut microbiota also have an important role in NAFLD. For instance, one study indicated a substantial difference in microbiota profiles between obese and lean individuals with NAFLD.[107] Lean patients with NASH had specific gut microbiota composition that showed pathogenesis of liver injury that was independent from food consumption.[116] More studies are needed that address these particular mechanisms of action that can lead to the development of NAFLD in non-obese people.[117] As treatment strategies evolve for NAFLD, these differences will need to be kept in mind as one treatment approach might not work for all patients.

Our estimated prevalence of lean NAFLD within the lean population (10·6%) is similar to that of a meta-analysis by Shi and colleagues,[118] who reported an NAFLD prevalence of 10·2% in the lean population. Our estimated prevalence of non-obese NAFLD in the non-obese general population (18·3%) was also similar to the non-obese NAFLD prevalence reported by Shi and colleagues[118] in the non-obese population (15·7%). Previous studies have shown that metabolic status, including diabetes, arterial hypertension, and dyslipidaemia, was associated with NAFLD independently of BMI.[93] Together these results suggest that non-obese and lean NAFLD are not uncommon and that BMI by itself should not be used as an exclusionary criterion to determine whether further testing is warranted to confirm or rule out NAFLD. Our findings have also expanded this previous work by quantifying the prevalence of lean and non-obese NAFLD, which could be used for economic modelling and to assist policy makers in their decision making.

Another notable area for which data were scarce was determining the incidence of NAFLD in lean and non-obese individuals. In this study, we found that the incidence of NAFLD in lean people is 23·2 per 1000 person-years, which closely matches the incidence of NAFLD in the non-obese population (24·6 per 1000 person-years). We also found that the non-obese NAFLD group was more likely to be insulin-resistant, have higher plasma triglyceride concentrations, and, if not diabetic, to have a metabolic milieu similar to that of obese patients with NAFLD. Additionally, non-obese individuals were noted to not only have abnormal laboratory findings but also elevated blood pressure as per the new American College of Cardiology (ACC) guidelines (systolic blood pressure 120–129 mm Hg, diastolic blood pressure <80 mm Hg).[119] These factors again suggest that BMI alone should not be the sole criterion on which to determine the testing threshold for NAFLD, as many patients with NAFLD have metabolic abnormalities.

Furthermore, we found that the incidence of diabetes within the non-obese NAFLD population was 12·6 per 1000 person-years compared with the global estimate for adults (aged >18 years) in 2014 (8·5%),[120] indicating that individuals with non-obese NAFLD carry a substantial disease burden associated with diabetes.[120] The presence of diabetes also increases the burden of liver disease due to an increased risk of progression to liver cirrhosis and hepatocellular carcinoma.[121,122]

Therefore, when non-obese patients present with elevated glycated haemoglobin (HbA_{1c}) concentrations, elevated glucose, plus elevated cholesterol or elevated blood pressure, or both, as defined by the ACC, health-care providers should not rule out NAFLD.[119] And although we do not have long-term data to determine the reversal of NAFLD progression when individuals with NAFLD receive treatment for diabetes, current studies provide some promising evidence that treatment of diabetes is beneficial for lowering the risk of progression of liver disease or reversing disease progression.[122–126]

We surmise that many non-obese individuals with NAFLD might have NASH, since we found that among those with liver histology data, the proportion of non-obese or lean individuals with NAFLD who had NASH was 39%, similar to the NASH prevalence of 37% reported in an analysis of 1600 obese patients who had undergone bariatric surgery[127] and the prevalence of 53% we found in our small analysis of obese individuals with NAFLD. The proportion of non-obese individuals with NAFLD and fibrosis (≥stage 2) was 29%, whereas the proportion of obese patients with NAFLD and fibrosis (≥stage 2) was 38%; this finding is important since the stage of fibrosis independently predicts mortality. Previous studies have suggested that once NASH is present, it is not the presence of obesity that causes further liver degradation but the presence of other variables such as diabetes, suggesting that non-obese NAFLD is not a benign disease.[1,76,128–130] Further studies are needed to ascertain the true natural history of lean NAFLD versus obese NAFLD since our study was not designed to make this comparison.

The incidence of all-cause mortality for non-obese individuals with NAFLD in our study (12·1 per 1000 person-years) was similar to the overall mortality for NAFLD reported in a previous study (15·4 per 1000 person-years).[1] Liver-related mortality was almost two times higher in the non-obese NAFLD population than in the obese NAFLD population and five times higher than previous reported data for the overall (obese and non-obese) NAFLD population (0·77 per 1000 person-years);[1] however, because of the scarcity of separate data for non-obese and obese populations, further research is necessary before any conclusions are made.

A strength of our analysis was that most studies used ultrasound as their diagnostic method. Although ultrasound has its limitations, it is currently the recommended method for diagnosis of NAFLD as other more precise methods are under investigation.[131] We were also able to provide global data by country and by regions, which provides countries with the necessary data as they develop policies to address this rising cause of liver disease. Additionally, our study built on a recent meta-analysis on this topic by providing long-term outcome data, more updated and more comprehensive data as well as a more in-depth subgroup analysis with inclusion of more studies than the previous meta-analysis (93 studies compared to 45 studies).[118]

However, this study is not without its limitations. We were unable to include many relevant abstracts in this meta-analysis as enough detail was not available in the abstracts to do a quality analysis. We were also unable to report on the occurrence of cancer in individuals with NAFLD, which is an area that needs further exploration as solid tumours, especially gastric, colon, and pancreatic cancers, are seen more frequently in individuals with NAFLD than in those without NAFLD.[132] Additionally, the general population in our study might not represent the average patient population since our definition included obese and non-obese individuals and those with and without NAFLD from both epidemiological surveys as well as health-care clinics and other clinical facilities. There was high heterogeneity across the majority of our results. We did subgroup analyses to better understand where the heterogeneity might have occurred; however, because of the small number of studies in many of our subgroup analyses, we were not able to analyse subgroups by potential risk strata, and high heterogeneity remained; results should therefore be interpreted with caution, especially those that had fewer than two studies or those with small sample sizes. Further research into non-obese NAFLD is needed for a more complete understanding[133] of this chronic liver disease.

In conclusion, non-obese NAFLD constitutes just over 40% of the NAFLD population and is common in both eastern and western countries. People with non-obese NAFLD are metabolically unhealthy and many have NASH (40%) and fibrosis (≥stage 2; 30%); mortality is high (12·1 per 1000 person-years). As such, BMI should not be the sole criterion for screening of NAFLD; instead, the presence of metabolic diseases such as diabetes, hypercholesterolaemia, or elevated blood pressure, or both elevated blood pressure and hypercholesterolaemia, should warrant further investigation into the presence of NAFLD. We recommend that clinical trials of interventions for NAFLD keep in mind the different profiles of people with NAFLD to make sure all groups are adequately represented.

Contributors

QY, YHY, and MHN contributed to study design. QY, JL, DQH, YW, HY, CL, LYK, XXET, NC, ST, CDS, TH, and MHN contributed to data acquisition. QY, BZ, YHY, and MHN contributed to data analysis. QY, LH, and MHN drafted the manuscript. All authors contributed to data interpretation and review and revision of the manuscript. MHN was responsible for study concept and study supervision.

Declaration of interests

TH reports speaking fees and educational funds from Gilead. RCC reports research support from Gilead. MHN reports research support from Gilead and Pfizer; and consulting and advisory board fees from Intercept and Gilead. All other authors declare no competing interests.

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