***Title*: The global epidemiology of lean nonalcoholic fatty liver disease: a systematic review and meta-analysis**

Short title: Lean NAFLD epidemiology

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List of Abbreviations

NAFLD: nonalcoholic fatty liver disease; CI: confidence interval; BMI: body mass index; MAFLD: metabolic dysfunction-associated fatty liver disease; CKD: chronic kidney disease; CVD: cardiovascular disease; OR: odds ratio; SMD: standardized mean difference.

Contributors

FBL and MHZ conceived and designed the study. FBL, KIZ and RSR acquired the data. FBL and MHZ analyzed and interpreted the data. FBL, KIZ and RSR drafted the initial manuscript. MHZ, GT and CDB critically revised the manuscript for important intellectual content. All authors approved the final version of the report.

Declaration of conflicts of interest

We declare no competing interests.

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Abstract

Background and Aim: Lean nonalcoholic fatty liver disease (NAFLD) is a potentially metabolically unhealthy state that refers to NAFLD occurring in non-overweight/non-obese subjects. Yet its global epidemiology and metabolic characteristics are not extensively elucidated.

Methods: PubMed, EMBASE, Web of Science and Cochrane databases were searched for eligible studies to January 2020. Random-effects/fixed-effects models were used to estimate the global prevalence of lean NAFLD and to compare clinical characteristics among lean non-NAFLD, lean NAFLD and overwight/obese NAFLD subjects. 'Lean' NAFLD was defined by ethnic-specific body mass index measurements in the normal range. Meta-regression and subgroup analyses were performed to determine potential sources of heterogeneity.

Results: 33 observational studies were included with 205,307 individuals from 14 countries. The global prevalence of lean NAFLD was 4.1% (95%CI: 3.4-4.8%). In lean subjects the prevalence of NAFLD was 9.7% (95%CI: 7.7-11.8%). The prevalence of lean NAFLD with diabetes, hypertension, metabolic syndrome, dyslipidemia or central obesity was 0.6% (95%CI: 0.4-0.9%), 1.8% (95%CI: 1.2-2.5%), 1.4% (95%CI: 1.0-1.9%), 2.8% (95%CI: 1.9-3.7%) and 2.0% (95%CI: 1.6-2.4%), respectively. The prevalence of lean NAFLD showed an upward trend between 1988 and 2017. Asian individuals had the highest prevalence of lean NAFLD (4.8%, 95%CI: 4.0-5.6%). Middle-aged people (45-59 years old) had the highest prevalence of lean NAFLD (4.4%, 95%CI: 3.2-5.5%). The prevalence of metabolic complications in lean non-NAFLD, lean NAFLD and overweight/obese NAFLD groups increased sequentially.

Conclusions: Lean NAFLD occurs with metabolic complications and is not an

uncommon condition. The highest prevalence of lean NAFLD occurs in middle-aged individuals of Asian countries.

Keywords: Lean NAFLD, Non-overweight, Epidemiology, Body mass index, Meta-analysis, Metabolism

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of ≥5% of hepatic steatosis, diagnosed by imaging or histology, in the absence of significant alcohol consumption and other known causes of liver diseases.[1] Due to the heterogeneity of the pathogenesis of NAFLD and its strong association with metabolic dysfunction, it has recently been proposed that NAFLD should be renamed as metabolic dysfunction-associated fatty liver disease (MAFLD), which may also in turn aid international researchers in trial recruitment.[2] It is well known that NAFLD may progress to liver fibrosis and hepatocellular carcinoma and is also a risk factor for important extra-hepatic complications [i.e., cardiovascular disease (CVD) and chronic kidney disease (CKD)], irrespective of coexisting metabolic disorders, such as obesity, type 2 diabetes and dyslipidemia.[3-5] The rising tide of NAFLD has become a significant public health problem worldwide as it is significantly associated with increased mortality from liver-related and liver-unrelated causes.[6]

NAFLD is strongly associated with central overweight or obesity, but NAFLD also occurs in lean subjects, which is described as lean NAFLD.[7] 'Lean' is mainly defined by body mass index (BMI), while BMI cutoffs vary across published studies. At present, the most frequently used definition for lean NAFLD is a BMI <23 kg/m^2 for Asian subjects and BMI <25 kg/m^2 for non-Asian subjects, respectively. These two BMI thresholds are consistent with the World Health Organization's recommended thresholds for defining overweight in Asian and non-Asian individuals.[8] Recent studies have shown that lean NAFLD is commonly accompanied by metabolic abnormalities and even associated with metabolic complications.[9] Some studies have also reported that lean NAFLD is associated with a higher risk of liver-related

mortality and morbidity than overweight and obese NAFLD.[10] Presently, however, due to the normal values of BMI, the presence of lean NAFLD is often ignored by both patients and health-care professionals. Therefore, we consider that a comprehensive evaluation of the global epidemiology of lean NAFLD and associated metabolic complications is required to inform future prevention and treatment strategies for this patient population.

The aim of our systemic review and meta-analysis was to estimate the global prevalence, clinical metabolic risk factors, and metabolic-related complications of lean NAFLD in order to inform the potential global burden of this condition and to provide a reference for future strategies to prevent and treat this burdensome liver disease.

Methods

The study evaluation and protocol description were conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/). According to the meta-analysis of observational studies in epidemiology (MOOSE) guideline, data were extracted by two independent investigators and any discrepancy in collection of data were resolved by a third investigator. For detailed information on the search strategy, selection criteria, data analysis and role of the funding source, see Supplementary File 1.

Results

Figure 1A displays the selection process and PRISMA flow-diagram for the global prevalence of lean NAFLD. There were 33 observational studies (26 cross-sectional,

4 prospective, and 3 retrospective) with a total of 205,307 individuals from 14 countries that were eligible for the systematic review (for references see Supplementary File 2). As shown in Figure 1B, no studies were available in the literature for Africa, South America and Antarctica. The characteristics of all included studies are summarized in Supplementary File 3. According to the checklist developed by the Joanna Briggs Institute Reviewer's Manual, the overall quality of each included study is reported in Supplementary File 4. Most of these studies were well designed and had a low risk of bias. Only one study had unclear population risk because individuals with age <20 years were excluded.

As shown in Figure 2, the pooled global prevalence of lean NAFLD in the overall population was 4.1% (95% CI: 3.4-4.8%), whereas the pooled global prevalence of NAFLD in the lean population was 9.7% (95% CI: 7.7-11.8%). Within the NAFLD subjects, 16.7% (95% CI: 14.9-18.5%) of population were lean. The global prevalence of lean NAFLD with type 2 diabetes, hypertension, metabolic syndrome, dyslipidemia or central obesity were 0.6% (95%CI: 0.4-0.9%), 1.8% (95%CI: 1.2-2.5%), 1.4% (95%CI: 1.0-1.9%), 2.8% (95%CI: 1.9-3.7%) and 2% (95%CI: 1.6-2.4%), respectively. As shown in Supplementary File 5, the prevalence of overweight/obese NAFLD was higher than that of lean NAFLD in different time periods. In the overall population, regardless of lean or overweight/obese status, the prevalence of NAFLD showed a general upward trend in recent years, while the prevalence of non-NAFLD has generally declined. Among the lean or overweight/obese groups, the prevalence of NAFLD also showed an increasing trend. In addition, by analyzing the prevalence of lean NAFLD in each continent, we found that the prevalence of lean NAFLD was the highest in Asia (4.8%, 95% CI: 4.0-5.6%) and the lowest in Europe (2.2%, 95% CI:

0.2-4.2%). The prevalence of lean NAFLD was around 3% in North America (3.1%, 95% CI: 2.3-3.8%) and Oceania (3.5%, 95% CI: 3.1-3.8%), respectively.

We also estimated the prevalence of lean NAFLD in each country. To reduce bias, at least two studies were needed to estimate the prevalence of lean NAFLD in each country. Interestingly, the prevalence of lean NAFLD varied among different countries (Supplementary File 6). The United States had the lowest prevalence of lean NAFLD (3.1%, 95% CI: 2.3-3.8%), whereas China had the highest prevalence (5.5%, 95% CI: 2.5-8.5%), followed by South Korea (5.0%, 95%CI: 4.4-5.6%), Iran (4.3%, 95% CI: 1.2-7.5%) and Japan (3.8%, 95% CI: 3.2-9.1%), respectively.

A number of eligible studies reported prevalence estimates stratified by age, sex, or type of population. We then performed subgroup analyses to estimate the global prevalence of lean NAFLD for each of these subgroups. As shown in Supplementary File 7, the prevalence of lean NAFLD calculated from health examination-based studies (4.4%, 95% CI: 3.8-5.0%) was essentially comparable to that calculated from population-based studies (4.3%, 95% CI: 3.0-5.6%), but it was higher than that calculated from either community-based (3.0%, 95% CI: 0.7-5.3%) or hospital-based studies (2.0%, 95%CI: 1.0-5.1%). We also found that compared with other age groups, middle-aged subjects (45-59 years old) had the highest prevalence of lean NAFLD (4.4%, 95% CI: 3.2-5.5%), and that the prevalence of lean NAFLD was higher in men (4.5%, 95% CI: 3.8-5.2%) than in women (3.9%, 95% CI: 3.0-4.8%). In addition, we used data from 14 eligible studies to compare lean NAFLD prevalence between men and women within studies (for references see Supplementary File 8). As shown in Supplementary File 9, meta-analysis of within-study comparisons of lean NAFLD

prevalence confirmed that the prevalence of lean NAFLD was higher in men than in women, although there was a high heterogeneity across studies (odds ratio=1.52, 95% CI: 1.13-2.04).

We further analyzed the features of the prevalence of lean NAFLD in Asia, where the prevalence is the highest as we estimated above (for references see Supplementary File 10). As shown in Supplementary File 11, lean NAFLD in both the overall and the lean populations showed a general upward trend toward a higher prevalence in recent years in Asia. Compared to the prevalence of lean NAFLD calculated from either health examination-based (4.5%, 95% CI: 3.9-5.2%) or community-based studies (3.0%, 95% CI: 0.7-5.3%), the population-based studies (5.7%, 95% CI: 3.6-7.7%) showed the highest prevalence of lean NAFLD. We also found that middle-aged Asian individuals had the highest prevalence of lean NAFLD (4.7%, 95% CI: 3.4-6.0%), and that the prevalence of lean NAFLD in Asia was higher in men (5.1%, 95% CI: 4. 3-5.8%) than in women (3.9%, 95% CI: 2.7-5.0%) (detailed data are shown in Supplementary File 12). Eleven eligible studies were used to compare lean NAFLD prevalence between men and women in Asia within studies (for references see Supplementary File 13). This analysis confirmed that in Asia, the prevalence of lean NAFLD was higher in men than in women, although there was a high heterogeneity across studies (odds ratio=1.53, 95% CI: 1.03-2.26).

A meta-regression analysis revealed that the sample size of the study was associated with significant heterogeneity for studies with more than 16,000 and 3,000-16,000 subjects. Moreover, the study region also resulted in high heterogeneity between European and Asian countries (P<0.01). In addition, the study year significantly

affected the prevalence estimates of lean NAFLD (Table 1), whereas the study type, the population type, and the diagnostic methods used for diagnosing NAFLD were non-significant factors contributing to the observed heterogeneity.

We also estimated the average clinical and biochemical characteristics with 95% confidence intervals of lean NAFLD and lean non-NAFLD individuals across studies by meta-analysis. Then, we compared these characteristics between lean NAFLD and lean non-NAFLD individuals within studies. Among the 33 eligible studies, 12 studies provided available data for these two groups of individuals (for references see Supplementary File 14). As shown in Figure 3, metabolic comorbidities associated with lean NAFLD included pre-existing type 2 diabetes (12%, 95% CI: 7-16%), metabolic syndrome (32%, 95% CI: 17–46%), hypertension (37%, 95% CI: 21-53%), central obesity (42%, 95% CI: 17-68%) and dyslipidemia (52%, 95% CI: 44-60%), respectively. Compared to lean non-NAFLD subjects, patients with lean NAFLD were more likely to be male, older, smokers, and had greater adiposity measures (BMI and waist circumference), higher blood pressure, a more atherogenic lipid profile and higher levels of fasting glucose, hemoglobin A1c and serum liver enzymes. Patients with lean NAFLD also had a greater prevalence of type 2 diabetes, metabolic syndrome, hypertension, dyslipidemia and central obesity and were less engaged in physical activity compared to their lean counterparts without NAFLD, although with a considerable heterogeneity across studies (detailed data are shown in Table 2).

In addition, the average clinical and biochemical characteristics of lean NAFLD and overweight/obese NAFLD individuals were also analyzed and compared. A total of 13 studies were included for analysis (for references see Supplementary File 15). As

shown in Figure 4, metabolic comorbidities associated with overweight/obese NAFLD included pre-existing type 2 diabetes (43%, 95% CI: 23-64%), metabolic syndrome (60%, 95% CI: 44–76%), hypertension (52%, 95% CI: 31-73%), central obesity (85%, 95% CI: 75-95%) and dyslipidemia (60%, 95% CI: 57-62%), respectively. Compared to lean NAFLD subjects, patients with overweight/obese NAFLD were more likely to be male, and had greater adiposity measures (BMI and waist circumference), lower levels of high-density lipoprotein cholesterol, higher blood pressure, higher levels of hemoglobin A1c and liver enzymes. Patients with overweight/obese NAFLD also had a greater prevalence of type 2 diabetes, metabolic syndrome, hypertension, dyslipidemia and central obesity compared to lean NAFLD, although with considerable heterogeneity across studies (detailed data are shown in Table 3).

Finally, in order to assess the stability of the overall prevalence estimates of lean NAFLD, we have also re-analyzed all data after that a logit transformation was applied. As a result, the overall prevalence estimates of lean NAFLD were essentially superimposable both before (4.1%, 95% CI: 3.4-4.8%) and after (4.0%, 95% CI: 3.4-4.6%) logit transformation.

Discussion

In this updated and comprehensive systematic review and meta-analysis of 33 observational studies from 14 countries (involving a total of 205,307 individuals), we have estimated that the global prevalence of lean NAFLD was 4.1% (95% CI: 3.4-4.8%) in the overall population, whereas the global prevalence of NAFLD was 9.7% (95% CI: 7.7-11.8%) in the lean population. It is worth mentioning that the prevalence of lean NAFLD showed a general upward trend in recent years, which has occurred in

parallel with the increasing dietary fat and fructose consumptions both in Asia and in Western countries.[11] Similar to risk factors for overweight/obese NAFLD, lifestyle changes (e.g. decreased physical activity, sedentariness, high fat and fructose intakes) may be also acquired risk factors for lean NAFLD.[12] Therefore, as the global burden of lean NAFLD increases, special attention should be paid to lean subjects with coexisting risk factors for the development of NAFLD.

Previous studies indicated that the pooled prevalence estimates of NAFLD did not differ by geographical regions in the general population.[13] A recent meta-analysis reported the highest prevalence of NAFLD in the Middle East and South America.[14] Moreover, Shi and colleagues found that the prevalence of NAFLD in the lean/non-obese populations in Western studies was higher than that observed in Eastern studies.[15] Interestingly, our findings show that the prevalence of lean NAFLD in the overall population was the highest in Asia (4.8%) followed by Oceania (3.5%), North America (3.1%) and Europe (2.2%), respectively, despite a much lower daily caloric intake in Asia.[16] This phenomenon might be partly dependent on greater intra-abdominal visceral fat accumulation and higher genetic susceptibility in Asian individuals, such as conferred by the rs738409 variant in the *patatin-like phospholipase domain-containing protein 3* (*PNPLA3*), which is the genetic variant most robustly associated with the presence and severity of NAFLD in non-obese populations.[17, 18] More importantly, compared with other regions, Asia has a higher proportion of lean subjects defined by BMI,[19] which could not reflect accurately body fat distribution and visceral fat accumulation. In addition, ethnic characteristics and cultural factors closely related to lean NAFLD, such as sedentary lifestyles, are also likely to lead to variation in the geographic prevalence of lean NAFLD.[15, 20] It is easy

to overlook that the diagnostic methods used in different studies may affect the assessment of the prevalence of NAFLD.[18]

The direct relationship between sex and susceptibility to NAFLD remains uncertain and is amenable of further study as the Asian guidelines on NAFLD have also recently reported.[18] A number of studies have reported that the global prevalence of lean NAFLD is higher in men than in women. However, in contrast a few studies have reported that lean NAFLD occurs more frequently in women than men.[21] In our meta-analysis, we confirmed that the global prevalence of lean NAFLD was more frequent in men than in women, although the causes of this sex-related difference are not entirely understood. Studies suggested that sex hormones, sex-hormone-binding globulin and muscle mass could affect body fat distribution and insulin resistance, which might partly explain the sex-related difference in the prevalence of lean NAFLD.[22] In addition, the sex-related difference in lean NAFLD might also be partly attributable to differences in exposure to the risk factors for NAFLD, such as less alcohol consumption and smoking among women. It should be noted that due to the difficulty in extracting data from the eligible studies, we have not compared the prevalence of lean NAFLD in men and women during menopause, but some studies have reported that the prevalence of imaging-defined NAFLD in postmenopausal women was higher than that in men.[23] Further investigations are certainly required to confirm whether there exists a sex-specific difference in the prevalence of lean NAFLD between men and post-menopausal women.

The link between aging and NAFLD is very complex and poorly elucidated. A number of studies have suggested that a gradual decline in physical activity, sex

hormones, growth hormone, and insulin-like growth factor-1 with aging might contribute to the development of NAFLD.[23] The results of our meta-analysis show that patients with lean NAFLD are likely to be older than those with lean non-NAFLD, suggesting that advancing age is a risk factor for lean NAFLD. Surprisingly, many studies found that NAFLD occurs more frequently in middle-aged populations, which is consistent with our results.[24] The latest Japanese review also reported that older age was a risk factor for hepatic steatosis, but the authors did not find that the elderly had a higher prevalence than the middle-aged.[23] Eguchi et al. found that the middle-aged male had the highest prevalence of NAFLD and the prevalence of disease decreased at the age of 50 or 60 years, which has been defined as an "inverted U shaped curve".[25] This phenomenon of decreased prevalence of NAFLD in older age may also reflect selectively a decreased survival in those with NAFLD.[26] In addition, changes in circulating sex hormone levels with ageing may also affect the development of lean NAFLD in older age. Nishioji et al. showed that the highest prevalence of lean NAFLD among men occurs in the middle-aged population. In contrast, in women, the highest prevalence of lean NAFLD was observed in the elderly (possibly due to the decline of estrogen levels with menopause).[27] Kojima et al. estimated that the prevalence of NAFLD in men tended to rise gradually with age and declined at the age of 60-70 years, which is approximately 10 years earlier than in women.[28] However, it should be noted that NAFLD is not associated with an increased risk of mortality in older age. Although the prevalence of lean NAFLD decreases in older age relative to middle age, the rates of both metabolic comorbidities and all-cause mortality are rising.[23]

In this meta-analysis, we adopted a recognized method to define lean NAFLD, which

is based on age and ethnic-specific BMI cutoffs. Our estimated prevalence of NAFLD in the lean population (9.7%) was essentially superimposable to that reported by Shi and colleagues (10.2%).[15] In addition, Shi and colleagues found that the prevalence of NAFLD in lean subjects has increased in recent years, and lean/non-obese NAFLD patients had a lower prevalence of male sex, hypertension, lower waist circumference and higher high-density lipoprotein cholesterol levels than non-lean/obese patients, which is similar to our results. Our findings have also developed previous work by quantifying the prevalence of lean NAFLD and its metabolic complications in the general population. We have further analyzed the features of the prevalence of lean NAFLD in the general population and compared risk factors, metabolic characteristics and complications among the lean NAFLD, lean non-NAFLD and overweight/obese NAFLD groups. In our meta-analysis, the pooled characteristics showed that lean NAFLD patients had a worse metabolic profile and anthropometric parameters compared to lean non-NAFLD patients, and some of these parameters were also considered as risk factors for lean NAFLD in Asian countries.[29] The pooled prevalences of type 2 diabetes, metabolic syndrome, hypertension, central obesity and dyslipidemia in lean NAFLD patients were, respectively, 12%, 32%, 37%, 42% and 52%, which are significantly higher than the pooled prevalences observed in the lean non-NAFLD population. This finding further reinforces the notion that lean NAFLD and metabolic diseases are closely interrelated, and risk factors involved in the development of metabolic diseases may be also useful predictors of lean NAFLD[30]. The comparison between lean NAFLD and overweight/obese NAFLD further supports the notion that all groups have similar risk factors (e.g. smoking and physical inactivity). Conversely, lean NAFLD patients had significantly lower values of waist circumference and blood pressure, lower levels of hemoglobin A1c and liver enzymes,

higher level of high-density lipoprotein cholesterol and a lower prevalence of type 2 diabetes, metabolic syndrome, hypertension, central obesity and dyslipidemia; compared with the overweight/obese NAFLD group (43%, 60%, 52%, 85% and 60%, respectively). A previous study has reported a lower prevalence of hypertension and central obesity in lean NAFLD than in overweight/obese NAFLD.[9] Cruz et al. also showed that lean NAFLD patients have fewer individual components of metabolic syndrome and lower insulin resistance compared to overweight-NAFLD patients.[31] Collectively, these results suggest that lean NAFLD patients may have better indicators related to metabolic syndrome and a lower prevalence of metabolic complications than overweight/obese NAFLD patients.

Our meta-analysis has some important limitations that are strictly inherent to the studies included in the meta-analysis. First, there was a significant heterogeneity between studies, which might be largely due to differences in geographic regions, study year, and sample size. Also, differences in the population types and methods used for diagnosing NAFLD might also lead to higher heterogeneity, which was not completely explained by our subgroup analyses and meta-regressions. Second, some studies defined lean NAFLD using different BMI cutoffs and the prevalence of lean NAFLD varied widely according to these criteria.[7] In our meta-analysis, we adopted the most frequently used definition of lean NAFLD (as defined above in the Methods section and in Supplementary file 1) to select all eligible studies, which might lead to selection bias. Based on these above-mentioned diagnostic criteria of lean NAFLD, we were not able to obtain any epidemiological data on lean NAFLD in Africa and South America and, therefore, some of the most important underdeveloped countries were under-represented in our meta-analysis. Finally, the eligible studies were

included according to the search strategy that was developed to address the aims of our study. Unfortunately, the included studies lacked sufficient data for meta-analysis to compare the genetic factors (e.g. *PNPLA3* and other genetic variants) and the outcome indicators (such as liver pathology and mortality) among lean NAFLD, lean non-NAFLD and obese NAFLD subjects.

Conclusion

The results of our updated and comprehensive meta-analysis show that lean NAFLD occurs with metabolic complications and is not an uncommon condition worldwide that is also increasing in prevalence over time. The highest prevalence of lean NAFLD occurs in middle-aged individuals, especially in Asian countries. Our meta-analysis now provides a reference for the future management and prevention strategies of this burdensome condition.

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TABLE LEGENDS

Table 1. Multivariable meta-regression of included studies to identify heterogeneous sources affecting the global prevalence of lean NAFLD.

Table 2. Meta-analysis of within-study comparisons of characteristics between lean NAFLD patients and lean non-NAFLD subjects.

Table 3. Meta-analysis of within-study comparisons of characteristics between lean NAFLD patients and overweight/obese NAFLD patients.

FIGURE LEGENDS

Figure 1. (A) Flow diagram of the assessment of the studies identified in the systematic review of the global prevalence of lean NAFLD. (B) Included studies in the global lean NAFLD prevalence meta-analysis, stratified by continent. 33 observational studies with a total of 205,307 subjects from four different continents were eligible for the systematic review and meta-analysis. No studies were available in the literature for Africa, Antarctica and South America.

Figure 2. Forest-plot of the prevalence of lean NAFLD in the overall and lean populations. Overall mean estimate and 95% confidence limits are calculated from a random-effects meta-analysis.

Figure 3. Meta-analysis of within-study comparison of both clinical (A) and laboratory (B) characteristics between lean NAFLD and lean non-NAFLD

populations. Pooled mean and 95% confidence limits are calculated by random-effects or fixed-effects meta-analysis. (C) Meta-analysis of within-study comparison of sex, smoking, physical inactivity and metabolic complications between lean NAFLD and lean non-NAFLD populations. Average prevalence and 95% confidence limits are calculated by random effects or fixed effects meta-analysis. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, TG = triglyceride, LDL = low-density lipoprotein cholesterol, TC = total cholesterol, BUN = blood urea nitrogen, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, UA = uric acid, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = γ -glutamyl transferase, EH = hypertension, DM = type 2 diabetes mellitus, MS = metabolic syndrome, DL = dyslipidemia. * $P < 0.05$, # $P > 0.05$ (not significant).

Figure 4. Meta-analysis of within-study comparison of clinical (A) and laboratory (B) characteristics between lean NAFLD and overweight/obese NAFLD populations. Pooled mean and 95% confidence limits are calculated by random-effects or fixed-effects meta-analysis. (C) Meta-analysis of within-study comparison of sex, smoking, physical inactivity and metabolic complications between lean NAFLD and overweight/obese NAFLD populations. Average prevalence and 95% confidence limits are calculated by random effects or fixed effects meta-analysis. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP =

diastolic blood pressure, HDL = high-density lipoprotein cholesterol, TG = triglyceride, LDL = low-density lipoprotein cholesterol, TC = total cholesterol, BUN = blood urea nitrogen, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, UA = uric acid, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = γ -glutamyl transferase, EH = hypertension, DM = type 2 diabetes mellitus, MS = metabolic syndrome, DL = dyslipidemia. * $P < 0.05$, # $P > 0.05$ (not significant).

SUPPLEMENTARY FILE LEGENDS

Supplementary File 1. Detailed description of the methods section.

Supplementary File 2. References for included studies used to analyze the global prevalence of lean NAFLD.

Supplementary File 3. Extracted characteristics of all included studies.

Supplementary File 4. Quality assessment of included studies in the global epidemiology of lean NAFLD.

Supplementary File 5. The prevalence of NAFLD in different populations over time in recent years

Supplementary File 6. Prevalence of lean NAFLD in each study country ($n \geq 2$).

Supplementary File 7. Subgroup analysis. The global prevalence of lean NAFLD.

Supplementary File 8. References for included studies used to compare the prevalence of lean NAFLD between men and women.

Supplementary File 9. Meta-analysis of within-study comparisons of lean NAFLD

prevalence in men vs. women.

Supplementary File 10. References for included studies used to analyze the prevalence of lean NAFLD in Asia.

Supplementary File 11. The prevalence of NAFLD in different populations over time in recent years in Asia.

Supplementary File 12. Subgroup analysis - prevalence of lean NAFLD in Asia.

Supplementary File 13. References for included studies used to compare the prevalence of lean NAFLD between men and women in Asia.

Supplementary File 14. References for included studies used to compare the characteristics (i.e., clinical parameters, laboratory variables, male sex, smoking, physical inactivity, complication rate) between lean NAFLD and lean non-NAFLD subjects.

Supplementary File 15. References for included studies used to compare the characteristics (i.e., clinical parameters, laboratory variables, male sex, smoking, physical inactivity, complication rate) between lean NAFLD and overweight/obese NAFLD subjects.