

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

3

4 **Short title:** Lean NAFLD epidemiology

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8

9 **List of Abbreviations**

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

14

15 **Contributors**

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

20

21 **Declaration of conflicts of interest**

22 We declare no competing interests.

23

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1 **Abstract**

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

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

13 **Results:** 33 observational studies were included with 205,307 individuals from 14
14 countries. The global prevalence of lean NAFLD was 4.1% (95%CI: 3.4-4.8%). In
15 lean subjects the prevalence of NAFLD was 9.7% (95%CI: 7.7-11.8%). The
16 prevalence of lean NAFLD with diabetes, hypertension, metabolic syndrome,
17 dyslipidemia or central obesity was 0.6% (95%CI: 0.4-0.9%), 1.8% (95%CI:
18 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:
19 1.6-2.4%), respectively. The prevalence of lean NAFLD showed an upward trend
20 between 1988 and 2017. Asian individuals had the highest prevalence of lean NAFLD
21 (4.8%, 95%CI: 4.0-5.6%). Middle-aged people (45-59 years old) had the highest
22 prevalence of lean NAFLD (4.4%, 95%CI: 3.2-5.5%). The prevalence of metabolic
23 complications in lean non-NAFLD, lean NAFLD and overweight/obese NAFLD
24 groups increased sequentially.

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

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

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

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1 **Introduction**

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

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

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

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

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14 **Methods**

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

22

23 **Results**

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

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

10
11 As shown in Figure 2, the pooled global prevalence of lean NAFLD in the overall
12 population was 4.1% (95% CI: 3.4-4.8%), whereas the pooled global prevalence of
13 NAFLD in the lean population was 9.7% (95% CI: 7.7-11.8%). Within the NAFLD
14 subjects, 16.7% (95% CI: 14.9-18.5%) of population were lean. The global prevalence
15 of lean NAFLD with type 2 diabetes, hypertension, metabolic syndrome, dyslipidemia
16 or central obesity were 0.6% (95%CI: 0.4-0.9%), 1.8% (95%CI: 1.2-2.5%), 1.4%
17 (95%CI: 1.0-1.9%), 2.8% (95%CI: 1.9-3.7%) and 2% (95%CI: 1.6-2.4%),
18 respectively. As shown in Supplementary File 5, the prevalence of overweight/obese
19 NAFLD was higher than that of lean NAFLD in different time periods. In the overall
20 population, regardless of lean or overweight/obese status, the prevalence of NAFLD
21 showed a general upward trend in recent years, while the prevalence of non-NAFLD
22 has generally declined. Among the lean or overweight/obese groups, the prevalence of
23 NAFLD also showed an increasing trend. In addition, by analyzing the prevalence of
24 lean NAFLD in each continent, we found that the prevalence of lean NAFLD was the
25 highest in Asia (4.8%, 95% CI: 4.0-5.6%) and the lowest in Europe (2.2%, 95% CI:

1 0.2-4.2%). The prevalence of lean NAFLD was around 3% in North America (3.1%,
2 95% CI: 2.3-3.8%) and Oceania (3.5%, 95% CI: 3.1-3.8%), respectively.

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4 We also estimated the prevalence of lean NAFLD in each country. To reduce bias, at
5 least two studies were needed to estimate the prevalence of lean NAFLD in each
6 country. Interestingly, the prevalence of lean NAFLD varied among different
7 countries (Supplementary File 6). The United States had the lowest prevalence of lean
8 NAFLD (3.1%, 95% CI: 2.3-3.8%), whereas China had the highest prevalence (5.5%,
9 95% CI: 2.5-8.5%), followed by South Korea (5.0%, 95%CI: 4.4-5.6%), Iran (4.3%,
10 95% CI: 1.2-7.5%) and Japan (3.8%, 95% CI: 3.2-9.1%), respectively.

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12 A number of eligible studies reported prevalence estimates stratified by age, sex, or
13 type of population. We then performed subgroup analyses to estimate the global
14 prevalence of lean NAFLD for each of these subgroups. As shown in Supplementary
15 File 7, the prevalence of lean NAFLD calculated from health examination-based
16 studies (4.4%, 95% CI: 3.8-5.0%) was essentially comparable to that calculated from
17 population-based studies (4.3%, 95% CI: 3.0-5.6%), but it was higher than that
18 calculated from either community-based (3.0%, 95% CI: 0.7-5.3%) or hospital-based
19 studies (2.0%, 95%CI: 1.0-5.1%). We also found that compared with other age groups,
20 middle-aged subjects (45-59 years old) had the highest prevalence of lean NAFLD
21 (4.4%, 95% CI: 3.2-5.5%), and that the prevalence of lean NAFLD was higher in men
22 (4.5%, 95% CI: 3.8-5.2%) than in women (3.9%, 95% CI: 3.0-4.8%). In addition, we
23 used data from 14 eligible studies to compare lean NAFLD prevalence between men
24 and women within studies (for references see Supplementary File 8). As shown in
25 Supplementary File 9, meta-analysis of within-study comparisons of lean NAFLD

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

4

5 We further analyzed the features of the prevalence of lean NAFLD in Asia, where the
6 prevalence is the highest as we estimated above (for references see Supplementary
7 File 10). As shown in Supplementary File 11, lean NAFLD in both the overall and the
8 lean populations showed a general upward trend toward a higher prevalence in recent
9 years in Asia. Compared to the prevalence of lean NAFLD calculated from either
10 health examination-based (4.5%, 95% CI: 3.9-5.2%) or community-based studies
11 (3.0%, 95% CI: 0.7-5.3%), the population-based studies (5.7%, 95% CI: 3.6-7.7%)
12 showed the highest prevalence of lean NAFLD. We also found that middle-aged Asian
13 individuals had the highest prevalence of lean NAFLD (4.7%, 95% CI: 3.4-6.0%),
14 and that the prevalence of lean NAFLD in Asia was higher in men (5.1%, 95% CI: 4.
15 3-5.8%) than in women (3.9%, 95% CI: 2.7-5.0%) (detailed data are shown in
16 Supplementary File 12). Eleven eligible studies were used to compare lean NAFLD
17 prevalence between men and women in Asia within studies (for references see
18 Supplementary File 13). This analysis confirmed that in Asia, the prevalence of lean
19 NAFLD was higher in men than in women, although there was a high heterogeneity
20 across studies (odds ratio=1.53, 95% CI: 1.03-2.26).

21

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

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

4

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

22

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

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

13
14 Finally, in order to assess the stability of the overall prevalence estimates of lean
15 NAFLD, we have also re-analyzed all data after that a logit transformation was
16 applied. As a result, the overall prevalence estimates of lean NAFLD were essentially
17 superimposable both before (4.1%, 95% CI: 3.4-4.8%) and after (4.0%, 95% CI:
18 3.4-4.6%) logit transformation.

19 **Discussion**

21 In this updated and comprehensive systematic review and meta-analysis of 33
22 observational studies from 14 countries (involving a total of 205,307 individuals), we
23 have estimated that the global prevalence of lean NAFLD was 4.1% (95% CI:
24 3.4-4.8%) in the overall population, whereas the global prevalence of NAFLD was 9.7%
25 (95% CI: 7.7-11.8%) in the lean population. It is worth mentioning that the prevalence
26 of lean NAFLD showed a general upward trend in recent years, which has occurred in

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

7

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

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

3

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

23

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

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

1 is based on age and ethnic-specific BMI cutoffs. Our estimated prevalence of NAFLD
2 in the lean population (9.7%) was essentially superimposable to that reported by Shi
3 and colleagues (10.2%).¹⁵ In addition, Shi and colleagues found that the prevalence of
4 NAFLD in lean subjects has increased in recent years, and lean/non-obese NAFLD
5 patients had a lower prevalence of male sex, hypertension, lower waist circumference
6 and higher high-density lipoprotein cholesterol levels than non-lean/obese patients,
7 which is similar to our results. Our findings have also developed previous work by
8 quantifying the prevalence of lean NAFLD and its metabolic complications in the
9 general population. We have further analyzed the features of the prevalence of lean
10 NAFLD in the general population and compared risk factors, metabolic characteristics
11 and complications among the lean NAFLD, lean non-NAFLD and overweight/obese
12 NAFLD groups. In our meta-analysis, the pooled characteristics showed that lean
13 NAFLD patients had a worse metabolic profile and anthropometric parameters
14 compared to lean non-NAFLD patients, and some of these parameters were also
15 considered as risk factors for lean NAFLD in Asian countries.²⁹ The pooled
16 prevalences of type 2 diabetes, metabolic syndrome, hypertension, central obesity and
17 dyslipidemia in lean NAFLD patients were, respectively, 12%, 32%, 37%, 42% and
18 52%, which are significantly higher than the pooled prevalences observed in the lean
19 non-NAFLD population. This finding further reinforces the notion that lean NAFLD
20 and metabolic diseases are closely interrelated, and risk factors involved in the
21 development of metabolic diseases may be also useful predictors of lean NAFLD³⁰.
22 The comparison between lean NAFLD and overweight/obese NAFLD further
23 supports the notion that all groups have similar risk factors (e.g. smoking and physical
24 inactivity). Conversely, lean NAFLD patients had significantly lower values of waist
25 circumference and blood pressure, lower levels of hemoglobin A1c and liver enzymes,

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

11

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

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

6

7 **Conclusion**

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

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1 **TABLE LEGENDS**

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

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

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

8

9 **FIGURE LEGENDS**

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

16

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

20

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

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

14

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

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

8

9 **SUPPLEMENTARY FILE LEGENDS**

10 **Supplementary File 1.** Detailed description of the methods section.

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

13 **Supplementary File 3.** Extracted characteristics of all included studies.

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

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

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

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

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

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

1 prevalence in men vs. women.

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

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

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

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

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

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