The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis

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To cite this article: Feng-Bin Lu, En-De Hu, Lan-Man Xu, Lu Chen, Jin-Lu Wu, Hui Li, Da-Zhi Chen & Yong-Ping Chen (2018) The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis, Expert Review of Gastroenterology & Hepatology, 12:5, 491-502, DOI: 10.1080/17474124.2018.1460202

To link to this article: https://doi.org/10.1080/17474124.2018.1460202

Published online: 02 Apr 2018.

Article views: 108

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The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis

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ABSTRACT

Introduction: A number of researches have explored the association between obesity and nonalcoholic fatty liver disease (NAFLD) liver function, histopathology, complications, genetic factors and prognosis, but the results were conflicting and inconclusive.

Areas covered: In this meta-analysis, the liver function, histopathology, metabolic complications, patatin-like phospholipase domain-containing protein 3 (PNPLA3) genetic polymorphism and prognosis were compared between non-obese and obese NAFLD.

Expert commentary: This meta-analysis indicated that for NAFLD patients, obesity (according to ethnic-specific BMI cut-off points to define obesity) could predict a worse long-term prognosis. However, obesity may not be an independent factor for the development of NASH or advanced fibrosis in NAFLD patients and NAFLD should be considered as potential population for pharmacologic treatment regardless of obesity. In addition, PNPLA3 rs738409 may be more relevant to the progression of non-obese NAFLD when compared to obese NAFLD. Importantly, large-sample, long-term follow-up cohort studies based on liver biopsy are highly needed due to limited liver pathology and long-term follow-up data at present.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of ≥5% of hepatic steatosis (HS), without other liver disease etiologies. Presentation of the disease ranges from nonalcoholic fatty liver to non-alcoholic steatohepatitis (NASH) [1]. Similar to other chronic liver diseases, NAFLD can induce fibrosis process and gradually develop into cirrhosis, liver cancer, and its complications. In addition, NAFLD is significantly associated with metabolic diseases, which can lead to cardiovascular events [2]. Today, global prevalence of NAFLD is 25.24% [3]. Despite the higher prevalence of NAFLD in obese individuals, the disease may be present in the nonobese subjects [4]. Especially in Asia, a considerable portion of NAFLD (8–20%) had been reported to develop at lower BMI [5]. Similar to obese NAFLD, patients with nonobese NAFLD also have higher transaminase levels and a higher prevalence of metabolic complications than nonobese individuals without NAFLD [6]. Recently, some studies suggest that dysfunction of adipose tissue has a greater impact on metabolism relative to the severity of adiposity [7].

Over the past several decades, with change in diet and activity patterns, the global prevalence of obesity gradually increased to 12% in 2008 [8]. Previous studies have shown that obesity and its related diseases have been one of the significant causes of death [9,10]. Recently, studies confirmed that obesity is an important risk factor for NAFLD [11]. A number of researches have explored the association between obesity and NAFLD liver function, histopathology, complications, genetic factors, and prognosis, but the results were conflicting and inconclusive [12–15]. Although previous meta-analysis have confirmed that the metabolism-related serological indicators of obese NAFLD patients were significantly higher than those of lean NAFLD patients (BMI < 25 kg/m²), the difference of the risk of metabolic complications was still unknown [16]. In addition, Sookoian et al. also discovered that obese NAFLD had a higher fibrosis score, higher NAFLD activity score (NAS), and the risk of NASH than lean NAFLD (BMI < 25 kg/m²) by a systematic review [17]. However, their definition of lean NAFLD includes overweight NAFLD for Asians but excludes overweight NAFLD for non-Asians. Thus, the difference between obese NAFLD and nonobese NAFLD needs further study based on the definition of obesity in different populations. Moreover, advanced fibrosis was significantly associated with liver-related mortality [18], but the relationship of advanced fibrosis between nonobese and obese NAFLD remains controversial. Genetic factors are...
important in the development of NAFLD, especially PNPLA3 rs738409 genetic polymorphism [19]. So far, few studies have evaluated the differential role of rs738409 in nonobese versus obese NAFLD patients, but their results were not consistent [16]. Therefore, by meta-analysis, comparing the G allele of PNPLA3 rs738409 in nonobese and obese NAFLD is of great importance. In this study, based on ethnic-specific BMI cutoff points to define obesity (BMI ≥ 25 kg/m² for Asians and BMI > 30 kg/m² for non-Asians) [20], we performed a systematic review and meta-analysis to compare the clinical features between nonobese NAFLD and obese NAFLD in order to discover the relationship between obesity and NAFLD liver function, histopathology, complications, genetic factors, and prognosis. The information could be contributed to understanding the pathogenesis of NAFLD and developing a management strategy for NAFLD to relieve the burden on public health care.

2. Methods

2.1. Search strategy

A systematic search was performed in PubMed, EMBASE, and Cochrane database to identify eligible studies up to July 2017. The search terms were conducted as follows: ‘nonobese’ OR ‘nonobese’ OR ‘lean’ OR ‘obese’) AND ((((((‘non-alcoholic fatty liver disease’) OR ‘non alcoholic fatty liver disease’) OR ‘fatty liver’) OR ‘nonalcoholic fatty liver disease’) OR ‘nonalcoholic fatty liver’ OR ‘non-alcoholic steatohepatitis’) OR ‘NAFLD’) OR ‘NASH’) AND (cohort OR prospective OR longitudinal OR case-control OR follow-up). References of all publications identified as relevant were reviewed for further studies. All selected articles were reviewed for inclusion by two independent readers and any disagreements were resolved by a third investigator.

2.2. Study selection

Inclusion criteria for the meta-analysis were as follows: (1) USG, CT, MRI, or liver biopsy confirmed the diagnosis of NAFLD after the exclusion of other known causes; (2) the studies provided sufficient information for comparison between nonobese NAFLD and obese NAFLD. We define obesity according to ethnic-specific BMI cutoffs: for adult Asians, BMI ≥ 25 defined as obesity; for non-Asians, BMI ≥ 30 defined as obesity; and (3) data were available in English.

The study exclusion criteria included the following: (1) the diagnosis of NAFLD did not exclude other causes of liver disease; (2) lack of specific information for patients with NAFLD; (3) the study was carried out in population with pre-existing disease, such as human immunodeficiency virus coinfected; (4) the study was carried out in children; (5) diagnosis of NAFLD by abnormal liver function; (6) the study diagnosed NAFLD postmortem; and (7) abstracts or unpublished data.

2.3. Data extraction

According to the meta-analysis of observational studies in epidemiology (MOOSE) guideline, data were extracted by two independent investigators and any discrepancies were resolved by a third reader. If two articles came from the same study or population, the article with higher quality was included. The authors of included studies without available information were contacted for additional data when required. From each study, the following characteristics were extracted: author name, publication year, study design, region, selected population characteristics (such as BMI, mean age, sex, liver function, liver histopathology, complications, prognosis), diagnostic method, and number of NAFLD.

2.4. Definition

Hypertension was considered present in patients on treatment for hypertension or/and when a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg; diabetes mellitus was diagnosed when fasting plasma glucose (FPG) was ≥126 mg/dL and/or receiving treatment for diabetes mellitus; hypertriglyceridemia was diagnosed as serum triglyceride ≥150 mg/dL (1.7 mmol/L); metabolic syndrome was defined according to the ethnic-specific criteria by the International Diabetes Federation.

2.5. Assessment of methodological quality

The quality of included studies was evaluated by the Newcastle–Ottawa Scale (NOS). The NOS for observational studies is based on assessing selection of the study groups (0–4 stars), comparability of cases and controls (0–2 stars), or cohorts, and ascertainment of exposure/outcome (0–3 stars). A study awarded 6 stars or more is considered as a high-quality study.

2.6. Statistical analysis

All analyses were performed using STATA, version 12.0 (STATA, College Station, TX, USA). The odds ratio (OR) or standardized mean difference (SMD) was used as the measure of the relationship between obesity and NAFLD liver function, liver histopathology, or complications. The OR was calculated for bivariate analysis and the continuous variable analysis was performed by estimating SMD. Both OR and SMD were given 95% confidence interval (95%CI). Heterogeneity among studies was assessed by Cochran’s Q and I² statistics. For Cochran’s Q statistic, substantial heterogeneity was defined as P < 0.1. The I² value of 25%, 50%, and 75% indicates low, moderate, or high heterogeneity, respectively. Both the fixed- and random-effects models were used to calculate the pooled OR or SMD. If substantial heterogeneity was found, we presented the results from random-effects models, and random-effects meta-regression, subgroup analysis, or article elimination was performed to determine potential sources of heterogeneity. A sensitivity analysis was performed to assess the stability of the overall results of the meta-analysis by omitting one study at a time. Egger’s test was used to evaluate publication bias (P < 0.05 was considered significant).

3. Results

3.1. Literature search and study characteristics

In Figure S1, a flow diagram was demonstrated for the selection process. There were 13 publications including 12 cross-sectional
and 1 cohort with a total of 11,043 participants from 7 countries perform the systematic review [12–15,21–29]. Liver biopsy was available in 1256 NAFLD patients (330 nonobese and 926 obese patients). Additional characteristics of all included studies are summarized in Table 1. According to NOS, the quality of the included studies was assessed in Table S1. As shown in Table S1, all included articles evaluated more than five stars, suggesting that the overall quality of the included studies is good.

3.2. Meta-analysis between obesity and NAFLD liver function

Figure 1(a,c) shows the forest plots for nonobese NAFLD versus obese NAFLD. The summary SMDs for alanine aminotransferase (ALT) and aspartate transaminase (AST) were 0.27 (95%CI: 0.15–0.38; P < 0.001; I² = 79.6%) and 0.21 (95%CI: 0.12–0.30; P < 0.001; I² = 63.8%), respectively. By meta-regression analysis, we found that geographic regions (Japan and Korea vs. other countries) were associated with significant heterogeneity (P < 0.001 for ALT and P = 0.001 for AST). In order to assess the stability of the results of the meta-analysis, sensitivity analysis was conducted by excluding one study at a time. As shown in Figure 1(b,d), no matter which study was excluded, the results of meta-analysis were not significantly altered, suggesting the results were robust. In addition, Egger’s test was used to calculate publication bias, but there was no evidence of publication bias (P = 0.063 for ALT; P = 0.082 for AST).

3.3. Meta-analysis between obesity and NAFLD liver inflammation

In Figure 2(a), we performed a meta-analysis to compare the degree of HS in nonobese NAFLD and obese NAFLD. The summary SMD for HS was 0.32 (95%CI: 0.18–0.45; P < 0.001; I² = 51.7%), indicating that obesity can aggravate HS in NAFLD, although with moderate heterogeneity across studies. By exploring heterogeneous source, we found that heterogeneity was significantly reduced after Alam et al.’s study [12] was removed, suggesting that Alam et al.’s study may be a source of heterogeneity (SMD: 0.40; 95%CI: 0.25–0.55; P < 0.001; I² = 0%). As shown in Figure 2(b), no matter which study was excluded, the results of meta-analysis were not significantly altered, suggesting the results were robust. No publication bias was found by Egger’s test (P = 0.345). Moreover, we also performed a meta-analysis to compare the NAS in nonobese NAFLD and obese NAFLD. As shown in Figure 2(c), there was significant difference in NAS between nonobese NAFLD and obese NAFLD (SMD: 0.31; 95%CI: 0.10–0.51; P = 0.004; I² = 54.3%) with moderate heterogeneity across studies. By exploring heterogeneous source, we found that heterogeneity was significantly reduced after Alam et al.’s study [21] was removed (SMD: 0.42; 95%CI: 0.27–0.57; P < 0.001; I² = 0%). Importantly, the sensitivity analysis showed that the pooled SMD calculated by excluding Alam et al.’s study [12,21] was significantly different from those conducted by excluding Leung et al.’s study (Figure 2(d)), which means that the relationship between obesity and NAS in NAFLD was controversial and need further research. No publication bias was found by Egger’s test (P = 0.377). In addition, the correlation between NASH and obesity in NAFLD was also assessed by meta-analysis. In Figure 2(e), the pooled OR was 1.45 (95%CI: 0.84–2.51; P = 0.185; I² = 56.9%), indicating that there was no significant difference in the prevalence of NASH between nonobese NAFLD and obese NAFLD. As the sensitivity analysis shows, excluding the Alam et al.’s study [12], the results of meta-analysis were signifi-

Table 1. The characteristics of all included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Continent</th>
<th>Publication year</th>
<th>Study design</th>
<th>Diagnostic method</th>
<th>Obesity definition</th>
<th>Number of NAFLD nonobese/obese (n)</th>
<th>Age of NAFLD patients (mean ± SD) (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung, J.C.F</td>
<td>Asia</td>
<td>2017</td>
<td>Cohort</td>
<td>Liver biopsy</td>
<td>BMI ≥ 25 kg/m²</td>
<td>72/235</td>
<td>Nonobese: 54.0 ± 11.0 Obese: 51.0 ± 12.0</td>
</tr>
<tr>
<td>Vos, B.</td>
<td>Europe</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>Liver biopsy</td>
<td>BMI ≥ 30 kg/m²</td>
<td>31/48</td>
<td>Nonobese: 40 (22)a Obese: 49 (19)a</td>
</tr>
<tr>
<td>Alam, S.</td>
<td>Asia</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>119/346</td>
<td>Nonobese: 41.7 ± 10.9 Obese: 40.5 ± 9.6</td>
</tr>
<tr>
<td>Kim, J.Y.</td>
<td>Asia</td>
<td>2016</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>136/211</td>
<td>Nonobese: 53.4 ± 9 Obese: 54.5 ± 10.2</td>
</tr>
<tr>
<td>Kwon, Y.M.</td>
<td>Asia</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>3014/3025</td>
<td>Nonobese: 49.4 ± 10.4 Obese: 47.7 ± 11.1</td>
</tr>
<tr>
<td>Nishioji, K.1</td>
<td>Asia</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>130/142</td>
<td>Nonobese: 55.3 ± 10.6 Obese: 53.6 ± 8.9</td>
</tr>
<tr>
<td>Nishioji, K.2</td>
<td>Asia</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>411/394</td>
<td>Nonobese: 59.5 ± 10.3 Obese: 55.9 ± 10.5</td>
</tr>
<tr>
<td>Wang, Z.</td>
<td>Asia</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>514/680</td>
<td>Nonobese: 52.6 ± 12.3 Obese: 54.2 ± 13.9</td>
</tr>
<tr>
<td>Wei, J.L.</td>
<td>Asia</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>H-MRS</td>
<td>BMI ≥ 25 kg/m²</td>
<td>135/127</td>
<td>Nonobese: 51.0 ± 9.0 Obese: 51.0 ± 10.0</td>
</tr>
<tr>
<td>Chen, C.H.</td>
<td>Asia</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>61/291</td>
<td>Nonobese: 18–39 (18); 40–64 (36); ≥65 (7)b Obese: 18–39 (91); 40–64 (161); ≥65 (39)b</td>
</tr>
<tr>
<td>Lankarani, K.B.</td>
<td>Asia</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>29/147</td>
<td>Nonobese: 49.8 ± 13.9 Obese: 48.3 ± 10.8</td>
</tr>
<tr>
<td>Kumar, R.</td>
<td>Asia</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>USG</td>
<td>BMI ≥ 25 kg/m²</td>
<td>64/141</td>
<td>Nonobese: 39.7 ± 13.4 Obese: 40.9 ± 12.8</td>
</tr>
<tr>
<td>Honda, Y.</td>
<td>Asia</td>
<td>2016</td>
<td>Cross-sectional</td>
<td>Liver biopsy</td>
<td>BMI ≥ 25 kg/m²</td>
<td>134/406</td>
<td>Nonobese: 56.6 ± 13.6 Obese: 48.5 ± 13.9</td>
</tr>
</tbody>
</table>

aData are expressed as median (interquartile range); bdata are expressed as age range (n).
cantly altered (OR: 1.73; 95%CI: 1.15–2.61; \( P = 0.009; \, I^2 = 11.2\% \)) (Figure 2(f)), suggesting that the result was unstable. No publication bias was discovered by Egger’s test (\( P = 0.346 \)).

### 3.4. Meta-analysis between obesity and NAFLD liver fibrosis

In Figure 3(a), we performed a meta-analysis to compare the prevalence of liver fibrosis in nonobese NAFLD and obese NAFLD. The pooled OR was 3.22 (95%CI: 2.13–4.87; \( P < 0.001; \, I^2 = 0.0\% \)), indicating that obesity was significantly associated with liver fibrosis in patients with NAFLD. By sensitivity analysis, we found that the result of meta-analysis was robust (Figure 3(b)). No publication bias was found by Egger’s test (\( P = 0.519 \)). In addition, liver advanced fibrosis (\( F > 2 \)) was further compared between nonobese NAFLD and obese NAFLD. The summary OR was 1.49 (95%CI: 0.93–2.39; \( P = 0.096; \, I^2 = 43.3\% \)), suggesting that there was no correlation between obesity and liver advanced fibrosis in NAFLD (Figure 3(c)). The sensitivity analysis also showed that the result of meta-analysis was unstable (Figure 3(d)). No publication bias was discovered by Egger’s test (\( P = 0.230 \)).

### 3.5. Meta-analysis between obesity and NAFLD complications

In Figure 4(a), the prevalence of hypertension in nonobese NAFLD and obese NAFLD was compared by meta-analysis. The pooled OR was 1.85 (95%CI: 1.32–2.59; \( P < 0.001; \, I^2 = 49.6\% \)). By exploring heterogeneous source, we found that heterogeneity was significantly reduced after Vos et al.’s study [15] was removed, suggesting that Vos et al.’s study may be a source of heterogeneity (OR: 1.67; 95%CI: 1.32–2.11; \( P < 0.001; \, I^2 = 0.0\% \)). The sensitivity analysis showed that the result of meta-analysis was robust (Figure 4(b)). No publication bias was found by Egger’s test (\( P = 0.272 \)).

In Figure 4(c), the prevalence of diabetes mellitus in nonobese NAFLD and obese NAFLD was compared by meta-analysis. The pooled OR was 1.35 (95%CI: 1.09–1.68; \( P = 0.006; \, I^2 = 16.8\% \)), suggesting that obesity is significantly associated with diabetes mellitus in patients with NAFLD, although with low heterogeneity across studies. The sensitivity analysis showed that the result of meta-analysis was robust (Figure 4(d)). In addition, publication bias was found by Egger’s test (\( P = 0.015 \)). However, after excluding Kumar et al.’s study [21], no publication bias was found by Egger’s test (\( P = 0.050 \)), and the pooled OR was 1.29 (95%CI: 1.04–1.61; \( P = 0.024; \, I^2 = 0.0\% \)).

As shown in Figure 5(a), we performed a meta-analysis to compare the prevalence of hypertriglyceridemia in nonobese
NAFLD and obese NAFLD. The pooled OR was 1.51 (95%CI: 1.08–2.13; P = 0.018; $I^2 = 62.2$%), suggesting that obesity is associated with the occurrence of hypertriglyceridemia in NAFLD. Moreover, after excluding Alam et al.’s research [12], the heterogeneity disappeared (OR: 1.66; 95%CI: 1.49–1.84; P < 0.001; $I^2 = 0.0$%). However, when excluding another study once a time, the results of meta-analysis were significantly altered (Figure 5(b)), indicating that the result was unstable. No publication bias was found by Egger’s test (P = 0.823).

As shown in Figure 5(c), the prevalence of metabolic syndrome in nonobese NAFLD and obese NAFLD was compared by meta-analysis. The pooled OR was 2.66 (95%CI: 1.83–3.86; P < 0.001; $I^2 = 53.1$%), indicating that obesity is associated with the occurrence of metabolic syndrome in NAFLD. By exploring heterogeneous source, we found that heterogeneity was significantly reduced after Kumar et al.’s study [21] was removed, suggesting that Kumar et al.’s study may be a source of heterogeneity (OR: 2.20; 95%CI: 1.69–2.87; P < 0.001; $I^2 = 0.0$%). In addition, the sensitivity analysis also showed that the result of meta-analysis was robust (Figure 5(d)). No publication bias was found by Egger’s test (P = 0.233).

### 3.6. Meta-analysis between obesity and NAFLD PNPLA3 rs738409 genetic polymorphism

In Figure 5(e), the frequent of the G allele of PNPLA3 rs738409 in nonobese NAFLD and obese NAFLD was compared by meta-analysis. The pooled OR was 0.60 (95%CI: 0.45–0.80; P < 0.001; $I^2 = 42.7$%), suggesting that nonobese NAFLD subjects had a more frequent of G allele of PNPLA3 rs738409 than obese NAFLD, although with moderate heterogeneity across studies. By exploring heterogeneous source, we found that...
heterogeneity was significantly reduced after Honda et al.’s study [21] was removed, suggesting that Honda et al.’s study may be a source of heterogeneity (OR: 0.51; 95% CI: 0.37–0.72; \(P < 0.001\); \(I^2 = 15.4\%\)). In addition, the sensitivity analysis also showed that the result of meta-analysis was robust (Figure 5(f)). No publication bias was found by Egger’s test \((P = 0.508)\).

3.7. Obesity and NAFLD prognosis

So far, there are few published articles about the correlation between obesity and NAFLD prognosis, and their results are conflicting. After 49 months of follow-up for 77 nonobese and 235 obese patients with NAFLD, Leung et al. found that more clinical events (most of them are cardiovascular events) occurred among obese patients with NAFLD (for obese NAFLD, 6 patients died, 2 developed hepatocellular carcinoma, and 1 had liver failure), suggesting nonobese NAFLD may have a better prognosis than obese NAFLD [14]. By using the Third National Health and Nutrition Examination Survey (NHANES) and linked mortality data to assess the association of obesity with overall and liver-specific mortality in patients with NAFLD, Stepanova et al. and Otgonsuren et al. showed that obesity could be independent predictors of liver-related mortality in patients with NAFLD [30,31]. However, in a retrospective multi-ethnicity cohort study of 1090 patients with biopsy-proven NAFLD (published in abstract form), subjects with BMI < 25 kg/m\(^2\) had higher mortality (follow-up of 133 ± 81.3 months) than obese NAFLD [32]. Unfortunately, no other studies confirmed their observation. In addition, one large-scale long-term follow-up study of NAFLD patients also indicated that obesity was not independent risk factors for HCC \((P = 0.300)\) [33].

4. Discussion

This systematic review and meta-analysis study for the first time elucidated the correlation between obesity (according to ethnic-specific BMI cutoff points to define obesity) and NAFLD liver function, histopathology, complications, genetic factors, or prognosis. Thirteen studies with a total of 11,043 participants (11.4% patients have hepatic pathological information) were finally included. The results of the meta-analysis suggest that obese NAFLD have a higher level of transaminase, higher degree of HS, higher NAS and increased risk of liver fibrosis, hypertension, diabetes mellitus, hypertriglyceridemia, and metabolic syndrome than those with nonobese NAFLD. In contrast, nonobese NAFLD subjects have more frequent of the G allele of PNPLA3 rs738409 than those with obese NAFLD. There was no correlation between obesity and liver advanced fibrosis or NASH in patients with NAFLD. Importantly, except for NAS, NASH, advanced fibrosis and hypertriglyceridemia, the relationship between obesity and liver function, fibrosis, genetic factors, or complications (hypertension, diabetes mellitus, and...
metabolic syndrome) in patients with NAFLD was further confirmed by the sensitivity analysis, suggesting these results were robust. Although this meta-analysis found that obese NAFLD has a higher NAS and increased risk of hypertriglyceridemia than nonobese NAFLD, and there was no correlation between obesity and NASH or liver advanced fibrosis in patients with NAFLD, the sensitivity analysis showed that these results are unstable, indicating more research is needed to support these conclusions. Moreover, due to the lack of relevant data, we did not compare the risk of hypercholesteremia between obese and nonobese NAFLD. However, by comparing blood cholesterol levels, we found that there was no significant difference in blood cholesterol levels between obese and nonobese NAFLD (P = 0.051, Figure S2). In addition, for the association of obesity with HCC or mortality in patients with NAFLD, few studies have been reported, indicating that it needs further study.

There was substantial heterogeneity across those included studies. By meta-regression analysis, geographic regions were identified as possible sources of heterogeneity when assessing the relationship between obesity and liver function of NAFLD. Moreover, in the meta-analysis to compare the risk of hypertension, Vos et al.’s research (European population) was considered as a possible source of heterogeneity, which may be related to regional difference of included participants. Because of gender differences, Alam et al.’s study (the proportion of males in nonobese NAFLD is higher than that in obese NAFLD) or Honda et al.’s study (the proportion of males in NAFLD patients was smallest) was also considered as possible source of heterogeneity when comparing the risk of hypertriglyceridemia or the frequent of the G allele of PNPLA3 rs738409 between nonobese NAFLD and obese NAFLD. In addition, Kumar et al.’s study (the average age of included population was smallest) was identified as possible sources of heterogeneity in the meta-analysis to compare the risk of metabolic syndrome, which may be related to the average age difference of the included population. Importantly, meta-analysis results have not been altered after excluding the heterogeneity, suggesting heterogeneity had little effect on the results and further evidence that the meta-analysis results were credible.

Recently, obesity has been considered to be an independent risk factor for NAFLD [11] and was significantly associated with metabolic disorders (such as insulin resistance and dyslipidemia), tissue inflammation, and liver fibrosis [34–37]. In patients with obesity, the increasing burden of lipid accumulation leads to adipocytes death and cytokine secretion, which contributes to the activation and chemotaxis of inflammatory cells [38]. Moreover, studies have shown that insulin-resistant adipocytes can cause chronic inflammation by secreting free fatty acids which may able to activate NF-κB pathway and increase diacylglycerol (DAG) content in the liver [39]. Thus, chronic inflammation triggered by lipid accumulation in
individuals with obesity has important roles in the progression of NAFLD, which may be the reason why obese NAFLD has a higher degree of HS or NAS, and increased risk of liver fibrosis, metabolic complications than those with nonobese NAFLD. Honda et al. have reported that the factors associated with increased AST and ALT were different in nonobese and obese NAFLD [29]. In our study, we found that obese NAFLD has a higher level of transaminase than those with nonobese NAFLD, which may be associated with a higher BMI or prevalence of diabetes mellitus in obese NAFLD patients, but the specific mechanism needs to be further studied. Interestingly, our meta-analysis results also showed that obesity can not increase the risk of NASH and liver advanced fibrosis in NAFLD, indicating factors other than obesity come into play as the disease advances further, such as the G allele of PNPLA3 rs738409, which plays a crucial role in the development of NAFLD [25]. Through meta-analysis, we found that nonobese NAFLD subjects have more frequent of the G allele of PNPLA3 rs738409 than those with obese NAFLD, suggesting PNPLA3 rs738409 was strongly associated with the development and progression of nonobese NAFLD. In addition, the ‘two hits thesis’ might be applied to explain above phenomenon, with obesity as the ‘first hit’ and oxidative stress, adipokines or metabolic abnormalities as the ‘second hit,’ which may lead to NASH or liver advanced fibrosis [40,41]. Moreover, ‘multiple parallel hits thesis,’ which holds that there are many parallel hits that lead to NASH and liver advance fibrosis, also supports our results [42,43]. Regarding the impact of obesity on the incidence of liver cancer and mortality in patients with NAFLD, the number of studies is small and the results are inconsistent,
suggested that large-scale multicenter long-term follow-up cohort studies are needed to further analyze the impact of obesity on the prognosis of NAFLD.

With the increase of obesity and NAFLD, their effects on future health should be taken seriously. The relationship between obesity and the severity of NAFLD provides a reference for health management institutions to better estimate the social burden of NAFLD. In this system review and meta-analysis, we found that obesity could aggravate the severity of NAFLD, suggesting that obesity could predict a worse long-term prognosis in NAFLD. In addition, weight loss may be helpful to prevent or delay the progression of NAFLD. Some studies have confirmed that weight loss can improve NAFLD and its metabolic abnormalities [44]. Weight loss is also recommended by the latest guidelines to reduce steatosis in NAFLD [1]. Moreover, bariatric surgery has been regarded as a potential treatment option for NAFLD [45]. However, the results of meta-analysis also showed that there was no significant difference in the risk of NASH and liver advanced fibrosis between nonobese NAFLD and obese NAFLD, which may support the hypothesis that obese and nonobese NAFLD are likely to gradually progress to NASH and liver advanced fibrosis, and they all should be considered as potential population for pharmacologic treatment [according to European guidelines for the management of NAFLD, pharmacotherapy should be reserved for patients with significant fibrosis (F > 2)].

The present study had several limitations. First, there was substantial heterogeneity between studies, which might be attributed to the different source of populations and geographic regions. Meta-analysis using individual-level data from multiple studies might provide the best available evidence for the association [46]. Second, as liver biopsy is a kind of invasive examination and has a certain risk of complications, the clinical study of NAFLD patients (especially nonobese NAFLD) with liver biopsy is limited. In this meta-analysis, only 1256 NAFLD patients have useful hepatic pathological information, which may affect the reliability of the results. Sensitivity analysis also suggested that the results of comparison of the risk of NASH and liver advanced fibrosis between obese and nonobese NAFLD are unstable, so further studies are needed to confirm these results. Third, as all included studies were observational, we cannot exclude the residual confounding factors to improve the accuracy of the results. Fourth, most of the included studies did not provide complete information, such as weight changes, medication, lifestyle, etc., which will affect the disease of NAFLD. Fifth, this meta-analysis included 12 studies from Asia and 1 study from Europe; additional investigations in other continents are warranted. Sixth, other genetic information (except PNPLA3 rs738409) which is involved in the progression of NAFLD, such as TM6SF2, is limited. Few studies have reported the relationship between obesity and other genetic information in NAFLD patients. Although Leung et al. showed that there was no significant difference in the proportion of patients carrying the TM6SF2T allele between obese and nonobese NAFLD (18.1% vs. 17.1%) [14], the relationship between obesity and other genetic information in NAFLD needs to be further studied. Seventh, liver cirrhosis is significantly associated with the prognosis of NAFLD, but we did not analyze the relation between obesity and NAFLD—cirrhosis due to lack of related data. Finally, publication bias is a concern in the meta-analysis because few studies report negative results.

5. Conclusions

In conclusion, obese NAFLD has a higher level of transaminase, higher degree of HS and increased risk of liver fibrosis, hypertension, diabetes mellitus, and metabolic syndrome than those with nonobese NAFLD. Moreover, obesity may also increase the NAS and the risk of hypertriglyceridemia in NAFLD. All of these results supported that obesity could predict a worse long-term prognosis in NAFLD patients. However, this meta-analysis also found no correlation between obesity and liver advanced fibrosis or NASH in patients with NAFLD, indicating that obesity may not be an independent factor for NASH and advanced fibrosis in NAFLD and NAFLD should be considered as potential population for pharmacologic treatment regardless of obesity. In addition, we found that nonobese NAFLD subjects have more frequent of the G allele of PNPLA3 rs738409 than those with obese NAFLD, suggesting that compared to obese NAFLD, PNPLA3 rs738409 may be more relevant to the development and progression of nonobese NAFLD. Importantly, large-sample, long-term follow-up cohort studies based on liver biopsy are highly needed due to limited liver pathology and long-term follow-up data, which help to confirm our results and analyze the impact of obesity on the prognosis of NAFLD.

6. Expert commentary

As a common cause of chronic liver disease, NAFLD is a serious threat to human health, and its pathogenesis has not been elucidated. Obesity has been considered as an important risk factor for NAFLD [11]. However, a considerable portion of NAFLD occurs in nonobese population, which has attracted the attention of many scholars. A number of studies have explored the difference between nonobese NAFLD and obese NAFLD in order to discover the underlying pathogenesis of NAFLD, but the results were conflicting and inconclusive. Recently, relative to obese NAFLD, some researchers also put forward the concept of lean NAFLD which have no uniform definition up to now (there are different BMI cutoff points to define lean, such as BMI < 23 kg/m², BMI < 25 kg/m², or BMI < 30 kg/m²) [15,47]. Previous meta-analysis have confirmed that the metabolism-related serological indicators of obese NAFLD patients were significantly higher than those of lean NAFLD patients (BMI < 25 kg/m²), but the difference of the risk of metabolic complications was still unknown [16]. Genetic factors are important in the development of NAFLD, especially PNPLA3 rs738409 genetic polymorphism. Few studies also have evaluated the differential role of rs738409 in nonobese versus obese NAFLD patients, but their results were not consistent. In addition, due to the difference of the definition of obesity in Asian and non-Asian, there was still no systematic assessment of the differences between obese NAFLD and nonobese NAFLD based on ethnic-specific BMI cutoff points to define obesity. Moreover, advanced fibrosis was significantly associated with
the prognosis of NAFLD [18]. So far, there was still no meta-analysis on the systematic comparison of advanced fibrosis between nonobese and obese NAFLD. Thus, based on ethnic-specific BMI cutoff points to define obesity (BMI > 25 kg/m² for Asians and BMI > 30 kg/m² for non-Asians), a comprehensive comparison of clinical features between nonobese NAFLD and obese NAFLD is needed.

Based on ethnic-specific BMI cutoff points to define obesity, this meta-analysis indicated that for NAFLD patients, obesity could predict a worse long-term prognosis, which further supported the importance of weight loss in patients with NAFLD. Interestingly, by meta-analysis, there was no significant difference of the risk of NASH or liver advanced fibrosis between nonobese and obese NAFLD. It indicated that obesity may not be an independent factor for the development of NASH or advanced fibrosis in NAFLD patients. According to European guidelines for the management of NAFLD, pharmacotherapy should be reserved for patients with significant fibrosis (F > 2) [48]. Thus, the results further suggested that both obese and nonobese NAFLD patients should be considered as potential population for pharmacologic treatment. In this study, the comparison of genetic polymorphisms also showed that PNPLA3 rs738409 may be more relevant to the progression of nonobese NAFLD when compared to obese NAFLD, indicating pathogenesis or risk factors for progression of NAFLD might be different between obese and nonobese. In summary, this meta-analysis comprehensively compared clinical features between nonobese NAFLD and obese NAFLD, which could contribute to understanding the pathogenesis of NAFLD and developing a management strategy for NAFLD to relieve the burden on public health care. Furthermore, this result of meta-analysis also provides a reference to the definition of lean NAFLD. However, what we need to be aware of is that only 1256 NAFLD patients have useful hepatic pathological information in this study. Moreover, sensitivity analysis also suggested that the results of comparison of the risk of NASH and liver advanced fibrosis between obese and nonobese NAFLD are unstable. Thus, further studies are needed to confirm these results.

7. Five-year view

Regarding the impact of obesity on the incidence of liver cancer and mortality in patients with NAFLD, the number of studies is small and the results are inconsistent, suggesting that large-sample, long-term follow-up cohort studies based on liver biopsy are needed to further analyze the impact of obesity on the prognosis of NAFLD.

Key issues

- Obesity and NAFLD are two major global issues. NAFLD can occur not only in the obese population, but also in non-obese people.
- A systematic comparison of the clinical characteristics between non-obese NAFLD and obese NAFLD contributes to understanding the pathogenesis of NAFLD and developing a management strategy for NAFLD to relieve the burden on public healthcare.
- So far, a number of researches have explored the differences in liver function, histopathology, complications, genetic factors and prognosis between non-obese NAFLD and obese NAFLD, but the results were conflicting and inconclusive.
- For the first time, this study fully compared the clinical features (liver function, histopathology, complications, genetic factors and prognosis) between non-obese NAFLD and obese NAFLD according to ethnic-specific BMI cut-off points to define obesity (BMI<25 kg/m² for Asians and BMI<30 kg/m² for non-Asians).
- Obese NAFLD may have a higher level of transaminase, higher degree of hepatic steatosis and increased risk of liver fibrosis, metabolic complications than those with non-obese NAFLD, indicating that for NAFLD patients, obesity could predict a worse long-term prognosis.
- There was no correlation between obesity and liver advanced fibrosis or NASH in patients with NAFLD, suggesting that obesity may not be an independent factor for the development of NASH and advanced fibrosis in NAFLD patients and NAFLD should be considered as potential population for pharmacologic treatment regardless of obesity.
- Non-obese NAFLD subjects have more frequent of the G allele of PNPLA3 rs738409 than those with obese NAFLD, indicating that compared to obese NAFLD, PNPLA3 rs738409 may be more relevant to the development and progression of non-obese NAFLD.

Funding

National Natural Science Foundation of China (81570514 and 81500477); Natural Science Foundation of Zhejiang Province (LY15H030017 and LQ15H030006); Public Welfare Science and Technology Project of Wenzhou (Y20150014); Medical Award Fund, Beijing, China (YJHYXKYJJ-162); Scientific and Technological Innovation Team of the Early Warning and Intervention to End-stage Liver Disease of Wenzhou (C20150005); and National Major Scientific and Technological Special Project during the Twelfth Five-year Plan Period, China (2013ZX10005002-001-008, 2013ZX10002003 and 2012ZX10002004).

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Papers of special note have been highlighted as either of interest (+) or of considerable interest (++) to readers.

++ The guideline provides a recognized definition and management of NAFLD.
This article gives a detailed overview of the status of NAFLD in Asia.


This article describes the global trend of obesity and overweight.


This article describes a detailed comparison of metabolic factors between obese and lean NALFD patients.


- This article presents a new theory of the progression of NAFLD.

- The guideline provides a recognized definition and management of NAFLD.