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Association between polycystic ovary syndrome and risk of non-alcoholic fatty liver disease: a meta-analysis

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Abstract

Introduction: There have been many studies assessing whether abnormal metabolic and hormone levels among women with polycystic ovary syndrome (PCOS) are associated with a greater risk of non-alcoholic fatty liver disease (NAFLD). However, previous studies reported no consistent outcomes. To provide a comprehensive evaluation regarding the role of PCOS in the risk of NAFLD, we updated the published literature and conducted this systemic review and meta-analysis.

Material and methods: Electronic databases (Web of Science and PubMed) were searched for literature up to October 2022. We used STATA 12.0 software to compute odds ratios (ORs) and 95% confidence intervals (CIs), to evaluate the association between PCOS and risk of NAFLD.

Results: The study indicated that PCOS was significantly related to an elevated risk of NAFLD (OR = 2.93, 95% CI 2.38 to 3.62, $I^2 = 83.7\%$, $p < 0.001$). Meta-regression analysis showed that age and body mass index (BMI) were not responsible for heterogeneity across the studies (age: $p = 0.096$; BMI: $p = 0.418$). Sensitivity analysis indicated no alteration in the direction of effect when any study was eliminated. Begg's test, Egger's test, Begg's test, and funnel plot indicated a significant risk of publication bias (Egger's test: $p = 0.028$; Begg's test: $p < 0.001$).

Conclusion: This meta-analysis reported that PCOS was associated with an elevated risk of NAFLD. Early proper detection of NAFLD for PCOS women is essential. All patients with PCOS should undergo appropriate diagnostics for early detection of fatty liver and fibrosis.

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Key words: *meta-analysis; non-alcoholic fatty liver disease; polycystic ovary syndrome*

Introduction

Polycystic ovary syndrome (PCOS) is known as a highly prevalent endocrine disease affecting approximately 10% of reproductive age women globally [1]. Women with PCOS are often confronted with reproductive (hyperandrogenism, menstrual disturbances, polycystic ovaries, and infertility), and metabolic (dyslipidaemia, hypertension, obesity, hyperinsulinaemia, and insulin resistance) and psychological features (depression and anxiety) [2, 3]. PCOS is regarded as the most common cause of anovulatory infertility and a risk factor for certain cardiometabolic diseases including type 2 diabetes mellitus (T2DM), myocardial infarction, and stroke [4, 5]. However, the exact aetiology of PCOS remains unknown. PCOS is considered a multifactorial disease associated with genetic, endocrine, and environmental factors [6].

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease, which is related to increased mortality of cardiovascular disease, malignancy, and liver disease [7, 8]. NAFLD comprises a spectrum of liver disorders, ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) [9]. NASH is a more severe form of NAFLD and is characterized by the presence of NAFL plus inflammation with liver injury, which potentially progresses to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [10, 11]. The prevalence of NAFLD has increased from 15% in 2005 to 25% in 2010 among adults all over the world, and the rate of NASH has almost doubled around the same time [12]. Considering the increasing incidence of NAFLD and NASH, the numbers of patients who need liver transplantation because of cirrhosis and end-stage liver disease will increase [13].

There have been many studies assessing whether the abnormal metabolic and hormone levels among women with PCOS are associated with a greater risk of NAFLD. However, previous studies reported no consistent outcomes. Some studies showed a significant association between PCOS and increased risk of NAFLD [14–16], while other studies showed no association

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[17]. To provide a comprehensive evaluation regarding the role of PCOS in the risk of NAFLD, we updated the published literature and conducted this systemic review and meta-analysis.

Material and methods

Search strategy, inclusion criteria, and exclusion criteria

Electronic databases (Web of Science and PubMed) were searched for published literature up to October 2022. We used the following search terms: ("polycystic ovary syndrome" OR "PCOS") AND ("non-alcoholic fatty liver disease" OR "NAFLD"). After removing duplicates, we included 232 studies. Two independent reviewers determined study eligibility by reading the scanned abstracts, studies, and citations. Discrepancies were resolved through consultation. We included studies according to the following inclusion criteria: (1) studies that explored PCOS and NAFLD; (2) studies that were performed in humans; (3) studies that reported in English language; and (4) studies that used abdominal ultrasound for fatty liver. We excluded studies according to the following exclusion criteria: (1) studies not designed as case-control or cohort studies; (2) articles that did not provide sufficient information to acquire odds ratios (ORs) and their 95% confidence intervals (CIs) regarding the association between PCOS and risk of NAFLD; and (3) reviews, case reports, and meta-analyses.

Data collection and meta-analysis

Data extracted from each study included the author and publication year, study type, located country, sample number, age of participants, body mass index (BMI), diagnosis criteria of PCOS and NAFLD, and NAFLD cases. If data of the above categories were not reported in the primary study, this item was marked as "not reported (NR)". We used STATA 12.0 software to compute ORs and 95% CIs to evaluate the association between the prevalence of PCOS in women with PCOS and controls. If the ORs and corresponding 95% CIs were given explicitly, crude ORs and 95% CIs were used. Heterogeneity was calculated with I^2 and Cochran's Q test. While heterogeneity was high ($I^2 \geq 50\%$, p value for Q test ≤ 0.05), a random effect model was applied; conversely, a fixed effects model was used [18]. Subgroup studies were applied to investigate source of heterogeneity. Meanwhile, meta-regression analysis was applied to assess the effect of age and BMI on the different results. Sensitivity analysis was used to assess stabilization of meta-analyses. Publication bias was assessed by Egger's test, Begg's test, and funnel plot.

Result

Characteristics of studies

Table S1 (Supplementary File) illustrates the characteristics of the studies. Figure S1 (Supplementary File) illustrates the selection procedures. 32 studies [14–17, 19–46] (including 145,131 PCOS patients and 50,832,503 controls) were included in the study.

Meta-analysis results

The study indicated that PCOS was significantly related to an elevated risk of NAFLD with a random effects model (OR = 2.93, $p < 0.001$, 95% CI 2.38 to 3.62, $I^2 = 83.7\%$, p-value for Q test < 0.001, Fig. 1). Subgroup analysis indicated an increased risk of NAFLD in PCOS in both prospective and retrospective studies (prospective studies: OR = 3.00, $p < 0.001$, 95% CI: 2.36 to 3.81; retrospective studies: OR = 2.78, $p < 0.001$, 95% CI 1.79 to 4.32; Fig. 2). Subgroup analysis reported an increased risk of NAFLD in PCOS in both Caucasian and Asian populations (Caucasian populations: OR = 2.66, $p < 0.001$, 95% CI: 2.06 to 3.44; Asian: OR = 3.01, $p < 0.001$, 95% CI 2.11 to 4.30; Fig. 3). Meta-regression analysis showed that age and BMI were not responsible for heterogeneity across studies (age: $p = 0.096$; BMI: $p = 0.418$). Sensitivity analysis indicated no alteration in the direction of effect when any study was eliminated (Fig. 4). Egger's test, Begg's test, and funnel plot indicated a significant risk of publication bias (Egger's test: $p = 0.028$; Begg's test: $p < 0.001$; Fig. 5).

Discussion

In this systemic review and meta-analysis of 32 studies with 145,131 PCOS patients and 50,832,503 controls, we explored the association between PCOS and risk of NAFLD. We updated previous results of meta-analysis and expanded the number of included studies to 32. Our findings revealed that compared to controls, women with PCOS were at greater risk for NAFLD (OR =2.93, 95% CI: 2.38 to 3.62). This result was in accordance with previous results. A meta-analysis demonstrated that NAFLD prevalence was higher in women with PCOS compared with healthy controls (OR = 3.93, 95% CI: 2.17 to 7.11) [47]. A meta-analysis published in 2017 and including 17 studies showed that there was a significant association between PCOS and an elevated risk of NAFLD (OR = 2.54, 95% CI 2.19 to 2.95) [48]. In our meta-analysis, subgroup analysis also reported significant associations between PCOS and increased risk of NAFLD in both Caucasian and Asian populations (Caucasian: OR = 2.66, 95% CI: 2.06 to 3.44; Asian: OR = 3.01, 95% CI: 2.11 to 4.30). Shengir *et al.* also reported that women who were diagnosed with PCOS were at 2.5-fold higher risk for NAFLD than healthy controls (OR = 2.49, 95% CI: 2.20 to 2.82), and the remarkable relationship between PCOS and NAFLD was found almost all over the world (South America/Middle East: OR = 3.55, 95% CI: 2.27 to 5.55; Europe: OR =2.22, 95% CI: 1.85 to 2.67; Asia: OR = 2.63, 95% CI: 2.20 to 3.15) [49].

The present study showed high heterogeneity across the included studies. The subgroup analysis reported that different study types and ethnicities could not explain the high heterogeneity across the studies. In addition, meta-regression analyses showed that age and BMI were not responsible for heterogeneity across the studies. The result was inconsistent with a recent meta-analysis, which reported that BMI might

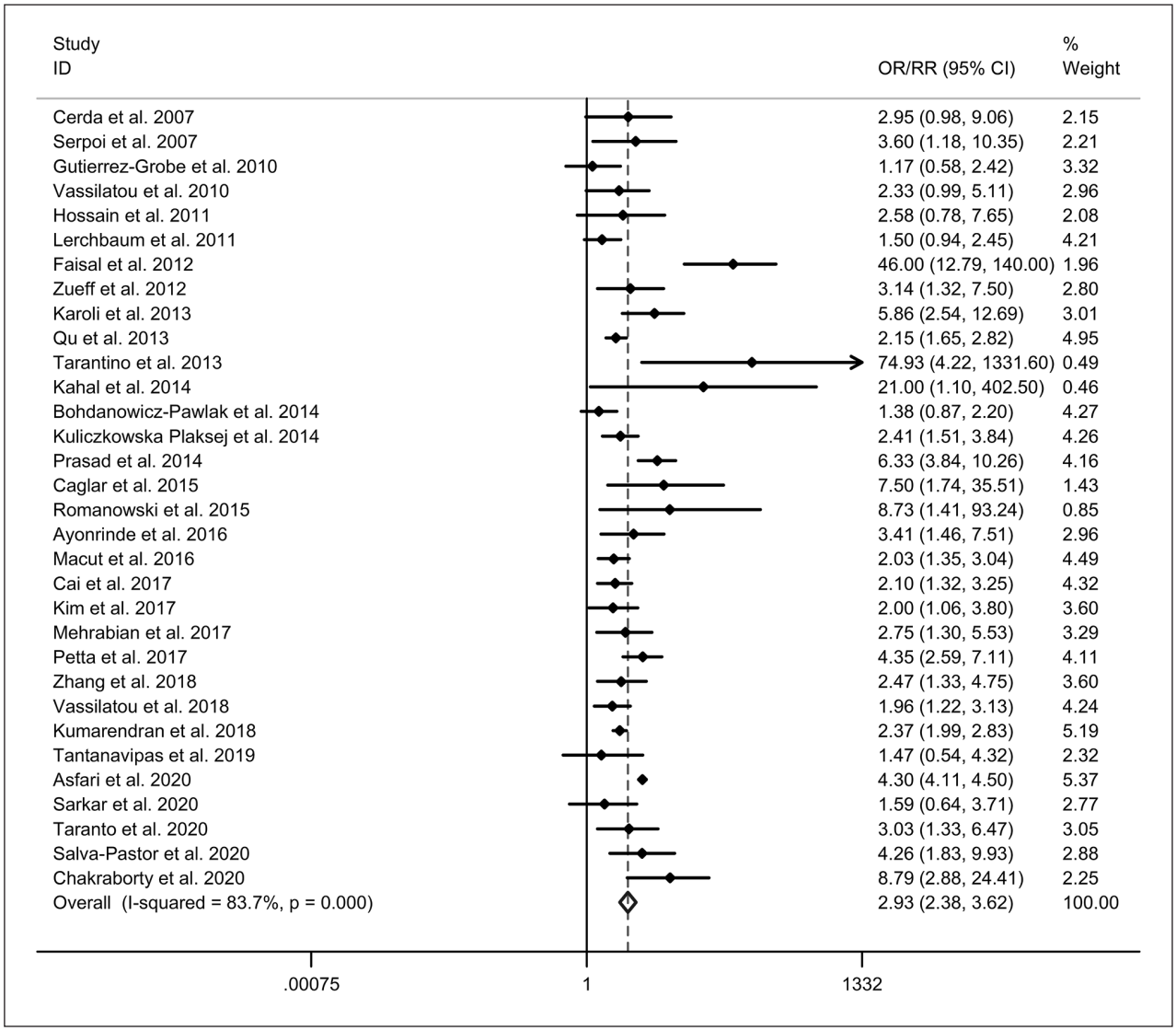

Figure 1. *Forest plots of association between polycystic ovary syndrome (PCOS) and risk of non-alcoholic fatty liver disease (NAFLD). CI — confidence intervals; OR — odds ratio; RR — relative risk*

contribute to the heterogeneity across studies (50). Heterogeneities might be derived from heterogeneity of included participants and different detection methods of NAFLD between studies. Characteristics of participants included age, BMI, and homeostasis model assessment of insulin resistance (HOMA-IR). In addition, most studies included in the meta-analysis used ultrasound scan.

NAFLD is not only considered as a chronic liver disease, but also as a metabolic disease with multiple organ involvement. The extra-hepatic manifestations of NAFLD include T2DM, cardiovascular disease, chronic kidney disease, osteoporosis, and obstructive. Thus, NAFLD is usually seen as "hepatic manifestation" of metabolic syndrome [51]. Unfortunately, the exact mechanism between PCOS and NAFLD remains elusive. However, the association between PCOS and NAFLD is more than coincidental, because these 2 diseases share many risk factors including insulin resistance, hyperandrogenaemia, and chronic inflammation [52]. IR and hyperandrogenaemia were thought to be predictors of NAFLD among PCOS women [53]. IR and hyperinsulinaemia are considered as major causes that contribute to the pathophysiology of PCOS [54]. Previous studies showed that hepatic steatosis may be associated with IR rather than obesity [55] because there were high rates of NAFLD – almost 40% among lean and young women diagnosed with PCOS according to previous studies [56]. IR is universal in T2DM patients, and a meta-analysis found that the pooled NAFLD prevalence among T2DM patients was 59.67% on the basis of 24 included studies with a total of 35,599 patients [57]. Also, the vicious circle of IR and inflammation promoted the development of NAFLD and other metabolic disorders in the pres-

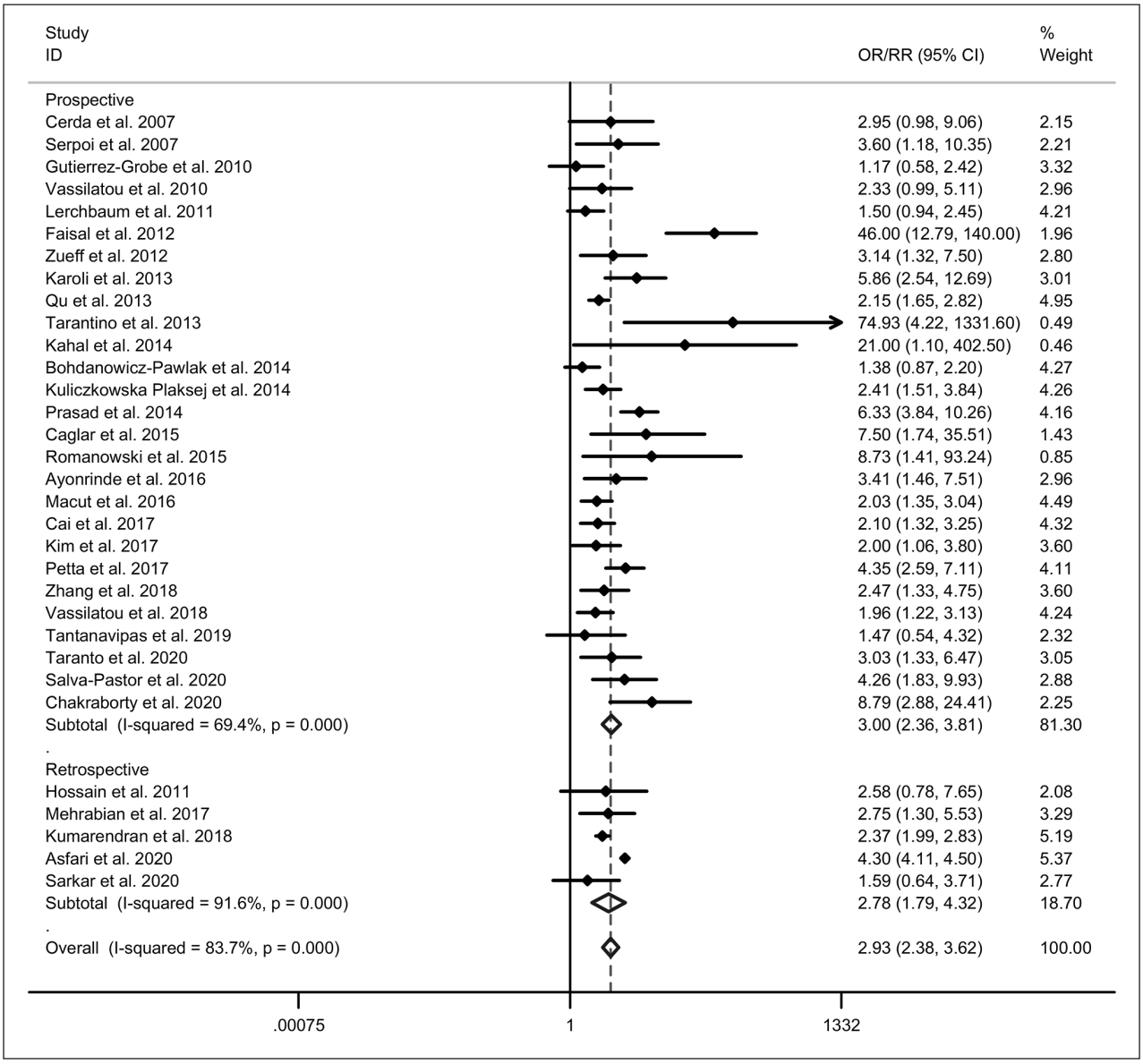

Figure 2. *Subgroup analysis of association between polycystic ovary syndrome (PCOS) and risk of non-alcoholic fatty liver disease (NAFLD) in different study types. CI — confidence intervals; OR — odds ratio; RR — relative risk*

ence of lipotoxicity [58]. Hyperandrogenaemia may also contribute to the pathogenesis of NAFLD in PCOS. Androgens may induce excess lipid accumulation in the liver by extending the half-life period of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) via inhibiting the LDL-receptor expression [59]. Compared with PCOS women with normal androgens, PCOS women with increased androgens showed elevated levels of LDL, triglycerides, and homeostasis model assessment of insulin resistance (HOMA-IR) [60]. Kumarendran et al. conducted a prospective study using a large primary care database and found that serum testosterone > 3.0 nmol/L was related to an increased risk of NAFLD among PCOS women [46].

There are some limitations to this systemic review and meta-analysis. First, a certain shortcoming of the study is the reliance on ultrasound in the diagnosis of steatosis, which is somewhat subjective and does not reflect the essence of the problem, which is the fibrosis accompanying NAFLD. Ultrasound scan is the most commonly used testing method for NAFLD, but it can only detect when there is over 33% of fat content in the liver [61]. However, the gold standard for detecting NASH is invasive liver biopsy [62]. In addition, non-invasive assessment of steatosis and fibrosis (e.g. controlled attenuation parameter [CAP] and liver stiffness measurement [LSM]) is not yet widely used. Hence, most of included studies used ultrasound scanning, which may inexactly evaluate the proportion of

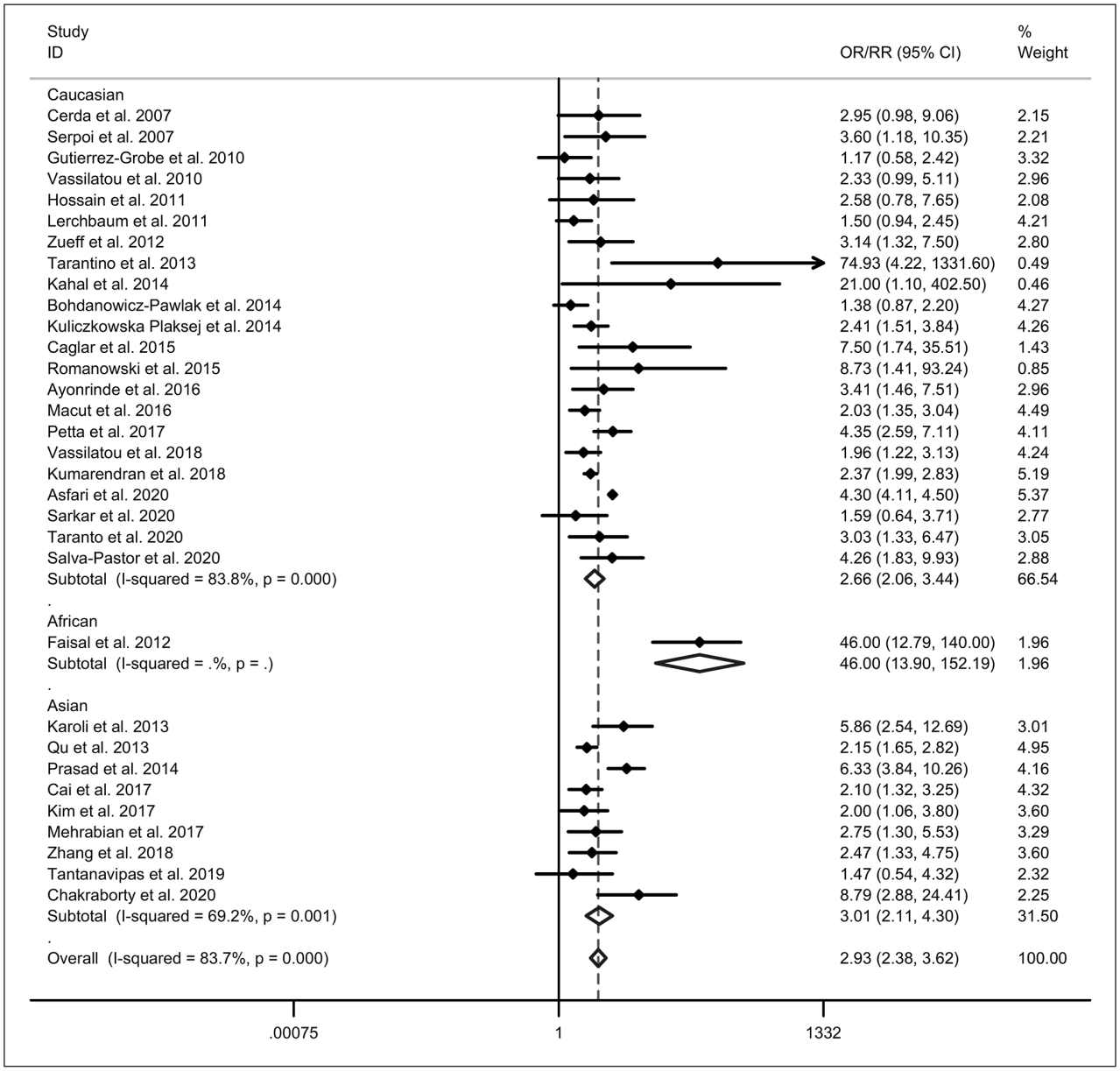

Figure 3. *Subgroup analysis of association between polycystic ovary syndrome (PCOS) and risk of non-alcoholic fatty liver disease (NAFLD) in different ethnicities. CI — confidence intervals; OR — odds ratio; RR — relative risk*

NAFLD among PCOS women. Second, the included studies used different diagnostic criteria of PCOS, which may affect the doctors' judgement. Third, several confounding factors such as diet, smoking, and excessive drinking were not taken into account.

Conclusion

This meta-analysis reported that there was a significant association between PCOS and an elevated risk of NAFLD. Early proper detection of NAFLD for PCOS women is essential. All patients with PCOS should undergo appropriate diagnostics for early detection of fatty liver and fibrosis.

Ethics statement

Ethics section header: The present study is a meta-analysis. Thus, an ethics section header is not applicable.

Ethical approval

The present study is a meta-analysis. Thus, ethical approval is not applicable.

Conflicting interests

No conflict of interest.

Funding

No funding.

Data statement

Data can be acquired from corresponding author.

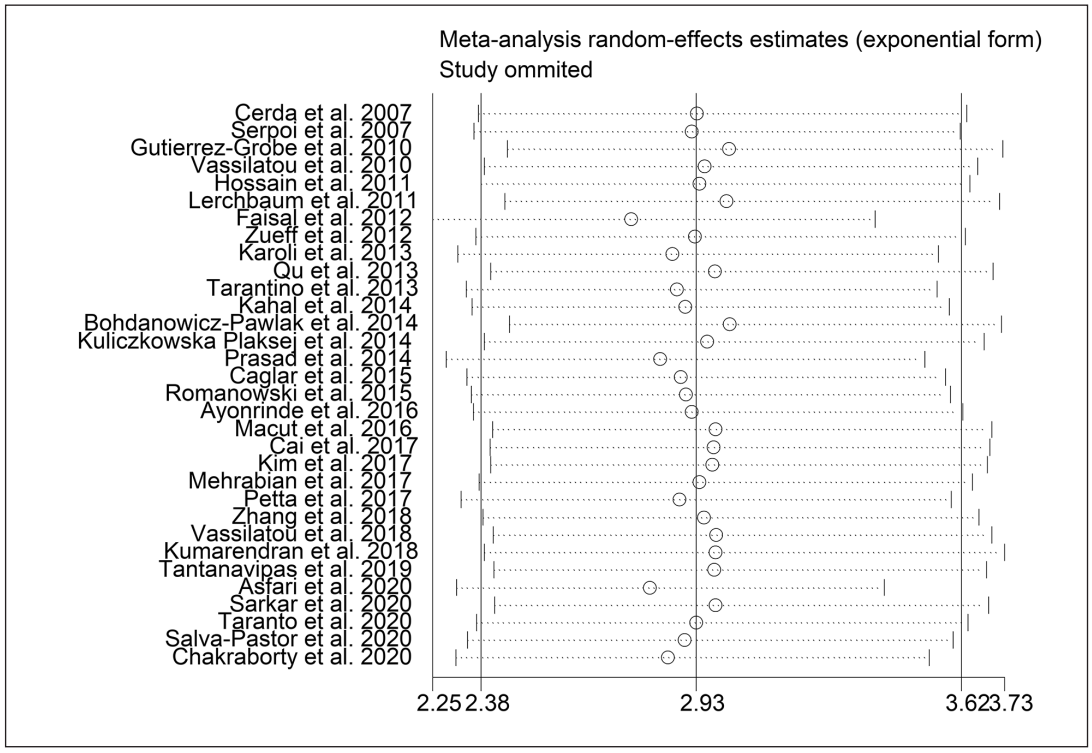

Figure 4. *Sensitivity analysis of association between polycystic ovary syndrome (PCOS) and risk of non-alcoholic fatty liver disease (NAFLD) in different ethnicities*

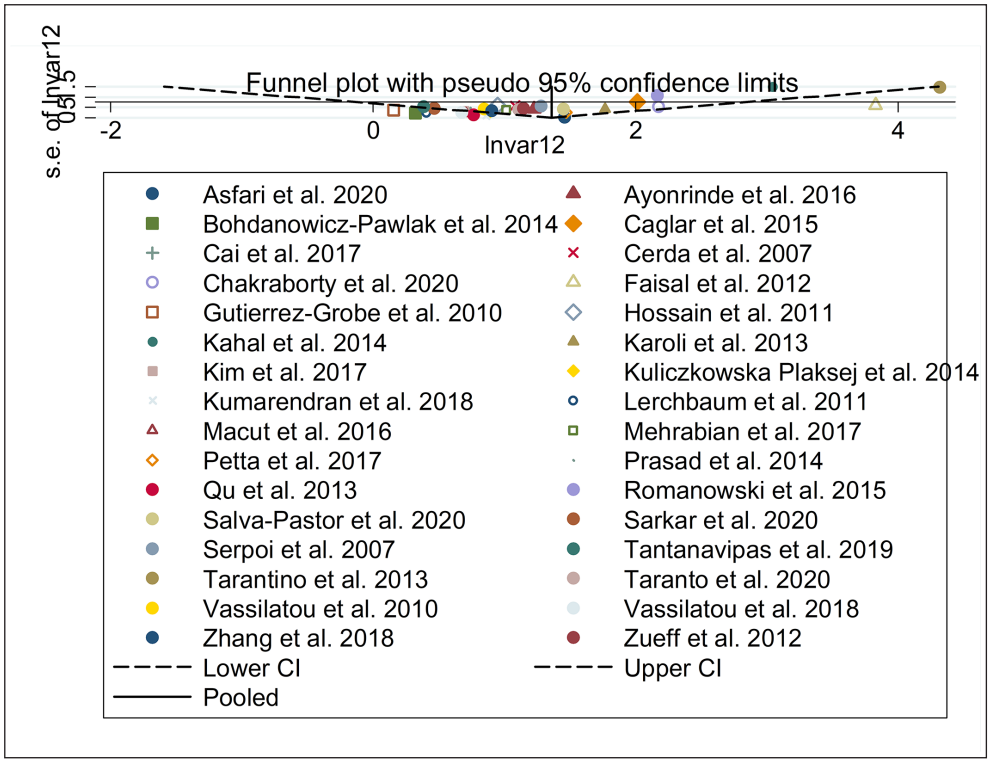

Figure 5. *Funnel plot of association between polycystic ovary syndrome (PCOS) and risk of non-alcoholic fatty liver disease (NAFLD) in different ethnicities*

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