


ORIGINAL ARTICLE

# Non-alcoholic fatty liver disease in premenopausal women with polycystic ovary syndrome: A systematic review and meta-analysis

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## Key words

BMI, geographic region, NAFLD, pooled odds ratio, study quality.

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**Authors contributions:** Mohamed Shengir was involved in study concept and design, acquisition of data, interpretation of data, analysis, and drafting of manuscript. Tianyan Chen was involved in study concept, acquisition and interpretation of data, critical revision of manuscript, and overall study supervision. Elena Guadagno created the search strategy and was involved in the revision of manuscript. Ramana V Ramanakumar performed the meta-analysis and was involved in the revision of manuscript. Peter Ghali, Marc Deschenes, Philip Wong, and Srinivasan Krishnamurthy were involved in study concept and critical revision of manuscript. Giada Sebastiani was involved in study concept and design, acquisition and interpretation of data, analysis and drafting of manuscript, critical revision of manuscript, and overall study supervision. All authors declare that they have participated in the preparation of the manuscript and have seen and approved the final version.

## Abstract

**Background and Aim:** Non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS) are prevalent conditions sharing common pathogenic factors. We performed a systematic literature review and meta-analysis aiming to investigate the association between NAFLD and PCOS among premenopausal PCOS patients.

**Methods:** Relevant studies were systematically identified from scientific databases until 2019. We calculated pooled odds ratio (OR) using a random-effect model, and heterogeneity was addressed through  $I^2$ . Subgroup analyses and meta-regression for various covariates were performed.

**Results:** Of the 1833 studies retrieved, 23 studies with 7148 participants qualified for quantitative synthesis. The pooled result showed that women with PCOS had a 2.5-fold increase in the risk of NAFLD compared to controls (pooled OR 2.49, 95% confidence interval [CI] 2.20–2.82). In subgroup analyses comparing PCOS to controls, South American/Middle East PCOS patients had a greater risk of NAFLD (OR 3.55, 95% CI 2.27–5.55) compared to their counterpart from Europe (OR 2.22, 95% CI 1.85–2.67) and Asia (OR 2.63, 95% CI 2.20–3.15). Insulin resistance and metabolic syndrome were more frequent in the PCOS group (OR 1.97, 95% CI 1.44–2.71 and OR 3.39, 95% CI 2.42–4.76, respectively). Study quality and body mass index (BMI) were the only covariates that showed a relationship with the outcome in the meta-regression, with a regression coefficient of  $-2.219$  (95% CI  $-3.927$  to  $-0.511$ ) and  $-1.929$  (95% CI  $-3.776$  to  $-0.0826$ ), respectively.

**Conclusions:** This meta-analysis indicates that premenopausal PCOS patients are associated with 2.5-fold increase in the risk of NAFLD, and BMI seems to be the main cofactor.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a growing global health problem, affecting almost a quarter of the world's population, and is currently recognized as the most common cause of chronic liver disease globally.<sup>1,2</sup> NAFLD is defined as the detection of >5% fat accumulation within the liver, either by imaging or histology in the absence of other identifiable causes of hepatic steatosis, particularly in the absence of excessive alcohol consumption.<sup>3</sup> The disease encompasses a spectrum of conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) to fibrosis, cirrhosis, and eventually hepatocellular carcinoma.<sup>4</sup> The estimated global prevalence of NAFLD ranges from 6.3 to 33%, with a median of 20%.<sup>5</sup> However, its risk is considerably higher in some populations such as obese and type 2 diabetics, where the prevalence reaches 69.4%.<sup>6</sup> NASH, the progressive form of NAFLD, is presently the second indication for liver transplantation and is projected to become the leading indication in the coming decade.<sup>7</sup> NASH is already the most frequent indication in women.<sup>8</sup> Parallel to its liver-related outcomes, there is growing body of evidence supporting that NAFLD is a multisystemic disease, and it has strong clinical associations with many extrahepatic conditions.<sup>9</sup> Insulin resistance (IR), which is considered the gameplayer in NAFLD pathogenesis, seems to be the culprit risk factor for most of these associations.<sup>10</sup>

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence up to 20%.<sup>11</sup> It is characterized by oligoamenorrhea, clinical or biochemical hyperandrogenism, and/or polycystic ovary morphology on ultrasonography.<sup>12</sup> In addition to these main features, metabolically, most PCOS patients have IR with compensatory hyperinsulinemia as an intrinsic feature. Notwithstanding that, obesity, which is frequently associated with PCOS, can also cause IR.<sup>13</sup> Several studies demonstrated that nonobese PCOS patients have higher IR in comparison with non-PCOS women.<sup>14–16</sup> The association between PCOS and IR may come with a high prevalence of NAFLD among women with PCOS. NAFLD and PCOS are considered the hepatic and ovarian manifestations of the metabolic syndrome, respectively.<sup>17–23</sup> However, while some studies reported a higher prevalence of NAFLD in PCOS patients compared to controls, others were inconclusive. One meta-analysis reported a significant association between PCOS and NAFLD, but independent of obesity and geographic region.<sup>24</sup>

In this study, we aim to conduct a systematic review and meta-analysis to estimate the strength of association between NAFLD and premenopausal women with PCOS, as well as identifying cofactors associated with NAFLD.

## Methods

**Search strategy.** This systematic literature review was conducted following a designated protocol and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines<sup>25</sup> (Appendix S1). The protocol was submitted to the international prospective register of systematic reviews (PROSPERO),<sup>26</sup> registration # CRD42020154363. The following databases were searched from inception until 1st June 2018 and then updated on 1st February 2020 with inputs from a medical

librarian (EM), who ran the former search, and study investigators (MS, TC, GS). The following databases were searched: Africa-Wide Information (Ebsco), Biosis (Ovid & Clarivate Analytics), Cochrane (Wiley), Embase (Ovid), Global Health (Ovid), Global Index Medicus (WHO), Medline (Ovid), and Web of Science (Clarivate Analytics) to identify articles that addressed the association between NAFLD and PCOS using the following variations in text words found in the title, abstract or keyword fields, and relevant subject headings: Fatty liver OR hepatic steatosis OR non-alcoholic fatty liver disease OR NAFLD OR non-alcoholic steatohepatitis OR NASH OR liver fibrosis OR cirrhosis AND polycystic ovary syndrome OR PCOS. The search was neither limited to defined geographic area nor specific language. See Appendix S2 for the full search strategy.

**Eligibility criteria.** Eligible studies were selected according to the following criteria: (i) original observational (cohort, case-control, or cross-sectional) studies; (ii) conducted on premenopausal women  $\geq 18$  years old; (iii) a diagnosis of PCOS according to one of the following criteria: Rotterdam criteria, National Institutes of Health (NIH) criteria, or Androgen excess and PCOS Society (AES) criteria; (iv) NAFLD diagnosis determined by either imaging studies or noninvasive biomarkers; and (v) reported the measure of association (odds ratio [OR]) or provided sufficient data to be calculated.

**Data extraction.** All retrieved articles in the initial search were read independently by two reviewers (MS and TC), starting with titles and abstracts screening, followed by the full-text reading, and concluded by data extraction.<sup>27</sup> Any disagreements were resolved by mutual discussion or by a third independent reviewer (GS) if necessary. The following data were retrieved from the full text of the selected articles: geographic region, first author, year of publication, country, age, body mass index (BMI), number of participants, enrollment period, PCOS criteria, NAFLD diagnosis modality, prevalence of NAFLD, cofactors of NAFLD, and ORs with confidence intervals (CIs). Data were extracted from each article and sorted into customized tables.

**Quality assessment.** Evaluation of risk of bias for each paper was performed by two independent reviewers (MS, TC) using the Newcastle-Ottawa Scale (NOS)<sup>28</sup> for nonrandomized studies. The scale judges three broad perspectives: the selection of participants, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies. As there is no specific scale available for cross-sectional studies from the original source, an adjusted NOS<sup>29</sup> has been adapted. Further modifications have been applied based on the purpose of this review (S1 "coding manuals"). In this scale, each study will be given an overall quality score; this score is the sum of subscores assigned for each domain that was used to categorize overall study quality.<sup>30</sup> The selection of participant domain subscore was amended (using  $\geq 2$  star points instead of  $\geq 3$  for fair to good threshold) to account for all study designs. For the interpretation of overall scores, modified dichotomous limits (good vs poor) were applied for simplification purposes. The original description of overall scores were as follows: good ( $>7$ ), fair (5–7), and poor ( $<5$ ); however, we replaced it with the following thresholds: fair to good ( $>5$ ) and poor ( $<5$ ) (Table 1).

**Table 1** Quality assessment for (a) cross-sectional studies and (b) case-control studies

Author, year	Selection				Comparability		Outcome		
	Representative of sample (*)	Sample size (*)	Non-respondents (*)	Ascertainment of the exposure (*)	Control for weight and/or IR (*)	Control for additional factors (*)	Assessment of the outcome (**)	Statistical test (*)	Total (9*)
Cerda, 2007	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	—	6
Serpo, 2007	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	—	6
Lerchbaum, 2011	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Karoli, 2012	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Ou, 2013	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Tarantino, 2013	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	—	6
Pawlak, 2014	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Plaksei, 2014	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Prasad, 2014	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Romanowski, 2015	*(b)	—	—	*(a)	—	—	***(a)	—	4
Macut, 2016	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Cai, 2017	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Mehrabian, 2017	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Munir, 2017	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	—	6
Petta, 2017	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Zhang, 2018	*(b)	—	—	*(a)	*(a)	*(b)	*(b)	*(a)	6
Vassiliadou, 2018	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7
Tantanavipas, 2019	*(b)	—	—	*(a)	*(a)	*(b)	***(a)	*(a)	7

Author, year	Selection			Comparability		Exposure		
	Case definition (*)	Representativeness of cases (*)	Selection of controls (*)	Definition of controls (*)	Ascertainment of exposure (*)	Same method of ascertainment for cases/controls (*)	Nonresponse rate (*)	
Vassiliadou, 2010	*(a)	*(a)	—(b)	*(a)	*(a)	*(a)	—(C)	7
Zueff, 2012	*(a)	*(a)	—(c)	*(a)	—(c)	*(a)	—(C)	5
Oztaşi, 2014	*(a)	*(a)	—(b)	*(a)	—(c)	*(a)	—(C)	5
Çağlar, 2015	*(a)	*(a)	—(c)	*(a)	—(c)	*(a)	—(C)	5
Kim, 2017	*(a)	*(a)	*(a)	*(a)	***(a,b)	*(a)	—(C)	8

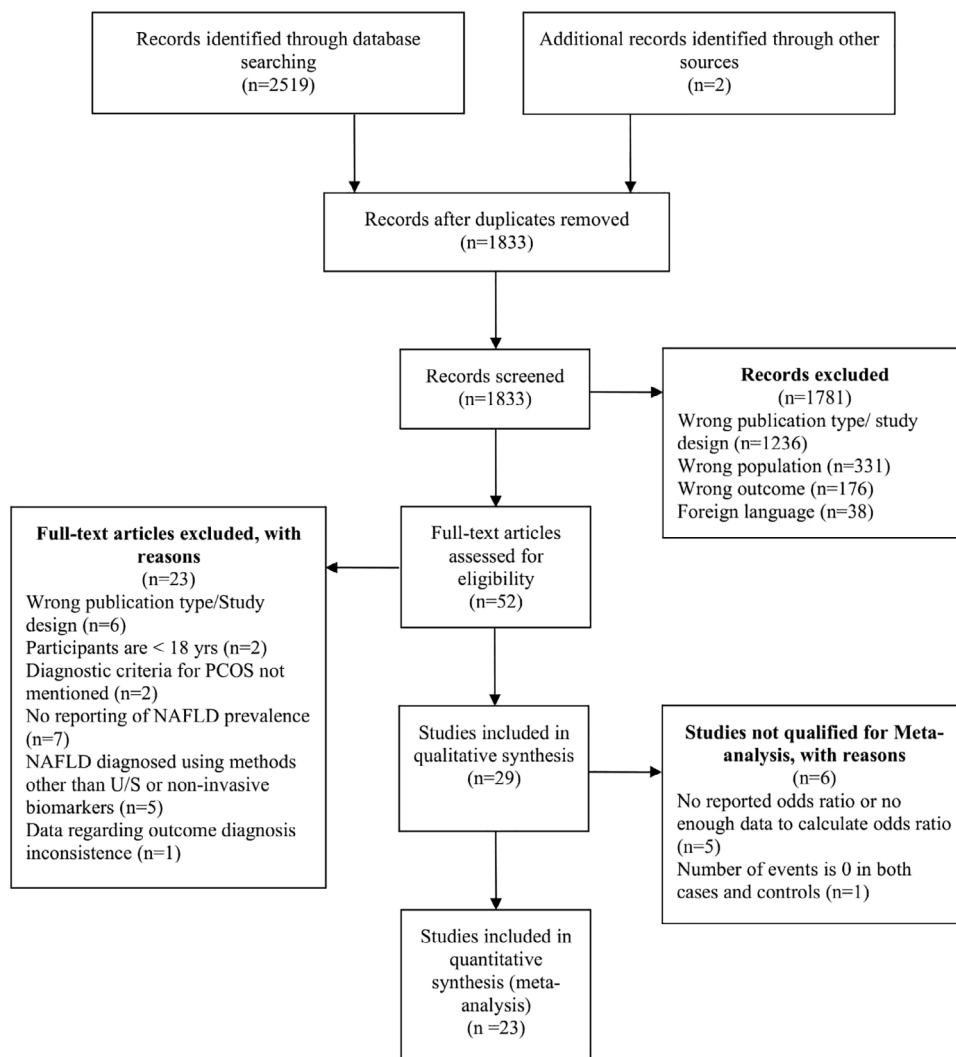
Interpretation of total scores: fair to good (>5) and poor (<5).

IR, insulin resistance.

**Outcome measures.** The primary outcome was to study the association between NAFLD and PCOS among premenopausal women with PCOS. The secondary outcome was to determine cofactors of NAFLD.

**Statistical analysis.** In the meta-analysis, forest plots were provided to illustrate pooled ORs and corresponding 95% confidence intervals [CIs] using a random-effect model.<sup>31</sup> As only seven studies have reported adjusted ORs (aOR), we calculated crude OR for all reviews in order to obtain a standardized measure of association. Statistical heterogeneity was assessed using the inconsistency ( $I^2$ ) index. Sensitivity analyses were performed by excluding: (i) poor-quality studies, defined as total NOS score <5 and/or sub-score thresholds <2 in selection of participants and ascertainment of exposure and outcome and <1 in comparability domain, and (ii) studies that weighed <5%. Publication bias was examined visually via a funnel plot, which is represented as a scatterplot of the degree of association of NAFLD in women with PCOS against sample size.<sup>32</sup> Subgroup analyses were performed by: (i) geographic

region, (ii) study design, (iii) NAFLD identification tool, (iv) PCOS diagnostic criteria, (v) presence of IR, (vi) presence of metabolic syndrome, and (vii) BMI. For BMI, eligible studies were stratified into two categories, lean (BMI <25 kg/m<sup>2</sup>) and overweight/obese (>25 kg/m<sup>2</sup>). The allocation to either group was based on the following criteria: (i) the study explicitly stated that it investigated NAFLD in either lean or overweight/obese PCOS,<sup>22,33–35</sup> (ii) there were data on either (or both) group(s) that allow us to calculate ORs for that subset of patients,<sup>17,23,36</sup> and (iii) studies in which PCOS and controls were matched for body weight and both groups had mean BMI <25 or >25 kg/m<sup>2</sup> were placed accordingly.<sup>18–20,37–43</sup> Using the above-mentioned BMI categories, further subanalyses investigating the presence of IR and the frequency of metabolic syndrome in each BMI subgroup was also conducted. Finally, we evaluated the effect of frequently reported cofactors on the desired outcome (NAFLD) through a meta-regression. Statistical analyses were performed using STATA 14.2 (STATA Corp. LP, College Station, Texas, USA) and funnel plots using R 3.5.1 (The R Foundation for Statistical Computing).



**Figure 1** Prisma flow chart.

**Table 2** Studies included in (a) qualitative synthesis and (b) quantitative analysis

(a)									
ID	Region	Author	Year	Country	Study design	Enrollment period	PCOS criteria	NAFLD diagnosis	Cofactors of NAFLD
1	Europe	Serpoi	2007	Romania	Prospective	—	Rotterdam	Ultrasound	—
2		Markou	2010	Greece	Prospective	—	Rotterdam	Ultrasound + CT	—
3		Vassiliadou	2010	Greece	Prospective	2006–2008	AES	Ultrasound + Transaminases	FAI, HOMA-IR
4		Ciotta	2011	Italy	Prospective	2010–2011	NIH	Ultrasound	—
5		Lerchbaum	2011	Austria	Prospective	2006–2010	NIH	FLI + APRI + FIB-4	—
6		Tarantino	2013	Italy	Prospective	2009–2011	Rotterdam	Ultrasound	—
7		Pawlak	2014	Poland	Prospective	—	Rotterdam	Ultrasound	ALT, BMI, estradiol/testosterone ratio, fasting blood sugar
8		Kozakowski	2014	Poland	Prospective	—	Rotterdam	Ultrasound	—
9		Plaksej	2014	Poland	Prospective	—	Rotterdam	Ultrasound	—
10		Maceut	2016	Serbia & Greece	Prospective	2008–2013	Rotterdam	NAFLD-liver fat score	HOMA-IR, lipid accumulation product
11		Petta	2017	Italy	Prospective	2005–2015	Rotterdam	HSI, FIB-4	FAI, WC
12		Vassiliadou	2018	Greece	Prospective	2007–2010	Rotterdam	Ultrasound	BMI
13	Asia	Ma	2011	China	Prospective	—	Rotterdam	Ultrasound	—
14		Karoli	2012	India	Prospective	2008–2010	Rotterdam	Ultrasound	HDL, HOMA-IR
15		Qu	2013	China	Prospective	2008–2010	Rotterdam	Ultrasound	BMI, HOMA-IR, triglycerides, waist-hip ratio
16		Prasad	2014	India	Prospective	2013–2014	Rotterdam	Ultrasound	HDL, HOMA-IR
17		Cai	2017	China	Prospective	2013–2016	Rotterdam	Quantitative Ultrasound	BMI, FAI, HOMA-IR, CRP, liver fat content
18		Munir	2017	Pakistan	Prospective	2016	Rotterdam	Ultrasound	—
19		Kim	2017	Korea	Prospective	2004–2014	Rotterdam	Ultrasound	FAI, free testosterone
20		Zhang	2018	China	Prospective	2014–2015	Rotterdam	Ultrasound	BMI, HOMA-IR, triglycerides
21		Tantanavipas	2019	Thailand	Prospective	2017–2018	Rotterdam	Ultrasound	WC
22	South America	Cerda	2007	Chile	Retrospective	2005–2006	Rotterdam	Ultrasound	—
23		Zueff	2012	Brazil	Prospective	2009–2010	Rotterdam	Ultrasound	—
24		Tock	2014	Brazil	Prospective	—	Rotterdam	Ultrasound	—
25		Romanowski	2015	Brazil	Retrospective	2008–2009	AES	Ultrasound	—
26	Middle East	Oztas	2014	Turkey	Prospective	2009–2011	AES	Ultrasound	anti-Müllerian hormone, sd-LDL
27		Çağlar	2015	Turkey	Prospective	—	Rotterdam	Ultrasound	ALT, VLDL
28		Mehrabian	2017	Iran	Retrospective	2013–2014	Rotterdam	Ultrasound	ALT, BMI, IR
29	North American	Gambarin-Geiwan	2007	USA	Retrospective	2004	NIH	Ultrasound	—

(b)												
PCOS							Controls					
ID	Author	n	Age (years)	BMI (kg/m <sup>2</sup> )	Metabolic syndrome	NAFLD % (n)	n	Age (years)	BMI (kg/m <sup>2</sup> )	Metabolic syndrome	NAFLD (%), n	OR (95% CI)
1	Cerda, 2007	41	24.6 ± 7	30.3 ± 7	14.6%	42% (17)	31	27.9 ± 7	29.3 ± 5	16.1%	19% (6)	2.95 (0.99–8.74)
2	Serpoi, 2007	44	29.3 ± 7	27.3 ± 6	27%	55% (24)	20	31.8 ± 6	26.9 ±	5%	25% (5)	3.6 (1.11–11.63)
3	Vassiliadou, 2010	57	27 ± 8	28.3 ± 8	14%	37% (21)	60	27.6 ± 7	27 ± 8	6.6%	20% (21)	2.33 (1.02–5.35)

ID	Author	PCOS						Controls					
		n	Age (years)	BMI (kg/m <sup>2</sup> )	Metabolic syndrome	NAFLD % (n)	OR (95% CI)	n	Age (years)	BMI (kg/m <sup>2</sup> )	Metabolic syndrome	NAFLD (%)	n
4	Lerchbaum, 2011	611	27 (23–31) <sup>‡</sup>	24.5 (21.4–29.4) <sup>‡</sup>	12.1%	23% (43)	1.49 (0.92–2.43)	139	30 (26–37) <sup>‡</sup>	24.1 (20.9–28.8) <sup>‡</sup>	4.9%	17% (23)	
5	Karoli, 2012	54	28.5 ± 6	27.2 ± 5	35%	67% (35)	5.39 (2.36–12.30)	55	27.8 ± 8	26.8 ± 7	7%	25% (14)	
6	Zueff, 2012	45	31.6 ± 4	34.7 ± 3	—	73% (33)	3.14 (1.29–7.59)	45	31.7 ± 4	34.5 ± 3	—	47% (21)	
7	Ou, 2013	602	28.7 ± 4	29.1 ± 3	—	33% (198)	2.15 (1.64–2.81)	588	28.1 ± 4	23 ± 3	—	19% (109)	
8	Tarantino, 2013	40	27.7 ± 6	28.1 ± 7	—	65% (26)	61.08 (3.52–1057.84)	20	26.2 ± 4	22.1 ± 2	—	0	
9	Pawlak, 2014	184	—	—	—	58% (106)	1.38 (0.87–2.17)	125	—	—	—	50% (62)	
10	Oztas, 2014	58	24.4 ± 3	21.9 ± 2	—	41% (24)	6.70 (1.42–31.52)	21	24.5 ± 3	21.8 ± 1	—	10% (2)	
11	Plaksej, 2014	172	25.3 ± 6	28.7 ± 7	—	53% (92)	2.41 (1.49–4.19)	125	27.7 ± 6	26.4 ± 6	—	32% (40)	
12	Prasad, 2014	162	27.6 ± 7	27.6 ± 6	36%	66% (106)	6.21 (3.82–10.09)	165	27.9 ± 8	26.9 ± 7	8%	23% (38)	
13	Çağlar, 2015	34	26 ± 3	22 ± 1	5.8%	44% (15)	7.5 (1.50–37.39)	21	26 ± 3	22.1 ± 2	0%	10% (2)	
14	Romanowski, 2015	101	26.8 ± 5	28.5 ± 6	32.7%	24% (24)	8.72 (1.12–67.56)	30	33.7 ± 7	26.1 ± 4	26.6%	3% (1)	
15	Macut, 2016	600	25.6 (25.1–26.1) <sup>†</sup>	30.7 (30.1–31.3) <sup>†</sup>	35.7%	51% (366)	2.51 (1.67–3.76)	125	31.4 (30.4–32.4) <sup>†</sup>	29.4 (28.1–30.7) <sup>†</sup>	29.4%	34% (42)	
16	Cai, 2017	400	25.8 ± 5	25.6 ± 5	—	56% (225)	2.09 (1.33–3.28)	100	26.8 ± 6	24.7 ± 5	—	38% (38)	
17	Kim, 2017	275	30.4 ± 5	20.3 ± 2	2.9%	6% (15)	2 (1.03–3.85)	892	35.1 ± 4	19.9 ± 2	1.3%	3% (25)	
18	Mehrabian, 2017	75	—	24.7 ± 2	33.3%	39% (29)	2.74 (1.30–5.77)	75	—	24.6 ± 2	10.7%	19% (14)	
19	Munir, 2017	30	25.8 ± 6	31.9 ± 6	—	73% (22)	6.05 (1.59–22.90)	16	30.6 ± 7	29.2 ± 6	—	31% (5)	
20	Petta, 2017	202	33.2 ± 6	25.7 ± 3	—	69% (139)	4.34 (2.61–7.23)	101	34.9 ± 8	23.9 ± 3	—	33% (34)	
21	Zhang, 2018	188	27.1 ± 5	25.1 ± 3	—	45% (84)	2.47 (1.31–4.66)	65	26.9 ± 5	24.2 ± 3	—	25% (16)	
22	Vassilatou, 2018	145	27.5 ± 7	31.8 ± 7	—	54% (78)	1.96 (1.22–3.13)	145	32.1 ± 8	30.5 ± 7	—	37% (55)	
23	Tantanavipas, 2019	42	27.7 ± 5	27 ± 6	14.2%	52% (22)	1.46 (0.51–4.21)	21	31.4 ± 6	25.7 ± 5	14.2%	43% (9)	

Data expressed in mean ± SD or percentage, unless otherwise indicated.

AES, androgen excess and PCOS society; ALT, alanine aminotransferase; APRI, aspartate aminotransferase (AST) to platelets ratio index; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CT, computerized tomography; FAI, free androgen index; FIB-4, fibrosis 4; FLI, fatty liver index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HSI, hepatic steatosis index; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NIH, national institutes of health; OR, odds ratio; PCOS, polycystic ovary syndrome; sd-LDL, small-density low-density lipoprotein; VLDL, very-low-density lipoprotein; WC, waist circumference.

<sup>†</sup>Mean and 95% CI.

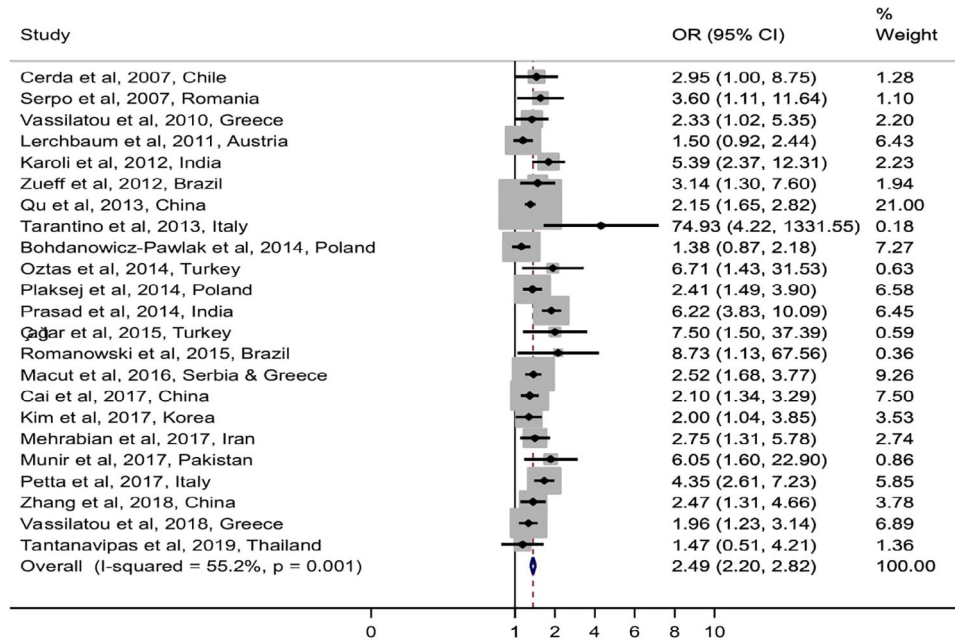
<sup>‡</sup>Median with interquartile range.

**Results**

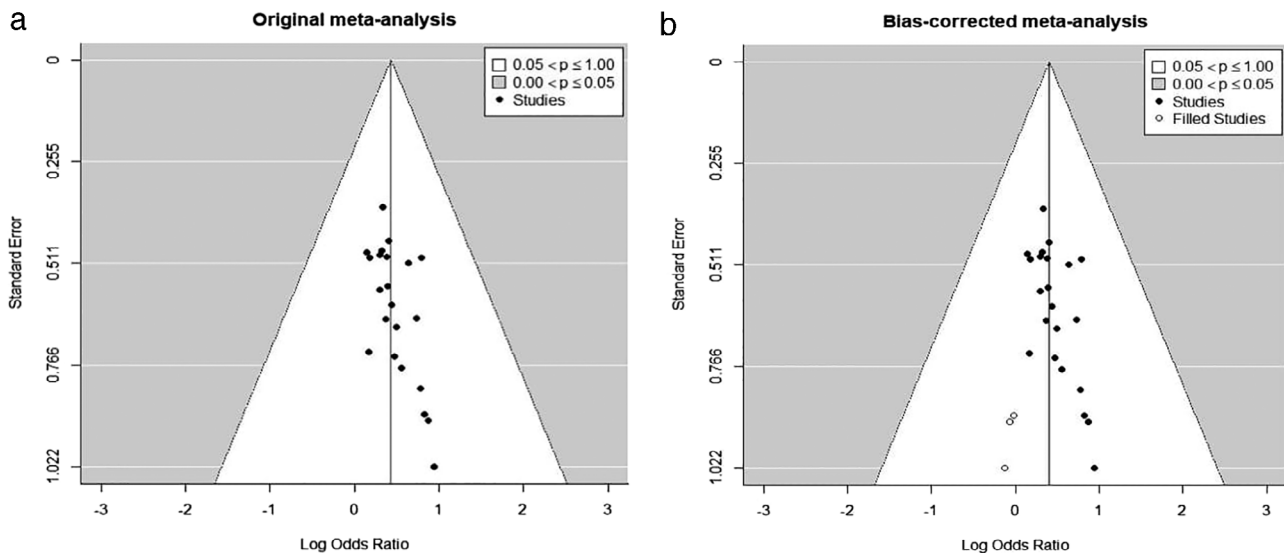
**Study selection.** The PRISMA flowchart is shown in Figure 1. The search strategy retrieved 1833 records after excluding duplicates. Upon applying our eligibility criteria using Rayyan web application,<sup>27</sup> titles and abstract screening resulted in an elimination of 1781 citations for different reasons; the remaining 52 studies met the criteria for full-text reading. Ultimately, 29 articles published between 2007 and 2019

were found to qualify for the systematic review. Of these, 23 studies were eligible for quantitative synthesis. Six studies were not included in the analysis; five were excluded due to a lack of sufficient data, and one article was excluded because the number of events was zero in both the PCOS and control groups.

**Study characteristics.** We divided our inputs from 29 studies into two tables. Table 2a shows articles selected for the



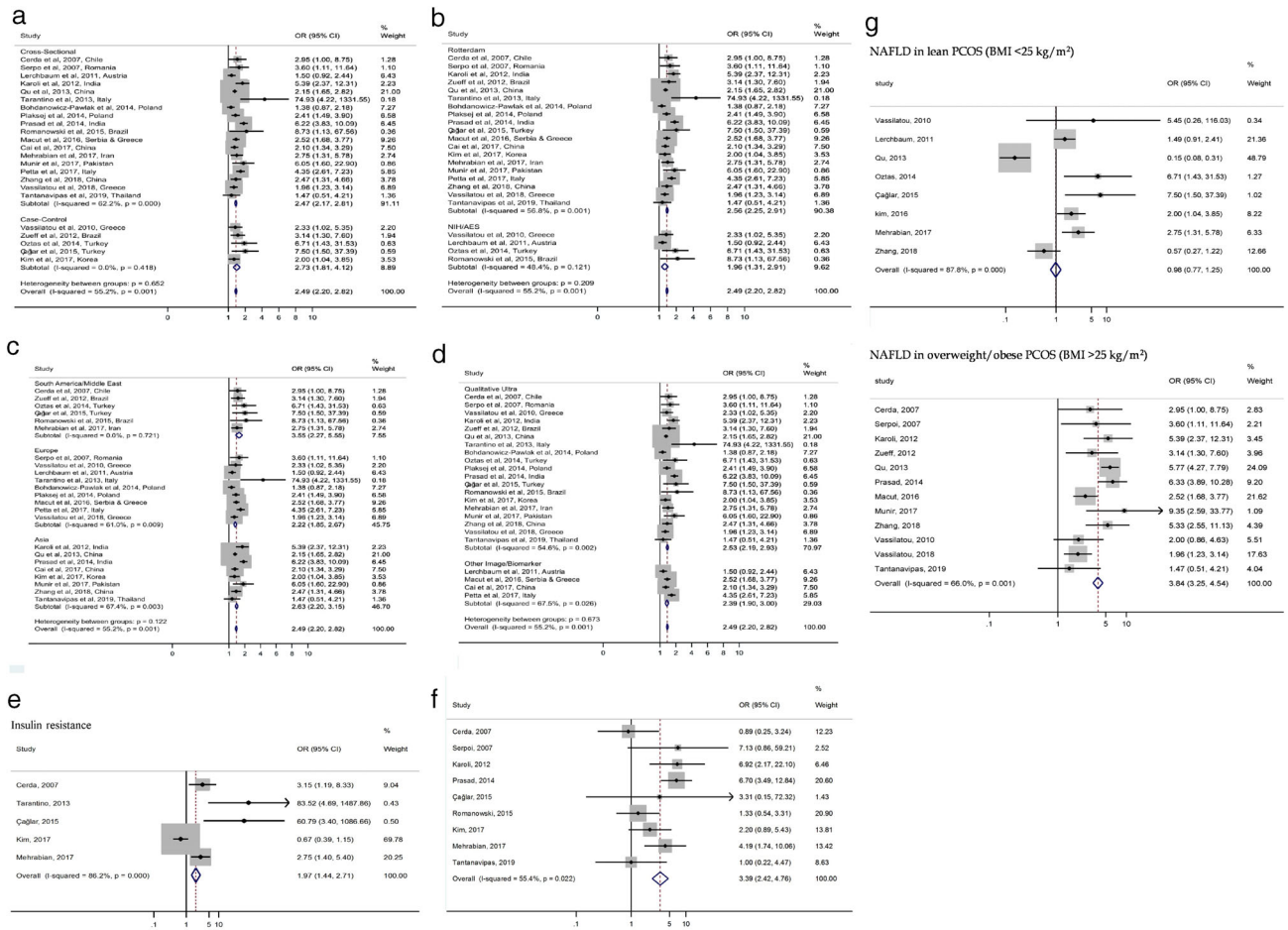
**Figure 2** Forest plot of studies investigated the association of non-alcoholic fatty liver disease and polycystic ovary syndrome.



**Figure 3** Funnel plots of the meta-analysis. Funnel plots of the meta-analysis before (panel a) and after (panel B) applying the trim-and-fill method. The closed dots indicate the observed studies, and the open dots indicate the missing studies imputed by the trim-and-fill method. The dashed lines that create a triangular area indicate the 95% confidence limits, and the vertical solid line represents the overall effect size.

systematic review. These were divided according to their geographic areas: 1–12 Europe, 13–21 Asia, 22–25 South America, 26–28 the Middle East, and 29 North America. The majority of

these articles (25 studies) have used qualitative ultrasonography (alone or combined with additional method) as a diagnostic tool for NAFLD. We also noticed that the Rotterdam criteria were, by



**Figure 4** Subgroup analyses: A, study design; b, polycystic ovary syndrome criteria; c, geographic region; d, non-alcoholic fatty liver disease diagnostic tool; e, insulin resistance; f, metabolic syndrome; g, body mass index (BMI) (1. BMI <25 kg/m<sup>2</sup>, 2. BMI >25 kg/m<sup>2</sup>).

**Table 3** Subgroup analyses for risk of NAFLD in PCOS patients

Stratification	Subgroup	Number of studies	Odds ratio (95% CI)	I <sup>2</sup> (%)	P-value
Study design	Cross-sectional	18	2.47 (2.17–2.81)	62.2	<0.001
	Case-control	5	2.73 (1.81–4.12)	0	0.418
	Rotterdam	19	2.56 (2.25–2.91)	56.8	0.001
PCOS criteria	AES/NIH	4	1.96 (1.31–2.91)	48.4	0.121
	Rotterdam	6	3.55 (2.27–5.55)	0	0.721
Geographic region	South America/Middle East	9	2.22 (1.85–2.67)	61	0.009
	Europe	8	2.63 (2.20–3.15)	67.4	0.003
	Asia	8	2.63 (2.20–3.15)	67.4	0.003
NAFLD diagnosis	Ultrasound	19	2.53 (2.19–2.93)	54.6	0.002
	Other imaging/non-invasive biomarkers	4	2.39 (1.90–3.00)	67.5	0.026
Insulin resistance	PCOS versus Controls	1	1.97 (1.44–2.71)	86.2	<0.001
Metabolic syndrome	PCOS versus Controls	9	3.39 (2.42–4.76)	55.4	0.022

AES, androgen excess and PCOS society; HOMA-IR, homeostatic model assessment of insulin resistance; NAFLD, non-alcoholic fatty liver disease; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome.



far, the predominant standards utilized (23 studies) to identify patients with PCOS. All except four studies were prospective studies. Cofactors of NAFLD determined through multivariate logistic regression analyses were reported only in 12 studies. The three most frequently stated ones were IR measured by homeostatic model assessment (HOMA), BMI, and free androgen index (FAI), in descending order. Table 2b depicts the quantitative data such as the number of participants, age, BMI, NAFLD proportion, and ORs with 95% CIs in both arms—PCOS and controls.

**Meta-analysis.** Across 23 studies that were included in the meta-analysis, with 4164 PCOS cases and 2984 matched controls, pooled OR using the random-effect model was estimated to be 2.49 (95% CI 2.20–2.82), an almost 2.5-fold increase in the risk of NAFLD in PCOS compared to controls (Fig. 2). The results were significant, with moderate heterogeneity ( $I^2 = 55.2\%$ ,  $P = 0.001$ ). Publication bias was addressed using the trim-and-fill method developed by Duval and Tweedie.<sup>44,45</sup> The adjusted result from the random-effect model, after accounting for the missing studies (Fig. 3), was an OR of 2.56 (95% CI 2.07–3.17), which indicates that the result of the present meta-analysis is reliable. Furthermore, sensitivity analyses excluding poor-quality studies and studies that weighed <5% both displayed similar results, with an OR of 2.38 (95% CI, 2.09–2.71) and 2.36 (95% CI, 2.05–2.70), respectively. Subgroup analyses were conducted to explore potential sources of heterogeneity (Fig. 4). The pooled ORs of most subgroups were not markedly changed by the study characteristics. However, stratification by geographic location revealed that South American/Middle East populations with PCOS had a greater risk of NAFLD than those without PCOS (OR 3.55, 95% CI 2.27–5.55) compared to their European (OR 2.22, 95% CI 1.85–2.67) and Asian (OR 2.63, 95% CI 2.20–3.15) counterparts. When we stratified based on IR and the presence of metabolic syndrome, PCOS patients had a significantly higher risk of NAFLD, compared to controls (OR 1.97, 95% CI 1.44–2.71 and OR 3.39, 95% CI 2.42–4.76, respectively). Additional stratification by BMI showed a substantial risk of NAFLD in overweight/obese PCOS patients (OR 3.84, 95% CI 3.25–4.54) as opposed to weight-matched controls, whereas no risk was noted in lean PCOS (OR 0.98, 95% CI 0.077–1.25). Although normal BMI was not associated with an increased risk of NAFLD among PCOS patients, IR and metabolic syndrome were more frequent than in non-PCOS individuals (Fig. S1). We also noticed that the risk of NAFLD was lower with the NIH/AES criteria (OR 1.96, 95% CI 1.31–2.91) compared to the Rotterdam criteria (OR 2.56, 95% CI 2.25–2.91). Significant heterogeneity was observed in subgroup analyses for study design (cross-sectional,  $I^2 = 62.2\%$ ,  $P = <0.001$ ; case-control,  $I^2 = 0\%$ ,  $P = 0.418$ ), PCOS diagnostic criteria (Rotterdam,  $I^2 = 56.8\%$ ,  $P = 0.001$ ; NIH/AES,  $I^2 = 48.4\%$ ,  $P = 0.121$ ), and geographic area (Asia,  $I^2 = 67.4\%$ ,  $P = 0.003$ ; Europe,  $I^2 = 61\%$ ,  $P = 0.009$ ; Middle East & South America,  $I^2 = 0\%$ ,  $P = 0.721$ ). For all groups of NAFLD diagnostic modality (qualitative ultrasonography,  $I^2 = 54.6\%$ ,  $P = 0.002$ ; imaging/noninvasive biomarkers,  $I^2 = 67.5\%$ ,  $P = 0.026$ ), IR ( $I^2 = 86.2\%$ ,  $P = <0.001$ ), metabolic syndrome ( $I^2 = 55.4$ ,  $P = 0.022$ ), BMI <25 kg/m<sup>2</sup> ( $I^2 = 87.8\%$ ,  $P = <0.001$ ), and BMI >25 kg/m<sup>2</sup> ( $I^2 = 66\%$ ,  $P = 0.001$ ), heterogeneity reached statistical significance. Nonetheless, the degree

of heterogeneity remained unaltered from the main result (Table 3). Of note, only three among the included studies looked for the association between PCOS and severity of NAFLD, evaluated via ultrasound. There was no significant difference in NAFLD severity between PCOS patients and controls, possibly because of the relative limited patient populations.<sup>33,43</sup> One of these studies reported the prevalence of significant liver fibrosis in PCOS patients to be 4.7% as determined by transient elastography.<sup>43</sup>

**Meta-regression.** General study characteristics such as the presence of matching and aOR, as well as study design and NAFLD diagnostic modalities, revealed no significant association except for study quality, which is defined as (i) fair to good when the total NOS score is >5 given that the subscores for the selection of participants and ascertainment of exposure and outcome domains are  $\geq 2$  and for comparability domain is  $\geq 1$  and (ii) poor when the total NOS score is <5 given that the subscores for the selection of participants and ascertainment of exposure and outcome domains are <2 and for comparability domain is <1 (regression coefficient –2.219, CI –3.927 to –0.511) (Table S1). Moreover, among most frequently reported risk factors, only BMI showed an elevated risk with the desired outcome (regression coefficient –1.929, 95% CI –3.776 to –0.082) (Table S2).

## Discussion

As NAFLD is becoming the most common cause of chronic liver disease globally, health-care authorities and many well-known liver organizations are currently advocating for NAFLD screening in high-risk groups such as people with obesity and type 2 diabetes mellitus.<sup>46–49</sup> Therefore, identifying populations at risk is the first step toward implementing an effective screening strategy that might help in alleviating the burden of NAFLD-related outcomes, including cirrhosis, hepatocellular carcinoma, and liver transplantation. Over the past decade, there has been increasing interest in researching NAFLD in women with PCOS as the relationship seems extremely relevant in clinical settings: both conditions are common, and their coexistence may synergistically increase the risk of catastrophic consequences of progressive NAFLD, especially in a relatively young PCOS population. Moreover, menstrual and reproductive factors, as well as the use of exogenous hormones, have been associated with the risk of NAFLD in women.<sup>50</sup> Finally, NASH already represents the first indication for liver transplant in women.<sup>8</sup> So far, some studies have found a positive relationship between PCOS and NAFLD when compared to non-PCOS counterparts.<sup>17–19,22,23,33,34,36,37,39,40,42,43,51–55</sup> At the same time, others could not determine this association, either because there were no differences between both groups and/or the prevalence in the PCOS group was lower than the general population.<sup>21,35,38,56</sup> To date, data regarding this topic are inconsistent and still evolving.

When we reviewed the literature, we found three previous meta-analyses that investigated the relationship between NAFLD and PCOS. First, a report that included seven studies found that NAFLD was markedly prevalent among PCOS patients presumably due to shared risk factors such as obesity and IR.<sup>57</sup> A subsequent meta-analysis that included 17 studies has confirmed

frequent NAFLD occurrence in the PCOS cohort. In addition, the report shed a light on hyperandrogenemia as an additional risk factor contributing to the development of NAFLD in the PCOS population.<sup>58</sup> Finally, another meta-analysis that included 17 studies showed results that were also in total agreement with previous findings. However, the authors were also aiming to identify if these higher figures of NAFLD were related to the presence of PCOS itself or were caused by common risk factors.<sup>24</sup> Indeed, determining the culprit factor(s) contributing to a higher prevalence of NAFLD, especially in PCOS, is a challenging task as this raises the argument of PCOS-defining criteria. AES and NIH definitions mandate the presence of hyperandrogenemia to establish the diagnosis of PCOS. Therefore, PCOS and hyperandrogenemia are relatively synonymous in this context. The only criteria that include a subset of PCOS patients without exhibiting any signs of either clinical or biochemical androgen excess is Rotterdam criteria. Discussing the etiology of NAFLD in PCOS patients is beyond the scope of this study. Although all aforementioned meta-analyses suggested frequent comorbidity of NAFLD in PCOS patients, each of them has its limitation in terms of generalizability. The former meta-analysis has a small sample size,<sup>57</sup> and the other two meta-analyses had quit limited search, they only searched for English language articles from two databases.<sup>24,58</sup> To include a larger, more representative sample and add robustness to the argument that PCOS patients are, in fact, at higher risk of NAFLD, we carried out a systematic literature review searching eight scientific databases and meta-analyses of studies that have reported the prevalence of NAFLD in PCOS patients up to 2020 without any restrictions in the search strategy. Our summary result indicates that PCOS patients are at higher risk of NAFLD (OR 2.49, 95% CI 2.20–2.82), a 2.5-fold increase compared to controls. Although this result is in line with previous meta-analyses,<sup>24,57,58</sup> the present study confirms, updates, and adds more strength to the previous findings because it includes more reviews, a total of 29 publication, and thus a larger sample size of 7148 participants compared to 17 studies with 5334 participants in the most recent meta-analysis<sup>24</sup> and 7 studies with 1185 participants in the oldest one,<sup>57</sup> a total increase of 12 and 22 studies, respectively. The characteristics of included studies are variable in terms of study design, PCOS definition, quality appraisal, and results. However, our subgroup and sensitivity analyses suggest that all these factors did not impact the overall results.

Epidemiological studies found different prevalence for NAFLD in the general population across continents. The highest figures were reported from South American and the Middle East, with a prevalence of around 30% for each region.<sup>59</sup> Thus, when we stratified according to geographic locations, we combined these two areas based on the similarity that both ethnicities exhibited. Our results depict that NAFLD risk was also considerably elevated in PCOS patients from these geographic regions. Factors associated with a higher risk of NAFLD reported in most included studies were increased IR,<sup>21,22,34,37,39</sup> worse metabolic profile,<sup>21,37</sup> and hyperandrogenemia.<sup>33</sup> In this meta-analysis, we conducted subgroup analyses for various risk factors aiming to investigate their association with the risk of NAFLD. Apart from geographic area that was previously mentioned, higher BMI and IR were correlated with an increased risk of NAFLD. Likewise, metabolic syndrome was highly prevalent among the PCOS

population. Importantly, PCOS patients with normal BMI showed no significant risk for NAFLD compared to weight-matched controls. To our knowledge, this is the first meta-analysis researching IR and metabolic syndrome in a PCOS setting. On top of the aforementioned factors, genetic predisposition seems to be an undisputed contributing factor to the high prevalence of NAFLD in South Americans, where the rs738409 G allele of the patatin-like phospholipase domain-containing protein 3 gene is highly prevalent despite much lower daily caloric intake than in North America and western Europe.<sup>59</sup>

Our meta-regression identified an association between study quality and the frequency of NAFLD in women with PCOS. Conversely, other general study characteristics such as matching, study design, adjusted OR, and NAFLD diagnostic tool did not show any significant results. Among most frequently reported risk factors including age, HOMA-IR, and FAI, only BMI indicated an elevated risk for the desired outcome.

This study has several strengths. We broadened our literature search to include eight databases without search strategy restrictions in order to provide a representative sample size that can reflect the PCOS population in general. In addition, studies that have used aminotransferase as a method to diagnose NAFLD were excluded to be consistent with the NAFLD definition. Clinically meaningful factors were investigated in subgroup analysis, adding strength to the existing knowledge. Although our study allows for a clinically meaningful expansion of the literature, it is not without limitations. First, the included studies were all observational, which might be biased due to unmeasured confounders. Second, our summary result was based on crude ORs as only seven reviews reported adjusted ORs. Although some studies were adjusted for main confounders, other modifiable factors were not accounted for in all these studies, such as family history, dietary habits, and/or exercise. The presence of adjusted ORs for all studies and taking into account all possible relevant confounders may have influenced the overall result. Third, ultrasonography was the predominant method for diagnosing NAFLD rather than the gold-standard liver biopsy. This can be justified by the difficulty in applying such an invasive procedure for research purposes. Ultrasonography is a readily available, cheap, noninvasive technique with discrete sensitivity and specificity for epidemiological studies.

In conclusion, our findings indicate that PCOS patients are at higher risk of NAFLD, and BMI seems to be the main driving factor. This risk is increased in women from South America and the Middle East. Therefore, early detection and initiation of intervention plans, including counseling on weight loss and linkage to hepatology care, will be crucial and can reduce or even eliminate the possibility of disease progression as these women can develop NAFLD at a relatively young age. Future research efforts should target the association between PCOS and severity of NAFLD, including liver fibrosis and clinical outcomes.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Appendix S1.** Supporting Information.

**Appendix S2.** Supporting Information.

**Figure S1.** Insulin resistance and metabolic syndrome in lean PCOS patients and in overweight/obese PCOS patients.

**Table S1.** Meta-regression of study characteristics.

**Table S2.** Meta-regression of cofactors of NAFLD.