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REVIEW

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

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Abstract
Purpose Non-alcoholic fatty liver disease (NAFLD) is an insidious pathologic condition that can manifest from simple steatosis to steatohepatitis (NASH) with potential progression to cirrhosis. Like the polycystic ovary syndrome (PCOS), NAFLD is associated with obesity, diabetes mellitus, insulin resistance and metabolic syndrome. PCOS women have an increased risk of NAFLD, but it is debatable which features of PCOS, either specific (androgen excess) or unspecific (metabolic derangements) affect the NAFLD risk.
Methods We performed a systematic review and meta-analysis of studies that addressed the association of PCOS and NAFLD. We selected 17 studies published between 2007 and 2017 that included 2734 PCOS patients and 2561 controls of similar age and body mass index (BMI).
Results PCOS patients have increased prevalence of NAFLD (odds ratio 2.54, 95% confidence interval 2.19–2.95). PCOS women with hyperandrogenism (classic phenotype) have a higher prevalence of NAFLD compared to women with PCOS without hyperandrogenism, even after correction for confounding variables. Among women with PCOS, those with NAFLD have higher serum total testosterone (mean difference 0.40 nmol/L, 95% CI 0.29–0.50 nmol/L) and free androgen index (mean difference 4.46, 95% CI 3.53–5.39) than those without NAFLD. The studies that used multivariate analysis controlling for age, BMI, triglycerides, and insulin resistance index confirmed that serum androgens are independent predictors of NAFLD in women with PCOS.
Conclusion The prevalence of NAFLD is increased in women with PCOS and the presence of NAFLD is associated with high serum androgen levels, in addition to obesity and insulin resistance.

Keywords Polycystic ovary syndrome · Non-alcoholic fatty liver disease · Infertility · Obesity · Metabolic syndrome

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of clinical–pathological conditions that can manifest as simple steatosis, characterized by accumulation of lipids in the liver parenchyma, or non-alcoholic steatohepatitis (NASH), characterized by hepatocyte injury, inflammation, and fibrosis [1]. The worldwide prevalence of NAFLD has been estimated to range from 6 to 35% depending on the diagnostic method used [2]. NAFLD is the most common chronic liver disease in industrialized countries, with increasing prevalence in Asia [3]. The disease is strongly associated with obesity, diabetes mellitus (DM), insulin resistance (IR), and metabolic syndrome (MS). Thus, approximately 3/4 of the obese adults have NAFLD and 1/5 have NASH [4]. Although rarely, NAFLD can progress to cirrhosis and hepatocellular carcinoma [3, 5, 6].

The findings that characterize NASH include hepatocellular ballooning, acute and chronic lobular inflammation, and perisinusoidal fibrosis. These findings are similar to alcoholic steatohepatitis, except by the history of

alcohol consumption. Fat accumulation in visceral adipose tissue and hepatocytes, which occurs in obesity and NAFLD, favors the development of a low-grade chronic inflammation [7–11], in which many components are involved in the classical inflammatory response such as increased systemic adipokines, inflammatory cytokines and chemokines, activation, and recruitment of leukocytes into inflamed tissues [8, 9, 12].

The gold standard for the diagnosis of NAFLD is liver biopsy [13]. However, liver biopsy is limited by invasiveness, high costs, sampling error, procedure-related morbidity, and mortality. Liver biopsy should be considered in NAFLD patients who are at increased risk of having steatohepatitis and advanced fibrosis or for those with MS [13]. NAFLD can be detected by imaging methods such as abdominal ultrasonography, which has been used as a screening method to detect fatty liver infiltration, with an acceptable level of sensitivity (approximately 80% in the presence of more than 30% of fat infiltration) [14–17], besides short time required for the examination and low cost. Ultrasound is often used in combination with serum aminotransferases for the detection of NAFLD. Transaminase levels are not sensitive enough for screening, since they may be normal in patients with NASH [13].

Polycystic ovary syndrome (PCOS) is another common condition with a spectrum of clinical presentations and strongly associated with obesity, IR, MS, and low-grade chronic inflammation [18–20]. PCOS has been estimated to affect 6% to 10% of reproductive age women, considering the classical definition of the syndrome by the presence of hyperandrogenism and ovulatory dysfunction. With the use of the Rotterdam criteria, the prevalence of PCOS rises to about 18%, since this definition also includes milder phenotypes without the evidence of hyperandrogenism, provided that polycystic ovaries are found on ultrasound examination. Multiple genetic, metabolic, and hormonal factors interact in PCOS [5, 18, 21, 22].

We performed a systematic review of the literature to find out what evidence supports the association between PCOS and NAFLD. Our hypothesis is that being complex, multifactorial and multifaceted conditions, PCOS and NAFLD should have one or more contact points rather than a full, mandatory coexistence. Moreover, we aimed at exploring what is the evidence linking the risk of NAFLD to the presence of androgen excess in women with PCOS.

Methods

Criteria for considering studies for this review

We performed a comprehensive review of published studies that addressed the association of PCOS and NAFLD between May 2007 and May 2017. Cross-sectional, cohort, and case–control studies were considered eligible for review, whereas small case-series and case reports were excluded. Only articles with an abstract in English were considered.

Search methods for identification of studies

The following databases and search strategies were used in the initial screening: Pubmed, using the sentence [("Non-alcoholic Fatty Liver Disease" (Mesh)) OR cirrhosis OR steatosis OR Non-alcoholic Steatohepatitis] AND "Polycystic Ovary Syndrome" (Mesh); Scopus, using TITLE-ABS-KEY ("non-alcoholic fatty liver disease" OR "cirrhosis" OR "steatosis" OR "non-alcoholic steatohepatitis") AND TITLE-ABS-KEY ("polycystic ovary syndrome"); Google Scholar, using allintitle: "polycystic ovary syndrome" "non-alcoholic fatty liver disease"; and Scielo, using ("non-alcoholic fatty liver disease") AND ("polycystic ovary syndrome"). This initial search returned 324 records that were shortened to 242 after excluding duplicates (Fig. 1). Title screening eliminated 84 records, and abstract reading excluded 104 items, leaving 54 full-text articles to be assessed for eligibility. Finally, 26 articles were included in the qualitative synthesis and 17 were eligible for meta-analysis (Fig. 1).

Statistical analysis

Data were extracted independently by two authors and analyzed using Review Manager version 5.3. Publication bias was assessed with the funnel plot method, which evaluates whether the results from smaller studies are more likely to be at the same side of the estimate of larger studies [23]. Heterogeneity of study results was tested with χ^2 and I^2 calculation, which measures approximately the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) [23].

The association between PCOS and NAFLD was quantified as odds ratio with 95% confidence interval. Total testosterone (nmol/L) and free androgen index (FAI) were meta-analyzed comparing PCOS women with NAFLD vs. PCOS women without NAFLD. For this analysis, unpublished data of two studies [43, 44] were obtained directly from the authors. All data were entered as mean ± standard deviation. When the original results were reported only as medians and quartiles, we estimated the means and standard deviations using the formula proposed by Wan et al. [24].

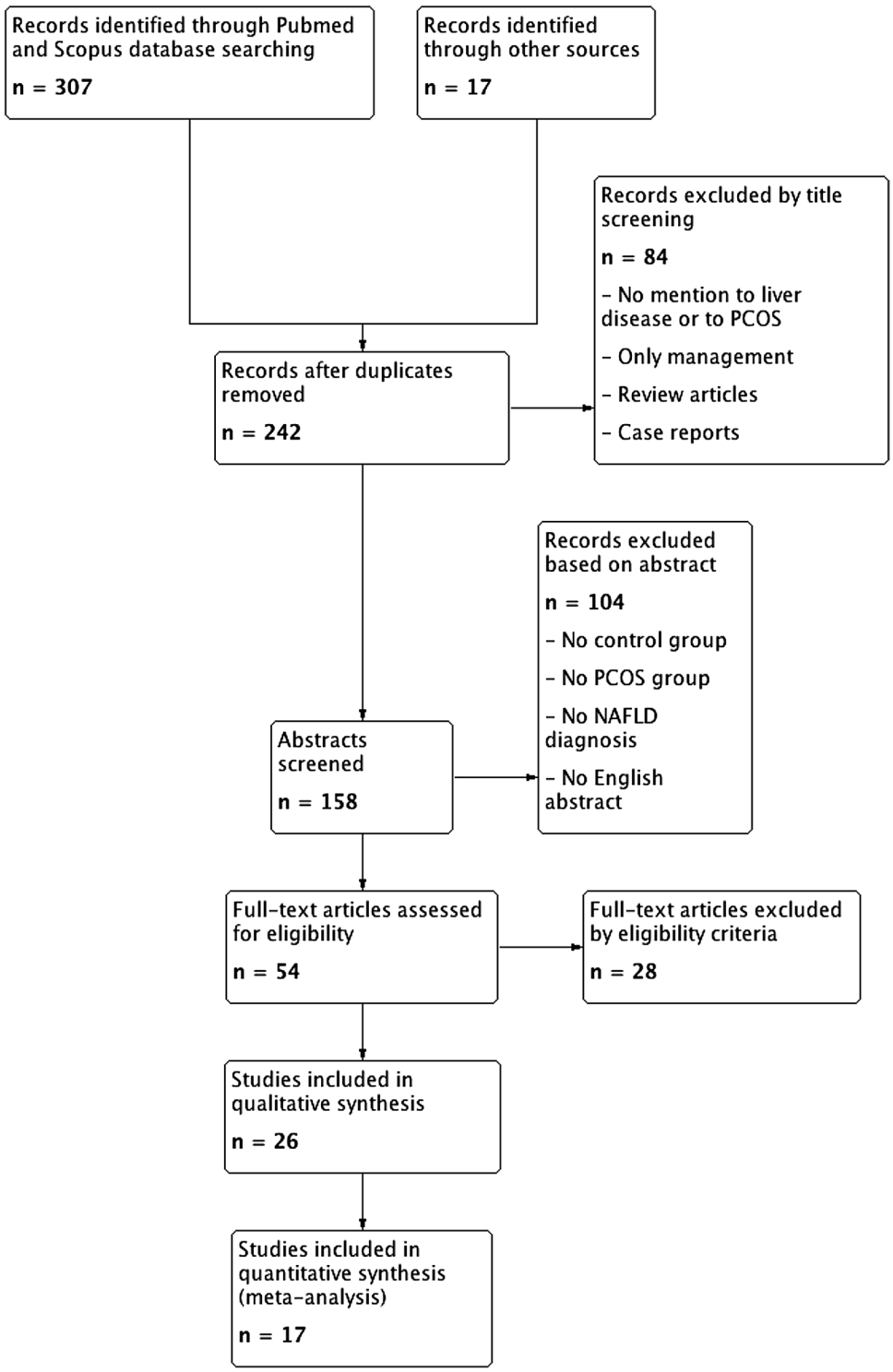

Fig. 1 PRISMA flow diagram

Results

We found 20 studies that evaluated the prevalence of NAFLD in women with PCOS [25–44]. All but one of these studies [29] also reported the prevalence of NAFLD in a control group matched to the PCOS group by age and BMI. The study by Markou et al. [32] was not entered in the quantitative synthesis, because the prevalence of NAFLD (number of events) was 0 both in cases and controls. The study by Polyzos et al. [36] was not included in the meta-analysis, because NAFLD diagnosis was not established dichotomously; instead, cases and controls were compared for a NAFLD score calculated from biochemical parameters and the women with PCOS had a

significantly higher NAFLD liver fat score compared to their matched controls [36].

All included studies diagnosed NAFLD prospectively, using liver enzymes (all studies) and liver ultrasound (15 studies). Most studies diagnosed PCOS prospectively using the same standard criteria for all patients, although the studies differed as they adopted the National Institutes of Health (NIH), the Rotterdam, or the Androgen Excess and PCOS Society (AES) criteria (Table 1).

Figure 2 shows the forest plot for the association between PCOS and NAFLD. Based on the meta-analysis of 2734 cases and 2561 controls from 17 studies, we found that patients with PCOS had a 2.5-fold increase in the risk of NAFLD [odds ratio 2.54, 95% confidence interval (CI) 2.19–2.95] compared to controls. The statistical heterogeneity of the results was moderate ($I^2 = 57\%$) and visual inspection of the funnel plot (Fig. 3) suggests symmetrical distribution of smaller studies, arguing against publication bias. Sensitivity analysis excluding (i) three studies that defined PCOS by criteria other than the Rotterdam [25, 31, 40], (ii) one study that did not use liver ultrasound or biopsy to diagnose NAFLD [37], or (iii) two studies on very low [44] or very high [27] BMI strata did not modify the results. In these three reanalyses, the combined odds ratios for the association between PCOS and NAFLD were 2.49 (95% CI 2.13–2.90), 2.65 (95% CI 2.26–3.11), and 2.57 (95% CI 2.20–3.00), respectively.

We found 13 studies that evaluated the relationship between serum androgen levels in women with PCOS and the coexistence of NAFLD [30, 33, 37–41, 43–48]. Multivariate analysis controlling for age, BMI, triglycerides, and IR confirmed that serum total testosterone levels and FAI are independent predictors of NAFLD in women with PCOS [30, 43, 44]. One study did not find such independent association, but NAFLD was detected only with a clinical and biochemical score without liver imaging or biopsy [37]. Other studies found positive linear correlations between testosterone or FAI and serum liver enzymes [47], grade of NAFLD [34], and visceral adiposity [48].

Figure 4 shows the quantitative synthesis (meta-analysis) of the mean serum androgen levels of PCOS women with NAFLD vs. PCOS women without NAFLD. Eight studies comprising 1106 PCOS cases reported serum total testosterone separately for those with ($n = 542$) and without ($n = 564$) NAFLD (Fig. 4a). Overall, PCOS women with NAFLD had higher total testosterone levels (mean difference 0.40 nmol/L, 95% CI 0.29–0.50 nmol/L) compared to PCOS women without NAFLD. Six of these studies also reported FAI for both subgroups of PCOS patients. The women with associated NAFLD had much higher FAI than those without NAFLD (mean difference 4.46, 95% CI 3.53–5.39, Fig. 4b).

Discussion

The present study confirms and updates the results of a previous meta-analysis assessing the risk of NAFLD in women with PCOS [49], expanding the number of studies included (from 7 to 17) and the number of subjects evaluated (from 616 to 2734 PCOS cases and from 569 to 2561 controls). In addition, this is the first meta-analysis of serum androgen levels in PCOS women with and without NAFLD. We found evidence that NAFLD is more prevalent in women with PCOS than in healthy controls of similar age and BMI.

The studies reviewed here have some degree of heterogeneity in their design and results. Most studies defined PCOS by the Rotterdam criteria, but one used the NIH criteria [40] and two used the AES criteria [25, 31]. One study did not include ultrasound nor biopsy in NAFLD diagnosis [37], and two studies enrolled women with very low [44] or very high BMI [27]. However, sensitivity analyses excluding these studies confirmed the significant association of PCOS and NAFLD, suggesting that such differences in study designs did not impact the overall results.

Women with PCOS have a high prevalence of obesity, IR, dyslipidemia, hypertension, and thus MS, which increases their cardiovascular risk [21, 37, 50–52]. The prevalence of both PCOS and NAFLD increases with the degree of IR and body fat mass [2, 53]. NAFLD is considered a hepatic manifestation of MS [5]. Therefore, a first link between NAFLD and PCOS is established through IR, which is often caused by obesity and promotes both fat accumulation in the liver and ovarian dysfunction with excess androgen synthesis, arrested follicle development and chronic anovulation.

However, the obesity–IR link does not tell the whole story about NAFLD and PCOS (Fig. 5). The studies included in the present meta-analysis compared PCOS cases and healthy controls of the same BMI, avoiding the confounding bias of overweight and obesity (Table 1). In addition, studies using multivariate analysis confirmed the risk of NAFLD in women with hyperandrogenism after statistical adjustment for IR [30, 43, 44].

The elevated prevalence of NAFLD in young patients with PCOS, regardless of the presence of obesity and/or MS, shows that this association is not explained only by the overlap of obesity in both conditions, but also by other pathophysiological mechanisms in PCOS [46].

Table 1 Characteristics of the studies included in the meta-analysis

Study	PCOS			Controls			Enrollment	Setting	PCOS diagnosis	PCOS criteria	NAFLD diagnosis	Liver ultrasound	Refs.
	Number	Age (yearrs)	BMI (kg/m^2)	Number	Age (year)	BMI (kg/m^2)							
Ayonrinde, 2016	32	17.0 ± 0.0	26.1 ± 6.0	167	17.0± 0.0	22.6 ± 3.6	2007–2008	Community-based cohort in Australia.	Prospect.	NIH	Prospect.	Yes	[40]
Bohdanowicz-Pawlak, 2014	184	25.3 ± 6.0	>25.0[b]	125	27.7± 7.0	–[a]	–[a]	University medical center in Poland.	Prospect.	Rotterdam	Prospect.	Yes	[39]
Cerda, 2007	41	24.6 ± 7.2	30.4 ± 7.1	31	27.9± 7.0	29.3 ± 5.3	2005–2006	Two University Hospitals in Chile.	Retrosp.	Rotterdam	Prospect.	Yes	[28]
Chen, 2010	273	24.5 ± 5.1	24.7 ± 5.9	278	25.1± 4.3	20.9 ± 3.5	2003–2009	University Hospital in Taiwan.	Prospect.	Rotterdam	Prospect.	Yes	[30]
Guierrez-Grobe, 2010	50	33.1 ± 7.7	25.6 ± 5.6	90	38.6± 7.4	27.2 ± 5.0	2009–2009	University Hospital in Mexico.	Retrosp.	–[a]	Prospect.	Yes	[26]
Hossain, 2011	34	38.6 ± 9.9	45.3 ± 6.1	32	38.3± 9.9	44.5 ± 8.4	2001–2009	Research center in the USA.	Prospect.	Rotterdam	Prospect.	No[d]	[27]
Jie, 2017	400	25.9 ± 5.5	25.7 ± 5.3	100	26.9 ± 6.2	24.8 ± 5.5	2013–2016	Academic Hospital in China.	Prospect.	Rotterdam	Prospect.	Yes	[43]
Karoli, 2012	54	28.5 ± 6.2	27.2 ± 5.4	55	27.8 ± 7.5	26.8 ± 6.7	2008–2010	Endocrine clinic of a teaching hospital in India.	Prospect.	Rotterdam	Prospect.	Yes	[38]
Kim, 2017	275	30.4 ± 5.2	20.3 ± 2.1	892	35.1 ± 4.0	19.9 ± 2.0	2004–2014	Academic Hospital in Korea.	Prospect.	Rotterdam	Prospect.	Yes	[44]
Macut, 2016	600	25.6 ± 5.9	30.6 ± 6.9	125	31.4 ± 5.3	29.6 ± 6.8	2008–2013	University hospitals in Serbia and Greece.	Prospect.	Rotterdam	Prospect.	No	[37]
Qu, 2010	306	30.2 ± 2.8	–[c]	286	31.2 ± 2.9	–[c]	2008–2009	Academic hospital in China.	Prospect.	Rotterdam	Prospect.	Yes	[35]
Romanowski, 2013	101	26.8 ± 5.0	28.5 ± 6.0	30	33.7 ± 7.0	26.1 ± 4.0	2008–2009	Tertiary referral center in Brazil.	Retrosp.	AES	Prospect.	Yes	[25]
Srinivas-Prasad, 2014	162	27.5 ± 6.5	27.6 ± 5.6	165	27.9 ± 7.5	26.9 ± 6.9	2013–2014	Medical college and research hospital in India.	Prospect.	Rotterdam	Prospect.	Yes	[41]
Tarantino, 2013	60	26.0 ± 8.7	27.1 ± 7.1	20	26.3 ± 3.5	22.1 ± 1.6	2009–2011	University Hospital in Italy.	Prospect.	Rotterdam	Prospect.	Yes	[42]
Vassilatou, 2010	57	27.0 ± 7.9	28.3 ± 7.6	60	27.6 ± 7.2	27.1 ± 7.5	2006–2008	Tertiary referral centers in Greece.	Prospect.	AES	Prospect.	Yes	[31]
Zheng, 2008	60	24.0 ± 7.0	30.0 ± 7.0	60	27.0 ± 7.0	29.0 ± 5.0	2005–2007	Public hospital in China.	Prospect.	Rotterdam	Prospect.	Yes	[34]
Zueff, 2012	45	31.6 ± 4.1	34.8 ± 2.9	45	31.8 ± 4.1	34.6 ± 3.1	2009–2010	Contraception program at academic hospital in Brazil.	Prospect.	Rotterdam	Prospect.	Yes	[33]

AES Androgen Excess and PCOS Society, *BMI* body mass index, *NIH* National Institutes of Health, *Prospect* prospective diagnosis, *Retrosp* retrospective diagnosis

[a] Information not available

[b] All patients were overweight, but the mean BMI is not reported

[c] The cases were stratified by BMI groups, but the mean BMI was not reported

[d] Liver biopsies were available for 73% of PCOS patients and 78% of controls. Age and BMI are summarized as means ± standard deviations

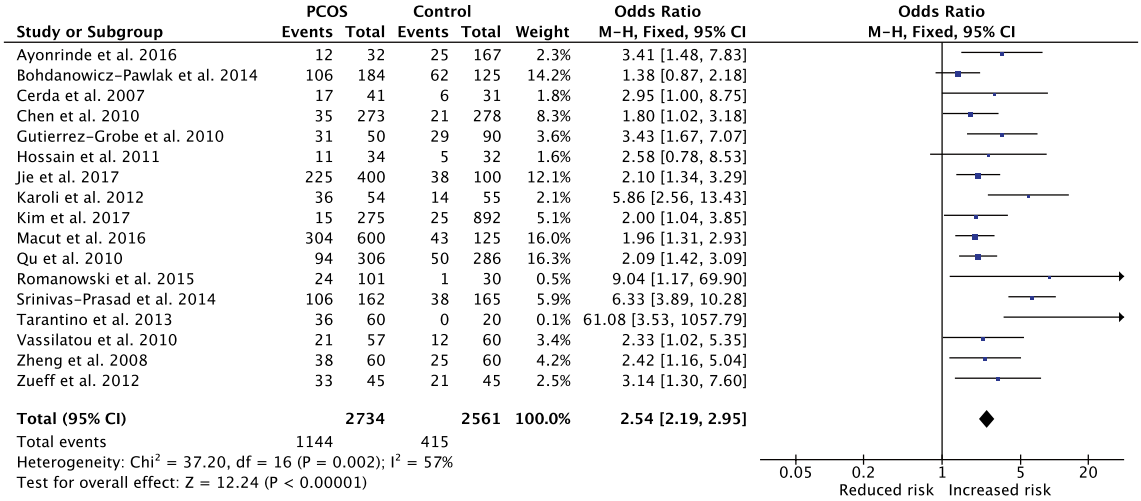

Fig. 2 Quantitative synthesis of studies evaluating the association of PCOS and NAFLD

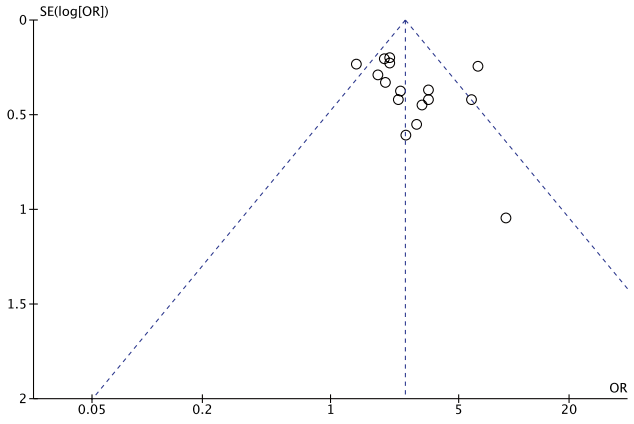

Fig. 3 Funnel plot of the studies included in the meta-analysis

Androgen excess is the most likely mechanism of increased abdominal visceral adiposity in women with PCOS [48]. Accordingly, PCOS women with hyperandrogenism (classic phenotype) have a higher prevalence of NAFLD compared to women with PCOS without hyperandrogenism, even after covariate adjustment for potential confounders, such as differences in body mass, adiposity, and IR index [46]. In contrast, PCOS women with normal androgen levels had liver function markers similar to healthy controls [46], suggesting that high androgen levels may contribute to fat deposition in the liver.

Our meta-analysis found robust evidence that both total testosterone and FAI are higher in women with PCOS and NAFLD than in women with only PCOS. We also reviewed evidence that high FAI correlates with quantitative or semi-quantitative liver disease markers [34, 47, 48] and remains a risk factor to NAFLD after statistical adjustment to the confounder effect of IR [30, 43, 44]. Thus, hyperandrogenism is a feature of PCOS that further increases the risk of NAFLD (Fig. 5).

Early detection of NAFLD in PCOS patients is important, because these women can develop NAFLD at a relatively young age. Moreover, intervention at an early stage of NAFLD can reduce or even eliminate the possibility of disease progression [54]. Weight loss of 5–10% of initial body weight should be implemented as first-line therapy in all patients with NAFLD and is generally sufficient to reduce fatty liver and improve liver function tests [54]. Even a modest (i.e., 5%) weight loss through lifestyle modification may reverse histologic features of NASH and improve liver fibrosis in a fair proportion of cases [55]. More advanced cases should be treated with drugs that correct IR and metabolic disorders [56, 57] or specific drugs for the treatment of liver disease, such as anti-oxidants and anti-inflammatory agents [54].

Plasma aminotransferase measurements and liver imaging with abdominal ultrasonography should be considered in patients with hyperandrogenic PCOS, even in the non-obese ones. Liver biopsy may be justifiable when NAFLD is detected in association with MS or with elevated liver enzymes (Fig. 5). Changes in lifestyle with weight loss of 5–10% of body weight and regular physical activity should be encouraged and recommended to patients with PCOS as an adjunctive treatment to improve reproductive outcomes and prevent long-term comorbidities [58]. Diets with energy restriction lead to significant improvements in body composition in obese women with PCOS, including reduction in fat mass, abdominal fat, and waist circumference [18].

The main limitation of this review is the lack of longitudinal studies following patients with a healthy liver until the onset of NAFLD; therefore, the available data

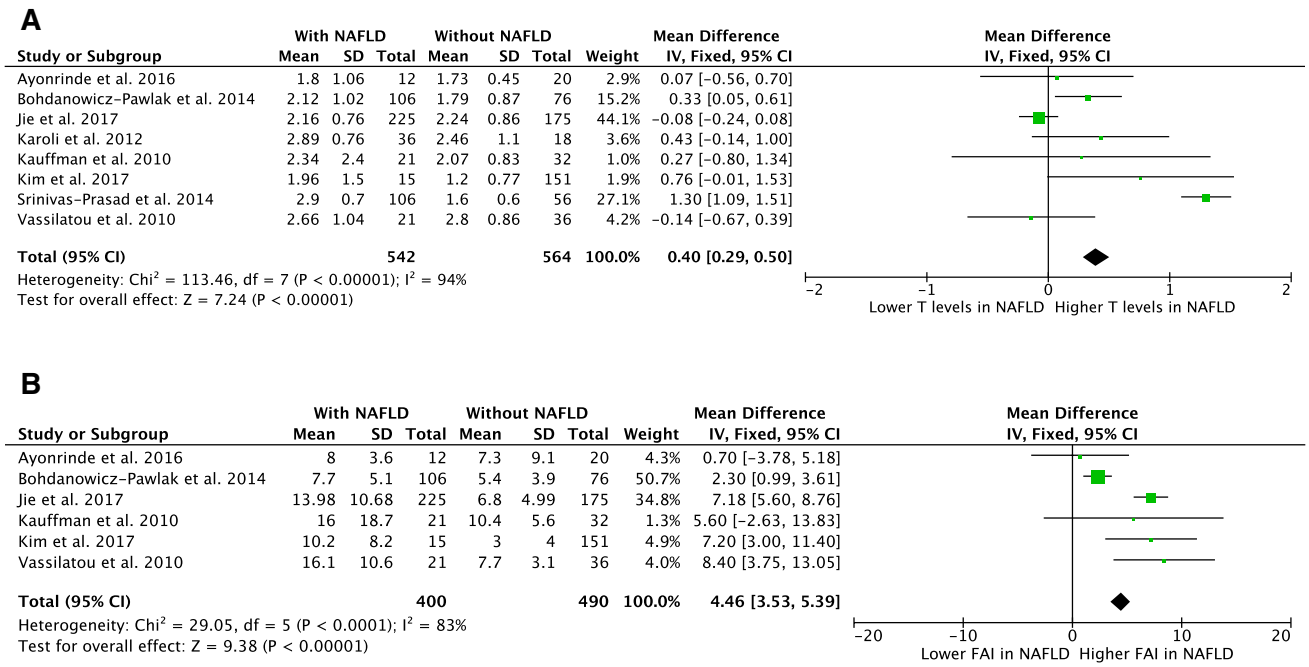

Fig. 4 Quantitative synthesis of serum androgen levels in PCOS women with NAFLD vs. PCOS women without NAFLD. **a** Total testosterone (T, nmol/L); **b** free androgen index (FAI)

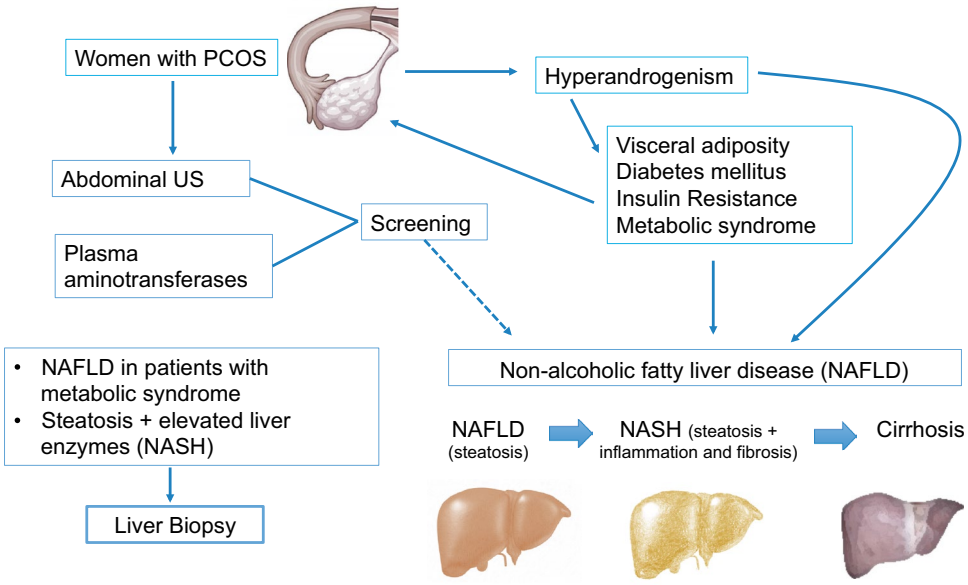

Fig. 5 Putative mechanisms involved in the increased risk of NAFLD in women with PCOS and proposed diagnostic workflow

are insufficient to clarify whether the presence of any PCOS feature (e.g., androgen excess or IR) is a cause, a consequence, or an epiphenomenon of the liver disease. Thus, new prospective cohort studies with periodic evaluation of liver function and imaging together with a standardized assessment of biometric, biochemical, and hormonal markers are needed to establish the temporal sequence of events and elucidate a possible cause–effect relationship between them.

In conclusion, the prevalence of NAFLD is increased in women with PCOS. The presence of NAFLD is associated with high serum total testosterone and FAI, in addition to obesity and IR.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human subjects performed by any of the authors.

Informed consent No informed consent.

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