Received: 6 July 2018 | Revised: 6 August 2018 | Accepted: 8 August 2018

DOI: 10.1111/cen.13828

REVIEW ARTICLE

WILEY

Comorbidities and complications of polycystic ovary syndrome: An overview of systematic reviews

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Summary

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting reproductive-aged women with adverse reproductive, metabolic and psychological outcomes. It has a complex pathophysiology and therefore requires a multidiscipline clinical approach. However, there remains limited research synthesizing the broad clinical implications of PCOS which would assist clinicians in the management of PCOS.

Objective: To summarize and appraise methodological quality of systematic reviews and meta-analyses evaluating complications and comorbidities associated with PCOS.

Methods: A literature search from MEDLINE, EMBASE, CINAHL PLUS and PROSPERO was performed until 15 September 2017. Article selection, data extraction and quality appraisal of included reviews using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool were performed in duplicate. A narrative synthesis of the findings was conducted.

Results: Twenty-three reviews were included. All reviews were of low (n = 2) to moderate quality (n = 21). PCOS was associated with adverse pregnancy outcomes (n = 2), impaired glucose tolerance (n = 6), insulin resistance (n = 6), increased risk of type 2 diabetes (n = 1), cardiovascular disease (n = 10), metabolic syndrome (n = 2), psychological stress (n = 7), endometrial cancer (n = 1) and vitamin D deficiency (n = 1). Obesity exacerbates many of these outcomes.

Conclusions: There is a large body of reliable evidence for adverse metabolic outcomes and smaller, but consistent evidence for psychological issues in PCOS. We identified a shortage of systematic reviews regarding pregnancy outcomes of PCOS and significant gaps in knowledge of the association between PCOS and subclinical hyperthyroidism, vitamin D levels and cancers which future studies could aim to address.

KEYWORDS

comorbidity, hyperandrogenism, insulin resistance, metabolic syndrome, obesity, PCOS, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder among reproductive-aged women. Depending on the diagnostic criteria used and the population studied, its prevalence PCOS ranges between 9 and 18%[1] with a higher prevalence among women who are overweight[2] or of an Indigenous background.[3,4]

The Rotterdam Consensus (2003) is the most widely accepted diagnostic criteria for PCOS and requires the presence of at least two of the following characteristics: (a) clinical and/or biochemical hyperandrogenism, (b) oligo-/anovulation or (c) polycystic ovaries on ultrasound, with exclusion of secondary causes of hyperandrogenism.[5] The recently developed international evidence-based guideline for the assessment and management of PCOS[6] has refined the Rotterdam criteria in adolescence to hyperandrogenism and oligo-/anovulation and recommended against ultrasound due to poor specificity of polycystic ovaries in this age group. While the aetiology of PCOS remains unclear, it is likely to be multifactorial. Insulin resistance (IR) and hyperandrogenism are the two key hormonal disturbances that underpin PCOS, with obesity, genetic inheritance, lifestyle and environment also contributing to the multifactorial aetiology of PCOS.[7,8]

Women with PCOS may present with a number of reproductive,[9] metabolic,[10,11] psychological[12] and anthropometric[13] complications. The most common PCOS feature is ovarian dysfunction driven by hyperandrogenism which leads to chronic oligo-/anovulation and menstrual disturbances.[14] Hyperandrogenism also causes dermatological complaints such as hirsutism,[9] acne and male pattern alopecia.[15,16] PCOS is the most common cause of anovulatory infertility, but infertility is not necessarily impaired in all affected women.[14] However, those who do become pregnant are at an increased risk of pregnancy and foetal complications regardless of the mode of conception.[17,18]

PCOS has metabolic implications including IR,[19] dyslipidaemia[20,21] and abnormal glucose metabolism.[22,23] Moreover, women with PCOS also show a propensity for excess weight gain which exacerbates these symptoms.[24] Cardiovascular risk factors such as chronic inflammation, oxidative stress[25] and impaired fibrinolysis are increased[24] with some evidence of a higher prevalence of cardiovascular disease (CVD).[11,26] Furthermore, affected women are more likely to experience moderate-to-severe depression and anxiety symptoms,[27] low self-esteem, negative body image and psychosexual function compared to healthy women.[28] PCOS also negatively impacts health-related quality of life (HRQoL)[29,30] and may limit a woman's ability to optimize healthy lifestyle.[31]

PCOS is a multisystem, polygenic and multifactorial disorder. It has diverse implications that can change throughout a woman's life. It is imperative that the information available to clinicians and researchers is evidence based and generated by high-quality research studies. A systematic review is widely considered to provide the highest level of evidence compared to other study methodologies,[32] and recent years have seen an increasing number summarizing the assessment of PCOS. However, many of these reviews present conflicting results, highlighting the need for synthesis and critical appraisal of the pertaining literature to reach more consistent conclusions. The aim of this review was therefore to conduct an overview of systematic reviews evaluating comorbidities and complications of PCOS and to appraise their quality and synthesize the results. We also aimed to explore alignment between the evidence and recent evidence-based guidelines in PCOS adopted across 37 international societies.[6]

2 | METHODS

2.1 | Protocol and registration

This review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[33] An a priori study protocol was registered with PROSPERO (CRD42016052649). Ethics application was not required.

2.2 | Literature search

The electronic databases MEDLINE in-process and other non-indexed citations (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present), Ovid EMBASE (EBM Reviews—Cochrane Database of Systematic Reviews 2005 to 15 September 2017 EBM Reviews—ACP Journal Club 1991 to September 2017, EBM Reviews—Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM reviews—Cochrane Central Register of Controlled Trials September 2017, EBM Reviews—Cochrane Methodology Register 3rd quarter 2012, EBM Reviews—Health Technology Assessment 4th Quarter 2016, EBM Reviews—NHS Economic Evaluation Database 1st Quarter 2016) and CINAHL PLUS were searched to identify relevant articles. Additional ongoing reviews were identified from searching the international prospective register of systematic reviews PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). The literature search was last updated on 15 September 2017. The search terms used included "PCOS," "polycystic ovary syndrome," "Stein Leventhal," "systematic," "review" and "meta-analysis" with the complete search strategy for each database provided in Appendix S1 (Supporting Information). The search strategy was limited to human studies only.

2.3 | Eligibility criteria and study collection

Articles were included if they met the following inclusion criteria: (a) article was an original systematic review or meta-analysis; (b) PCOS was the primary focus of the review and if PCOS was assessed as a secondary condition as part of a broader topic the article was excluded; (c) a clear search strategy was reported with at least keywords or terms included, documentation of search returns and some form of quality appraisal of the included studies performed; (d) the study was published in English; and (e) the study was published

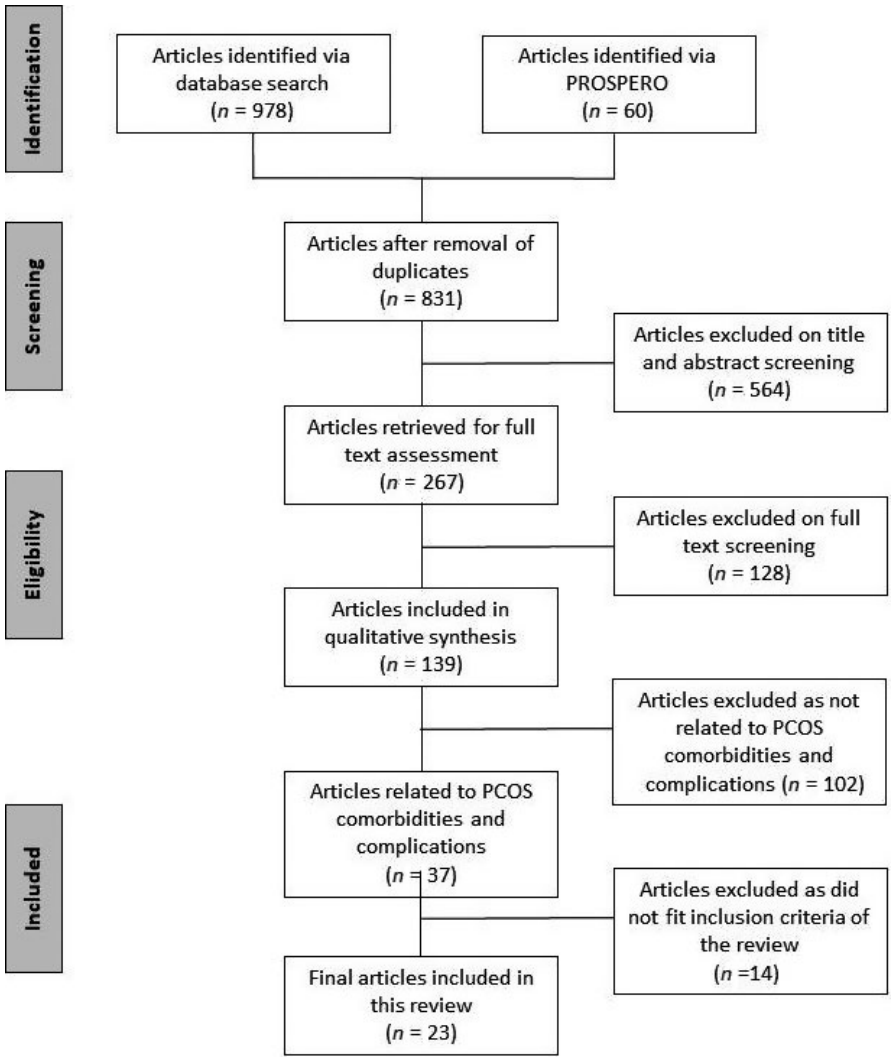

FIGURE 1 Selection study process

from year 2009 onwards given this was when the PRISMA statement was published to guide reporting of systematic reviews and meta-analyses.[33]

For this particular review, articles assessing the comorbidities and complications associated with PCOS were included for analysis. The outcomes of interest were PCOS comorbidities and complications related to reproduction (pregnancy, foetal and neonatal complications), metabolism (CVD and cardiovascular risk factors, diabetes and markers of IR, manifestations of metabolic syndrome and obesity), psychological (quality of life, depression and anxiety) and other (cancer and vitamin D level) outcomes.

2.4 | Study selection and data extraction

Identified articles from the literature search were screened in a two-step process. First, the titles and abstracts were screened for suitability. Second, all articles that appeared to meet the inclusion criteria from the first step were retrieved for detailed full-text assessment to determine eligibility. Study selection was performed independently in duplicate by a combination of investigators (L.J.M., E.W.G., C.T.T. and D.S.H.) with any discrepancies resolved by consensus.

Data collected from the eligible articles included authorship, publication year, country of authors' origin, types of study eligible for the systematic review, date of literature search, language restriction, adherence to a systematic review guideline, presence of meta-analysis, the authors' interpretation of quality assessment of the included studies, number of included studies and participants involved and the Participant, Intervention, Comparison, Outcomes and Studies (PICOS) framework of the study. If the authors did not interpret the quality of the included studies nor summarize the overall quality of the entire study, the section on quality assessment was documented as "unclear." Data extraction was conducted independently in duplicate (L.J.M., E.W.G., C.T.T. and D.S.H.) with any discrepancies resolved by consensus.

2.5 | Quality assessment (AMSTAR)

The Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool was employed to appraise the quality of the included systematic reviews.[34] AMSTAR evaluates the methodological aspects of systematic reviews using 11 items. These are (a) the provision of an a priori design; (b) duplication of study selection and data

TABLE 1 Study characteristics

Author (year)	Country	Included study type	Date of last literature search	Language	Systematic review guideline followed	Meta-analysis performed	Paper (n)	Total number of included participants (n)	Population and PCOS diagnostic criteria
Barry (2011)[27]	UK	All study types (exclude reviews, case studies)	Dec-10	All	No	Yes	12	2257	Women with PCOS Diagnostic criteria not stated
Barry (2014)[40]	UK	All study types (exclude reviews, or single case studies)	Oct-13	All	Yes	Yes	11	72 973	Women with or without PCOS Diagnostic criteria not stated
Bazarganipour (2015)[29]	Iran	Not stated	Dec-13	English only	Yes	Yes	6	1140	Women with PCOS Diagnostic criteria not stated
Behboudi-Gandevani (2016)[19]	Iran	Observational studies	Dec-13	English only	Yes	Yes	27	3037	Women with or without PCOS Diagnostic criteria not stated
de Groot (2011)[11]	Netherlands	Controlled studies (exclude reviews)	2008	All	Yes	Yes	5	767 988	Women with or without PCOS NIH, ESHRE/ASRM, AES, WHO II anovulation
Dokras (2012)[37]	US	Cross-sectional	Apr-08	All	Yes	Yes	9	827	Women with or without PCOS NIH, ESHRE/ASRM
He (2015)[38]	US	All study types	Jan-15	English only	No	Yes	30	3182	Women with or without PCOS NIH, ESHRE/ASRM
Kaczmarek (2016)[47]	Switzerland	Qualitative, cross-sectional, or interventional studies	Sep-15	English or French only	Yes	No	9	213	Women with PCOS aged 13-24 y Diagnostic criteria not stated
Li (2011)[30]	China, Sweden	All study types	May-10	English or Chinese only	No	Yes	10	459	Women with or without PCOS Diagnostic criteria not stated
Li (2017)[35]	China	Not stated	Jan-14	English only	No	Yes	13	827	Obese adolescents with PCOS aged 11-20 yr NIH, ESHRE/ASRM, AES
Lim (2012)[2]	Australia	All study types	Nov-10	English only	No	Yes	106	15 129	Women with PCOS NIH, ESHRE/ASRM
Lim (2013)[43]	Australia	All study types	Nov-10	English only	No	Yes	30	3344	Women with PCOS NIH, ESHRE/ASRM
Meyer (2012)[39]	USA	Peer-reviewed primary articles	Nov-10	English only	Yes	Yes	27	2812	Women with PCOS NIH, ESHRE/ASRM, AES
Moran (2010)[23]	Australia, USA	Not stated	Apr-09	All	No	Yes	35	77 823	Women with PCOS NIH, ESHRE/ASRM

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Included study type	Date of last literature search	Language	Systematic review guideline followed	Meta-analysis performed	Paper (n)	Total number of included participants (n)	Population and PCOS diagnostic criteria
Pergialiotis (2017)[46]	Greece	Observational studies (prospective and retrospective cohort studies). Exclude case reports, review articles and animal studies	2016	All	Yes	Yes	12	2654	Women with PCOS with subclinical hypothyroidism or with normal thyroid function Diagnostic criteria not stated
Ramezani-Binabaj (2014)[44]	Iran	All study types (exclude review, case report, letter to editor, editorial and commentarial papers)	Jun-13	All	No	Yes	7	1185	Women with PCOS Diagnostic criteria not stated
Shobeiri (2016)[45]	Iran	Cohort, case-control, cross-sectional	Jun-15	All	No	Yes	8	45 470	Women with PCOS Diagnostic criteria not stated
Sprung (2013)[41]	UK, Australia	Observational	Jul-05	Not stated	No	Yes	21	1474	Women with PCOS NIH, ESHRE/ASRM, AES
Toulis (2009)[17]	Greece	Observational studies (exclude retrospective investigation of PCOS prevalence, ovarian drilling treatment, reviews or letters to the editor)	Jun-07	All	No	Yes	16	98 226	Women with PCOS NIH, ESHRE/ASRM
Veltman-Verhulst (2012)[42]	UK, Netherlands	All studies	Nov-11	All	No	Yes	28	5089	Women with PCOS NIH, ESHRE/ASRM, AES
Yang (2016)[36]	China	Cross-sectional	Nov-14	English or Chinese only	No	Yes	32	9556	Women with PCOS with or without hyperandrogenism ESHRE/ASRM, AES
Yu (2016)[18]	China	All studies (excluded editorials, reviews and letters to the editors)	Jan-16	All	Yes	Yes	40	17 186	Pregnant women with PCOS Diagnostic criteria not stated
Zhao (2016)[26]	China	Case-control and cohort studies (exclude meta-analyses, letters, reviews and editorial articles)	Apr-16	All	No	Yes	10	104 392	Women with PCOS Diagnostic criteria not stated

AES, Androgen Excess and PCOS Society; ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome; WHO II anovulation, World Health Organization II anovulation.

TABLE 2 Results of systematic reviews regarding reproductive comorbidities of PCOS

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Pregnancy, foetal and neonatal complications					
Toulis (2009)[17]	Moderate	Unclear	GDM	Women w/PCOS vs women w/out PCOS	GDM: 2.89 RR (95% CI 1.68 to 4.98)
Yu (2016)[18]	Moderate	35 high, 5 moderate	Neonatal: Foetal hypoglycaemia, perinatal death, LGA, SGA, FGR, congenital malformation, macrosomia, RDS	Women w/PCOS vs women w/out PCOS	Foetal hypoglycaemia: 2.85 RR (95% CI 1.93 to 4.22) Perinatal death: 1.83 RR (95% CI 1.06 to 3.1)
			Maternal: Preeclampsia, Preterm delivery, caesarean delivery, miscarriage, GDM, PIH, preterm premature membrane rupture, oligohydramnios, polyhydramnios		Preeclampsia: 2.79 RR (95% CI 2.29 to 3.38) GDM: 2.78 RR (95% CI 2.27 to 3.40) PIH: 2.46 RR (95% CI 1.95 to 3.09) Preterm delivery: 1.52 RR (95% CI 1.22 to 1.90) Caesarean delivery: 1.25 RR (95% CI 1.15 to 1.36) Miscarriage: 2.87 RR (95% CI 1.65 to 4.98)

CI, confidence interval; FGR, foetal growth restriction; GDM, gestational diabetes; LGA, large for gestational age; N/A, not applicable; PCOS, polycystic ovarian syndrome; PIH, pregnancy-induced hypertension; RDS, respiratory distress syndrome; RR, risk ratio; SGA, small for gestational age.

extraction; (c) conduction of a comprehensive literature search; (d) inclusion of grey literature in the review; (e) availability of a list of the included and excluded studies; (f) description of the characteristics of the included studies; (g) clear documentation of the scientific quality of the included studies; (h) consideration of the scientific quality of the included studies in formulating conclusions; (i) appropriate analysis of results depending on heterogeneity; (j) assessment of publication bias; and (k) consideration of conflict of interest of both the systematic review and the included studies. Each item was given one point if it was determined as "yes" and zero point if it was determined as either "no" or "not applicable." The reviews were categorized as low quality, moderate quality and high quality if the total AMSTAR score was ≤3, between 4 to 7 and ≥8, respectively. Quality assessment of all eligible systematic reviews was conducted independently in duplicate by a combination of investigators (L.J.M., E.W.G., C.T.T. and D.H.) with any disagreements resolved by consensus.

2.6 | Data synthesis

Results of included reviews were presented in tabular format organized according to morbidity category. Statistically significant outcomes of interest were presented if a meta-analysis was performed by the review. Otherwise, a narrative description of the findings was given.

3 | RESULTS

3.1 | Literature search

In total, 1068 reviews were identified for screening. Following removal of duplicates, review of title and abstract and full-text evaluation, 23 studies were included for this overview of systematic reviews. The PRISMA flow diagram is illustrated in Figure 1. The list of excluded articles is available in Appendix S2 (Supporting Information).

3.2 | Study characteristics

The study characteristics and PICO framework of the included systematic reviews are summarized in Table 1. The country of origin of the authors included China (n = 5),[18,26,30,35,36] USA (n = 4),[23,37-39] United Kingdom (UK) (n = 4),[27,40-42] Australia (n = 4),[2,23,41,43] Iran (n = 4),[19,29,44,45] Greece (n = 2),[17,46] the Netherlands (n = 2),[11,42] Sweden (n = 1)[30] and Switzerland (n = 1).[47]

N = 9 reviews included all study types.[2,18,27,38,40,42-44,48] N = 5 reviews included observational studies only[11,17,19,41,46]; n = 2 included cohort and case-control studies only[26,47]; and n = 2 reviews explicitly included cross-sectional studies only.[37,49] N = 1 review included cohort, case-control or cross-sectional studies[45] and n = 1 included peer-reviewed primary articles.[39] N = 3 reviews did not state an inclusion criteria for the study type.[23,29,35]

N = 12 reviews did not set a language restriction in their literature search.[11,17,18,23,26,27,37,40,42,44-46] N = 7 reviews restricted their search to English publications only.[2,19,29,35,38,39,43] N = 2 reviews restricted their language to English and Chinese[30,49] and n = 1 reviews restricted its language to English and French.[47] N = 1 reviews did not state if any language restriction was applied.[41]

N = 9 reviews reported following a guideline on good practice in conducting systematic reviews[11,18,19,29,37,39,40,46,47]; n = 22 systematic reviews included meta-analyses[2,11,17-19,23,26,27,29,30,35,37-46,49]; and n = 10 did not provide a clear statement as to the overall quality of

TABLE 3 Results of systematic reviews regarding metabolic comorbidities of PCOS

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Cardiovascular disease and risk factors					
de Groot (2011)[11]	Moderate	2 high, 3 low	Fatal/nonfatal CHD or stroke	Women w/PCOS vs women w/out PCOS	CHD/stroke: 2.02 RR (95% CI 1.47 to 2.76)
He (2015)[38]	Moderate	Unclear	TC, HDL-C, LDL-C, TG	Women w/PCOS, VDD vs women w/PCOS non-VDD	HDL-C: −0.58 SMD (95% CI −0.86 to −0.30)
				Correlation of Vitamin D with parameters in women w/PCOS	HDL-C: 0.35 SMD (95% CI 0.22 to 0.47) TG: −0.69 SMD (95% CI −0.91 to −0.16)
				Postintervention of Vitamin D vs Preintervention	TG: −0.45 SMD (95% CI −0.73 to −0.17)
				Postintervention of Vitamin D vs postintervention of placebo	N/A
Li (2017)[35]	Moderate	Moderate	TC, HDL-C, LDL-C, TG	Normal weight adolescents (BMI <30 or BMI <25 for Asian-Pacific population) w/PCOS vs obese adolescents (BMI >30 or BMI >25 for Asian-Pacific population) w/PCOS	TC: 11.82 MD (95% CI 0.85 to 22.79) HDL-C: −8.00 MD (95% CI −12.119 to −3.89) LDL-C: 14.36 MD (95% CI 5.30 to 23.42)
				Obese adolescents w/PCOS vs obese adolescents w/out PCOS	LDL-C: 6.88 MD (95% CI 0.62 to 13.14)
Lim (2013)[43]	Moderate	Moderate	TC, HDL-C, LDL-C, TG	Overweight or obese women (BMI >25 or >23 for Asian population) w/PCOS vs normal weight women (BMI <25 or BMI <23 for Asian population) w/PCOS	TC: 0.35 MD (95% CI 0.07 to 0.64) HDL-C: −0.23 MD (95% CI −0.38 to −0.07) LDL-C: 0.35 MD (95% CI 0.23 to 0.48) TG: 0.37 MD (95% CI 0.23 to 0.50)
				Overweight women (BMI 25-29.9 or BMI 23-24.9 for Asian population) w/PCOS vs normal weight women w/PCOS	HDL-C: −0.08 MD (95% CI 0.14 to 0.01) TG: 0.13 MD (95% CI 0.01 to 0.25)
				Obese women (BMI ≥30 or BMI ≥25 for Asian population) w/PCOS vs normal women w/PCOS	TC: 0.62 MD (95% CI 0.44 to 0.80) HDL-C: −0.29 MD (95% CI −0.49 to −0.08) LDL-C: 0.53 MD (95% CI 0.36 to 0.70) TG: 0.57 MD (95% CI 0.25, 0.89)
				Obese women w/PCOS vs overweight women w/PCOS	N/A
Meyer (2012)[39]	Moderate	Unclear	CIMT	Women w/PCOS vs women w/out PCOS	High-quality studies—CIMT: 0.072 SMD (95% CI 0.040 to 0.105) Good quality studies—CIMT: 0.084 SMD (95% CI 0.042 to 0.126)
Pergialiotis (2016)[46]	Moderate	11 low, 1 N/A	TC, HDL-C, LDL-C, TG, systolic BP, diastolic BP	Women w/PCOS, normal thyroid function vs women w/PCOS, subclinical hypothyroidism	HDL: −3.92 MD (95% CI −6.56 to −1.29) TG: 26.91 MD (95% CI −3.79 to 50.02).
Sprung (2013)[41]	Moderate	Unclear	FMD	Women w/PCOS vs women w/out PCOS	FMD: −3.4% pooled mean (95% CI 1.9 to 4.9)
Yang (2016)[36]	Moderate	Unclear	TC, HDL-C, LDL-C, TG	Women w/PCOS vs women w/PCOS, HA	HDL: −0.22 SMD (95% CI −0.39 to −0.06)

(Continues)

TABLE 3 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Yu (2016)[18]	Moderate	14 high, 6 low	TC, HDL-C, LDL-C, TG, systolic, BP, diastolic BP	Pregnant women w/PCOS vs pregnant women w/out PCOS	Systolic BP: 4.21 MD (95% CI 0.23 to 8.19) Diastolic BP: 3.17 MD (95% CI 0.07 to 6.28)
Zhao (2016)[26]	Moderate	1 high, 9 medium	CVD	Women w/PCOS vs women w/out PCOS	CVD: (1.30 OR, 95% CI 1.09 to 1.56)
			Subgroup analysis (type of CVD): CHD, MI		CHD: 1.44 OR (95% CI 1.13 to 1.84)
Diabetes and markers of insulin resistance					
Behboudi-Gandevani (2016)[19]	Moderate	High	HOMA-IR, QUICKI, ISI	Women w/PCOS, obese	IR: 4.38 pooled mean (95% CI 3.84 to 4.92)* QUICKI: 0.32 pooled mean (95% CI 0.30 to 0.34) ISI: 4.06 pooled mean (95% CI 2.95 to 5.17)
				Women w/out PCOS, obese	IR: 2.44 pooled mean (95% CI 2.06 to 2.82) QUICKI: 0.34 pooled mean (95% CI 0.33 to 0.36) ISI: 5.94 pooled mean (95% CI 4.55 to 7.33)
				Women w/PCOS, nonobese	IR: 2.68 pooled mean (95% CI 2.16 to 3.20) QUICKI: 0.33 pooled mean (95% CI 0.32 to 0.33) ISI: 8.62 pooled mean (95% CI 6.68 to 10.56)
				Women w/out PCOS, nonobese	IR: 1.34 pooled mean (95% CI 1.06 to 1.63) QUICKI: 0.37 pooled mean (95% CI 0.36 to 0.37) ISI: 10.39 pooled mean (95% CI 8.09 to 12.68)*
He (2015)[38]	Moderate	Unclear	FBG, FI, HOMA-IR, HOMA-β, IS (QUICKI)	Women w/PCOS, VDD vs women w/PCOS non-VDD	FBG: 0.31 SMD (95% CI 0.10 to 0.53) FI: 0.63 SMD (95% CI 0.42 to 0.85) HOMA-IR: 1.11 SMD (95% CI: 0.51 to 1.71) HOMA-β: 0.43 SMD (95% CI 0.15 to 0.71)
				Correlation of vitamin D with parameters in women w/PCOS	FBG: −0.23 SMD (95% CI −0.38 to 0.07) FI: −0.29 SMD (95% CI −0.37 to −0.21) QUICKI: 0.19 SMD (95%C 0.07 to 0.30)
				Postintervention of vitamin D vs Preintervention in women w/PCOS	N/A
				Postintervention of vitamin D vs postintervention of placebo in women w/PCOS	N/A
Li (2017)[35]	Moderate	Moderate	FBG, FI, HOMA-IR, glucose 2 h-OGTT, insulin 2 h-OGTT	Normal weight adolescents (BMI <30 or BMI <25 for Asian-pPacific population) w/PCOS vs obese adolescents (BMI >30 or BMI >25 for Asian-Pacific population) w/PCOS	FI: 6.55 MD (95% CI 4.03 to 9.06) HOMA-IR: 1.24 MD (95% CI 0.71 to 1.77)
				Obese adolescents w/PCOS vs obese adolescents w/out PCOS	FI: 9.10 MD (95% CI 1.83 to 16.36)

(Continues)

TABLE 3 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Lim (2013)[43]	Moderate	Moderate	FI, FBG, HOMA-IR, glucose 2 h-OGTT, insulin 2 h-OGTT, IFG/IGT	Overweight or obese women (BMI >25 or >23 for Asian population) w/PCOS vs normal weight women (BMI <25 or BMI <23 for Asian population) w/PCOS	FI: 39.75 MD (95% CI 29.95 to 49.55) FBG: 0.25 MD (95% CI 0.13 to 0.37) HOMA-IR: 1.58 MD (95% CI 1.00 to 2.16) Glucose 2 h-OGTT: 0.95 MD (95% CI 0.31 to 1.59) Insulin 2 h-OGTT: 443.30 MD (95% CI 303.89 to 582.71)
				Overweight women (BMI 25-29.9 or BMI 23-24.9 for Asian population) w/PCOS vs normal weight women w/PCOS	FI: 36.37 MD (95% CI 12.74 to 59.99) FBG: 0.33 MD (95% CI 0.15 to 0.52) HOMA-IR: 1.00 MD (95% CI 0.40 to 1.60) IFG/IGT: 5.10 MD (95% CI 1.91 to 13.62)
				Obese women (BMI≥30 or BMI ≥25 for Asian population) w/PCOS vs normal weight women w/PCOS	FI: 123.13 MD (95% CI 60.28 TO 185.97) FBG: 0.59 MD (95% CI 0.42 to 0.77) HOMA-IR: 3.75 MD (95% CI 1.69 to 5.81) IFG/IGT: 6.18 MD (95% CI 2.78 to 13.75)
				Obese women w/PCOS vs overweight women w/PCOS	FI: 72.17MD (95% CI 41.30 to 103.04 FBG: 0.26 MD (95% CI 0.05 to 0.46) HOMA-IR: 2.41 MD (95% CI 0.89 to 3.93)
Moran (2010)[23]	Moderate	Unclear	IGT, T2DM	Women w/PCOS vs women w/out PCOS	IGT: 2.48 OR (95% CI 1.63 to 3.77); BMI-matched studies 2.54 OR (95% CI 1.44 to 4.47) DM2: 4.43 OR (95% CI 4.06 to 4.82); BMI-matched studies 4.00 OR (95% CI 1.97 to 8.10)
Pergialiotis (2016)[46]	Moderate	11 low, 1 N/A	HOMA-IR, FBG, 2-h OGTT	Women w/PCOS, normal thyroid function vs women w/PCOS, subclinical hypothyroidism	HOMA-IR: 0.82 MD (95% CI 0.15 to 1.50)
Yang (2016)[36]	Moderate	Unclear	HOMA-IR, incidence of IR	Women w/PCOS vs women w/PCOS, HA	HOMA-IR: 0.28 SMD (95% CI 0.11 to 0.44) IR: 3.11 SMD (95% CI 2.32 to 4.17)
Yu (2016)[18]	Moderate	14 high, 6 low quality	FBG	Pregnant women w/PCOS vs pregnant women w/o PCOS	N/A
Obesity					
Lim (2012)[2]	Moderate	17 high, 89 low quality	Prevalence of overweight, obesity or central obesity	Women w/PCOS vs women w/out PCOS	Overweight: 1.95 RR (95% CI 1.52 to 2.50) Obesity: 2.77 RR (95% CI 1.88 to 4.10) Central obesity: 1.73 RR (95% CI 1.31 to 2.30)
Pergialiotis (2017)[46]	Moderate	11 low, 1 N/A quality	Body mass index (BMI), waist circumference, waist-to-hip ratio	Women w/PCOS, normal thyroid function vs women w/PCOS, subclinical hypothyroidism	N/A
Metabolic syndrome and NAFDL					

(Continues)

TABLE 3 (Continued)

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Moran (2010)[23]	Moderate	Unclear	Metabolic syndrome	Women w/PCOS vs women w/out PCOS	Metabolic syndrome: 2.88 OR (95% CI 2.40 to 3.45); BMI-matched studies 2.20 OR (95% CI 1.36 to 3.56)
Ramezani-Binabaj (2014)[44]	Moderate	Unclear	NAFLD	Women w/PCOS vs women w/out PCOS	NAFLD: 3.93 OR (95% CI 2.17 to 7.11)
Yang (2016)[36]	Moderate	Unclear	Metabolic syndrome	Women w/PCOS vs women w/PCOS, HA	Metabolic syndrome: 2.21 OR (95% CI 1.88 to 2.59)

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; T2DM, diabetes mellitus type 2; FI, fasting insulin; FMD, flow-mediated dilation; HA, hyperandrogenism; HDL-C, high-density lipoprotein cholesterol; HOMA-β, Homeostatic Model Assessment of B cell function; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IGT, impaired glucose tolerance; IFG/IGT, impaired fasting glucose to impaired glucose tolerance ratio; ISI, insulin sensitivity index; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; N/A, not applicable; OR, odds ratio; PCOS, polycystic ovary syndrome; QUICKI, quantitative insulin sensitivity check index; RR, risk ratio; SMD, standardized mean difference; TC, total cholesterol; TG, triglycerides; VDD, vitamin D deficiency; 2-h OGTT, 2-h oral glucose tolerance test.

assessment of the included articles.[17,23,29,30,36-39,41,44,47] The number of studies included in each systematic review ranged from 5 to 106 and the total participants ranged from 213 to 767 988. N = 8 of the systematic reviews had 10 studies or fewer in total.[11,26,29,37,44,45,47,48]

3.3 | Methodological quality of systematic reviews

The AMSTAR scores of the included reviews are available in Appendix S3. None of the included reviews were of high quality, 21 (91%) reviews[2,11,17-19,23,26,27,29,30,37-46,49] scoring moderate quality and 2 (9%) reviews scoring low quality.[35,47] The most commonly unreported items were potential for conflict of interest of the included studies (n = 22, 96%) and presence of priori study design (n = 22, 96%). Other commonly unreported items were a list of included and excluded studies (n = 19, 83%) and whether duplicate study and data extraction were used (n = 19, 83%), inclusion of grey literature (n = 15, 65%) and formulation of study conclusion based on the scientific quality of the included studies (n = 15, 65%). Conducting a comprehensive literature search was reported in just under half of the reviews (n = 11, 48%), likelihood of publication bias was considered and tested in (n=17, 74%) reviews and studies were combined using appropriate methods in all but two reviews (n = 21, 91%). All systematic reviews reported the study characteristic of the included studies.

3.4 | Reproductive comorbidities of PCOS

N = 2 moderate quality reviews evaluated reproductive comorbidities of PCOS[17,18] (Table 2). A total of 56 papers and 115 412 adult women were included.

3.4.1 | Pregnancy, foetal and neonatal complications

Both reviews assessed maternal and/or foetal complications in pregnant women with PCOS.[17,18] N = 1 review reported an increased prevalence of hypoglycaemia, perinatal death, gestational diabetes (GDM), preeclampsia, pregnancy-induced hypertension (PIH), preterm delivery, caesarean delivery and miscarriage among women with PCOS.[18] N = 1 review solely evaluated the risk of GDM in women with PCOS and similarly found women with PCOS to be at a significantly higher risk of GDM compared to women without PCOS.[17]

3.5 | Metabolic comorbidities of PCOS

N = 14 reviews evaluated metabolic comorbidities of PCOS (Table 3).[2,11,18,19,23,26,35,36,38,39,41,43,44,46] N = 13 were rated moderate quality and n = 1 was rated low quality. A total of 395 studies and 914 379 adolescent and adult participants were included.

3.5.1 | CVD and cardiovascular risk factors

CVD and associated risk factors of PCOS were assessed by n = 10 reviews.[11,18,26,35,36,38,39,41,43,46] N = 9 reviews were rated moderate

TABLE 4 Results of systematic reviews regarding psychological comorbidities of PCOS

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Quality of life					
Bazarganipour (2015)[29]	Moderate	Unclear	HRQoL mean scores in related dimensions	Women w/PCOS (no comparison)	Combined mean scores in the domains: Scores > mean of PCOSQ/MPCOSQ Emotional: 4.402 (95% CI 3.77 to 5.04) Infertility: 4.13 (95% CI 3.81 to 4.45 Weight: 3.88 (95% CI 2.33 to 5.42) Scores < mean of PCOSQ/MPCOSQ Menstruation: 3.84 (95% CI 3.63 to 4.04) Hirsutism: 3.81 (95% CI 3.26 to 4.35)
Kaczmarek (2016)[47]	Low	Unclear	HRQoL	Adolescents w/PCOS (13-24 y) vs adolescents w/out PCOS	9/9 studies reported PCOS significantly reduces HRQoL in adolescent girls. Body weight issues and BMI appeared to have the strongest effect on HRQoL; n = 2 studies reported a normalization of HRQoL scores after adjustment for BMI.
Li (2011)[30]	Moderate	Unclear	HRQoL	Women w/PCOS vs women w/o PCOS	Physical function: −5.46 MD (95% CI −8.52 to −2.41) Physical role function: −5.76 MD (95% CI −8.49 to −3.03) Body pain: −4.55 MD (95% CI −7.99 to −1.11) General health: −11.34 MD (95% CI −19.53 to −3.15) Vitality: −15.14 MD (95% CI −17.43 to −12.84) Social function: −15.95 MD (95% CI −18.57 to −13.33) Emotional role function: −23.86 MD (95% CI −27.51 to −20.21) Mental health: −13.83 MD (95% CI, −16.13 to −11.53)
Veltman-Verhulst (2012)[42]	Moderate	Moderate-high	Emotional subscales of HRQoL (emoQoL)	Women w/PCOS vs women w/o PCOS	EmoQoL (eight studies): 20.66 SMD (95% CI 20.92 to 20.410
Depression and anxiety					
Barry (2011)[27]	Moderate	11 moderate, 1 low	Depression and anxiety	Women w/PCOS vs women w/o PCOS	Depression: Hedges' g = 0.82 (95% CI 0.73 to 0.92) Anxiety: Hedges' g = 0.54 (0.33 to 0.75)
Dokras (2012)[37]	Moderate	Unclear	Anxiety	Women w/PCOS vs women w/o PCOS	Anxiety: 6.88 OR (95% CI 2.5 to 18.9)
Veltman-Verhulst (2012)[42]	Moderate	Moderate-high	Depression and anxiety	Women w/PCOS vs women w/o PCOS	Depression: 0.60 SMD (95% CI 0.47 to 0.73) Anxiety: 0.49 SMD (95% CI 0.36 to 0.63)

BMI, body mass index; CI, confidence interval; EmoQoL, emotional quality of life; HRQoL, health-related quality of life; MPCOSQ, modified polycystic ovary syndrome health-related quality of life questionnaire; NA, not applicable; MD, mean difference; OR, odds ratio; PCOS, polycystic ovary syndrome; PCOSQ, Polycystic Ovary Syndrome Health-related Quality of Life Questionnaire; RR, risk ratio; SMD, standardized mean difference.

TABLE 5 Results of systematic reviews regarding other comorbidities of PCOS

Reviews	AMSTAR	Quality of included studies	Outcomes assessed	Comparison	Significant results
Cancers					
Barry (2014)[40]	Moderate	Low-moderate	Endometrial cancer, ovarian cancer, breast cancer	Women w/PCOS vs women w/out PCOS	Endometrial cancer: 2.79 OR (95% CI 1.31 to 5.95)
				Women w/PCOS <54 y vs women w/out PCOS <54	Endometrial cancer: 4.05 OR (95% CI, 2.42 to 6.76) Ovarian cancer 2.52 OR (95% CI 1.08 to 5.89)
Shobeiri (2016)[45]	Moderate	4 moderate, 4 low	Breast cancer	Women w/PCOS vs women w/out PCOS	N/A
Vitamin D deficiency					
He (2015)[38]	Moderate	Unclear	Vitamin D levels	Women w/PCOS, VDD vs women w/PCOS non-VDD	Vitamin D: −0.74 SMD (95% CI −1.26 to −0.22)
				Correlation of vitamin D with parameters in women w/PCOS	N/A
				Postintervention of vitamin D vs Preintervention in women w/ PCOS	Vitamin D: 2.09 SMD (95% CI 1.28 to 2.91)
				Postintervention of vitamin D vs Postintervention of placebo in women w/PCOS	Vitamin D: 2.11 SMD (95% CI 0.85 to 3.37)

CI, confidence interval; NA, not applicable; MD, mean difference; PCOS, polycystic ovary syndrome; SMD, standardized mean difference; VDD, vitamin D deficiency.

quality and n = 1 was rated low quality. N = 2 reviews (n = 1 in adult women[43] and n = 1 in adolescent women[35]) assessed the effects of obesity on lipid metabolism by comparing the lipid profile of obese, overweight and/or normal weight individuals with PCOS. Compared to normal weight women with PCOS, overweight or obese adult women with PCOS had significantly higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) and significantly lower high-density lipoprotein cholesterol (HDL-C) levels[43] and obese adolescent women with PCOS had significantly higher TC and LDL-C and significantly lower HDL-C levels.[35] Subgroup analysis in the adolescent study reported significantly higher LDL-cholesterol levels for obese adolescents with PCOS compared to BMI-matched adolescents without PCOS.[35]

N = 1 review assessed the effects of obesity on lipid metabolism in the context of vitamin D deficiency (VDD).[38] Compared with non-VDD women with PCOS, VDD women with PCOS had significantly lower HDL-C levels but did not differ in any other lipid metabolism indexes. Vitamin D concentration was negatively correlated with TG and positively correlated with HDL-C.

N = 3 reviews examined lipid metabolism with respect to thyroid function,[46] hyperandrogenism (HA) and pregnancy.[18] Subclinical hypothyroidism was associated with decreased HDL-C levels and increased TG levels,[46] hyperandrogenism was associated with decreased HDL-C levels,[49] and no differences in the lipid profile were observed between pregnant women with or without PCOS.[18]

N = 2 reviews assessed how PCOS affects blood pressure, one review in the context of subclinical hypothyroidism[46] and one review in the context of pregnancy.[18] A significant increase in systolic and diastolic blood pressure was reported for pregnant women with PCOS when compared to nonpregnant women with PCOS. The presence of subclinical hypothyroidism failed to influence blood pressure in women with PCOS women.

N = 2 reviews examined the risk of early markers of CVD and reported women with PCOS were at a significantly increased risk for higher carotid intima-media thickness (CIMT)[39] and compromised flow-mediated dilatation (FMD).[41] N = 2 reviews assessed the prevalence of CVD and reported women with PCOS were at a significantly increased risk for coronary heart disease (CHD)[11,26] and stroke.[26]

3.5.2 | Diabetes and markers of insulin resistance

Glucose homeostasis-related PCOS outcomes were evaluated by n = 8 reviews, all of which were moderate quality.[18,19,23,35,36,38,43,46] Of these reviews, n = 3 assessed the effects of obesity on glucose homeostasis in adult and adolescent women with PCOS.[19,35,43] For all three reviews, compared with normal weight women with PCOS, overweight and obese adult and adolescent women with PCOS had significantly greater IR. Further subgroup analyses by one review reported that being overweight or obese significantly increased fasting insulin and fasting blood glucose compared to normal weight women with PCOS and being obese compared to overweight significantly worsened fasting insulin, fasting blood glucose and IR.[43]

N = 1 review investigated glucose homeostasis specifically in the context of VDD.[38] Compared with non-VDD women with PCOS,

VDD women with PCOS had significantly higher fasting blood glucose, fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR) and homeostatic model assessment-β-cell function (HOMA-Iβ). Circulating vitamin D negatively correlated with FI and FBG and positively correlated with the quantitative insulin sensitivity check index (QUICKI), a method for measuring insensitivity or inversely IR.

N = 3 reviews examined glucose homeostasis with respect to thyroid function,[46] hyperandrogenism[49] and pregnancy.[18] Subclinical hypothyroidism was associated with increased HOMA-IR,[46] hyperandrogenism was associated with significantly higher incidence of HOMA-IR and rate of IR, and no differences in glucose homeostasis were observed between pregnancies with or without PCOS.[18] N = 1 review assessed the prevalence and incidence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM2) in women with and without PCOS and reported compared to women without PCOS, women with PCOS had significantly increased prevalence of IGT and DM2.[23]

3.5.3 | Metabolic syndrome and nonalcoholic fatty liver disease (NAFLD)

The prevalence of metabolic syndrome was assessed by n = 2 reviews.[23,36] One review reported women with PCOS to have increased prevalence of metabolic syndrome for BMI and non-BMI-matched women without PCOS.[23] The other review assessed the effects of HA on the incidence of MS for women with PCOS and reported a significant higher incidence for women with PCOS and HA compared to women with PCOS without HA.[49] N = 1 review assessed the risk of NAFLD in women with PCOS and reported risk was significantly higher in women with PCOS compared to women without PCOS.[44]

3.5.4 | Obesity

N = 1 review assessed the association between PCOS with obesity and reported an increased prevalence of overweight, obesity and central obesity in women with PCOS compared to women without PCOS.[2] N = 1 review examined anthropometric alterations with respect to thyroid function in women with PCOS.[46] The presence of subclinical hypothyroidism did not significantly influence BMI, waist circumference or waist-to-hip ratio.

3.6 | Psychological comorbidities of PCOS

N = 6 reviews evaluated the psychological complications of PCOS[27,29,37,42,47,48] (Table 4). The reviews were of moderate quality (n = 5) and low quality (n = 1). A total of 74 studies and 9985 adult participants were involved.

3.6.1 | Quality of life

N = 4 studies evaluated HRQol[29,30,42,47] and reported PCOS to have a negative influence on HRQoL. N = 2 reviews examined the effect of PCOS on specific domains of HRQoL using the PCOS questionnaire (PCOSQ). Bazarganiour et al[29] reported hirsutism and menstruation as the most affected domain, while Kaczmarek et al[47] found BMI and body weight issues to have the strongest impact on HRQoL. N = 1 review[30] examined the effect of PCOS on specific domains of HRQoL (physical, emotional and social) using the 36-item short form survey (SF-36) questionnaire, and reported compared to healthy controls, women with PCOS had significantly lower values in each dimension of SF-36 (physical function, physical role function, body pain, general health, vitality, social function, emotional role function and mental health), particularly in the emotional role function. N = 1 review[42] evaluated the quality of life and emotional burden associated with PCOS using emotional subscales from all versions of QoL (quality of life) questionnaires (except PCOSQ) in women diagnosed with PCOS and reported higher emotional distress in women with PCOS.

3.6.2 | Depression and anxiety

N = 3 reviews assessed the prevalence of symptoms of depression or anxiety in women with PCOS.[27,37,42] In all the reviews, meta-analysis revealed significantly higher depressive and anxiety symptom scores in women with PCOS compared to women without.

3.7 | Other morbidities

There were three reviews that we could not classify as either reproductive, metabolic or psychological categories[38,40,45] (Table 5). The reviews were all of moderate quality. A total of 50 studies and 50 906 adult women were involved.

3.7.1 | Cancers

The risk of cancers in women with PCOS was assessed by n = 2 reviews. N = 1 review reported across their lifespan, and women with PCOS are at increased risk of developing endometrial but not breast or ovarian cancer compared with non-PCOS controls.[40] When only women under the age of 54 were included from the analysis, this further increased the risk of endometrial cancer. Shobeiri and Jenabi[45] found no significant association between PCOS and breast cancer.

3.7.2 | Vitamin D deficiency

N = 1 review assessed serum vitamin D levels in women with PCOS and reported compared to women without PCOS women with PCOS have significantly lower vitamin D levels.[38]

4 | DISCUSSION

The aim of this review was to summarize existing systematic reviews and meta-analyses evaluating comorbidities and complications of PCOS. Despite a large number of reviews (n = 23) that included 575 studies and over a million participants (1 090 072), there is a lack of high-quality systematic reviews or meta-analyses. We also aimed to

align evidence synthesis with the recent evidence-based guideline on PCOS, an international collaboration across 37 societies.[6]

For metabolic complications and comorbidities, we reported a worse lipid and cardiovascular risk profile[35,43] and higher prevalence of metabolic syndrome[23,49] for women with PCOS and this was exacerbated by being overweight or obese regardless of age[35] or ethnicity.[35,43] We found women with PCOS have an increased risk of surrogate markers for CVD (CIMT[39] and FMD[41]) and higher prevalence of CVD.[11,26] Despite our findings, we acknowledge the association between CVD and PCOS remains controversial. Evidence of higher prevalence of surrogate markers of CVD predominately comes from perimenopausal women with PCOS[50,51] but there is limited and conflicting evidence reporting if postmenopausal women with PCOS are truly at risk for CVD.[52] This confliction may be related to the decrease in hyperandrogenism experienced with age in PCOS[53] or apotential protective role of androgen excess against progression of CVD later in life.[54] Moreover, the large time gap (three to four decades) between PCOS diagnosis and CVD manifestation limits the number of large, well-phenotyped cohort studies with sufficient long-term follow-up in PCOS. Despite the controversies, these findings are consistent with current guidelines that recommended all women with PCOS should be screened for individual CVD risk factors with particular attention to excess body weight.[6,55-60] Another metabolic comorbidity assessed was NAFLD, which was increased in women with compared to those without PCOS.[44] However, this review only included seven studies of varied design of unknown quality, highlighting the need for more well-designed studies investigating the association of PCOS and NAFLD. Current guidelines and specialty societies acknowledged an association but no routine screening for NAFLD in women with PCOS has been recommended at this stage, as long-term health outcomes remain unclear.[59]

The majority of retrieved reviews reported worse insulin sensitivity and glucose tolerance in women with compared to women without PCOS. Excess weight further exacerbates IR regardless of age[35] or ethnicity.[35,43] The review by Yu et al,[18] comparing pregnant women with and without PCOS, was the only review to report no difference in markers of glucose metabolism, specifically FBG. We would have anticipated a negative additive effect of pregnancy and PCOS on glucose metabolism. One potential reason for this finding is that abnormalities in glucose tolerance in PCOS appear more likely to occur postprandially.[61] Past specialty society position statements acknowledged women with PCOS were at an increased risk of gestational diabetes,[29,56,59,62,63] yet few recommend early screening with an oral glucose tolerance test (OGTT) in pregnancy as good clinical practice.[59,64] The recent international guideline in PCOS[6] recommends an OGTT preconception or early in pregnancy at 24- to 28-week gestation and our findings support those recommendations. For nonpregnant women with PCOS, the international guideline recommends performing an OGTT, fasting glucose or HbA1c at baseline in all women but OGTT is preferred in high-risk women. Thereafter, assessment should be every 1 to 3 years, influenced by the presence of other diabetes risk factors.

We identified that having PCOS correlates with an increased risk of adverse pregnancy, foetal and neonatal events including preeclampsia, PIH, preterm delivery, caesarean delivery, miscarriage, perinatal death, neonatal hypoglycaemia[18] and GDM[17,18] which is line with the current evidence-based guidelines[6] and specialty society position statements.[55-59] However, these links should be interpreted with caution owing to the limited number of systematic reviews, their diverse quality and significant between-study heterogeneity including study size and different diagnostic criteria.

We also report that women with PCOS had a lower quality of life,[29,30,42,47] and an increased prevalence of depressive[27,42] and anxiety symptoms[37] compared to women without. Furthermore, a high BMI is associated with greater depression and anxiety in women with PCOS.[27] This is consistent with the prominent role of weight management in the first-line management of PCOS and suggests mood in PCOS could potentially be improved through weight control as reported in clinical trials.[65,66] The increased risk of psychological problems in PCOS may relate to coping with issues such as femininity, sexuality and fertility that are related to PCOS features underlining hirsutism[29] and irregular menstruation.[29] It may also relate to body weight issues[47] or the nature of living with a chronic disease. The new international guideline in PCOS[6] recognizes the PCOS-related psychological issues and emphasizes screening, assessment and management.

Two systematic reviews assessed the prevalence of obesity in women with PCOS[2,46] and reported a greater risk of obesity,[2] which was not altered by subclinical hypothyroidism status.[46] The international guideline in PCOS[6] recommends that BMI be assessed in all women with PCOS and that prevention of excess weight gain is vital. Weight loss is recommended for overweight or obese women and should be first-line treatment.[55,56,58-60,62,63] This is crucial given the recognition in both prior research and this current review of the key role of excess weight in worsening reproductive, metabolic and psychological outcomes in PCOS.

Two systematic reviews found a significant increase in risk of endometrial cancer in women with PCOS.[40,45] This may be the result of endometrial proliferation underlined by IR and oligomenorrhea,[67] prolonged endometrial exposure to unopposed oestrogen in anovulation[68] and/or related risk factors such as obesity[69] and T2DM.[70] While further high-quality evidence is required, the international guideline[6] recommends combined oral contraceptive pills (alone) in adult women with PCOS as first-line pharmacological management of hyperandrogenism and/or irregular menstrual cycles. Promotion of regular menses may be protective of endometrial cancer. It remains unknown whether dysregulation of vitamin D metabolism is a consequence or common comorbid manifestation of PCOS.[38] While there is some evidence to suggest poor vitamin D status may contribute to metabolic disturbance development, including IR and dyslipidaemia,[71] further investigation of a causal relationship is warranted. In general, there are limited data on vitamin D replacement in PCOS. For this reason, the international guideline does not make recommendations in this area.

There are several strengths of this study. Our search strategy was comprehensive, incorporated multiple databases and conducted in duplicate to reduce potential for random errors and bias. We note this overview of systematic reviews has some limitations. First, we restricted reviews to those published from 2009 onwards; the year the PRISMA statement was released,[33] which may exclude significant earlier studies assessing the comorbidities associated with PCOS, albeit potentially of lower quality. We also excluded non-English publications, thus potentially introducing a language bias. We also purposefully excluded reviews that focused on surrogate markers of unknown significance, for example, inflammatory cytokines and sex hormones and selected only reviews that clearly focused on PCOS comorbidities and complications that are more directly relevant to clinicians and patient care. We report the quality of the included systematic reviews were generally moderate with limitations in quality related to lacking a priori protocol driven approach or interpretation of the quality of individual studies. However, we note that performing quality assessment of each of the more than 500 included studies would be impractical. Quality of future systematic reviews may be strengthened by addressing issues including reporting conflict of interest of included studies, registering for a priori protocol, providing a list of excluded studies, and offering greater transparency to whether or not duplicate study and data extraction were used. Our findings also aligned with recent recommendations from the international evidence-based guidelines in PCOS.[6]

We report for the first time a comprehensive summary and quality assessment of systematic reviews assessing comorbidities and complications in women with PCOS. We confirm that PCOS has a range of reproductive, metabolic, psychological and other manifestations. We report many of the assessed outcomes were worsened by excess adiposity, highlighting the importance of weight management as first-line PCOS therapy. We draw attention to the shortage of systematic reviews regarding pregnancy outcomes of PCOS and significant knowledge gaps in the association between NAFLD, vitamin D levels and cancers with PCOS warranting future studies to elucidate the potential pathogenic associations. It is therefore imperative that clinicians are aware of the broad spectrum of complications and comorbidities associated with PCOS and rely only on the best available evidence to maximize the effectiveness of PCOS diagnosis, treatment and management.

ACKNOWLEDGEMENTS

The authors of this review would like to thank Angela Melder for contributing to the design of the study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this review.

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REFERENCES

1. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod*. 2010;25(2):544-551.
2. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(6):618-637.
3. Boyle JA, Cunningham J, O'Dea K, Dunbar T, Norman RJ. Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia. *Med J Aust*. 2012;196(1):62-66.
4. Roumain J, Charles MA, de Courten MP, et al. The relationship of menstrual irregularity to type 2 diabetes in Pima Indian women. *Diabetes Care*. 1998;21(3):346-349.
5. Chang J, Azziz R, Legro R, et al. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2014; 81(1):19-25.
6. Teede HJ, Misso ML, Costello MF, et al. ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril*. 2018;110(3):364-379.
7. Legro RS, Strauss JF III. Molecular progress in infertility: polycystic ovary syndrome. *Fertil Steril*. 2002;78(3):569-576.
8. Legro R, Castracane D, Kauffman R. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. *Obstet Gynecol Surv*. 2004;59(2):141-154.
9. Boomsma CM, Eijkemans M, Hughes E, Visser G, Fauser B, Macklon N. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update*. 2006;12:673-683.
10. Sharpless JL. Polycystic ovary syndrome and the metabolic syndrome. *Clin Diabetes*. 2003;21(4):154-161.
11. de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. *Hum Reprod Update*. 2011;17(4):495-500.
12. Himelein M, Thatcher S. Polycystic ovary syndrome and mental health: a review. *Obstet Gynecol Surv*. 2006;61(11):723-732.
13. Thathapudi S, Kodati V, Erukkambattu J, Katragadda A, Addepally U, Hasan Q. Anthropometric and biochemical characteristics of polycystic ovarian syndrome in south indian women using AES-2006 criteria. *Int J Endocrinol Metab*. 2014;12(1):e12470.
14. Brassard M, AinMelk Y, Baillargeon J-P. Basic infertility including polycystic ovary syndrome. *Med Clin North Am*. 2008;92(5):1163-1192.
15. Ozdemir S, Ozdemir M, Gorkemli H, Kiyici A, Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. *Acta Obstet Gynecol Scand*. 2010;89(2):199-204.
16. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet (London, England)*. 2007;370(9588):685-697.
17. Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I. Risk of gestational diabetes mellitus in women with

polycystic ovary syndrome: a systematic review and a meta-analysis. *Fertil Steril*. 2009;92(2):667-677.
18. Yu H-F, Chen H-S, Rao D-P, Gong J. Association between polycystic ovary syndrome and the risk of pregnancy complications: a PRISMA-compliant systematic review and meta-analysis. *Medicine*. 2016;95(51):e4863.
19. Behboudi-Gandevani S, Ramezani Tehrani F, Rostami Dovom M, et al. Insulin resistance in obesity and polycystic ovary syndrome: systematic review and meta-analysis of observational studies. *Gynecol Endocrinol*. 2016;32(5):343-353.
20. Wild RA, Painter PC, Coulson PB, Carruth KB, Ranney GB. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 1985;61(5):946-951.
21. Talbott E, Clerici A, Berga SL, et al. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *J Clin Epidemiol*. 1998;51(5):415-422.
22. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care*. 1999;22(1):141-146.
23. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2010;16(4):347-363.
24. Moran L, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update*. 2009;15(4):477-488.
25. Murri M, Luque-Ramirez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. *Hum Reprod Update*. 2013;19(3):268-288.
26. Zhao L, Zhu Z, Lou H, et al. Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis. *Oncotarget*. 2016;7(23):33715-33721.
27. Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod*. 2011;26(9):2442-2451.
28. Deeks A, Gibson-Helm M, Teede H. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. *Fertil Steril*. 2010;93(7):2421-2423.
29. Bazarganipour F, Taghavi S, Montazeri A, Ahmadi F, Chaman R, Khosravi A. The impact of polycystic ovary syndrome on the health-related quality of life: a systematic review and meta-analysis. *Iran J Reprod Med*. 2015;13(2):61-70.
30. Li Y, Li Y, Yu Ng EH, et al. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil Steril*. 2011;96(2):452-458.
31. Lin AW, Dollahite JS, Sobal J, Lujan ME. Health-related knowledge, beliefs and self-efficacy in women with polycystic ovary syndrome. *Hum Reprod*. 2018;33(1):91-100.
32. Hadorn DC, Baker D, Hodges JS, Hicks N. Rating the quality of evidence for clinical practice guidelines. *J Clin Epidemiol*. 1996;49(7):749-754.
33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:25-35.
34. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS ONE*. 2007;2(12):e1350.
35. Li L, Feng Q, Ye M, He Y, Yao A, Shi K. Metabolic effect of obesity on polycystic ovary syndrome in adolescents: a meta-analysis. *J Obstet Gynaecol*. 2017;37(8):1036-1047.
36. Yang R, Yang S, Li R, Liu P, Qiao J, Zhang Y. Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis. *Reprod Biol Endocrinol*. 2016;14:67.
37. Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. *Fertil Steril*. 2012;97(1):225-230 e222.
38. He C, Lin Z, Robb SW, Ezeamama AE. Serum vitamin D levels and polycystic ovary syndrome: a systematic review and meta-analysis. *Nutrients*. 2015;7(6):4555-4577.
39. Meyer ML, Malek AM, Wild RA, Korytkowski MT, Talbott EO. Carotid artery intima-media thickness in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(2):112-126.
40. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2014;20(5):748-758.
41. Sprung VS, Atkinson G, Cuthbertson DJ, et al. Endothelial function measured using flow-mediated dilation in polycystic ovary syndrome: a meta-analysis of the observational studies. *Clin Endocrinol*. 2013;78(3):438-446.
42. Veltman-Verhulst SM, Boivin J, Eijkemans MJ, Fauser BJ. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. *Hum Reprod Update*. 2012;18(6):638-651.
43. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev*. 2013;14(2):95-109.
44. Ramezani-Binabaj M, Motalebi M, Karimi-Sari H, Rezaee-Zavareh MS, Alavian SM. Are women with polycystic ovarian syndrome at a high risk of non-alcoholic Fatty liver disease; a meta-analysis. *Hepat Monthly*. 2014;14(11):e23235.
45. Shobeiri F, Jenabi E. The association between polycystic ovary syndrome and breast cancer: a meta-analysis. *Obstet Gynecol Sci*. 2016;59(5):367-372.
46. Pergialiotis V, Konstantopoulos P, Prodromidou A, Florou V, Papantoniou N, Perrea D. The impact of subclinical hypothyroidism on anthropometric characteristics, lipid, glucose and hormonal profile of PCOS patients: a systematic review and meta-analysis. *Eur J Endocrinol*. 2017;176(3):R159-R166.
47. Kaczmarek C, Haller DM, Yaron M. Health-related quality of life in adolescents and young adults with polycystic ovary syndrome: a systematic review. *J Pediatr Adolesc Gynecol*. 2016;29(6):551-557.
48. Li HW, Brereton RE, Anderson RA, Wallace AM, Ho CK. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. *Metabolism*. 2011;60(10):1475-1481.
49. Yang R, Yang S, Li R, Liu P, Qiao J, Zhang Y. Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis. *Reprod Biol Endocrinol*. 2016;14(1):67.
50. Carmina E, Campagna AM, Lobo RA. Emergence of ovulatory cycles with aging in women with polycystic ovary syndrome (PCOS) alters the trajectory of cardiovascular and metabolic risk factors. *Hum Reprod*. 2013;28(8):2245-2252.
51. Dokras A. Cardiovascular disease risk in women with PCOS. *Steroids*. 2013;78(8):773-776.
52. Gunning MN, Fauser BCJM. Are women with polycystic ovary syndrome at increased cardiovascular disease risk later in life? *Climacteric*. 2017;20(3):222-227.
53. Newbold T. What do patients and carers need in health apps - but are not getting. 2015. Accessed 27/05, 2018.
54. Khatibi A, Agardh CD, Shakir YA, et al. Could androgens protect middle-aged women from cardiovascular events? A population-based study of Swedish women: The Women's Health in the Lund Area (WHILA) Study. *Climacteric*. 2007;10(5):386-392.
55. Conway G, Dewailly D, Diamanti-Kandarakis E, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. *Eur J Endocrinol*. 2014;171(4):P1-P29.

56. Fauser B, Tarlatzis BC, Rebar RW, et al. Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Worshop Group Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod*. 2011;27:14-24.
57. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American association of clinical endocrinologists, American college of endocrinology, and androgen excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2. *Endocr Pract*. 2015;21(12):1415-1426.
58. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American association of clinical endocrinologists, American college of endocrinology, and androgen excess and PCOS society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome–part 1. *Endocr Pract*. 2015;21(11):1291-1300.
59. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565-4592.
60. Wild RA, Carmina E, Diamanti-Kandarakis E, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab*. 2010;95(5):2038-2049.
61. Colagiuri S, Hussain Z, Zimmet P, Cameron A, Shaw J. Screening for type 2 diabetes and impaired glucose metabolism. *Aust Exp*. 2004;27(2):367-371.
62. Alliance JHfWsHobotPA. Evidence-based guidelines for the assessment and management of polycystic ovary syndrome. 2015.
63. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Position statement: glucose intolerance in polycystic ovary syndrome—a position statement of the androgen excess society. *J Clin Endocrinol Metab*. 2007;92(12):4546-4556.
64. Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust*. 2011;195(6):S65-S112.
65. Thomson RL, Buckley JD, Moran LJ, et al. Comparison of aerobic exercise capacity and muscle strength in overweight women with and without polycystic ovary syndrome. *BJOG Int J Obstet Gynaecol*. 2009;116(9):1242-1250.
66. Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. *Am J Clin Nutr*. 2006;84(1):77-87.
67. Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: a significant risk factor of endometrial cancer. *Gynecol Oncol*. 2012;125(3):751-757.
68. O'Connor KA, Ferrell RJ, Brindle E, et al. Total and unopposed estrogen exposure across stages of the transition to menopause. *Cancer Epidemiol Biomark Prev*. 2009;18(3):828-836.
69. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet (London, England)*. 2008;371(9612):569-578.
70. Satija A, Spiegelman D, Giovannucci E, Hu FB. Type 2 diabetes and risk of cancer. *BMJ*. 2015;350:g7707.
71. Krul-Poel YH, Snackey C, Louwers Y, et al. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review. *Eur J Endocrinol*. 2013;169(6):853-865.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Gilbert EW, Tay CT, Hiam DS, Teede H, Moran LJ. Comorbidities and complications of polycystic ovary syndrome: An overview of systematic reviews. *Clin Endocrinol (Oxf)*. 2018;89:683–699. https://doi.org/10.1111/cen.13828