Systematic Review

Association between Polycystic Ovarian Syndrome, Impaired Kidney Function and Hyperuricaemia: A Systematic Review and Meta-analysis

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a gynaecological problem affecting women within reproductive age, accompanied by several metabolic anomalies, thus leading to alteration in kidney function and hyperuricaemia. Due to the high prevalence of cardiometabolic factors in PCOS, there is a need to anticipate an increased number of kidney impairments amongst these women. **Objectives:** This review aims to investigate the potential link between PCOS, impaired kidney function, and elevated uric acid levels. By elucidating this association, we hope to provide clinicians with a tool to stratify the risk of kidney disease in women diagnosed with PCOS, based on readily available kidney function parameters. **Materials and Methods:** The recommendations used for the analysis were outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Subsequently, eligible studies were identified using several databases (MEDLINE, ProQuest and EBSCOhost) between 1996 and 2022, with a total of 13 studies included. Serum uric acid, serum creatinine, as well as estimated glomerular filtration rate (eGFR) were evaluated as the outcome of interest. Quality assessment for cohort, case–control and cross-sectional studies was conducted utilising the Newcastle–Ottawa Scale, while Review Manager 5.4 was utilised for meta-analysis. **Results:** Uric acid was significantly higher in women with PCOS (mean difference [MD] = 0.70, 95% confidence interval [CI] [0.45–0.95], $P < 0.00001$). Meanwhile, serum creatinine and eGFR were statistically similar in each group (MD = 0.08, 95% CI [−0.05–0.21], $P = 0.22$ and MD = 3.54, 95% CI [−4.53–11.61], $P = 0.39$, respectively). **Interpretation:** This review showed that PCOS was significantly associated with elevated uric acid. However, no significant difference was found between eGFR and creatinine levels compared to healthy controls. Routine uric acid assessment in PCOS patients is recommended as a simple tool for risk stratification. **Limitations:** No body mass index (BMI) subgroup analysis was done due to limited BMI reporting in our included studies. Quantitative analysis of all kidney function parameters was also limited by sparse data on urea and albumin. **PROSPERO Registration Number:** CRD42023410092 (02 April 2023).

Keywords: *Creatinine, estimated glomerular filtration rate, kidney function, polycystic ovarian syndrome, uric acid*

Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent medical condition amongst women

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within reproductive age.[1] This syndrome is indicated by symptoms such as oligomenorrhoea, irregular ovulation, polycystic ovarian morphology and several metabolic abnormalities including hyperandrogenism, hyperinsulinaemia, gonadotropin imbalance, dyslipidaemia and is frequently accompanied by an increase in visceral fat.[2] As one of the most prevailing endocrinopathies, PCOS affects 4%–21% of women in the pre-menopausal population.[3]

PCOS is generally related to the progression of metabolic abnormalities, including dyslipidaemia, obesity, hypertension, as well as type 2 diabetes mellitus (T2DM).[4] These conditions are the major causes of kidney disease, characterised by changes in kidney function, including creatinine and estimated glomerular filtration rate (eGFR).[5] Studies suggest an indirect association between creatinine levels and PCOS, potentially mediated by the high prevalence of metabolic syndrome (MetS), especially in obese patients.[6] One best explanation is that elevated creatinine levels might be a potential indicator of glomerular injury, which could be triggered by the inflammatory processes associated with the PCOS itself, and creatinine is reported to be a significant marker of kidney damage ($P = 0.035$).[6] Moreover, elevated eGFR originating from hyperfiltration has been observed in diabetic patients, including those with MetS.[7] The pathogenesis of hyperfiltration is a combination of vascular and tubular factors, linked with reduced arterial stiffness as well as endothelial dysfunction,[8] indicating a representation of the unique physiological condition of systemic vascular dysfunction.[6] Consequently, there is a suggestion that the hyperfiltration condition represents overall alterations in microvascular and macrovascular function within the kidney's vasculature.[9]

Several women with PCOS suffer from an imbalance of reproductive hormones.[10] Previous research has shown that high levels of oestrogen and androgen can lead to decreased serum uric acid (SUA) levels.[11] Meanwhile, androgen reflects as a hyperuricaemia promoter in patients with PCOS.[12] By downregulating the expression of the human urate transporter gene, androgen promoted uric acid reabsorption in renal tubules and decreased uric acid secretion to accelerate the occurrence of hyperuricaemia.[13]

The outcomes of existing studies concentrating on kidney function and hyperuricaemia in PCOS are still inconclusive. Consequently, the purpose of this review was to determine the relationship between PCOS, kidney function and hyperuricaemia, as a way to help clinicians to stratify the risk of kidney diseases amongst PCOS women and provide a guide for future research.

Materials and Methods

The systematic review was designed and accomplished on the basis of the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[14]

Eligibility criteria

The studies included were the entirety of published observational studies investigating the risk of impaired kidney function and hyperuricaemia in women with PCOS. Furthermore, clinical and/or ovarian morphology was used as diagnosis criteria for PCOS, and articles published between 1996 and 2022 were included. Exclusion criteria were reviews, animal studies, pre-clinical studies, conference abstracts, book sections and commentaries/editorials, including articles with unavailability of full text and irrelevant topics.

Literature search and information sources

The search for eligible studies was carried out using MEDLINE, ProQuest and EBSCOhost electronic databases. Studies were identified by five independent authors using the following keywords: *((((((‘Polycystic Ovary Syndrome’[Mesh]) AND ‘Kidney Function Tests’[Mesh]) OR ‘Kidney Diseases’[Mesh]) OR ‘Creatinine’[Mesh]) OR ‘Urea’[Mesh]) OR ‘Glomerular Filtration Rate’[Mesh]) AND ‘Uric Acid’[Mesh]*.

All studies obtained were exported into the reference manager software of Mendeley and filtered for duplicates, titles, as well as abstracts. Subsequently, the analyses were examined and excluded independently when the title and/or abstract were not suitable for the aim of this review. The complete article of the specified studies was read by five authors for eligibility. Moreover, any disagreement was solved by consensus and the opinion of all reviewers.

Data collection process

Data extraction was accomplished independently by five authors. Any discrepancies that occurred were settled through discussion to get an agreement. The detailed information obtained from the analyses were first author, type of study, country, publication year, sample size, sample characteristic (age), kidney function measurement, PCOS diagnosis criteria, population matching and the outcome of interest. For bivariate data extraction, the collected studies were further classified based on eGFR, serum creatinine and uric acid from each group (PCOS and non-PCOS).

Data and outcome measures

Serum creatinine, eGFR and uric acid were expressed in mg/dL, mL/min/1.73 m^2 and mg/dL, respectively. The values obtained were shown as mean ± standard

deviation (SD) for normally distributed data. Initially, abnormal data were shown as median (interquartile range) but converted to a mean and SD to be computed in the meta-analysis.[15,16]

Summary measures

The standardised mean differences were used as the most appropriate effect sizes for continuous data, to determine the relationship between PCOS and kidney function measurement, namely eGFR, serum creatinine and uric acid. The *P* values were also included to show the significance of the results, with ≤0.05, being considered significant.

Assessment of risk of bias (quality assessment)

The Newcastle–Ottawa Scale was applied to evaluate each study, covering cohort, case–control and cross-sectional designs, with tools consisting of different evaluation aspects.[17] The overall score of each study will be graded into three categories, namely good, fair and poor quality. Each article was assessed by two reviewers independently and any differences were discussed by the review team to achieve an agreement.

Synthesis of results and statistical analysis

Review Manager (RevMan; Cochrane Collaboration) version 5.4 (Copenhagen, Denmark) was used to extract and pool the data to perform the quantitative synthesis. To facilitate the analysis, the mean difference was expressed as the difference of each kidney function parameter (creatinine, GFR and uric acid) between PCOS and non-PCOS groups. Subsequently, statistical analyses were carried out for between-group comparison. Data analysis was accomplished using totals and subtotals with 95% confidence interval (CI).

The results of several parameters were obtained using various calculation or assessment techniques, leading to a random effects model selection to perform the meta-analyses. This model assumes that the treatment impact will be distributed over certain populations and gives each study a more equal weighting. Moreover, the random effects model enables extrapolation to a larger sample of the population in cases when new studies are performed. The combined effects of the direct comparisons for individual interventions were compared using the inverse variance method for numerical (continuous) data, while the proportion data were examined with the Mantel–Haenszel method.

A funnel plots test was accomplished to evaluate the potential publication bias, where the effect of each trial was plotted by the inverse of standard error (SE). Subsequently, heterogeneity across trials was evaluated utilising the I^2 statistic, with value <25% considered subtle, 25% and 50% categorised low, 50% and 75% reflected moderate and above 75% represented high heterogeneity. When heterogeneity was present, possible causes were investigated through sensitivity analyses.

Results

Literature search

There were 348 studies obtained in the first literature search and 300 remained after removing duplicates. A total of 286 articles have incomplete criteria for the target population or exposure, including those with improper study design (review, conference abstract, book sections and commentaries/editorials, n = 55), studies in non-human subjects (*in vitro* or *in vivo*) n = 23, patients with any known acute or chronic illness or drug use that may affect the kidney function n = 8 and no relevant outcome n = 200. In addition, studies not mentioning the age group of participants were also excluded to mitigate the potential influence of age as a confounding factor. The screening on full text was carried out on the specified 14 studies, where 1 study failed to meet the outcome criteria. Consequently, 13 studies were used in the qualitative synthesis, as well as 9 with complete data extracted for the meta-analysis. A comprehensive flow diagram illustrating the literature search process is presented visually in Figure 1.

Characteristics of included studies

Table 1 shows the study's characteristics. Amongst 13 studies in this review, there were 1 cohort, 10 cross-sectional and 2 case–control studies. For the diagnosis criteria of PCOS, 9 studies used the definition of the Rotterdam ESHRE/ASRM 2003 criteria, 3 applied the definition of the US National Institutes of Health criteria, as well as 1 study determined the diagnosis based on normal or enlarged-sized ovary with numerous small subcortical follicles (diameter of 2–10 mm), together with the ovarian morphology evaluated by transvaginal ultrasound.

From 13 studies, the minimum range of age was 24.6 ± 5.4, as found in the PCOS group by Gozukara *et al*.,[8] while the maximum age was 33.4 ± 5.4, as obtained in Anttila *et al*.[18] Only 5 studies performed the age-matching population, such as El-Eshmawy *et al*.,[13] which recruited only obese patients; Can *et al*.[7] which divided individuals into two groups (normal and overweight obese); Luque-Ramírez *et al*.[19] which had three groups, consisting of lean, overweight and obese; Zhang *et al*.[20] which divided PCOS patients into normal weight, overweight and obese groups; and Pelluri *et al*.[21] which only investigated those with body mass index (BMI) ≥25 kg/m^2 and further divided PCOS patients into

Table 1: Study characteristics

Author, year, country	Types of study	Study participants				Diagnosis criteria of PCOS	Kidney function assessment	Population matching	Hormones and kidney function outcomes
		n		Age (year, mean±SD)					
		PCOS	Non-PCOS	PCOS	Non-PCOS				
Anttila *et al*., 1996, Finland[18]	Cross-sectional	38	20	27.9±5.6	33.4±5.4	Based on ovarian morphology: A normal-sized or enlarged ovary with multiple small subcortical follicles (2–10 mm in diameter), assessed by vaginal ultrasonography	SUA	All subjects were euthyroid and normoprolactinaemic, not use any hormonal medication for at least 2 months before the study	PCOS women display elevated levels of male hormones, and the testosterone-to-SHBG ratio, alongside a decrease in FSH, compared to healthy individuals UA levels were similar between women with PCOS and controls with matching BMI. Only two participants had UA levels above the reference range
Yarali *et al*., 2001, Turkey[22]	Case-control	30	30	27.9±6.1	31.4±6.5	US NIH criteria	SUA	N/A	The mean serum levels of all hormones remained comparable between the two groups SUA concentrations exhibited a statistically significant difference between the PCOS group and the control group (4.5±1.3 mg/dL vs. 3.8±0.8 mg/dL, $P<0.04$)
Luque-Ramírez *et al*., 2008, Spain[19]	Cross-sectional	40	40	24.5±5.8	25.6±6.0	US NIH criteria	SUA	Age and BMI	PCOS patients demonstrated elevated serum androgen concentrations and a greater degree of insulin resistance compared to control SUA levels exhibited a direct positive correlation with BMI, WHR and FAI
Lakhani *et al*., 2011, United Kingdom[23]	Cross-sectional	16	15	28.4±6.4	29.8±5.3	Rotterdam ESHRE/ASRM 2003	eGFR	N/A	No statistically significant difference of eGFR between PCOS women and healthy control (102.2±15.3 vs. 114.4±27.9 mL/min/1.73 m^2, $P=0.152$)

Contd...

Table 1: Contd..

Author, year, country	Types of study	Study participants				Diagnosis criteria of PCOS	Kidney function assessment	Population matching	Hormones and kidney function outcomes
		n		Age (year, mean±SD)					
		PCOS	Non-PCOS	PCOS	Non-PCOS				
Gozukara *et al*., 2015, Turkey[8]	Cross-sectional retrospective	140	60	24.6±5.4	25.2±4.38	Rotterdam ESHRE/ASRM 2003	GFR was estimated from SCr using the MDRD formula	N/A	PCOS women exhibited significantly elevated SUA levels (4.36±1.3 mg/dL) compared to control (3.2±0.7 mg/dL; *P*=0.002) No statistically significant differences in urea (*P*=0.72) or creatinine (*P*=0.09) levels between the two groups PCOS group demonstrated a significantly higher eGFR compared to controls (135.2±25.6 vs. 114.9±24.1 mL/min/1.73 m^2; *P*=0.001)
Leuștean *et al*., 2015, Romania[24]	Cross sectional	38	30	31.5*	35.5*	Rotterdam ESHRE/ASRM 2003	SUA	Age, history of chronic diseases, use of hypoglycaemic or hormonal drugs	No statistically significant differences of SUA between PCOS and control group (4.6 mg/dL in PCOS vs. 4.55 mg/dL in non-PCOS) No significant correlation was observed between SUA levels and either testosterone or LH concentrations
Mu *et al*., 2018, China[11]	Cross-sectional retrospective	1183	10,772	29.00 (27.00–31.00)*	31.00 (28.00–34.00)*	Rotterdam ESHRE/ASRM 2003	GFR and SUA	Age, BMI, eGFR	PCOS subjects exhibited significantly higher mean SUA compared to non-PCOS, with approximately two to four times higher A statistically significant positive association between SUA levels and testosterone levels (*r*=0.16, *P*<0.001), and elevated testosterone levels were independently associated with an increased risk of

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Table 1: Contd..

Author, year, country	Types of study	Study participants				Diagnosis criteria of PCOS	Kidney function assessment	Population matching	Hormones and kidney function outcomes
		n		Age (year, mean±SD)					
		PCOS	Non-PCOS	PCOS	Non-PCOS				
									hyperuricaemia (OR=1.75, 95% CI=1.45–2.11, *P*<0.001)
Song *et al*., 2019, China[5]	Cross-sectional	55	69	29.09±3.88	30.46±4.31	Rotterdam ESHRE/ASRM 2003	SCr, BUN, UACR, proteinuria marker	No specific kidney condition (acute kidney injury, nephrotic syndrome, diabetes and rheumatological conditions)	PCOS patients exhibited significantly elevated UACR levels compared to control subjects (*P*<0.05). Conversely, no statistically significant differences were observed in SCr or BUN levels between the two groups
Behboudi-Gandevani *et al*., 2020, Iran[25]	Population-based cohort study (follow-up period 12.9 (10.8–14.0) years)	156	1304	26.4 (8.5)*	28.7 (8.6)*	US NIH criteria	CKD (based on kidney disease outcome quality initiative guidelines)	All baseline characteristics were mostly not statistically significant, and adjustment was made for potential confounders: smoking status, BMI, hypertension and diabetes	Amongst 1460 women who free from CKD at baseline, no significant difference in CKD incidence between those with PCOS and healthy controls over 15 years. The adjusted hazard ratio for CKD in PCOS patients was 0.886 (95% CI: 0.633–1.328), indicating no increased risk compared to healthy women, and that PCOS does not pose an independent risk factor for CKD development
Can *et al*., 2020, Turkey[7]	Cross-sectional	56	48	24.00 (18–36)*	25.20 (18–36)*	Rotterdam ESHRE/ASRM 2003	Blood creatinine and eGFR	Age, BMI	No significant difference in kidney function (eGFR and other parameters) between PCOS and healthy control groups even within different BMI categories (obese/non-obese), suggesting that PCOS may not independently affect kidney function regardless of weight

Contd...

Table 1: Contd..

Author, year, country	Types of study	Study participants				Diagnosis criteria of PCOS	Kidney function assessment	Population matching	Hormones and kidney function outcomes
		n		Age (year, mean±SD)					
		PCOS	Non-PCOS	PCOS	Non-PCOS				
Pelluri *et al*., 2021, India[21]	Cross-sectional	80 (40 androgenic and 40 non-androgenic)	N/A	27.28±6.78	26.37±5.56	Rotterdam ESHRE/ASRM 2003	SUA	Age, BMI, history of chronic diseases, use of hypoglycaemic or hormonal drugs	Androgenic PCOS patients displayed elevated mean SUA levels and a significant association with hyperuricaemia (P<0.05), suggesting its potential role as an oxidative stress marker in this subgroup
Zhang *et al*., 2021, China[20]	Cross-sectional	199	N/A	BMI <25 kg/m^2=27.06±3.96 25≤ BMI <30 kg/m^2=28.25±5.22 BMI ≥30 kg/m^2=28.38±5.13	N/A	Rotterdam ESHRE/ASRM 2003	SUA	BMI-matched while calculating hyperuricaemia vs. hyperuricaemia	In PCOS patients, hyperuricaemia prevalence reached 28.64% and coincided with significantly higher weight and BMI compared to those without hyperuricaemia. SUA showed a strong positive correlation (r>0.4, P<0.001) with various adiposity measures, including total body fat percentage, arm, leg and trunk fat mass, waist-to-hip ratio and visceral adipose tissue mass
El-Eshmawy *et al*., 2022, Egypt[13]	Case-control	40**	40**	28.68±5.65**	26.98±6.67**	Rotterdam ESHRE/ASRM 2003	SUA, creatinine and UACR ratio	Age, BMI	Obese women with PCOS exhibited significantly elevated UA/Cr ratio compared to controls (4.38±0.69 vs. 3.94±0.88, P<0.001). Even after adjusting for confounding factors, UA/Cr ratio remained independent risk factors for PCOS in this population, with OR: 1.62 (1.13–4.58)

*Data presented as median (IQR), **All study subjects are obese. IQR=Interquartile range, NIH=National Institutes of Health, UACR=Urinary albumin to creatinine ratio, UA=Uric acid, WHR=Waist-to-hip ratio, FAI=Free androgen index, LH=Luteinising hormone, CI=Confidence interval, Scr=Serum creatinine, BUN=Blood urea nitrogen, CKD=Chronic kidney disease, SUA=Serum UA, N/A=Not available, GFR=Glomerular filtration rate, PCOS=Polycystic ovarian syndrome, SD=Standard deviation, BMI=Body mass index, eGFR=Estimated GFR, FSH=Follicle-stimulating hormone, OR=Odds ratio, SHBG=Sex hormone binding globulin , MDRD=Modification of diet in renal disease, ESHRE=European society of human reproduction and embryology, ASRM=American society for reproductive medicine

androgenic and non-androgenic groups. The remaining studies did not match for BMI.

Quality assessment

The Newcastle–Ottawa Scale was used for quality assessment towards case–control, cross-sectional and cohort studies, as shown in Supplementary Table 1a-c. Based on the results, studies obtained were categorised into several groups, including 4 very good quality, 6 good quality, 2 satisfactory and 1 poor study due to the absence of comparability.

Systematic review and meta-analysis results

Outcome for estimated glomerular filtration rate

The meta-analysis results based on four studies[7,8,11,23] showed that PCOS was not significantly associated with changes in eGFR compared to non-PCOS (mean difference [MD]: 3.54; 95% CI [−4.53–11.61]; P = 0.39, as presented in Table 2 and Figure 2a. A total of two studies[7,11] had higher eGFR in PCOS groups, while others[7,23] were greater in non-PCOS groups. Furthermore, two studies[7,11] reported a significant P value (0.001 and < 0.001, respectively) and others[6,23] reported non-significant P value (0.152 and 0.604, respectively). Behboudi *et al*.[25] did not find an increased risk of chronic kidney disease (CKD) in PCOS women (hazards ratio 0.911; 95% CI [0.600–1.383]; P 0.661) and did not present the eGFR values, both in PCOS and control groups. Regarding eGFR assessment, three studies used the MDRD formula to calculate eGFR[7,8,23] and only Mu *et al*. applied the CKD-EPI formula to calculate eGFR.[11]

The significant heterogeneity (I^2 = 89%) led to the implementation of a random effect model for the quantitative analysis. The funnel plot was symmetrical [Supplementary Figure 1a], suggesting there was no evidence of publication bias.

Outcome for creatinine

A total of four studies[5,7,8,13] were computed in the meta-analysis for creatinine levels. All studies reported statistically similar creatinine levels between PCOS and non-PCOS groups, with the P value ranging from 0.09 to 0.587. As shown in Table 2 and Figure 2b, no significant difference was discovered between creatinine levels in PCOS patients and healthy controls, based on meta-analysis results (MD: 0.08; 95% CI [−0.05, 0.21]; P = 0.22). The results of the I^2 test showed a significant heterogeneity (I^2 =96%), leading to the implementation of a random effect model for the analysis. The funnel plot presented in Supplementary Figure 1b was symmetrical, proposing no proof of bias in the publication.

Outcome for uric acid

A total of six studies[8,11,13,18,19,24] were included in the meta-analysis for uric acid, as shown in Table 2. Based on the results, four studies[8,11,13,22] showed that the PCOS

Table 2. Results of individual studies for eGFR, Creatinine, and Uric Acid (UA)

Results of Studies Included in the Meta-Analysis for eGFR				
Serial number	**Author, Year**	**eGFR (mL/min/1/. 73m², mean±SD)**		
		PCOS	**Non-PCOS**	***P****
1	Lakhani *et al*., 2011[23]	102.20±15.30	114.40±27.90	0.152
2	Gozukara *et al*., 2015[8]	135.20±25.60	114.90±24.10	0.001
3	Mu *et al*., 2018[11]	126.85±6.61	125.24±7.04	< 0.001
4	Can *et al*., 2020[7]	100.54±13.18	101.79±12.45	0.604
Results of Studies Included in the Meta-Analysis for Creatinine				
Serial number	**Author, Year**	**Creatinine (mg/dL, mean±SD)**		
		PCOS	**Non-PCOS**	***P****
1	Gozukara *et al*., 2015[8]	0.83±0.10	0.60±0.12	0.09
2	Song *et al*., 2019[5]	0.62±0.10	0.61±0.09	0.587
3	Can *et al*., 2020[7]	0.80±0.30	0.77±0.24	0.298
4	El-Eshmawy *et al*., 2022[13]	0.90±0.13	0.85±0.16	0.197
Results of Studies Included in the Meta-Analysis for UA				
Serial number	**Author, Year**	**UA (mg/dL, mean±SD)**		
		PCOS	**Non-PCOS**	***P****
1	Anttila *et al*., 1996[18]	4.54±0.87	4.22±0.79	NS
2	Yarali *et al*., 2001[22]	4.50±1.30	3.80±0.80	0.04
3	Luque-Ramirez *et al*., 2008[19]	4.30±1.09	4.10±1.09	0.35
4	Gozukara *et al*., 2015[8]	4.36±1.30	3.20±0.70	0.002
5	Mu *et al*., 2018[11]	5.19±1.20	4.54±0.89	< 0.001
6	El-Eshmawy *et al*., 2022[13]	5.78±0.92	4.86±0.75	< 0.001

*P<0.05 are assumed to be statistically significant

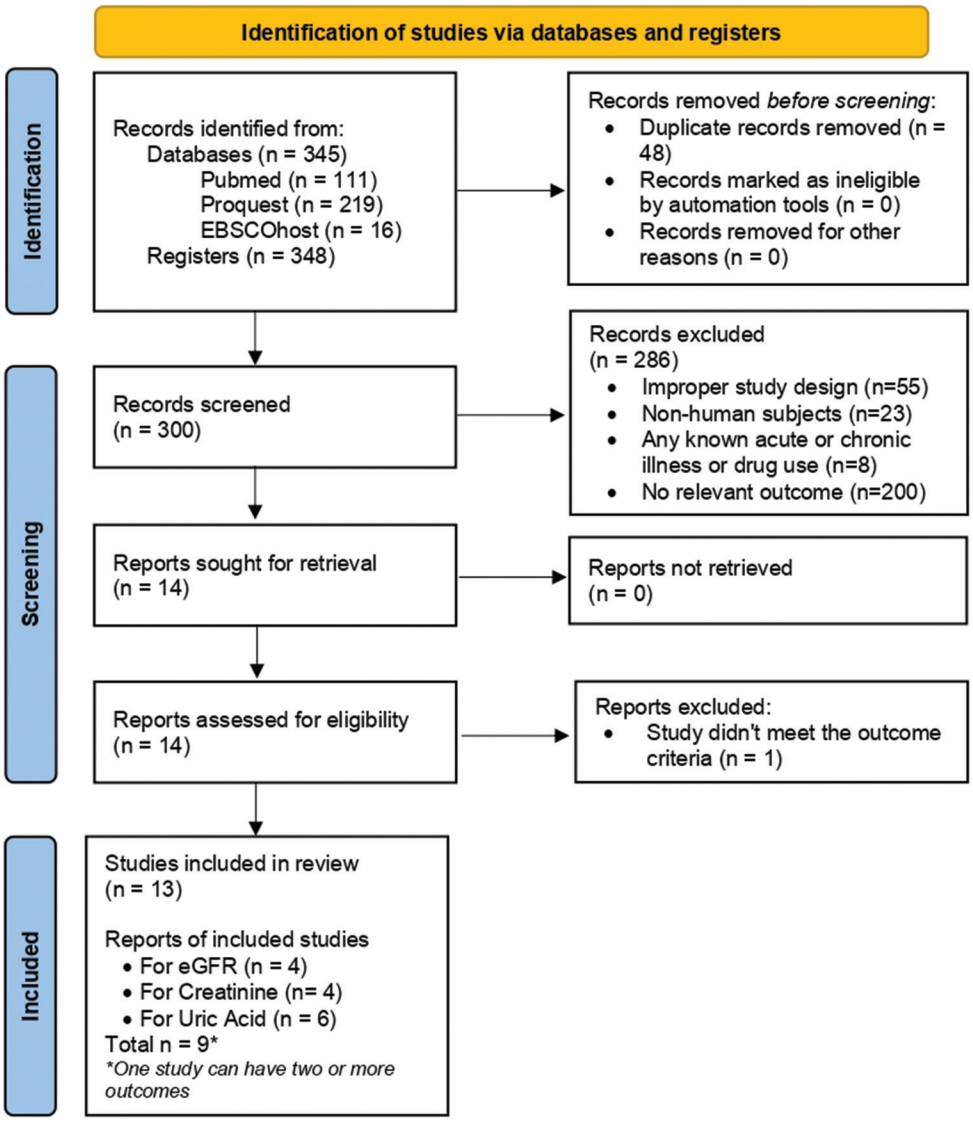

Figure 1: Flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses on included studies

group possessed significantly higher levels of SUA, with the *P* value ranging from < 0.001 to 0.04. The remaining two studies[18,19] showed no statistically significant differences in uric acid levels, but a higher value was obtained in the PCOS compared to the non-PCOS group.

There were three studies that could not be quantified in the meta-analysis. These included Zhang *et al*.,[20] which investigated the relationship between SUA levels as well as the distribution of body fat in PCOS patients. Consequently, the data presented solely consisted of SUA from PCOS patients (stratified by BMI) and no control group. According to SUA data, a high degree of visceral adipose tissue mass will significantly raise the hyperuricaemia risk in the patients ($P < 0.001$). Perulli *et al*.[21] only focussed on obese PCOS patients, who were further divided into androgenic and non-androgenic groups. The results showed higher levels of SUA in the PCOS group of androgenic ($P < 0.05$). The third study by Leustean *et al*.[24] reported that uric acid median values were 4.6 mg/dL in PCOS compared to 4.55 mg/dL in the non-PCOS group.

The pooled analysis shown in Figure 2c indicated that PCOS was significantly related to increased uric acid than the healthy controls (MD: 0.70; 95% CI [0.45–0.95]; $P < 0.00001$). The results of the I^2 test showed a significant heterogeneity ($I^2 = 75\%$), leading to the implementation of a random effect model for the quantitative analysis. The funnel plot was symmetrical [Supplementary Figure 1c], indicating no proof of bias in the publication.

Discussion

Resistance to insulin, dyslipidaemia, impaired glucose tolerance, obesity and hypertension, commonly known as metabolic disorders, are all associated with PCOS.[26]

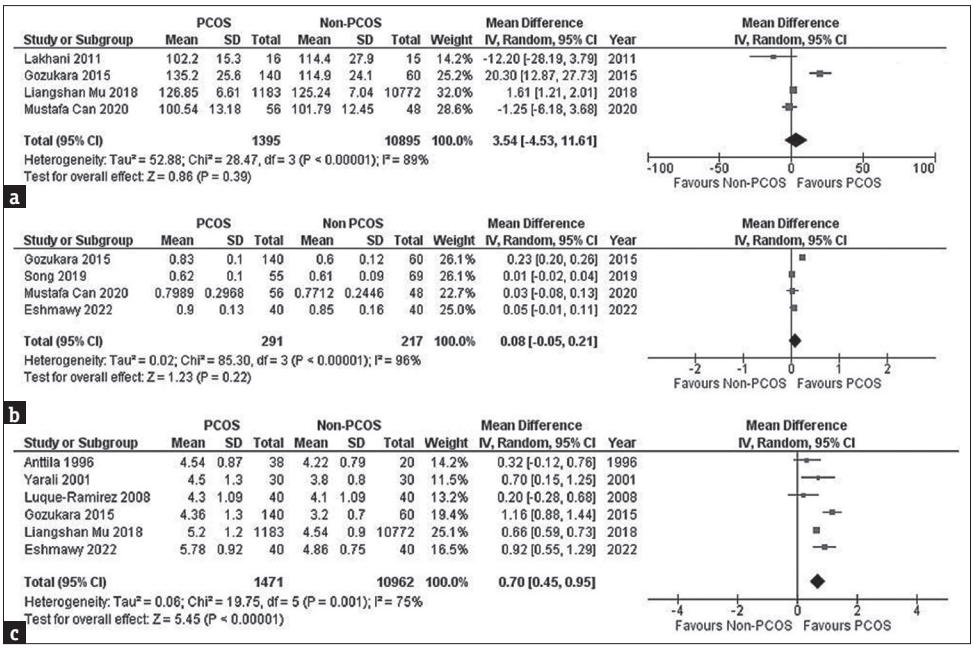

Figure 2: Meta-analysis results (forest plot) for: (a) Estimated glomerular filtration rate, (b) Creatinine, (c) Uric acid as a marker of kidney injury in polycystic ovarian syndrome patients

These conditions have the potential to cause alterations in kidney function, characterised by the presence of protein in the urine and changes in some kidney function parameters.[27] The changes in serum creatinine, eGFR and/or blood urea nitrogen from peripheral blood can be used to depict the reduction of kidney function.[28]

Obesity is considered a key factor in the development of renal disease in PCOS women.[29] Moreover, the level of creatinine is positively related to the majority of obesity-metabolic conditions of PCOS.[30-35] The results suggest that PCOS is related to the incidence of kidney injury as measured by the creatinine values.[36] However, this review showed no statistically significant association between PCOS and levels of creatinine. Data from four studies[5,7,8,13] showed that the PCOS group has statistically similar creatinine levels compared to the control group. Du *et al*. discovered a causal relationship between PCOS and creatinine, but the correlation status (direct or indirect) had not been established.[6] Furthermore, the sample was also obtained from European ancestry, thus limiting the generalisation of results to other races or ethnicities.[6]

Predominantly, the meta-analysis results found no significant difference in eGFR values between PCOS as well as non-PCOS groups. However, individual studies from Gozukara *et al*.[8] and Mu *et al*.[11] showed a statistically significant *P* value of 0.001 and < 0.001, respectively. This insignificance may be attributed to the limited number of studies and high heterogeneity.

The cumulative results of eGFR values in this review were within the normal limits or tended to be increased. Based on the current literature, the increasing trend of eGFR is commonly found in obese and diabetic patients,[37] a phenomenon called glomerular hyperfiltration.[38] Tonneijck *et al*. reported that hyperfiltration occurred in 6%–73% of T2DM patients.[39] A study of rat-induced PCOS models by Yanes *et al*. also showed an increase in eGFR due to metabolic disturbances occurring in PCOS.[40] The underlying mechanism of hyperfiltration related to diabetes and obesity in PCOS is complex and incorporates different mechanisms. Several vascular and tubular factors, including nitric oxide bioavailability, COX-2 prostanoids, atrial natriuretic peptide and angiotensin, caused a reduction in afferent arteriole resistance, with the uplift of efferent arteriole resistance (angiotensin-II, thromboxane A2 and endothelin-1).[41] This phenomenon led to the escalation of eGFR.[39] Growth hormone, with insulin-like growth factor-1, contributes to a hyperfiltration state by increasing the total renal blood flow.[39] Furthermore, the presence of tubular hypertrophy, proximal tubular reabsorption, increased abdominal pressure, as well as intrarenal fat accumulation by obesity compress the loop of Henle.[42] The intratubular pressure in Bowman's space will decline, thereby inducing the hyperfiltration state by promoting the net hydraulic pressure gradient.[43] Obesity also promotes intrarenal fat accumulation which gradually increases the kidney size, resulting in nephromegaly.[44] These conditions could lead to higher glomerular filtration surface area, thereby enhancing the filtration rate of the glomerulus, which might cause a hyperfiltration state.[39]

This meta-analysis demonstrated that PCOS was significantly related to the increment of uric acid levels compared to healthy controls. The results were in line with previous studies, where the PCOS group had significantly higher levels of uric acid.[25]

Women with PCOS have imbalanced levels of hormones, particularly reproductive hormones such as androgen, oestrogen and luteinising/follicle-stimulating hormone (LH/FSH) ratio.[45] Oyebanji *et al*.[46] showed that PCOS women have higher levels of total testosterone, oestrogen and the LH/FSH ratio compared to non-PCOS. These hormones are expected to play a role in uric acid regulation, but the mechanism remains unclear. Mu *et al*.[11] indicated that the level of testosterone was positively correlated to SUA level and also the hyperuricaemia prevalence in PCOS women. According to Pelluri *et al*.,[21] there were higher SUA levels in the androgenic PCOS group, resulting in a significant correlation with hyperuricaemia.

A study in the murine model also discovered that hyperandrogenaemia increased SUA by stimulating the hepatic metabolism of purine nucleotides, as well as improving purine renewal in the kidney.[47,48] However, Leustean *et al*.[24] showed that SUA levels were not elevated in PCOS patients compared to normal control, corresponded for age and BMI.

Obesity is thought to be the primary determinant of uric acid in PCOS women.[13,49] The potential mechanisms of increased levels of SUA in obesity might be explained by the overproduction of uric acid and low urinary urate excretion.[50,51] Furthermore, visceral fat accumulation increases the influx of plasma-free fatty acids into the hepatic portal vein. This condition can promote triglyceride synthesis, accompanied by an increase in uric acid production through the activated uric acid synthesis pathway.[52]

This meta-analysis summarises findings into the impact of PCOS on kidney function parameters. By encompassing three distinct observational study designs (cross-sectional, case–control and cohort), the analysis offers a comprehensive assessment of various outcome parameters, providing unprecedented insight into crucial aspects of PCOS evaluation and stratification.

However, the limitation of this review was the inability to perform a subgroup analysis based on the BMI group, since limited studies divided the populations according to their group. Furthermore, not all kidney function parameters were calculated in the meta-analysis, as urea and albumin were only reported by few studies, making it insufficient for a quantitative synthesis.

As there is a significant difference in uric acid levels between PCOS and non-PCOS subjects, consequently, a larger cohort with a broader research field should be carried out to obtain more extrapolated results and determine the presence of kidney dysfunction in a long-term duration of follow-up. This recommendation supported the results obtained, particularly regarding uric acid as an independent risk factor for kidney damage. Furthermore, clinicians are recommended to routinely assess the uric acid in PCOS patients, which serves as a simple tool for risk stratification.

Conclusion

Our review showed that a higher level of uric acid was significantly observed in women with PCOS. However, the results did not show differences in other kidney function parameters, specifically eGFR and creatinine levels.

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Authors' contribution

All authors conceived and designed the analysis. NDW, AFI and FGS drafted the protocol, which was then read and approved by all authors. AFI, FGS, RS and LL performed the database searches and extracted the data, which underwent verification by NDW. All authors contributed data or analysis tools, followed by meta-analysis conducted by NDW and FGS. All authors drafted the manuscript, which was reviewed and approved by all authors for the final version.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data that support the findings of this study are available within the article (and/or its Supplementary Material).

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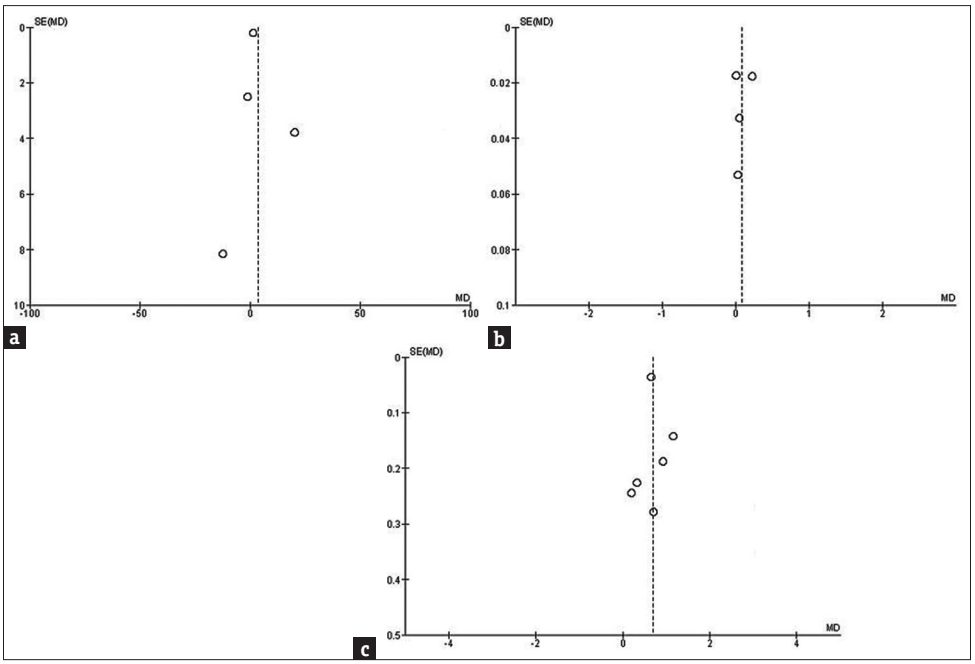

Supplementary Figure 1: Publication bias as funnel plot diagram for: (a) Estimated glomerular filtration rate, (b) creatinine and (c) uric acid as a marker of kidney injury in polycystic ovarian syndrome patients

Supplementary Table 1a: Bias Assessment Risk for Cohort Studies

Author, year	Selection				Comparability-C1	Outcome			Conclusion
	S1	S2	S3	S4		O1	O2	O3	
Behboudi-Gandevani *et al*., 2020[25]	☆	☆	☆	☆	☆☆	☆	☆	☆	Good quality study

☆=Score, S1=The exposed cohort representativeness, S2=The non-exposed cohort selection, S3=Exposure ascertainment, S4=Demonstration that the outcome of interest was absent at the study's outset, C1=Comparability, O1=The outcome assessment, O2=The duration of follow-up, and O3=Sufficiency of the cohort follow-up

Supplementary Table 1b: Bias Assessment Risk for Case-Control Studies

Author, year	Selection				Comparability -C1	Exposure			Conclusion
	S1	S2	S3	S4		E1	E2	E3	
El-Eshmawy *et al*., 2022[13]	☆	☆	☆	☆	☆☆	☆	☆	☆	Good quality study
Yarali *et al*., 2001[22]	☆	☆	☆	☆	-	☆	☆	☆	Poor quality study

☆=Score, S1=Is the case definition adequate, S2=The case representativeness, S3=The control selection, S4=The control definition, C1=Comparability, E1=The exposure ascertainment, E2=Similar ascertainment method for cases as well as controls, and E3=Non-response rate

Supplementary Table 1c: Bias Assessment Risk for Cross-Sectional Studies

Author, year	Selection				Comparability -C1	Outcome		Conclusion
	S1	S2	S3	S4		O1	O2	
Mu *et al*., 2018[11]	☆	☆	☆	☆☆	☆☆	☆☆	☆	Very good quality study
Gozukara *et al*., 2015[8]	☆	☆	☆	☆☆	-	☆☆	☆	Good quality study
Can *et al*., 2020[7]	-	-	☆	☆☆	☆☆	☆☆	☆	Good quality study
Zhang *et al*., 2022[20]	☆	-	☆	☆☆	☆☆	☆☆	☆	Very good quality study
Anttila *et al*., 1996[18]	☆	-	☆	☆☆	☆	☆☆	☆	Good quality study
Leuștean *et al*., 2015[24]	-	-	☆	☆☆	☆☆	☆☆	☆	Good quality study
Pelluri *et al*., 2021[21]	-	-	☆	☆☆	-	☆☆	☆	Satisfactory quality study
Song *et al*., 2019[5]	-	-	☆	☆☆	-	☆☆	☆	Satisfactory quality study
Luque-Ramirez *et al*., 2008[19]	☆	-	☆	☆☆	☆☆	☆☆	☆	Very good quality study
Lakhani *et al*., 2011[23]	☆	-	☆	☆☆	☆☆	☆☆	☆	Very good quality study

Bias assessment risk for cross-sectional studies; ☆=Score S1=The sample representativeness, S2=The size of samples, S3=Non-respondents, S4=The exposure ascertainment, C1=Comparability, O1=The outcome assessment, and O2=Statistical test