Circadian rhythm disruption and polycystic ovary syndrome: a systematic review and meta-analysis

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OBJECTIVE: The aim of our systematic review and meta-analysis was to determine if circadian rhythm disruption (CRD) is associated with polycystic ovary syndrome (PCOS). Our objective was to pool the overall mean differences in biomarkers of CRD (including melatonin levels, morning and evening cortisol levels, and sleep efficiency) between PCOS patients and controls. We hypothesized that CRD will be more prominent in patients with PCOS.

DATA SOURCES: A systematic search of PubMed, Scopus, Embase, ClinicalTrials.Gov, and the Cochrane Database of Systematic Reviews was conducted from inception until 2024 using the following MeSH terms "circadian rhythm" OR "sleep disturbance" OR "melatonin" AND "polycystic ovary syndrome." Citation search supplemented the systematic database search.

STUDY ELIGIBILITY CRITERIA: Inclusion criteria were women with PCOS, original case-control, cross-sectional, and cohort studies that identify parameters of CRD (melatonin, cortisol, and sleep disturbance). Exclusion criteria were women with endocrine and metabolic co-morbidities, menopausal women, case reports, review studies, animal studies, abstracts, and conference presentations. There was no time restriction for year of publication.

STUDY APPRAISAL AND SYNTHESIS METHODS: Two investigators (T.H. and P.R.) assessed the quality of the studies included using the Newcastle-Ottawa Scale. Forest plots were created using the Open Meta Analyst software. Publication bias was assessed in Egger's and Begg's tests.

RESULTS: A total of 16 studies were included in the systematic review and 12 studies were included in the meta-analysis (N=1,100 women [531 PCOS patients and 569 controls]). Pooled analysis showed that the mean difference in melatonin levels between PCOS patients and controls was 14.294 pg/mL, 95% CI [6.895, 21.693]. The overall mean difference in morning and evening cortisol between PCOS patients and controls was 1.103 pg/mL, 95% CI [−1.058, 3.265], and 3.574 pg/mL, 95% CI [1.741, 5.407], respectively. Pooled difference in mean sleep efficiency scores between PCOS patients and controls was −4.059, 95% CI [−6.752, −1.366]. Risk of bias assessment showed that NOS scores ranged from 7 to 9.

CONCLUSIONS: Our meta-analysis provides evidence that circadian rhythm disruption is positively associated with polycystic ovary syndrome. This is substantiated by differences in parameters indicative of circadian rhythm disruption, including melatonin levels, evening cortisol, and sleep efficiency.

Key words: polycystic ovary syndrome, circadian rhythm disruption, melatonin, cortisol, sleep quality

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 6.6% to 19.4% of women of reproductive age, impacting both hormonal and metabolic health.[1] PCOS is primarily characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries.[2] These metabolic disturbances contribute to clinical manifestations such as hirsutism, obesity, hypertension, type 2 diabetes mellitus, and amenorrhea.[3] It is widely acknowledged that ovulatory dysfunction is the leading cause of female infertility, with PCOS accounting for 90% to 95% of women seeking infertility treatment.[4]

Despite its long-standing recognition as a prevalent cause of infertility and metabolic complications, the precise pathophysiology of PCOS remains poorly understood. Various hypotheses have been proposed to explain the etiology of PCOS, with a growing body of evidence suggesting that circadian rhythm disruption (CRD) plays a key role.[5] Given the complex interactions between the hypothalamus—the body's central circadian pacemaker—and the endocrine system, CRD may influence both reproductive and metabolic processes in women with PCOS.[6] Disruptions in circadian rhythms have been implicated in both serum and ovarian follicle abnormalities in women with PCOS.[7]

While the role of melatonin in female reproduction is not yet fully elucidated, emerging data suggest a significant association between melatonin, ovarian function, and reproductive hormones.[8] A disrupted night-to-day melatonin

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The authors report no conflict of interest.

Tweetable statement: The role of melatonin and cortisol in circadian rhythm disruption in women with polycystic ovary syndrome.

Prospero: The study protocol was registered in the PROSPERO database (University of York, United Kingdom) [CRD42024507793] on February 29th, 2024. https://www.crd.york.ac.uk/prospero/.

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Why was this study conducted?

This systematic review and meta-analysis was conducted to elucidate the relationship between melatonin and cortisol on reproduction and circadian rhythm in women with and without PCOS to elucidate potential therapeutic targets that can prove promising in reducing the multifarious symptoms of PCOS.

Key findings

Women with PCOS experienced more circadian rhythm disruption as measured by melatonin and evening cortisol levels.

What does this study add to what is already known?

The pooled data that measures melatonin and cortisol, biomarkers for circadian rhythm, have never been assessed in the context of circadian rhythm disruption and sleep disturbance in women with PCOS compared to healthy women on a scale as large as this one. This provides potential targets for therapy and lays a foundation for further exploration into circadian rhythm and PCOS.

ratio, marked by increased daytime melatonin secretion, may contribute to anovulation, further supporting the role of CRD in the pathogenesis of PCOS.[9] However, the relationship between CRD and PCOS pathophysiology remains underexplored, with conflicting evidence regarding its precise impact.

Objective

The primary objective of our systematic review and meta-analysis was to evaluate whether CRD—measured through melatonin, cortisol levels, and sleep efficiency—is associated with PCOS. We hypothesized that CRD poses an increased risk of developing PCOS.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and protocols (PRISMA-P) statement.[10] The study protocol was registered in the PROSPERO database (University of York, United Kingdom) [CRD42024507793].

Review question according to PECO (population, exposure, control, outcome)

Our study question following the PECO format was: "In women of reproductive age (population), is CRD (exposure) more common in women with PCOS (outcome) than in women without PCOS (control)?"

Eligibility criteria, information sources, search strategy

A systematic search of PubMed, Scopus, Embase, ClinicalTrials.Gov and the Cochrane Database of Systematic Reviews was conducted using the following search strategy ("circadian rhythm" OR "sleep disturbance" OR "melatonin") AND ("polycystic ovary syndrome.") This was supplemented by citation search from the referenced literature. Citation files from the different databases were imported into Zotero reference management software and duplicates were removed. The titles and abstracts were independently screened for eligibility by two investigators (T.H. and P.R.), followed by full-text screening of studies that met criteria. Inclusion criteria were original case-control, cross-sectional, and cohort studies on women with PCOS. Patients with PCOS had to be diagnosed by the Rotterdam Criteria or the National Institute of Health (NIH) Criteria.[11] The parameters used to assess CRD were melatonin, cortisol, and sleep disturbance. Exclusion criteria were postmenopausal women, patients with endocrine and metabolic co-morbidities, case reports, review studies, animal studies, abstracts, and conference presentations. The search was not restricted to any language or year of publication.

Data extraction and assessment of bias

Data was extracted and inserted into an Excel file using the following headings: study, site, study design, sample size, PCOS criteria, parameters for CRD (including mean and standard deviation of melatonin and cortisol measurements or sleep efficiency score). Two investigators (T.H. and P.R.) assessed the quality of all studies using the Newcastle-Ottawa Scale (NOS).[12] The overall scores were recorded. Any discrepancy in scores was resolved through discussion. The NOS is a quality-assessment tool for nonrandomized studies in meta-analyses and systematic reviews based on study group selection, comparability, and determination of exposure and outcome.

Data synthesis and analysis

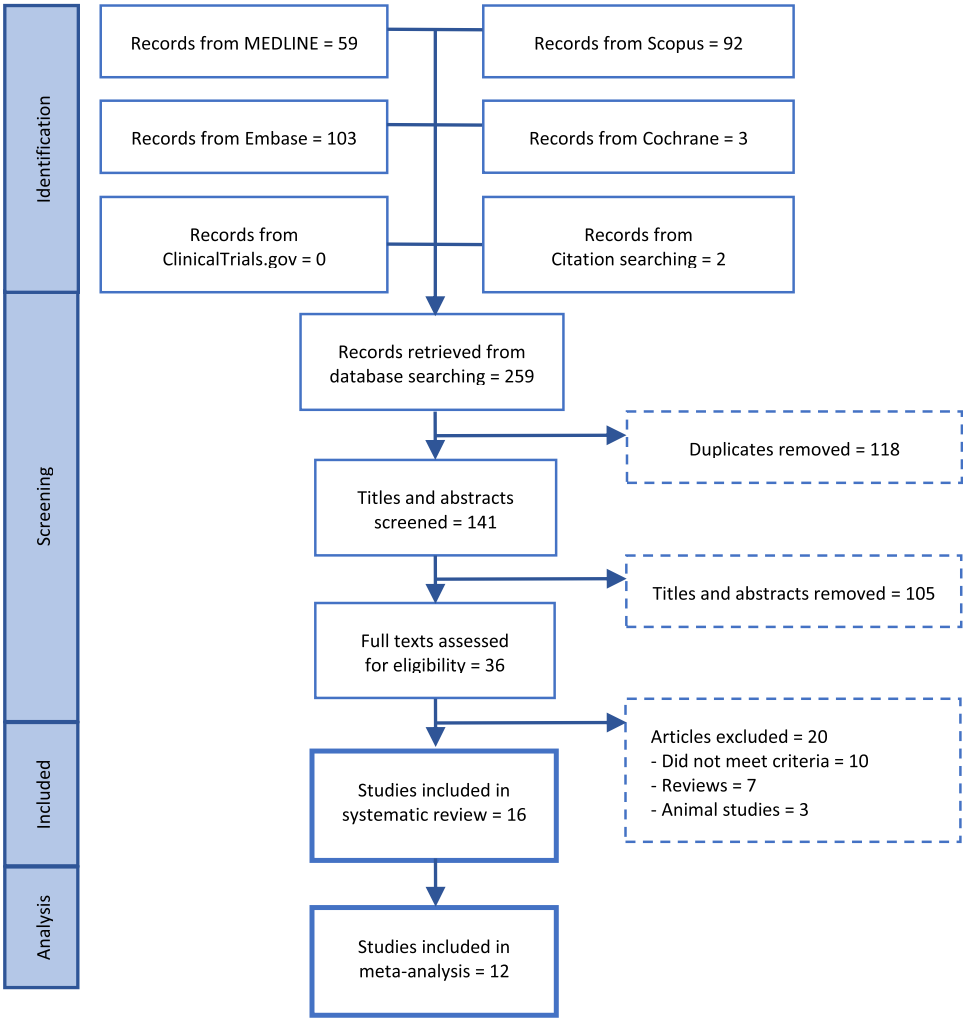
We used the Open Meta analyst software to perform pooled analyses and to create forest plots. The random-effects model was used to account for the heterogeneity in patient population due to differing ages, PCOS subtypes, and PCOS diagnostic criteria, to provide a conservative estimate of the overall mean differences. The extent of heterogeneity was assessed using the I^2 statistic. The calculation of I^2 is based on the Cochran's Q statistic, which tests whether the observed variance in study results is greater than what would be expected by chance. Value of $I^2 \geq 50$ indicate that there is a high level of variability, and that the studies may not be estimating a common effect. A P value of $<.05$ for all analyses was considered statistically significant. Publication bias was assessed through funnel plots and Egger's and Begg's tests.

Results

Study selection

Our database search yielded 257 articles. After removing duplicates, 139 titles and abstracts were screened. Thirty-six articles met eligibility for full-text review, of which 16 articles were included in the systematic review. Of these, 12 articles had sufficient data to be included in the meta-analysis. Study selection is shown in the PRISMA flow chart in Figure 1.

FIGURE 1
Flow diagram of included studies CRD and PCOS



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Study characteristics

For the 12 studies[9,13–29] included in the meta-analysis, there was a total of 1,100 patients, with 531 PCOS patients and 569 controls. The characteristics of the included studies are summarized in Table 1. The studies were conducted in 11 countries between 1996 and 2024. They had the following study designs: 8 experimental; 7 case-control; and 3 cross-sectional. Most studies (56%) used the Rotterdam criteria to diagnose PCOS, while the NIH criteria along with specific ultrasound and androgen testing were also used. CRD was assessed by measuring melatonin levels in 11 studies, whereas the remaining 7 studies assessed CRD by measuring either cortisol, sleep efficiency, or melatonin gene polymorphism.

Table 2 shows the measurements (mean and standard deviation) of the parameters indicative of CRD, including melatonin, evening cortisol, morning cortisol, and sleep efficiency. The mean melatonin and evening cortisol were higher for PCOS patients compared to controls in all studies, whereas the sleep efficiency scores were lower for PCOS patients compared to controls in all studies.

Meta-analyses

Melatonin

Six studies had data on melatonin levels, with 348 PCOS patients and 428 controls. Pooled analysis showed that PCOS patients had a mean melatonin level of 14.294 pg/mL higher than controls, with 95% CI [6.895, 21.693], $P<.001$. There was a large heterogeneity, with $I^2=97.78\%$, The forest plot is shown in Figure 2.

Evening cortisol

Three studies compared evening cortisol levels between 86 PCOS patients and 96 controls. Pooled analysis showed that PCOS patients had an overall mean of 3.574 pg/mL higher than controls, with 95% CI [1.741, 5.407], $P<.001$, $I^2=96.26\%$. This is strongly indicative of CRD in PCOS patients compared to controls. Results

TABLE 1
Characteristics of included studies in the systematic review and meta-analysis

Study	Country	Study Design	Criteria for PCOS	Criteria for CRD	NOS Score (max 9)
Tarquini et al[13]	Italy	Experimental	Diagnostic Criteria[a]	Circulating melatonin	6
Invitti et al[14]	Italy	Case-control	Ultrasound + Other	Circadian rhythmicity of cortisol release	8
Luboshitzky et al[15]	Israel	Experimental	3+ criteria	Melatonin production	9
Luboshitzky et al[16]	Israel	Experimental	3+ criteria	Urinary melatonin	9
Li et al[17]	China	Experimental	Rotterdam	Melatonin receptor gene polymorphisms	8
Shreeve et al[18]	UK	Case-control	Rotterdam	Urinary melatonin	8
Jain et al[19]	India	Case-control	Rotterdam	Serum melatonin	7
Terzieva et al[20]	Bulgaria	Case-control	Rotterdam	Melatonin, and melatonin: cortisol	8
Kialka et al[21]	Poland	Case-control	Not stated	Evening plasma cortisol	6
Suri et al[22]	India	Cross-sectional	Rotterdam	Sleep efficiency using ESS	8
Lim et al[23]	Singapore	Cross-sectional	Rotterdam	Melatonin and cortisol	8
Simon et al[24]	USA	Cross-sectional	NIH Criteria	Duration of melatonin secretion	9
Sun et al[25]	China	Experimental	Rotterdam	Circadian clock gene expression	7
Li et al[26]	China	Experimental	Rotterdam	Intrafollicular melatonin	9
Evans et al[9]	USA	Case-control	Rotterdam	Melatonin and sleep disturbance	7
Edan et al[27]	Iraq	Case-control	Rotterdam	Serum melatonin	7

[a] Reported diagnostic criteria not stated. *ESS*, epworth sleepiness scale; *NIH*, national institute of health.

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of the forest plot are illustrated in Figure 3.

Morning cortisol

Pooled analysis was done for 3 studies on morning cortisol, comparing 79 PCOS patients and 88 controls. The overall mean morning cortisol levels was similar for PCOS patients and controls, with a mean difference of 1.103 pg/mL, 95% CI [−1.058, 3.265], P=.317, I^2=93.57%. The forest plot is shown in Figure 4.

Sleep efficiency

Data from 5 studies was pooled to compare sleep efficiency. After comparing 163 PCOS patients and 104 controls, pooled analysis revealed a statistically significant mean difference in sleep efficiency scores. PCOS patients had a lower overall mean score of −4.059 than controls, 95% CI [−6.752, −1.366], P=.003, I^2=68.72%. The forest plot is shown in Figure 5.

Risk of bias assessment and publication bias

The NOS scores for all studies ranged from 6 to 9, with the majority of studies having a high-quality score. The funnel plot for publication bias is shown in Figure 6.

Comment

Principal findings

Our systematic review and meta-analysis provides evidence for the association of circadian rhythm disruption (CRD) in women with Polycystic Ovary Syndrome (PCOS). Our analysis indicates that women with PCOS exhibit higher serum melatonin and evening cortisol levels, along with reduced sleep efficiency, compared to women without PCOS. However, no significant difference was observed in morning cortisol levels. Thus, three out of the four parameters related to CRD that we examined showed significant differences between PCOS patients and the control group.

Comparison with existing literature

PCOS has long been recognized as a significant cause of infertility, insulin resistance, and a risk factor for diabetes and cardiovascular disease.[30] Despite eight decades of research, the exact mechanisms underlying PCOS remain unclear. Numerous studies have explored the risk factors and endocrine and metabolic disturbances associated with this condition.[31] Although variations in diagnosis contribute to the heterogeneity of PCOS, it is commonly diagnosed based on the Rotterdam criteria, which include hyperandrogenism, oligo/anovulation, and polycystic ovaries.[11]

One theory that attempts to explain the complex interplay between the hypothalamus, the endocrine system, and the reproductive system in PCOS involves the disruption of circadian rhythm.[32] A key hormone in regulating circadian rhythm, melatonin, is increasingly recognized for its role in female reproduction.[33] While the precise effect of melatonin on reproductive function is not fully established, growing

TABLE 2
Measurement differences between PCOS patients and controls

Study	Sample size	PCOS sample	PCOS mean	PCOS SD	Control sample	Control Mean	Control SD
Melatonin							
Tarquini et al[13]	11	4	52.8	6.49	7	30.7	4.49
Shreeve et al[18]	52	26	60.3	30.6	26	37.7	21.5
Jain et al[19]	100	50	63.27	10.97	50	32.51	7.55
Lim et al[23]	321	109	44.4	26	212	37.5	26.1
Simon et al[24]	92	59	9.06	1.2	33	4.89	1.3
Edan et al[27]	200	100	28.91	7.96	100	25.24	5.09
Morning cortisol							
Invitti et al[14]	17	9	5.7	0.9	8	3.2	0.3
Terzieva et al[20]	55	30	17.4	1	25	17.4	1.3
Kialka et al[21]	95	40	14.6	9.8	55	14.2	10
Evening cortisol							
Invitti et al[14]	15	7	3.7	0.8	8	1.5	0.2
Terzieva et al[20]	55	30	6	1.3	25	4.1	0.58
Kialka et al[21]	95	40	11.8	4.1	55	4.7	1.3
Sleep efficiency							
Shreeve et al[18]	33	15	82.8	4.7	18	85.6	4.3
Suri et al[22]	66	50	84.6	12.9	16	87.8	7.5
Simon et al[24]	92	59	81.3	7.1	33	84.1	5.3
Li et al[26]	41	17	86.3	3	24	94.5	5
Evans et al[9]	35	22	82	7.7	13	84	6.9

SD, standard deviation.

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evidence points to a significant relationship between melatonin, the ovaries, and reproductive hormones.[34] This relationship is particularly relevant in the context of PCOS, where disruptions in melatonin patterns are observed both in serum and within the ovarian follicle.[9] Melatonin levels follow a distinct circadian rhythm, typically rising in the evening, peaking during the night, and decreasing in the early morning.[35] Disruptions to this normal pattern can indicate CRD.[35]

While the mean melatonin levels provide insight into overall secretion, it is

FIGURE 2
Difference in melatonin levels

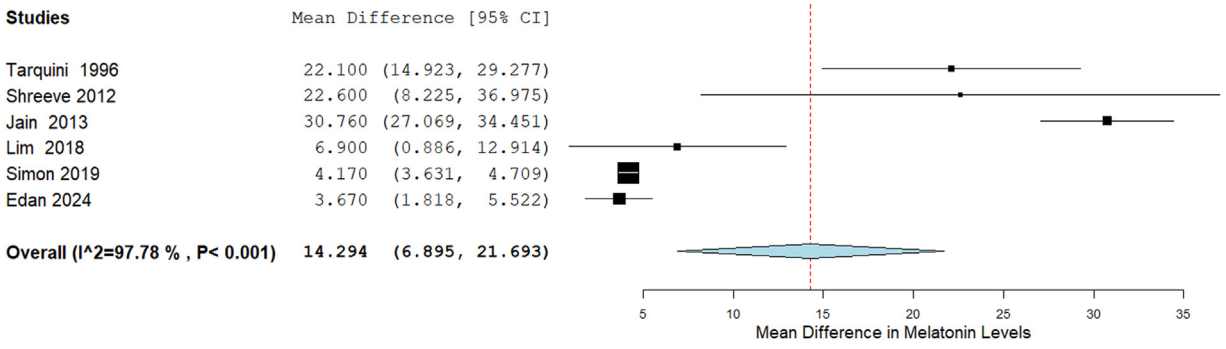

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FIGURE 3
Difference in morning cortisol levels

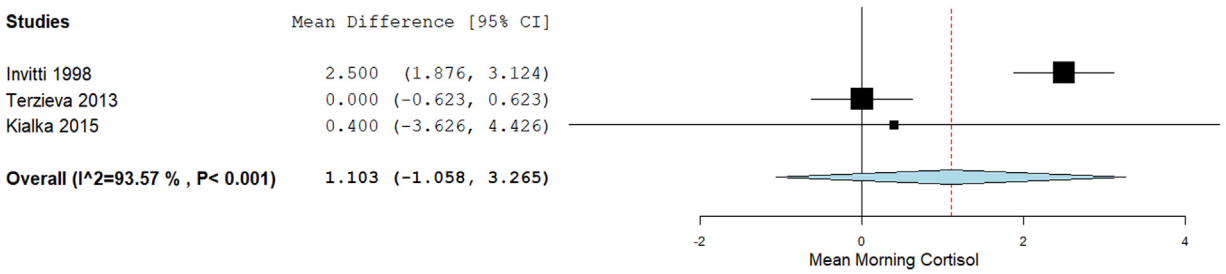

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FIGURE 4
Difference in evening cortisol levels

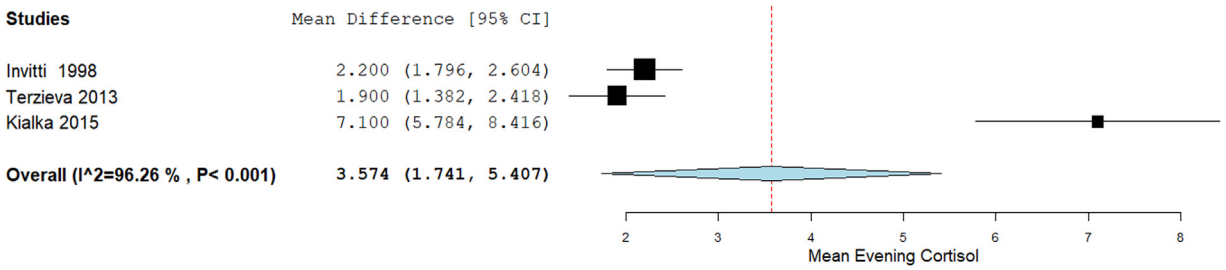

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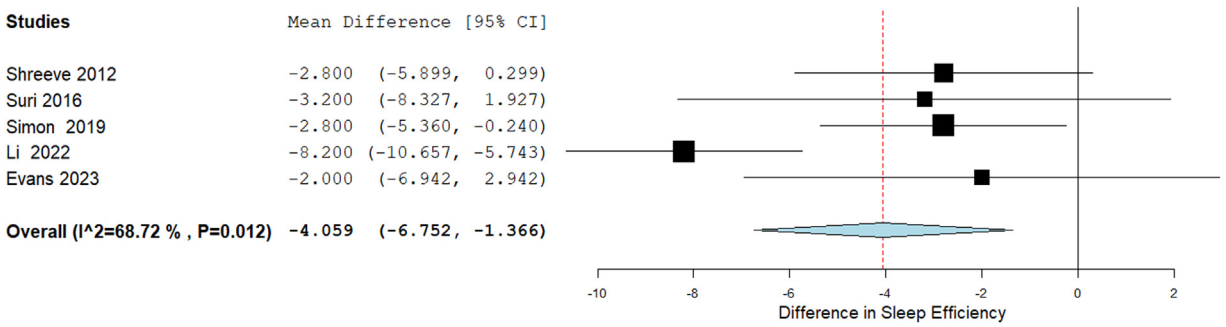
FIGURE 5
Difference in sleep efficiency



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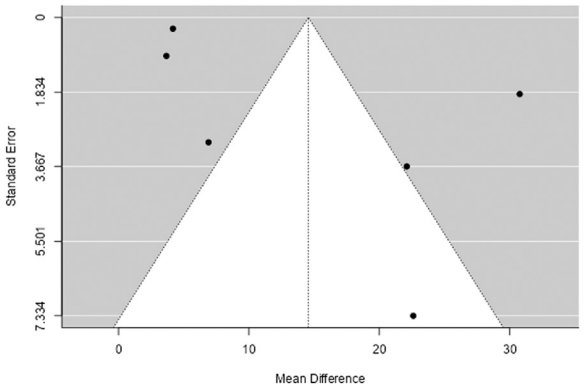
the timing and amplitude of melatonin fluctuations that play a fundamental role in regulating the circadian rhythm and sleep-wake cycles.[36] Even though our analysis primarily focused on the difference in mean melatonin levels, either daytime or nighttime, the diurnal variation of melatonin levels appears to be more critical than the mean melatonin levels.[37] This is exhibited in the study by Tarquini et al, in which the melatonin levels were consistently higher throughout the 24-hour cycle, especially in the nighttime hours, in patients with PCOS than in controls[13]. Notwithstanding, women with PCOS tend to have elevated serum melatonin levels, but paradoxically reduced melatonin concentrations within their ovarian follicles compared to women without PCOS.[38] This discrepancy may contribute to the oxidative stress and chronic inflammation observed in PCOS, both of which negatively impact oocyte health and ovulation.[39] The reduced intrafollicular melatonin may lead to suboptimal ovarian function, contributing to the oligo/anovulation characteristic of PCOS.[9] There is limited direct research suggesting that reduced intrafollicular melatonin could lead to increased serum melatonin as a compensatory mechanism.[40] Furthermore, the altered night-to-day melatonin ratio in women with PCOS suggests a misalignment of circadian rhythm, which could further

FIGURE 6
Funnel plot for publication bias



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compromise ovarian health and contribute to anovulatory conditions.[41]

The antioxidant properties of melatonin extend to the ovarian follicle, where it has been shown to upregulate antiapoptotic genes and reduce androgen production in granulosa cells.[42] In addition to its role in ovarian protection, melatonin supplementation has shown promise in improving oocyte maturation, reducing oxidative stress, and ameliorating hyperandrogenism in women with PCOS.[39] However, while these findings suggest a protective role for melatonin in ovarian function, the evidence remains inconclusive, necessitating further research.

CRD at the level of melatonin also has significant implications for sleep health in women with PCOS. Normally, melatonin follows a 24-hour circadian pattern, increasing to transition into bedtime and lowering to daytime levels upon waking.[34] However, in women with PCOS, the dim light melatonin offset (DLMOff)—the time when melatonin levels return to baseline—extends into the morning.[20] This misalignment is associated with increased free testosterone levels and insulin resistance, which are hallmark features of PCOS.[41] Additionally, the study by Li et al showed a difference in allelic frequencies of the MTNR1A gene between PCOS patients and controls, which possibly contribute to the observed metabolic disturbance in PCOS patients.[17]

In healthy adults, increased morning melatonin reduces insulin sensitivity, which could contribute to the insulin resistance observed in PCOS patients with circadian rhythm disruption.[24] Furthermore, melatonin supplementation has been shown to improve several aspects of PCOS, including hyperandrogenism, menstrual irregularities, and oocyte maturation.[43] However, more research, particularly large-scale randomized controlled trials, is needed to confirm these findings and determine the long-term safety and efficacy of melatonin supplementation. In patients with PCOS, decreased sleep efficiency, as a biomarker of CRD, may result from several interconnected factors, including hormonal imbalances, metabolic disturbances, and autonomic dysfunction.[44] Elevated androgen levels, for example, have been linked to increased sympathetic nervous system activity, which contributes to heightened arousal and sleep fragmentation.[45] Additionally, altered melatonin secretion can lead to difficulty falling asleep, frequent awakenings, and reduced overall sleep efficiency.[15] Moreover, the association between CRD and metabolic disturbances in PCOS is further supported by evidence from studies on night shift workers, who experience circadian misalignment.[46] These studies demonstrate reduced sleep time, impaired glucose tolerance, and increased markers of insulin resistance and inflammation, independent of sleep loss.[47] Our meta-analysis also supports this, as all five studies found that patients with PCOS had lower sleep efficiency compared to the controls.[9,18,22,24,26] This suggests that the misalignment itself directly impacts these health markers, making circadian disruption a potential risk factor for PCOS. Moreover, the psychological stress and metabolic disturbances commonly seen in PCOS can further exacerbate sleep fragmentation and circadian misalignment.[48] Although this misalignment worsens PCOS symptoms, it is important to recognize that there may be a bidirectional relationship between circadian disruption and PCOS.[49] This creates a vicious cycle, where poor sleep quality can further aggravate hormonal imbalances, thereby worsening the condition. Thus, decreased sleep efficiency in PCOS patients highlights the importance of addressing CRD as part of a comprehensive management strategy.[50] In addition to the overall increase in mean melatonin levels and reduced sleep efficiency, our analysis reveals that patients with PCOS also had higher evening cortisol levels compared to women without PCOS.[14,20,21] Cortisol, a key hormone in the hypothalamic-pituitary-adrenal (HPA) axis, follows a diurnal rhythm, with peak levels in the morning and gradual decline throughout the day, reaching a nadir at night.[51] In patients with PCOS, alterations in morning and evening cortisol levels suggest a disturbed circadian regulation of the HPA axis, which may contribute to metabolic dysfunction, sleep disturbances, and reproductive abnormalities.[52]

In a normal circadian rhythm, cortisol levels decline in the evening to promote sleep initiation and metabolic recovery.[53] However, patients with PCOS often exhibit elevated evening cortisol levels, a finding consistent across all three studies in our meta-analysis.[14,20,21] When cortisol levels fail to decrease in the evening, it can disrupt the circadian phase, alter melatonin secretion, and lead to difficulties falling asleep, poor sleep efficiency, and circadian misalignment.[54] Additionally, elevated evening cortisol increases nocturnal sympathetic activity, which can exacerbate hyperinsulinemia and dyslipidemia, thus worsening metabolic dysfunction.[55]

Furthermore, persistent activation of the HPA axis contributes to chronic low-grade inflammation, which plays a role in the reproductive and metabolic complications seen in PCOS.[56]

Although our pooled analysis did not show a statistically significant increase in morning cortisol levels, two studies reported higher levels in patients with PCOS.[14,21] Elevated morning cortisol has been associated with disrupted sleep architecture, as it may indicate impaired sleep homeostasis resulting from a weakened melatonin-cortisol interaction.[57]

Thus, both morning and evening cortisol dysregulation contribute to CRD in PCOS. Elevated morning cortisol exacerbates metabolic dysfunction and hyperandrogenism, while elevated evening cortisol disrupts sleep and perpetuates stress responses. Interventions targeting circadian restoration, such as light therapy, sleep optimization, and stress reduction techniques, may help regulate cortisol rhythms and improve PCOS outcomes.

Strengths and limitations

Our systematic review and meta-analysis has several limitations, including studies with relatively small sample sizes, phenotypic variations in PCOS diagnosis, high heterogeneity in melatonin and sleep efficiency data, and limited data on the relationship between circadian rhythm and PCOS. In addition, given the circadian variation of melatonin levels, our analysis did not account for these rhythmic differences. Besides, three of the studies included in the meta-analyses used a cross-sectional design, which limits the ability to infer causality. However, despite these limitations our systematic review is the first of its kind to assess the impact of circadian rhythm biomarkers on women with PCOS. Moreover, several indicators of CRD were investigated, including melatonin, morning and evening cortisol, and sleep efficiency. Our analysis provides a foundation for future research on the influence of CRD biomarkers melatonin and cortisol on the pathophysiology of PCOS.

Conclusions and implications

Our systematic review and meta-analysis found compelling evidence for the association between circadian rhythm disruption and PCOS, which may contribute to the endocrine and metabolic disturbances, as well as poor sleep health observed in this condition. This disruption could potentially underlie the serious manifestations of PCOS, such as cardiovascular disease, diabetes, obesity, and infertility. Further research is needed to elucidate the full impact of CRD on PCOS and explore potential therapeutic strategies.

Given the multifaceted nature of PCOS, establishing effective treatment is challenging but potentially rewarding. Although melatonin levels are already elevated in anovulatory states like PCOS, further exploration of the differences between endogenous (high serum, low intrafollicular) and exogenous (supplemental) melatonin could provide new insights. ■

CRediT authorship contribution statement

Tara Heydari: Writing — review & editing, Writing — original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. **Prakash V.A.K. Ramdass:** Writing — review & editing, Writing — original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation.

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