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REVIEW PAPER / GYNECOLOGY

Nonpharmacological mental health interventions for adolescent patients with polycystic ovary syndrome: a scoping review

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Abstract

Objectives: This study aimed to summarize nonpharmacological mental health interventions that are beneficial for adolescent patients with polycystic ovary syndrome (PCOS) and to identify the limitations of existing studies.

Material and methods: Following the recommendations of the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-SCR), we conducted a scoping review of nonpharmacological interventions aimed at improving mental health in adolescents with PCOS.

Results: Six randomized controlled trials (RCTs), two quasiexperimental studies, two case reports, one prospective study, one predictive correlation study, and one field trial study were included, resulting in 13 articles. Nonpharmacological interventions encompass a range of psychotherapies, dietary modifications, physical exercise, and traditional Chinese medicine therapies. Except for one study that has not yet reported findings, all included studies

reported significant improvements in patients' mental health through nonpharmacological interventions.

Conclusions: The evidence summarized in this study suggests that nonpharmacological interventions may be efficacious in improving the mental well-being of adolescent patients with PCOS. However, existing studies have limitations, including small sample sizes, the limited use of outcome indicators, and a lack of postintervention follow-up evaluations. Therefore, further RCTs should be conducted to validate the effectiveness and safety of current or alternative nonpharmacological interventions.

Keywords: PCOS; nonpharmacological intervention; mental health; adolescent; scoping review

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common gynecological endocrine disorder that affects patients from adolescence to postmenopause [1]. Owing to differing diagnostic criteria, the prevalence of PCOS in adolescents ranges between 5.29% and 22.60% [2, 3]. In addition to affecting the reproductive system, adolescents with PCOS are also susceptible to other metabolic derangements, including obesity, dyslipidemia, insulin resistance, and cardiovascular disease [3, 4], as well as the development of psychiatric disorders. The most common psychiatric disorders in adolescents with PCOS are anxiety and depression, with depression occurring in 50–60% and anxiety occurring in 38–58% of these individuals [5, 6]. Furthermore, although limited research has been conducted, adolescent PCOS patients are at increased risk for a variety of psychiatric disorders, including but not limited to bipolar disorder, sexual dysfunction, low self-esteem, social phobia, obsessive-compulsive disorder, attention deficit hyperactivity disorder, eating disorders and sleep disturbances [6, 7]. However, the co-occurrence of mental disorders significantly exacerbates the negative impact on the quality of life and prognosis of adolescents with PCOS. Studies have demonstrated a strong and independent correlation between insulin resistance and depression; however, the underlying mechanism remains unclear [8]. Moreover, recent research has revealed that although PCOS may contribute to infertility, its impact is more likely to be exacerbated by the patient's own emotional and mental disorders rather than being exclusively attributed to the disease itself [9]. In addition, an increasing body of research has demonstrated that untreated mental disorders in adolescent PCOS patients have the potential to persist into adulthood and progressively deteriorate, significantly impacting

their overall quality of life throughout their lifespan [10, 11]. Consequently, adolescence represents a critical period for public health practitioners to proactively intervene and prevent the onset of mental disorders among PCOS patients.

However, managing mental disorders in adolescents with PCOS can pose a challenge because of the potential increased harm caused by psychiatric medications in this population [7, 12–14]. Previous research has indicated that prolonged use of antipsychotic medications such as olanzapine and clozapine is linked to obesity, insulin resistance, and cardiovascular disease, whereas adolescents with PCOS are inherently predisposed to these conditions [12, 13]. Furthermore, medications such as sodium valproate, which is commonly used for the treatment of bipolar disorder, can lead to menstrual irregularities and trigger symptoms similar to those of PCOS [7].

A broad range of nonpharmacological interventions, including behavioral interventions, traditional Chinese medicine (TCM) treatments, and exercise interventions, are being researched to improve the mental health of PCOS patients [15–18]. However, there is considerable heterogeneity in the timing, frequency, outcome measures, and effect assessment of nonpharmacological interventions. Previous literature reviews have mostly examined nonpharmacological interventions for PCOS patients of childbearing age, whereas nonpharmacological interventions for adolescent PCOS patients are limited [14, 19]. Therefore, this study aimed to comprehensively review the intervention forms, outcome types, and effectiveness of nonpharmacological mental health interventions for adolescents with PCOS to identify existing issues within current nonpharmacological intervention programs and establish a foundation for future management strategies targeting the mental well-being of adolescents with PCOS.

MATERIAL AND METHODS

Review approach

We conducted a scoping review following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-SCR) [20]. A scoping review can examine and clarify broader areas than a systematic review; therefore, this method was chosen to allow for the inclusion of different study designs.

Research question establishment

This scoping review aimed to identify various nonpharmacological mental health interventions for adolescents with PCOS by mapping the literature in the field to inform policy and practice and provide recommendations for future research. The PubMed, Cochrane Library, Web of Science, CINAHL Complete, and Wiley Online Library databases were searched. We developed a search algorithm for PubMed (Table 1), also adapted for the other databases. The searches were completed in January 2024, and no time limit was set for inclusion in the study (no limit was placed on the range of publication years).

Table 1. PubMed search algorithm

PubMed Search Algorithm
(((((Polycystic ovary syndrome[MeSH Terms]) OR (PCOS[MeSH Terms])) OR (Polycystic ovar[MeSH Terms])) OR (POCD[MeSH Terms])) AND ((((intervention[MeSH Terms]) OR (treat[MeSH Terms])) OR (therapy[MeSH Terms])) OR (cure[MeSH Terms]))) AND ((((mood disorders [MeSH Terms]) OR (anxiety disorders [MeSH Terms])) OR(depressive disorder [MeSH Terms])) OR (mental block [MeSH Terms])) OR (psychological disorder [MeSH Terms])) AND ((((child [MeSH Terms]) OR (adolescent [MeSH Terms])) OR(young adult [MeSH Terms]))

Inclusion/exclusion criteria

We included articles that met four criteria:

- studies focused on young people aged 10–19 years,
- participants had a diagnosis of polycystic ovary syndrome,
- studies focused on mental disorders,
- studies focused on nonpharmacological interventions.

An age range of 10–19 years was chosen, as this is the World Health Organization's recommended age range for adolescents. If the average age of the study cohort was within this range, studies that included patients outside the age range of 10–19 years were included. We included a wide range of mental disorders in this review and articles focused on psychosis if the subjects met a diagnosis of any of the mental disorders (anxiety, depression, bipolar disorder, sexual dysfunction, eating disorders, etc.) or if at least one of the findings was related to mental health. We aim to include articles on the management of mental disorders associated with adolescent PCOS using a range of nonpharmacological interventions, such as diet, physical exercise, and psychological interventions. See Table 1 for more information about the search strategy and selection process.

Study selection and data extraction

The process of research collection and subsequent data extraction was independently conducted by two authors, with a third author resolving any inconsistencies. All article titles retrieved from different databases were downloaded into a Microsoft Excel spreadsheet, where two authors independently checked and selected studies using a four-stage screening process. The free web tool on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) website was subsequently utilized to create a flowchart.

Once eligible papers were identified, we followed Arksey and O'Malley's scoping research framework to help us determine the appropriate approach for charting the data, including the author, publication date, country, study type, PCOS diagnostic criteria, intervention details, and study outcomes, which were extracted and pooled for analysis. We did not assess the quality of the studies included in this review because this is not a mandatory requirement for scoping reviews.

RESULTS

Search results

Initially, 428 studies were identified through database searches. After 225 duplicate papers were eliminated, a preliminary screening excluded 180 of the remaining 203 papers based on their titles and abstracts. The remaining 23 papers were subsequently comprehensively evaluated. Ultimately, after further scrutiny, 10 articles were excluded, and only 13 met the inclusion criteria for this literature review. Figure 1 shows the PRISMA flow chart of the study selection process.

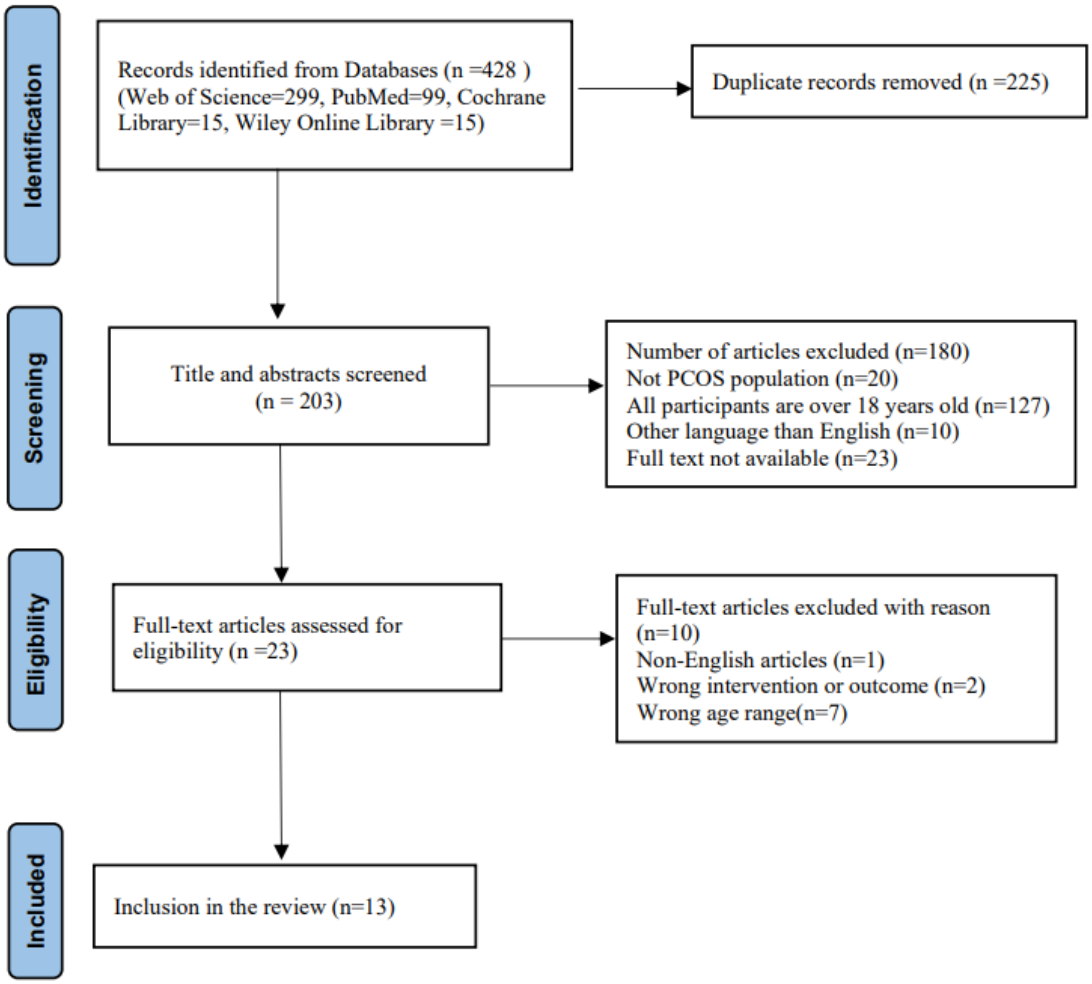

Figure 1. Flow diagram of database searches and study screenings

Study characteristics

There were thirteen studies, including six randomized controlled trials (RCTs) [15, 21–25], two quasiexperimental studies [17, 26], two case reports [27, 28], one prospective study [29], one predictive correlation study [30], and one field trial study [31]. The sample size of the included studies varied from 1 to 117 patients. Eighty-five percent of the studies focused exclusively on adolescent patients, with only two encompassing a broader age range [17, 23]. The participants' body mass indices (BMIs) ranged from 18.5 to 82.62 kg/m^2, and six of the studies exclusively included individuals who were overweight or obese. The included

studies employed inconsistent diagnostic criteria for PCOS, among which five utilized the Rotterdam criteria. Other basic features are shown in Table 2.

Table 2. Basic characteristics of the included studies

Author (year)	Country	Study type	Age (year)	BMI/Weight (Mean ± SD)	PCOS diagnostic criteria
Rofey (2009) [15]	USA	RCT	12–18 (n = 12)	39 ± 6 kg/m^2	Best practices and research in clinical endocrinology and metabolism (2006)
Rofey (2018) [29]	USA	Prospective study	13–20 (n = 117)	36.8 ± 8.8 kg/m^2	Best practices and research in clinical endocrinology and metabolism (2006)
Stefani (2014) [23]	Greece	RCT	15–40 (n = 46)	T1:21.53 ± 2.15 kg/m^2 T2: 23.70 ± 4.4 kg/m^2	The Rotterdam criteria
Salajeghh (2023) [17]	Iran	Quasiexperimental study	15–45 (n = 46)	T1: 70.92 ± 7.75 kg T2: 73.83 ± 8.79 kg	The Rotterdam criteria
Young (2021) [25]	USA	RCT	14–24 (n = 37)	Not specified	Adolescent medicine and pediatric endocrinology practice (2007)
Hajivandi (2021) [31]	Iran	Field trial study	15–21 (n = 72)	≥ 25 kg/m^2	Clinical gynecologic, endocrinology, and infertility (2011)
Bonab (2023)] [26]	Iran	Quasiexperimental study	14–18 (n = 40)	EG: 28.57 ± 0.07 kg/m^2 CG: 28.16 ± 0.8 kg/m^2	Not specified
Nidhi (2012) [21]	India	RCT	15–18 (n = 90)	18.5~23 (82.2%) kg/m^2 > 23 (17.78%) kg/m^2	The Rotterdam criteria
Wong (2015) [24]	USA	RCT	13–21 (n = 19)	EG: 36.2 ± 5.3 kg/m^2 CG: 33.9 ± 4.7 kg/m^2	The Rotterdam criteria
Bansal (2022) [27]	India	Case report	13–15 (n = 2)	Case 1: 27.17 kg/m^2 Case 2: 22.36 kg/m^2	Not specified
Adullhameed (2022) [30]	Egypt	Predictive correlation research	< 20 (n = 16) 20~30 (n = 34)	18.5~24.9 kg/m^2 (40%) 25~29.9 kg/m^2 (26%); > 30 kg/m^2 (34%)	Not specified
Hewawasam (2020) [22]	Australia	RCT	12–20 (n = 40)	BMI: not specified	Recommendations from the international evidence-based guideline for the assessment and management of PCOS
Farajzadh (2017) [28]	Iran	Case report	19 (n = 1)	BMI: 23.89 kg/m^2	The Rotterdam criteria

BMI — body mass index; PCOS — polycystic ovary syndrome; RCT — randomized controlled trial

Intervention categories

After a detailed review, interventions were grouped into 2 general categories, including (1) lifestyle interventions and (2) TCM therapy, as shown in Table 3. The most frequent

nonpharmacological interventions for PCOS patients were psychotherapy (n = 6), including mindfulness (n = 3), CBT (n = 2), and theory of planned behavior (TPB) (n = 1) interventions. The two included CBT studies were conducted by the same investigator, albeit nine years apart. Both CBT studies had similar schedules, consisting of eight weekly individual sessions and three family-based sessions, each of which included 15–30 minutes of physical activity. The intervention process and periods of the other studies are presented in Table 4.

Table 3. Categories of interventions

Category of intervention	**n (%)**
Lifestyle interventions	
Psychotherapy	6 (46%)
Exercise therapy	2 (15%)
Diet therapy	1 (8%)
Exercise combined with diet therapy	2 (15%)
TCM therapy	
TM	1 (8%)
EA	1 (8%)

EA — electroacupuncture; TM — transcendental meditation

Table 4. Intervention process and period

Author (year)	**Intervention process**	**Intervention period**
Rofey (2009) [15]	Eight weekly individual sessions for 45–60 min + three family-based sessions of CBT for 60 min	8 weeks
Rofey (2018) [29]	Eight weekly individual sessions for 45–60 min + three monthly booster sessions three family-based sessions of CBT	3 months
Stefani (2014) [23]	The intervention group: 30-min mindfulness stress management program once a day; the control group: received no training	8 weeks
Salajegh (2023) [17]	The intervention group: received MBSR sessions for 90-minute, twice a week; the control group: received routine care	1 month
Young (2021) [25]	Five 60–75 minutes consecutive weekly sessions	5 weeks

	based on MBI	
Hajivandi (2021) [31]	The intervention group: received educational intervention based on the TPB over 4 sessions; the control group: received no training	2 weeks
Bonab (2023) [26]	The exercise group (aerobics): performed aerobic exercises in three 60-minute sessions per week	12 weeks
Nidhi (2012) [21]	The yoga group: practiced a holistic yoga module 1 hour daily, 7 days a week for a total of 90 sessions. The control group: traditional physical exercise	12 weeks
Wong (2015) [24]	Participants were randomly assigned to receive either an LGL or LF dietary prescription	6 months
Bansal (2022) [27]	Case 1: structured exercise program (exercise + diet); Case 2: structured exercise program (exercise + diet) + oral contraceptive	3 months
Adullhameed (2022) [30]	Disease education + low-calorie diet + physical activities	1 year
Hewawasam (2020) [22]	The intervention group: practiced TM for 15 minutes, twice daily The control group sat comfortably for 15 minutes twice daily in a quiet room	8 weeks
Farajzadeh (2017) [28]	The first 2 weeks: twice per week; the next 6 weeks: once per week; The next 8 weeks: once every two weeks (duration and frequency were not changed over 14 EA sessions)	4 months

CBT — cognitive–behavioral therapy; CG — control group; EG — experimental group; MBSR — mindfulness-based stress reduction; MBI — mindfulness-based intervention; TPB — theory of planned behavior

Outcome measures

Almost all studies (n = 11) collected patients' psychological outcomes via objective measures, although two used researcher-made scales. A total of 10 assessment tools were used in 13 studies, as shown in Table 5. The outcome indicators were variable across studies: seven studies assessed patients' anxiety and depression symptoms, six studies assessed HRQOL, five studies assessed stress, and two studies assessed self-esteem. In addition to psychological measures, some studies collected BMI, testosterone, and patient menstrual

cycle data.

Table 5. Emotional categories and assessment tools

Emotional category	Assessment tools
Depression (n = 7)	DASS-21, PSS-14, CDI
Anxiety (n = 7)	DASS-21, PSS-14, CDI, STAI
Stress (n = 5)	DASS-21, PSS-14, CDI
Self-esteem (n = 2)	The Rosenberg self-esteem scale
HRQOL (n = 5)	PCOSQ, IWQoL-K, CHQ-CF87, SF-36, the Pediatric Quality of Life Inventory version 4.0

DASS-21 — the 21-item depression, anxiety, stress scale; PSS-14 — the perceived stress scale; STAI — the state-trait anxiety inventory; CDI — the children's depression inventory; CHQ-CF87 — the child health questionnaire; SF-36 — the short-form health survey; PCOSQ — the PCOS health-related quality of life questionnaire; HRQOL — health-related quality of life; IWQoL-K — the impact of weight on quality-of-life questionnaire-Kids.

Outcomes by intervention type

Twelve studies reported positive results from nonpharmacological interventions, but two of them had no significant effect on patients' mental health. Additionally, there is an ongoing trial for which no relevant outcomes have been reported [22]. Table 6 provides the categories of interventions and their clinical relevance.

Table 6. Clinical relevance of outcomes by category

Intervention type	Author (year)	Clinical relevance
Psychotherapy		
CBT	Rofey (2009) [15]	There were significant improvements in depression, BMI, quality of life, menstrual regularity and sleep-related breathing disorders.
CBT	Rofey (2018) [29]	Adolescents without a family history of psychiatric illness lost more weight than those who had a family history of psychiatric illness.
Mindfulness	Stefani (2014) [23]	With the intervention, these patients experienced reduced levels of stress, anxiety and depression and improved quality of life.
MBSR	Salajegh (2023) [17]	The mean score of worry in women with PCOS in the IG decreased.
MBI	Young (2021) [25]	The IG reported significantly higher nutrition self-efficacy and higher physical activity self-efficacy.
TPB	Hajivandi (2021) [31]	The attitude toward disease-related nutrition behavior in the IG was significantly improved compared with the CG.
Exercise therapy		
Aerobics	Bonab (2023) [26]	Prolactin, testosterone and lipid levels were significantly reduced.
Yoga	Nidhi (2012) [21]	The reduction in anxiety scores was significantly higher in the yoga group than in

		the exercise group.
Diet therapy	Wong (2015) [24]	Weight loss was significant, but quality of life was not significantly improved.
Exercise combined with diet		
Exercise + diet	Bansal (2022) [27]	Case 1: Anxiety, overweight, irregular menstruation all improved; Case 2: Anxiety and menstrual irregularity improved, but weight gain was noted.
Education + diet + exercise	Adullhameed (2022) [30]	The patients' cognition level of the disease was improved, and their inferiority and quality of life were significantly improved.
TCM therapy		
TM	Hewawasam (2020) [22]	Not yet reported.
EA	Farajzadeh (2017) [28]	Anxiety, depression and irregular menstruation improved significantly.

Psychotherapy

All six studies validated the effectiveness of psychotherapy in adolescents with PCOS. Two studies [23, 25] reported that mindfulness interventions significantly reduced anxiety, depression, and stress in adolescents with PCOS. In addition, one of the studies [25] reported that patients' nutritional self-efficacy improved significantly with the MBI, indicating that mindfulness interventions may treat eating disorders in adolescent girls with PCOS. The third mindfulness intervention [17] showed that the mindfulness intervention could reduce worry about the physical complications associated with the disease in adolescent girls with PCOS. Two of the included CBT studies [15, 29] were from the same researcher. One of these studies [15] showed that CBT is not only feasible for reducing obesity and depression but is also expected to improve sleep-related breathing disorders and menstrual irregularities. Another study [29] revealed that CBT could lead to weight loss and additional health benefits for obese adolescents with PCOS who had experienced childhood trauma. The last included psychotherapy was used in a field trial study [31] that validated the effectiveness of a 3-month TPB-based educational intervention in improving nutritional intentions in adolescents with PCOS.

Exercise therapy

The two exercise interventions had the same duration but distinct study designs [21, 26]. The first study [26] involved 12 weeks of aerobic training in patients who were obese (BMI ≥ 28 kg/m^2) and showed significant reductions in body weight, blood lipid levels, and prolactin levels, suggesting that exercise can reduce stress, depression, and the use of antidepressants. Another study [21] exclusively assessed anxiety as the primary outcome, and a significant majority of patients (82%) were neither overweight nor obese. After 12 weeks, yoga

demonstrated considerable superiority over traditional physical exercise in reducing anxiety symptoms among adolescents with PCOS, potentially given its capacity to regulate sympathetic nerve activity. Furthermore, yoga may also prevent long-term sequelae, such as cardiovascular disease and diabetes [32].

Diet therapy

The literature reporting the effects of various dietary patterns on the metabolic, reproductive, and psychological aspects of PCOS is scarce, with only one study focusing on adolescent participants. This investigation sought to examine the influence of LGL versus LF diets among overweight and obese adolescents diagnosed with PCOS [24]. The results demonstrated that exclusively implementing a dietary intervention led to notable advantages in weight reduction; nevertheless, it did not produce substantial improvements in quality of life.

Exercise combined with diet therapy

We included two studies that combined exercise and diet therapy [27, 30]. The first study [27] was a case report (n = 2) in which two girls underwent a supervised exercise program that included exercise and diet counseling. After three months of training, both girls' menstrual irregularities and anxiety symptoms improved significantly. Another study [30] educated participants about the disease on the basis of a combination of exercise and diet. After one year, the intervention significantly improved patients' awareness of PCOS, effectively mitigating their low self-esteem and improving their quality of life.

TCM therapy

The two TCM interventions included in this study were TM and EA [22, 28]. Previous research has demonstrated the effectiveness of meditation in addressing physical, psychological, and social-behavioral problems in children and adolescents [33]. However, no trials have specifically evaluated the effects of TM on adolescent girls with PCOS. The TM study included in this review was an RCT designed to assess the impact of TM on quality of life, psychological distress, cortisol levels, and blood pressure in girls with PCOS. Data from this study have not yet been reported [22]. The included EA study[28] was a single case report of a patient for whom four years of drug therapy had failed. EA significantly improved her symptoms of anxiety, depression, menstrual irregularity, and hyperandrogenemia by

modulating the sympathetic tone in the uterine and ovarian arteries and enhancing her circulatory reflexes through low-frequency muscle contractions, as demonstrated in another RCT involving 54 reproductive-age PCOS patients [34].

DISCUSSION

Over 80% (11 out of 13) of the included studies were published within the last decade, indicating a growing interest in mental health interventions for adolescents with PCOS despite limited evidence. Based on previous guidelines [1, 14], nonpharmacological interventions may serve as a first-line treatment strategy for adolescents with PCOS, with ongoing clinical studies on this topic. It is necessary to provide an extensive summary and perform an in-depth analysis of the existing evidence to provide a valuable reference for future research.

Diagnostic criteria for PCOS in adolescents

Owing to the overlap between features of normal adolescent development and the diagnostic criteria for PCOS in adults, diagnosing PCOS in adolescence poses a significant challenge. Consequently, the latest international evidence-based guidelines for adolescents have established standardized diagnostic criteria for PCOS during adolescence [14]. The variations observed in the diagnostic criteria used across the studies included in this review may be attributed to differences in geographical location and age range covered by the literature analyzed. Future research on the diagnosis of adolescents with PCOS should adhere to international consensus guidelines to increase diagnostic accuracy and prevent overdiagnosis.

Effectiveness of existing nonpharmacological interventions

This scoping review identified and summarized the scope and nature of 13 nonpharmacological interventions aimed at improving emotional outcomes in adolescents with PCOS. The studies were categorized into psychotherapy, dietary modifications, physical exercise, or TCM treatments based on the specific focus of each intervention. Overall, the included literature suggests that nonpharmacological interventions have beneficial effects on the mental health (mood, cognition, and quality of life) of adolescent POCS patients. Most of the included studies also analyzed physiological outcomes (hirsute, acne, BMI, waist-to-hip ratio, prolactin levels, testosterone levels, salivary cortisol levels, *etc*.) and, encouragingly,

reported statistically favorable outcomes.

Limitations of this scoping review

The studies we included in this review were limited to English, which may have led to bias. Two studies on CBTs from the same author were included in this review, which may have introduced selection bias in the data presented. Additionally, there was no quantitative assessment of the included studies, as this was beyond the scope (or purpose) of the review.

Summary of the gaps in the literature

The available literature on nonpharmacological interventions for managing mental disorders in adolescents with PCOS has several gaps that need to be addressed in the future to enhance our understanding and improve the mental well-being of this population: (1) Nearly half of the studies focused on overweight or obese adolescents, addressing psychological symptoms such as anxiety, depression, low self-esteem, sleep disorders, and eating disorders. However, insufficient attention has been given to emotional disorders that significantly impact the quality of life of adolescents with PCOS, including bipolar disorder, obsessive-compulsive disorder, and social phobias [5, 6, 14]. (2) None of the included studies performed follow-up assessments after the intervention to assess whether the reported benefits of the nonpharmacological interventions, dietary habits, or exercise behaviors persisted. (3) The high prevalence of mood disorders in adolescents with PCOS can have significant and enduring implications for their well-being, as well as for their families and society at large. However, the mental health issues associated with this condition remain widely underrecognized, underresearched, and undertreated.

CONCLUSIONS

Nonpharmacological interventions (behavioral interventions, dietary modifications, physical exercise, or TCM treatment) may improve the mental health of adolescents with PCOS and are a viable approach for those who cannot tolerate the side effects of medication or who are in poor physical condition. However, the published evidence supporting nonpharmacological interventions is limited, and more rigorous multicenter RCTs need to be designed to determine the effectiveness of these interventions and generalize the findings to a broader range of adolescents with PCOS.

Article information and declarations

Author contributions

Writing-original draft preparation, T.Z.; writing-review and editing, J.L. and J.C.; supervision, Y.H. and L.S.; funding acquisition, J.L. and L.H.W.

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Conflict of interest

The authors declare no competing interests.

Supplementary material

None.

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