SCOPING REVIEW OF POLYCYSTIC OVARY SYDROME STUDIES IN ADOLESCENTS: IDENTIFYING RESEARCH CHARACTERISTIC

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ABSTRACT

The consequences of polycystic ovary syndrome (PCOS) in adolescents go beyond infertility during reproductive age. Therefore, research on PCOS should be methodically designed to address gaps and enhance the diagnosis and clinical management of the condition. This scoping review aims to describe the characteristics of research on PCOS among adolescents, and summarise the available methods of diagnosing PCOS among adolescents in epidemiological research. This review followed the standard protocols by Arksey and O'Malley and adheres to the Preferred Reported Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review (PRISMA-ScR) 2018 statement checklist. We included studies of female adolescents aged 13 to 18 years old and published from January 2011 up to December 2023. 341 articles were reviewed. Majority of the studies were observational and primarily conducted in Western countries, indicating the paucity of research on PCOS in Asian adolescents. The main limitations of existing studies are small sample size and potential admission bias due to the non-community-based nature of research. Additionally, the use of adult definitions for PCOS diagnosis in adolescent studies is also debatable. This scoping review assembles and provides insights into the characteristics of current PCOS studies in adolescents, aiming to guide future research directions in the field of PCOS.

KEYWORDS: Adolescents, Polycystic Ovarian Syndrome, Diagnosis, Scoping Review.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common female reproductive disorder that often manifests during adolescence (Trent and Gordon 2020). The consequences of PCOS in adolescents go beyond infertility during reproductive age. There is an increased risk of various metabolic, reproductive, oncological, dermatological and psychological manifestations (Sidra et al. 2019). PCOS and its associated comorbidities, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease, have a negative impact on quality of life and lead to increased out-of-pocket expenditure (OOPE) (Satapathy and Dash 2024). Globally, PCOS occurs in 1.14% to 11.04% of adolescent girls (Christensen et al. 2013; Naz et al. 2019) with the prevalence doubling to 27% among those with obesity (Ybarra et al. 2018). In general, PCOS is defined by a combination of signs and symptoms of androgen excess (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology (PCOM)), provided that other specific diagnoses, such as hyperprolactinaemia and non-classic congenital adrenal hyperplasia, have been excluded (Azziz et al. 2009).

However, diagnosing PCOS in adolescents is not straightforward due to several factors associated with this transitional stage of physical and physiological development (Ramezani Tehrani and Amiri 2019). Firstly, PCOS symptoms may overlap with normal pubertal transition, complicating diagnosis (Trent and Gordon 2020). For example, functional variations in the hypothalamic-pituitary-ovarian axis during normal puberty leads to changes in reproductive hormones and menstrual patterns that mimic some of the features of PCOS, such as acne and menstrual irregularities (Carmina et al. 2010). Approximately 40-50% of adolescent girls have anovulatory cycles (Carmina et al. 2010). Research can help refine diagnostic criteria to distinguish between normal developmental changes and early signs of PCOS. Secondly, PCOS is a heterogeneous syndrome and shares symptoms with other conditions such as adrenal hyperplasia, thyroid disorders, and even normal developmental variations (Adone and Fulmali 2023). Research into adolescent-specific criteria can aid in distinguishing PCOS from these other conditions, leading to more accurate diagnoses and effective treatments. Identifying and diagnosing PCOS early in adolescents can impact long-term health outcomes. Adolescents who are diagnosed and managed early may experience better health outcomes in adulthood, including reduced risks of infertility, metabolic syndrome, and other associated conditions.

Therefore, research on PCOS should be prudently and adeptly designed to answer the research gaps and recuperate the diagnosis and clinical management of PCOS in adolescents. This scoping review aims to describe the characteristics of research on PCOS among adolescents, and summarise the available methods of diagnosing PCOS among adolescents in epidemiological research. These findings will serve as a guide for researchers in designing future studies of PCOS in adolescents.

MATERIALS AND METHODS

The scoping review was conducted according to standard protocols (Arksey and O'Malley 2005; Peters et al. 2015; Tricco et al. 2018). Ethical approval was not sought as only published data were used for this review. Reporting of the review adheres to the Preferred Reported Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review (PRISMA-ScR) 2018 statement checklist (Tricco et al. 2018).

Search Strategy and Eligibility Criteria

A systematic literature search for PCOS in adolescents was conducted using electronic databases for searching medical literature: PubMed, the Cochrane Library, and Science Direct. The search was restricted to articles published in the English language. Animal studies were excluded. Only studies that involved female adolescents aged 13 to 18 years old and published from January 2011 up to 7th December 2023 were included. The following keywords and MeSH terms were used: adolescen*, teen*, youth*, "Adolescent"[Mesh], polycystic ovary syndrome, polycystic ovarian syndrome, PCOS, and "Polycystic Ovarian Syndrome"[Mesh]. The terms were tailored to each database and combined (as appropriate) using the Boolean operands ‘AND’ and ‘OR’ (Table 1).

Table 1. Search algorithm for electronic database.

Search algorithm
((((adolescen*) OR (teen*)) OR (youth*)) OR (adolescent[MeSH Terms])) AND ((((("polycystic ovary syndrome") OR ("polycystic ovarian syndrome")) OR (PCOS)) OR (polycystic ovarian syndrome[MeSH Terms]))

Study selection

All searched articles were imported to EndNote Version 20 (Clarivate Analytics, PA, USA) and duplicates were removed. The screening process was conducted in a two-step approach, where the title and abstract of the records were first screened. Irrelevant articles were removed, and subsequently, the full text of the remaining articles were reviewed based on the inclusion criteria. The study selection process was performed by five groups of two independent researchers with input from a third researcher, who also arbitrated any disagreement. The final selection of articles was agreed upon by all three researchers.

Data extraction and synthesis

Data were extracted accordingly by each group, where one reviewer extracted data into an Excel spreadsheet and the second reviewer verified the data for completeness and accuracy. The following key information was extracted from the studies: year, study design, country, sample size, study objectives, criteria used to define PCOS and study limitations. The extracted data were analysed using descriptive statistics and were presented in a frequency table to summarize the characteristics of the included studies and the criteria used to diagnose PCOS. Research gaps were identified for future recommendations. The quality of the included studies was not analysed as it was not part of the scoping review objectives.

RESULTS

Search results

The database searches found 3,519 articles, with 2094 from PubMed, 319 from Cochrane Library, and 1,106 articles from Science Direct. After excluding duplicates (n = 351), 3,168 articles proceeded to title and abstract screening. Following that, 1,456 articles were identified for full-text screening. Among these, only 341 articles were included for quantitative synthesis, while 1,115 articles were omitted for reasons such as unfitting age range (i.e., articles among adults) (n = 819, 71.8%), articles not related to PCOS (n = 113, 10.1%), year of publication not within range (n = 14, 1.3%), language other than English (n = 27, 2.4%), articles with no full text available (n = 106, 9.5%), and other reasons (n = 36, 3.2%). This process is detailed in the PRISMA flowchart shown in Figure 1.

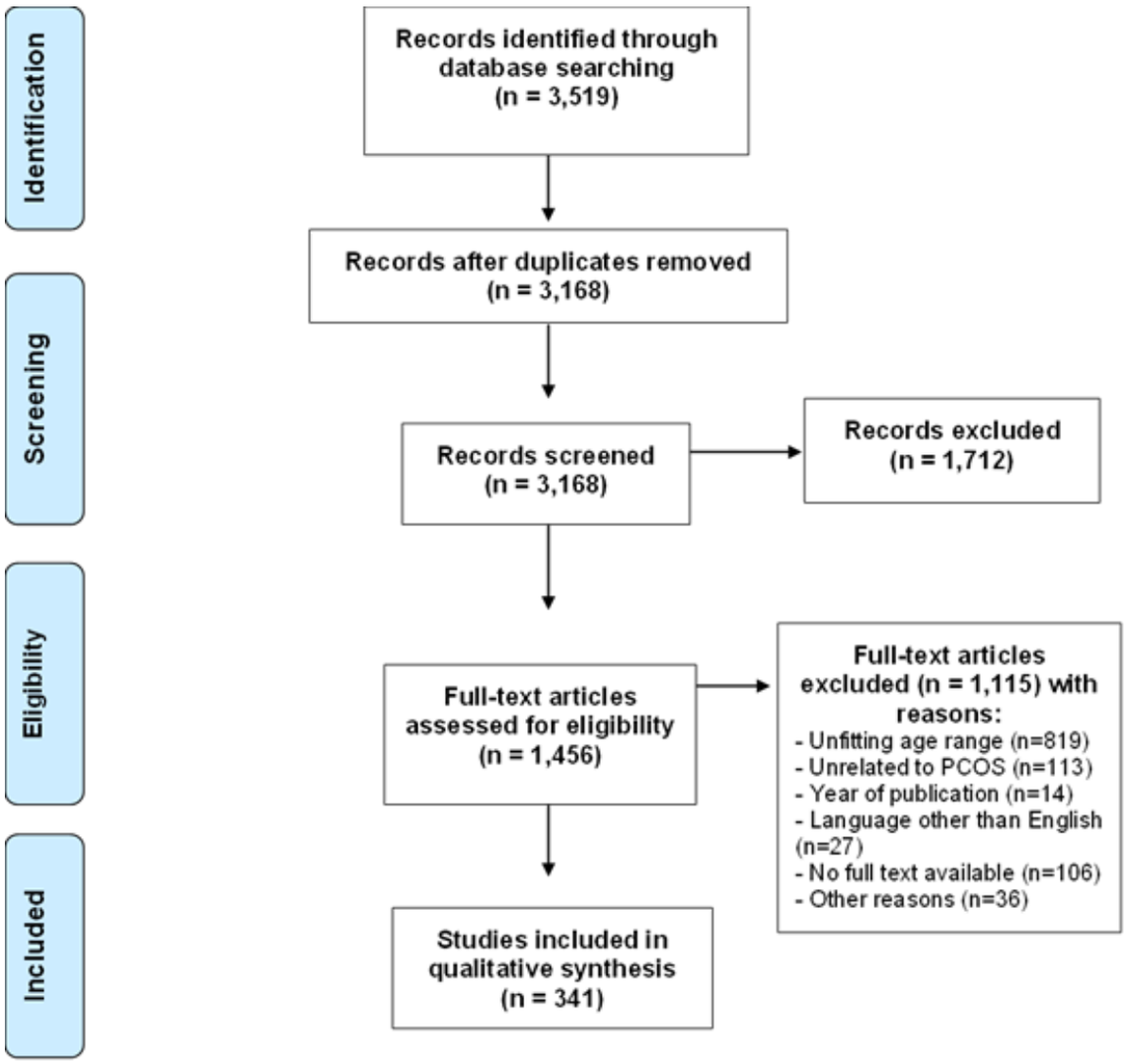

Figure 1. PRISMA Flow Diagram of Articles Through The Scoping Review.

Characteristics of included studies

This scoping reviews includes 341 articles published between January 2011 and December 2023 (Figure 2). There was a rapid increase in the number of publications between 2018 and 2020, peaking in 2020 with 45 articles worldwide. However, the number of publications declined from 2021 to 2022, likely due to the COVID-19 pandemic. Remarkably, the number of articles spike to 55 in 2023. Table 2 presents the characteristics of the articles included in this current review. By study design, many of the studies were observational (58.9%, n = 201), of which 50.3% (n = 101) were cross-sectional, 37.3% (n = 75) were case-control, and 12.4% (n = 25) were cohort studies. The remaining studies were reviews (24%, n= 82), experimental (9.1%, n = 31), case studies (5.3%, n = 18), qualitative studies (1.8%, n = 6), and others (1.2%, n = 4). Looking at the sub-category of the study designs, 72% (n = 59) of the review's articles were narrative reviews, and most experimental studies were randomised controlled trials (77.4%, n = 24), followed by 19.4% (n = 6) single-arm designs and 3.2% (n = 1) quasi-experimental studies. In addition, there was a huge difference in the sample size, ranging between 4 and 137,502 individuals.

Population-wise, 56.3% (n = 193) of the studies were conducted among Western populations, followed by Asians (28.1%, n = 79) and Middle-East (8.6%, n = 27). Among Asian studies, the majority were from Western Asians (56.8%, n = 41), while the least were from the South-Eastern population (2.3%, n = 2). Moreover, approximately 90% (n = 208) of the included articles have small sample sizes (n < 250). Scrutinising into publications by specific country (Figure 3), we found that the articles included were from 39 countries with the highest number of publications from the United States of

America (n = 82), followed by Turkey (n = 46), Poland (n = 20), India (n = 17), Australia (16), Iran (n = 13), Italy (n = 13) and Spain (n = 10). The remaining countries had fewer than 10 publications on PCOS in adolescents.

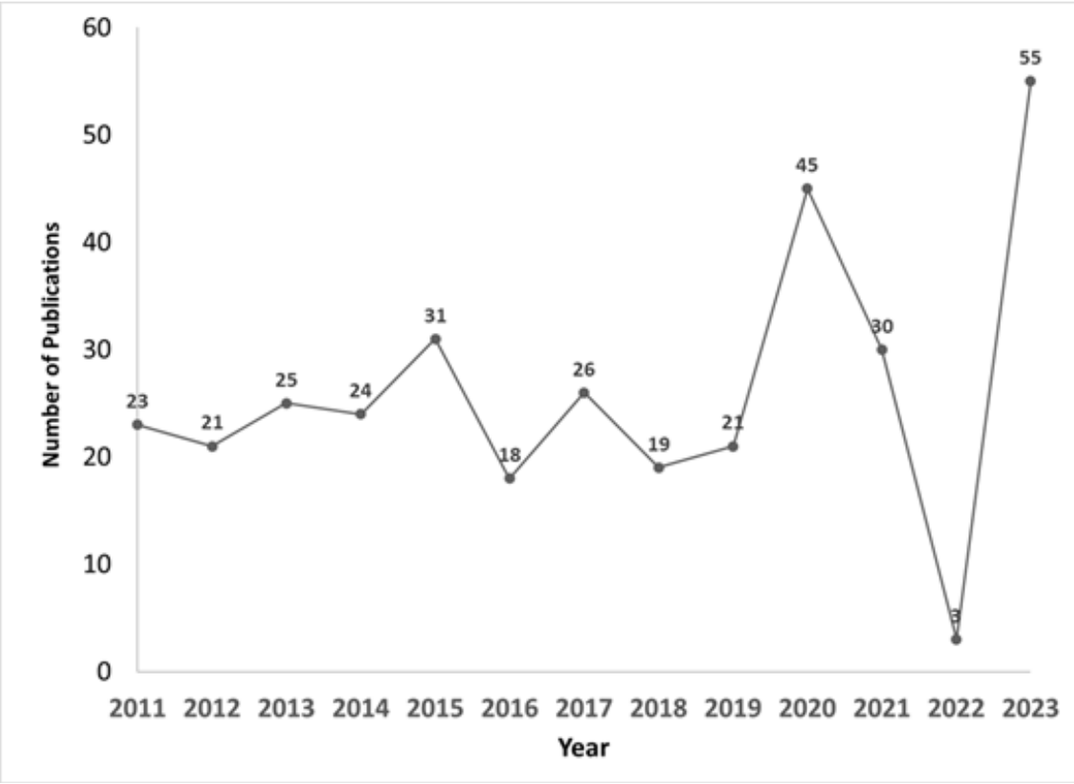

Figure 2. Articles published between 2011 and 2023.

Table 2. Study characteristics of research on PCOS among adolescents (2011-2023).

Characteristics		n (%)
Study design		
Observational (n=201, 58.9%)	Cross-sectional	101 (50.3)
	Case-control	75 (37.3)
	Cohort	25 (12.4)
Experimental (n=31, 9.1%)	Randomised Controlled Trial	24 (77.4)
	Quasi experimental	1 (3.2)
	Single arm	6 (19.4)
Reviews (n=82, 24%)	Systematic review	23(28.0)
	Narrative review	59 (72.0)
Qualitative study		6(1.8)
Case study		18 (5.3)
Others		4 (1.2)
Regions	Western	193(56.3)
	Middle East	27 (8.6)
	Asia	79(28.1)
	South-Eastern	2 (2.3)
	Southern	21 (23.9)

	Western	41 (56.8)
	Eastern	15 (17.0)
	Australasia/Oceania	5 (1.6)
Sample size range		4 – 137,502
Sample size category[a]		
250 and below		208 (88.8)
251 - 500		10 (42.9)
501 - 1000		1 (0.4)
Above 1000		13 (6.4)

a = observational and experimental studies

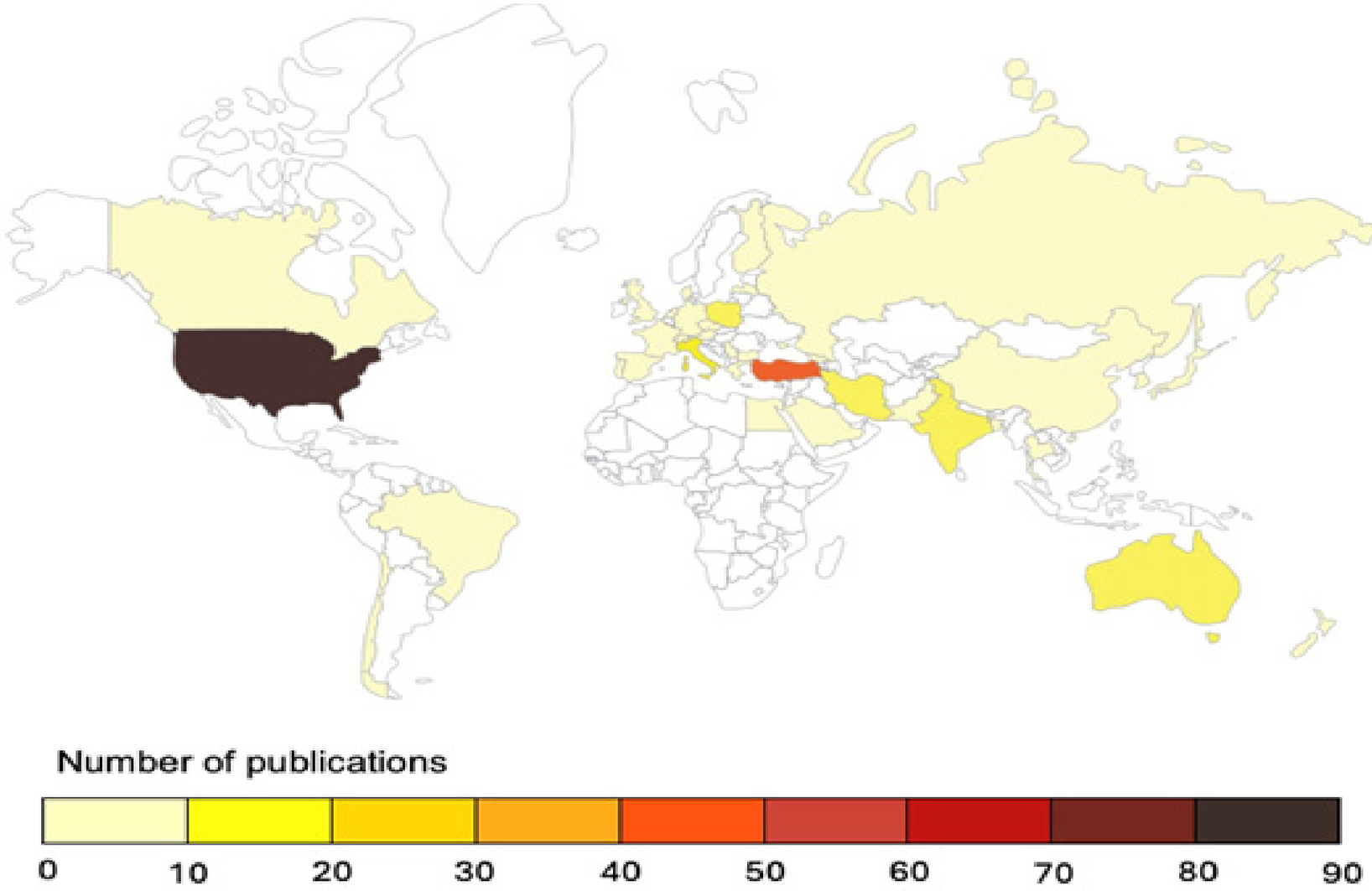

Figure 3. Map of the number of publications by country, with 39 countries represented.

Diagnostic criteria for PCOS in adolescents

Table 3 summarises the number of articles by the diagnostic criteria used in the diagnosis of PCOS among adolescents. In total 341 articles were reviewed. However, for the diagnostic criteria evaluation, we excluded 59 narrative reviews and 23 systematic reviews. Therefore only 259 articles were evaluated in Table 2. Out of the 259 articles, 47.7% (n = 124) used a single diagnostic definition of the standard PCOS definition, of which 68.5% (n = 85) used the 2003 Rotterdam criteria, followed by the National Institutes of Health (NIH) criteria (22.7%, n = 28), European Society of Human Reproduction and Embryology (ESRHRE) (4.0%, n = 5), Androgen Excess and PCOS Society (AEPCOSS) (2.4%, n = 3), and ICPE (2.4%, n = 3). Meanwhile,10.8% (n = 28) of the articles used combination of two or three of the standard PCOS definitions. Other types of diagnosis definition (26.9%, n = 70) were PCOS definition provided by other societies such as the Sultan and Paris's Criteria, the Pediatric Endocrine Society Guidelines and the International Consortium Update Reports. The remaining articles did not specify the exact criteria used for diagnosis. Instead, the diagnosis in the study population was based on a combination of several common criteria, such as evidence of hyperandrogenism, menstrual irregularities, or features of polycystic morphology, without adhering to any standard PCOS diagnostic definition.

Table 3. Number of articles by the diagnostic criteria used in the diagnosis of PCOS among adolescents (excluding reviews).

Diagnostic Method	Number of articles (n, %) N = 259
1.Total Single Method:	124 (47.9%)
Rotterdam	85 (68.5%)
NIH	28 (22.7%)
ESRHRE	5 (4.0%)
AEPCOSS	3 (2.4%)
ICPE	3(2.4%)
2. Multiple Methods	28 (10.8%)
3. Other Types	70(27.0%)
4. Not specify	37(14.3%)

NIH: National Institutes of Health; ESRHRE: European Society of Human Reproduction and Embryology; AEPCOSS: Androgen Excess and PCOS Society; ICPE: International Consortium of Pediatric Endrocrinology.

DISCUSSION

This scoping review aimed to describe the characteristics of PCOS studies and summarised the available diagnosing methods of PCOS among adolescents. Overall, we have observed an increasing trend in PCOS-related studies among adolescents, likely driven by the rising prevalence of obesity among children and adolescents worldwide (Cunningham et al. 2022; Horesh et al. 2021). Majority of the included studies were observational studies primarily conducted in the Western countries indicating the paucity of PCOS studies in Asian adolescents. In addition, the use of adult definitions for PCOS diagnosis in adolescents' studies is also debatable. Thus, this scoping review assembles and provides insights into the characteristics of current PCOS studies in adolescents to aid the direction of future research efforts in this area. Hence, this will help researchers to identify relevant research topics in PCOS among adolescents and preventing repetition and redundancy.

Characteristics of PCOS studies in adolescents

We found that more than half (~ 60%) of the included studies were observational, of which 50% were cross-sectional. The main limitations were small sample size and potential bias due to the non-community-based study (Glintborg et al. 2012; Simpson et al. 2020; Skrzynska et al. 2022). Thus, the results can only be applied to a subgroup of the population with similar characteristics. Furthermore, research on adolescent PCOS was primarily conducted in the West focusing mainly on White women. Therefore, we recommend PCOS studies in Asian adolescents, especially in the South-Eastern population, where the obesity prevalence is also on the rise.

Diagnosing methods of PCOS in adolescents

In this scoping review, we extend the information by summarising the diagnosis methods in adolescents' studies as a reference for researchers. The diagnosis of PCOS is primarily achieved through clinical history and physical findings. The principal features are hyperandrogenism (biochemical evidence of excess androgen production or hirsutism), irregular menstruation caused by chronic anovulation, and PCOM from ultrasound. PCOS studies in adolescents have been adopting the three commonly used definitions for adult PCOS namely; i) NIH criteria, ii) Rotterdam Criteria, and, iii) AEPCOSS (Escobar and Héctor 2018). Although differing in the combination of criteria used to define PCOS, all the above definitions include hyperandrogenism (clinical and/or biochemical), ovulatory dysfunction, and PCOM as part of the diagnostic criteria (Livadas and Diamanti 2013).

Most of our included studies adopted the 2003 Rotterdam criteria. Both the Rotterdam and the AEPCOSS definitions require transabdominal ultrasound to obtain ovary size and appearance. The use of transabdominal ultrasound to measure polycystic ovaries is highly dependent on the evolving quality of the machines and the operator's skill. Thus, potentially leading to variability in the diagnosis of polycystic ovaries. Additionally, visualisation of ovaries by transabdominal ultrasound can be challenging in obese individuals. The visibility of the ovaries may be hindered by the thickness of the abdominal wall and increased subcutaneous fat. Consequently, affecting the accuracy of the ovary's evaluation. In addition, PCOM is a common image of ovaries during puberty (Milczarek et al. 2019). Therefore, the role of ultrasound in the diagnosis of PCOS in adolescents is yet to be proven.

The absence of adolescent-specific diagnostic criteria and management guidelines when screening participants may lead to overdiagnosis of PCOS during in adolescents (Witchel et al. 2015; Pena and Metz 2018). The main diagnostic features of PCOS in adult women, such as irregular menstrual cycles, acne, and PCOM, may overlap with the normal pubertal physiological events (Legro et al. 2013; Witchel et al. 2015). Therefore, the adult cut-off may not be reliable or applicable to adolescents. Realising this, the ICPE recommended that diagnosis of PCOS in adolescent girls should be made based on the presence of irregular menstrual cycles well defined according to time post-menarche and clinical and/or biochemical evidence of hyperandrogenism after the exclusion of other pathological conditions that mimic PCOS (Witchel et al. 2019). PCOM from pelvic ultrasound is excluded to diagnose PCOS in adolescents as it can lead to overdiagnosis (Teede et al. 2019; Pena et al. 2020). This recommendation was supported by the Paediatric Endocrine Society (PES) and aligns with diagnostic criteria for adolescents in the 2018 International Evidence-Based Guidelines for the Assessment and Management of PCOS across the lifespan, resulting in the ICPE 2017. However, only three of our included studies were using this definition (Sari et al. 2020; Pena et al. 2022; Donbaloğlu et al. 2022). The ICPE 2017 was developed and recommended by an international panel of pediatric and endocrine experts (Rosenfield 2015) following an update on the pathophysiology, diagnosis, and treatment of PCOS specific to the management of adolescents with the disorder (Ibáñez et al. 2017). Thus, it may best suit the diagnosis of PCOS in adolescent girls and might be a consensus on PCOS diagnosis among adolescents.

Research approach and gaps of PCOS studies in adolescents

As mentioned previously, majority of the current research studies have reported on PCOS prevalence among adolescents. However, the absence of a consensus on adolescent-specific diagnostic criteria and management guidelines when screening participants makes comparison between studies difficult. Therefore, more evidence-based research can be directed towards refining the diagnostic criteria for PCOS in adolescents. For example, longitudinal studies to evaluate the changes of emerging PCOS biomarkers, such as the sex hormone-binding globulin (Qu and Donnelly 2020), insulin-like peptide-3 (Yetim et al. 2016), and inhibin A (Adu Gyamfi et al. 2020) as the disease progresses. These longitudinal studies of emerging biomarkers may aid in the diagnosis and treatment of adolescents with PCOS. It is worth noting that the diagnostic criteria for PCOS are continually evolving as our understanding of the condition improves. Therefore, ongoing research and refinement of the diagnostic criteria are necessary to ensure accurate diagnosis and optimal care for adolescents with PCOS.

Strength and limitations

To our knowledge, this is the first scoping review to identify characteristic and summarise the common diagnosing methods used in PCOS research among adolescents. This review captured a holistic view of how PCOS is diagnosed in adolescents across different studies. Thus, the review can guide researchers to focus on areas needing improvement, such as developing more accurate, less invasive, or more accessible diagnostic tools. The current review generally discussed on the common diagnostic tools used on adolescents across countries without considering factors that may influence PCOS diagnosis in adolescents apart from pubertal development. However, it is also important to highlight that

ethnicity may influence PCOS diagnosis in adolescents. In 2018, the International PCOS Network suggested that ethnic variations should be considered in the management of PCOS (Teede et al. 2018). Therefore, future reviews should discuss on ethnic variations in PCOS diagnosis among adolescents which will facilitate appropriate diagnostic,interventional,and preventive measures.

CONCLUSION AND FUTURE DIRECTION

A major gap in PCOS research among adolescents is the limited understanding of the condition's underlying mechanisms in this age group. Enhancing our knowledge of these mechanisms could improve the diagnosis of PCOS and subsequently assist in the development of evidence-based guidelines for its management and treatment. We propose that the primary goal of laboratory testing is to support the diagnosis of PCOS, rule out other potential causes of menstrual irregularity and clinical hyperandrogenism, and screen for associated clinical issues such as T2DM and hyperlipidemia. Thus, it could circumvent under- and overdiagnosis of PCOS in adolescents (Ibáñez et al. 2017; Pena and Metz 2018) for proper treatment and management.

We are now moving towards a more targeted and personalised approach in disease prevention and management, it is also suggestive that individualised management is the most promising strategy for optimal control of reproductive and metabolic outcomes for PCOS patients (Kostopoulou et al. 2020; Trent and Gordon 2020). As understanding of PCOS evolves, research can contribute to personalized treatment plans that consider the unique developmental stage of adolescents. This approach can improve treatment efficacy and patient satisfaction.

Author contributions

All authors contributed to the development of the research question and study design. SRA conducted the first stages of the scoping review by identifying relevant studies through database searching. All authors participated in the screening of relevant articles, abstract, and full text reviews. The first draft of the introduction and discussion was written by AKNZI, methods section by SRA, results section by NAZA, NAS, SSH, RMWMZ, YZT, FHM, FS, LAH, MKNK and SRA. All authors reviewed, edited, and provided extensive feedback on all portions and drafts of the manuscript. All authors read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT
The datasets used and/or analysed during the current study are included as supplementary (S1).

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CONFLICTS OF INTEREST
The authors declared no conflicts of interest.

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