Epidemiological Aspects of Polycystic Ovary Syndrome

Short title: Epidemiological Aspects of PCOS

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Abstract

Polycystic ovary syndrome (PCOS) affects 10–13% of women worldwide and is characterized by metabolic, reproductive, dermatological and psychological manifestations, with long term health implications. The aetiology of PCOS is complex and multifactorial, involving genetic predisposition and environmentally driven increases in obesity, manifesting as hyperandrogenism and insulin resistance. Research has been underfunded in this condition with significant remaining knowledge gaps, particularly in its pathophysiology, heterogeneity, and long-term natural history. Epidemiological research is essential for understanding the natural history of this chronic and complex condition with current insights gaps and future directions outlined herein.

In Brief

PCOS is one of the most common endocrine disorders in reproductive-aged women, causing diverse clinical manifestations with significant long-term health impacts. This review provides contemporary epidemiological evidence on PCOS outcomes while highlighting methodological limitations and research priorities.

Introduction

Polycystic ovary syndrome (PCOS) is a complex heterogeneous multisystem disorder affecting 10-13% of reproductive-aged women globally (1,2). The aetiology is multifactorial, involving epigenetic and genetic susceptibility, hypothalamic and ovarian dysfunction, hyperandrogenism, insulin resistance, and adiposity-related mechanisms (3). PCOS has traditionally been regarded as a reproductive disorder; however, it is now clear that PCOS is a chronic metabolic, reproductive, dermatologic and psychological condition. Metabolic

sequelae include obesity, metabolic syndrome, impaired glucose tolerance, type 2 diabetes (T2D), and increased cardiovascular disease whilst reproductive features include oligomenorrhoea, anovulation, subfertility and high-risk pregnancy (1). Dermatological features can be prominent including hyperandrogenic features including acne, female pattern hair loss and hirsutism. Psychological sequelae include depression, anxiety, eating disorders, and impaired quality of life (1,2,4). Diagnosis of PCOS is recommended based on the International PCOS Guideline criteria, with diagnosis confirmed in adults when two of out the following three criteria are met: i) oligo/amenorrhoea ii) hyperandrogenism (clinical or biochemical) and iii) polycystic ovary morphology or elevated anti-Müllerian hormone (AMH) levels. In adolescents, both oligo/amenorrhoea and hyperandrogenism (clinical or biochemical) criteria need to be met for diagnosis and ovarian markers are not applicable (1).

Epidemiological studies in PCOS

In seeking to understand the features, natural history, determinants and variation in this common condition, epidemiological studies are essential. The chronic and complex nature of PCOS lends itself well to epidemiological research. These observational studies capture and analyse disease occurrence and health outcomes in a population; they can also investigate associations between exposures and health outcomes. Study designs include cohort and cross-sectional studies, either at a single time point or following individuals over time to assess the incidence, association with exposure to risk factors, and natural history. Epidemiological studies are the only design that can address these key issues, yet they have both strengths and limitations. In the case of PCOS, epidemiological research is both essential and challenging. Diagnostic criteria have evolved over time and are variably applied, populations are often selected (clinical populations) and are mostly from high income regions, clinical features are variably defined and captured, and overall studies are often difficult to pool or aggregate. Here, we explore all various types of epidemiological

studies to explore current knowledge on PCOS prevalence, features, burden and natural history, whilst highlighting these challenges and noting next steps to strengthen evidence on these characteristics in PCOS.

Large-scale epidemiological studies provide valuable opportunities to assess the associated health impacts and economic burden. However, many existing longitudinal epidemiological studies rely on self-reported PCOS status without clinical or biochemical confirmation, due to logistical constraints and feasibility in large-scale population studies. Studies with clinically validated PCOS diagnoses can collect detailed data on each diagnostic criterion, enabling differentiation between PCOS subtypes, enhancing understanding of the syndrome's pathogenesis. Most importantly, we need longitudinal data to understand subtypes in relation to clinical implications. Studies using self-reported PCOS status or clinically validated PCOS status each have their strengths and weaknesses and provide distinct yet complementary contributions to the overall understanding of the condition.

Genome-wide association studies (GWAS) have identified candidate genes contributing to the heritability of PCOS and revealed a shared genetic architecture across its diverse phenotypic expressions. It is important to note that identified genetic loci only account for approximately 10% of its estimated 70% heritability (5). Emerging evidence implicates epigenetic alterations and disrupted developmental programming as contributory factors in the pathogenesis of PCOS (5). Manifestations of PCOS may emerge as early as childhood or during puberty, indicating a significant role of genetic susceptibility in its aetiology (6). PCOS exhibits strong heritability, with daughters of affected women having a five-fold increased risk of developing the condition compared to daughters of controls (7). Regardless of the diagnostic criteria used, whether NIH, Rotterdam, or self-reported, women with PCOS exhibit similar genetic profiles, supporting the heritable nature of the condition and reinforcing the validity of self-reported PCOS in epidemiological and genetic research (8).

The presence of genetically similar profiles across diverse PCOS phenotypes indicates that current diagnostic criteria may inadequately distinguish biologically distinct subtypes (9). Reclassifying individuals with PCOS into phenotypically defined subtypes may enhance the delineation of genetic, epigenetic, and other pathogenic mechanisms underlying the syndrome (9).

Despite PCOS being a prevalent endocrine disorder with significant metabolic, reproductive, and psychological consequences, natural history remains poorly understood due to the scarcity of large, community-based longitudinal studies. Most existing research is derived from clinic-based or cross-sectional cohorts, limiting generalizability and establishing only associations rather than causation. Clinic or hospital or insurance-based data sets, whilst they are more accessible, are likely not representative of community dwelling women. Whilst longitudinal studies provide critical insights into disease progression and long-term outcomes, their implementation is hindered by substantial logistical, financial and time constraints. Despite these challenges, such studies are essential for identifying modifiable risk factors, improving early intervention strategies, and refining clinical management to mitigate the long-term health burden of PCOS.

In large population-based studies, conducting physical or laboratory assessments to screen for PCOS is often impractical and unfeasible due to resource constraints. Consequently, other alternative approaches that are commonly used include self-reported PCOS status, self-reported symptoms consistent with PCOS, or self-reported physician-diagnosed PCOS. This facilitates the study of larger populations with longitudinal assessments over extended periods. The ongoing Australian Longitudinal Study on Women's Health (ALSWH) is a national, longitudinal, population-based study of more than 57,000 women in four age cohorts, with follow-up now for almost 30 years since 1996. This study utilizes self-report throughout. Self-reported physician-diagnosed PCOS has been validated against menstrual irregularity, a key diagnostic feature of PCOS (10). In contrast, the ongoing Northern Finland

Birth Cohort, consisting of 12,058 live births in 1966 with over 46 years of follow-up, has utilized a symptom-based PCOS diagnosis. This method has been validated, with studies demonstrating that 82.5% of women who self-reported hirsutism and irregular menses met the Rotterdam criteria (the prevailing criteria at the time these studies were completed) for PCOS upon clinical assessment, compared to only 14.4% of those without these symptoms (11). The sensitivity and specificity of self-reported symptoms in predicting PCOS using the Rotterdam criteria were 89% and 78%, respectively, highlighting the feasibility and acceptability of this approach in large-scale research (11). Studies relying on self-reported PCOS often lack sufficient detail on diagnostic criteria, limiting the ability to accurately define PCOS subtypes. While some large cohort studies have incorporated clinical assessments to establish a definitive diagnosis, this approach demands significantly greater resources, including time, funding, and specialized personnel. Consequently, the trade-off between study feasibility and diagnostic accuracy remains a key challenge in epidemiological research on PCOS.

To try to understand the natural history and epidemiology of PCOS, it is important to have longitudinal cohort studies to provide essential understanding of the progression and long-term outcomes of the syndrome. It is also essential to have the most generalizable and least medically biased population; including individuals without PCOS in epidemiologic studies will help establish population-specific normative ranges for various PCOS-related features (12). Key recommendations for conducting epidemiologic studies in PCOS include selecting appropriate populations and diagnostic criteria (which should ideally align with the International Guideline recommendations), ensuring broad and unbiased assessments of PCOS subtypes, and utilizing accurate detection methods (12). Study design should address statistical power, minimize biases, establish normative reference cohorts, and incorporate clear governance, ethical compliance, and standardized data collection (12). Adequate

resourcing, biobanking considerations, and open data access for qualified researchers are essential for maximizing study impact.

Global prevalence of PCOS and impact of BMI

Prior systematic reviews have also explored PCOS prevalence globally, yet limitations included focusing on adults or adolescents, excluding diagnosis based on self-report or International Classification of Diseases (ICD) codes), only including women from one ethnicity or region and not reporting according to ethnicity or region. For this reason, prevalence of PCOS was assessed on global meta-analysis in the recent 2023 updated of the 2023 International PCOS Guidelines, applying Rotterdam diagnostic criteria. Overall, 106,641 participants and 106 prevalence estimates were generated from 81 studies in the global meta-analysis. Prevalence of PCOS was 9.7% (95% CI 8.91, 10.53), indicating reasonably consistent prevalence. However, it was highest among women from the South-East Asian [pooled prevalence 12.8% (95% CI 9.92, 15.63)] and Eastern Mediterranean region [pooled prevalence 10.5% (95%CI 8.61, 12.41)] (2).

The Global Burden of Disease Study (GBD) 2019 also provided an assessment of the global, regional, and national burden of PCOS. The study indicates that the highest age-standardized incidence and disability-adjusted life years (DALYs) rates in 2017 were observed in Latin America, as was the largest percentage increases in both rates from 2007 to 2017 were seen in Tropical Latin America. In contrast to the meta-analysis, at the national level the GBD study suggested that countries such as Ecuador, Peru, Bolivia, Japan, and Bermuda had the highest age-standardized incidence rates and DALYs rates in both 2007 and 2017. It was also noted that the GBD in 2019 suggested there were 66.0 million prevalent cases of PCOS globally, with an age-standardized point prevalence of 1677.8 per 100,000 women, a 30.4% increase since 1990 (13). Variations in how PCOS was defined as a major limitation that prevented valid comparisons between different regions. Overall,

204 further research is needed to explore regional prevalence using similar diagnostic criteria
205 and considering health system access and other factors.
206
207 A key factor that impacts PCOS prevalence is the rising burden of obesity globally.
208 Environmentally-driven lifestyle factors, including food supply, high density caloric and ultra-
209 processed foods and limited physical activity in many world regions is driving a rise in
210 obesity prevalence. BMI, in turn, drives both the prevalence and severity of PCOS, with
211 higher rates of weight gain and obesity (1,2). Obesity contributes to insulin resistance, and
212 hyperandrogenism, both of which are reversed, along with other clinical features with
213 significant weight loss. In this context, population systems levels and policy interventions as
214 well as supporting individuals, are all critical to tackle the obesity epidemic and limit the
215 prevalence, severity, health and economic burden of obesity.
216
217 **Reproductive outcomes**

218 Reproductive symptoms in women with PCOS appear during adolescence, where women
219 with PCOS experience irregular menstrual bleeding. This is one of the diagnostic criteria in
220 women with PCOS, but importantly irregular cycles are common in the first year after
221 menarche in all adolescents. The definition of oligomenorrhoea when menstrual cycles < 21
222 days or > 35 days is not applicable until more than three years after menarche (1). The
223 irregular bleeding is due to ovulatory dysfunction, characterised by follicular arrest at the
224 antral stage, resulting in anovulation. The increased number of antral follicles is another key
225 element and diagnostic criteria in PCOS in adults, assessed by ultrasound or by AMH
226 measurement. In adolescents, polycystic ovary morphology is common and should not be
227 used for diagnosis. Importantly, weight gain worsens the ovulatory dysfunction whereas
228 weight loss has been shown to ameliorate ovulatory dysfunction and can restore menstrual
229 cycles (1,14).

The anovulation causes increased rates of infertility. Infertility attributable to PCOS has in fact increased over the years, with more than 12 million prevalent cases globally in 2019 (15). This increase is associated with greater health burdens for patients and elevated costs for health care systems. Many women with PCOS will seek infertility treatment during their reproductive years, with ovulation induction recommended as the first-line therapy (16,17). One study showed that by age 43 – 48, more than 50% of women with PCOS had experienced infertility issues, defined as unsuccessfully having tried to become pregnant for more than 12 months (17).

Being diagnosed with PCOS at an earlier age has recently been shown to improve fertility outcomes (18,19). A Swedish register study showed that women diagnosed with PCOS earlier in life had higher fecundity compared with women diagnosed later (19). A population-based cohort study from Australia showed that later diagnosis was associated with two times increased odds of giving birth at an advanced maternal age (18). Timely diagnosis and knowledge about reproductive implications of PCOS diagnosis can increase awareness of the need for family planning and the potential need for infertility treatment. One study recently showed that women with PCOS on average were three years younger compared with women in general when they started fertility treatment (20). As age is one of the most important determinants influencing infertility treatment results, this further underlines the importance of being diagnosed in a timely manner.

It is important to note that, with access to infertility treatment, the likelihood of having at least one child is comparable between women with and without PCOS in many studies (16,19,21,22). This is supported by evidence that before diagnosis, women with PCOS have lower fecundity, whereas following PCOS diagnosis, fertility rates are restored to that of the general population (16). A recent meta-analysis indicates that women with PCOS give birth at a younger age (23), however, data also support that a higher proportion of women with PCOS are giving birth at an advanced maternal age (i.e. >35 years) (18). Results regarding

the number of children at the end of the reproductive period are conflicting, and while some studies report a similar number of children (21,24), numerous other studies indicate that women with PCOS ultimately have a smaller family size (18,19,22).

During pregnancy, women with PCOS are more likely to experience pregnancy complications. Women have about 50% increased odds of experiencing a miscarriage (23). This can in part be due to differences in the endometrium between women with PCOS compared with healthy controls, contributing both to subfertility and poor reproductive outcomes (25). Hyperinsulinemia attributable to PCOS, compounded by the increased demands of pregnancy results in a 2.4-fold increased risk of gestational diabetes, after adjusting for age and BMI (23). Women with PCOS exhibit an increased prevalence of hypertensive disorders of pregnancy, with odds ratios of 2.2 for gestational hypertension and 2.3 for preeclampsia, and these associations persist after adjustment for age and BMI (23). Neonatal adverse outcomes are also increased, with offspring to women with PCOS more often being born preterm, and with lower birth weights and higher rates of fetal growth restriction (26). In the 2023 PCOS guideline, it is recommended that since women with PCOS have higher risk pregnancies, the PCOS status should be properly identified during antenatal care, so that appropriate pregnancy monitoring can be assured (1).

There are few prospective studies available on women with PCOS in peri- and postmenopausal age, but it seems that the ovarian function normalizes in the late reproductive age, with increased number of ovulatory cycles and more regular cycles (11). Natural menopause is reported to occur at a later age (21). This may be due to the increased number of follicles seen in women with PCOS, as menopause occurs when the number of ovarian follicles declines below a critical threshold (27). Follicle-stimulating hormone (FSH) levels remain lower in women with PCOS compared with those without, even up to senescence, indicating that this alteration may be part of PCOS pathophysiology (27).

Metabolic outcomes

Dyslipidaemia

Patients with PCOS display a dyslipidaemia that is similar to that of the metabolic syndrome, characterised by raised triglycerides (both fasting and post-prandial), reduced high density lipoprotein cholesterol (HDL-C) and increased small, dense low-density lipoprotein cholesterol (LDL-C) particles. Insulin resistance is a key driver of this dyslipidaemia, leading to increased hepatic very low-density lipoprotein (VLDL) triglyceride synthesis and increased hepatic apo-B100 production. A systematic review and meta-analysis of 30 studies of dyslipidaemia in patients with PCOS found that LDL-C and triglyceride concentrations were higher and HDL-C lower in PCOS subjects compared to controls (28). These differences are apparent across the weight spectrum of women with PCOS (29).

Hypertension

Meta-analyses have confirmed an increased prevalence of hypertension in young women with PCOS compared to controls (30). Longitudinal follow-up of community-based subjects in Australia showed that the risk of incident hypertension was significantly greater among women with PCOS than in controls (31). This risk was evident across all body mass index (BMI) categories but was exacerbated by obesity (31). A number of pathological alterations may contribute to an increased risk of hypertension, including sympathoexcitation, activation of the renin-angiotensin-aldosterone axis and reduced nitric oxide production (32); both insulin resistance and hyperandrogenism have been implicated as important drivers (32).

Cardiovascular disease

Studies of surrogate markers of cardiovascular risk have demonstrated elevated cardiovascular risk in PCOS. These include an increase in carotid intima media thickness (CIMT) (33), myocardial dysfunction (34), coronary artery calcification (35), arterial stiffness

(33), and endothelial dysfunction (36). However, until recently, studies had failed to confirm if these elevated risk measures led to an increase in cardiovascular events. In a longitudinal population study of >170,000 women diagnosed with PCOS in the UK, Berni *et al* observed a 26% increased risk of major adverse cardiovascular events (MACE) compared with controls (37). Weight gain, type 2 diabetes and indices of socioeconomic deprivation were predictive of progression to a cardiovascular event. These results were confirmed in the Northern Finland Birth Cohort, in which the BMI-adjusted hazard ratios for MACE were 2.33 and 2.47 for PCOS diagnosed by the Rotterdam or NIH criteria, respectively (38). In a systematic review and meta-analysis of 20 studies involving 1.06 million women (369, 317 with PCOS), PCOS was associated with a higher risk of composite cardiovascular disease (odds ratio [OR] 1.68), composite ischaemic heart disease (OR 1.48), myocardial infarction (OR 2.50) and stroke (OR 1.71) (39). These observations underscore the importance of recognizing PCOS as a risk factor for cardiovascular disease, and in undertaking a cardiovascular risk assessment as part of long-term patient management.

Overweight/obesity

Overweight and obesity are common comorbidities in patients with PCOS, with a pooled prevalence of obesity of 61% in a meta-analysis of over 100 studies (40). An increased risk of an elevated BMI was independent of PCOS diagnostic criteria, geographical region or age. Compared to non-PCOS populations, the prevalence of overweight was also increased, as was central obesity, more so among Caucasians than Asians (40). Whilst some studies indicate that fat accumulation is generalised (41), others have shown a predilection for the visceral compartment (42). Several mechanisms may be involved, including intra-adipose generated androgen production which drives lipotoxicity (43). Women with PCOS may thus be more metabolically impaired for the same BMI or overall fat accumulation. Bidirectional Mendelian randomisation analyses have shown a causal effect of BMI on PCOS but not vice versa (44). These studies emphasise the importance of weight

management in the prevention and management of PCOS, especially in early adulthood when weight increase may have a particular impact on PCOS emergence (45).

Insulin resistance, impaired glucose tolerance and type 2 diabetes

Insulin resistance, involving insulin receptor and post-receptor signalling defects, is a biochemical hallmark of PCOS, leading to reduced sex hormone binding globulin (and raised free androgens), altered gonadotrophin secretion and increased ovarian androgen production. Genetic studies implicate insulin resistance as an independent risk factor for the development of the disorder (8). A systematic review and meta-analysis of euglycaemic hyperinsulinaemic clamp studies, widely accepted as the gold standard measure of insulin sensitivity, confirmed a significant reduction in insulin sensitivity in women with PCOS (46). This was independent of BMI although a raised BMI was shown to exacerbate this and did so to a greater extent than in control women. The risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes (T2DM) is thus increased among subjects with PCOS, with a pooled analysis of 41 studies estimating odds ratios of 3.18, 3.90 and 2.87, respectively (1). Importantly, relying on HbA1c as a diagnostic method for type 2 diabetes has the potential to misdiagnose 50% of patients at a HbA1c threshold of 6.5% (47). The 2023 International PCOS guideline thus advocates the oral glucose tolerance test as the preferred method for screening and diagnosis of T2DM in this population.

Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) and PCOS are characterised by shared risk factors, such as metabolic syndrome and insulin resistance, hence it is not surprising that several studies have identified an increased risk of MASLD in women with PCOS (48). However, many studies are hampered by their retrospective nature and potential ascertainment bias among other limitations. Hyperandrogenism has been mechanistically implicated in some studies (48) although further work is needed to confirm this and any role that androgen excess may have in disease progression.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a common comorbidity in women with PCOS, with an estimated prevalence of 20-35% in systematic reviews of published studies (49). The risk of OSA is significantly greater than controls, unaffected by PCOS diagnostic criteria, and higher in subjects with obesity than in those with a normal BMI (49). However, many of the studies to date are limited by selection bias, restriction to more significant categories of obesity, and a failure to adjust for confounders.

Dermatological outcomes

Common dermatological manifestations associated with PCOS include hirsutism, acne, female pattern hair loss, and acanthosis nigricans (AN). Though a majority of patients with PCOS have at least one skin manifestation (estimated 70-90% of patients who meet Rotterdam criteria), there is striking heterogeneity in the prevalence of cutaneous signs and poor concordance between skin severity and hyperandrogenemia and other systemic outcomes of the condition (50). Cross-sectional studies suggest differences in dermatological signs depending on the age of presentation and in distinct populations. Multiple studies and multidisciplinary expert groups recognize hirsutism as the most sensitive cutaneous sign of PCOS, with acne and female pattern hair loss as weaker predictors of hyperandrogenism, especially in the absence of hirsutism (1). Though not classically identified as a cutaneous marker of hyperandrogenemia, AN is reported in up to 40% of patients with PCOS and may be strongly associated with biochemical hyperandrogenemia and a diagnosis of PCOS.

Acne vulgaris

Acne is a common skin finding in adult females and may indicate hyperandrogenemia and/or PCOS. The Androgen Excess and PCOS (AE-PCOS) Society expert task force on female

adult acne concluded that increased androgens play a significant role in triggering sebum alterations that can give rise to acne, which in turn is associated with significant quality of life impact, anxiety, and depression (51). Numerous epidemiological studies evaluating acne in patients with PCOS suggest a prevalence of adult acne that is 1.6-fold higher in patients with PCOS in comparison to the general female population (30-40% of patients with PCOS vs. 17% in the general female population). More severe presentations of acne may indicate hyperandrogenemia.

Hirsutism

Hirsutism is defined as the growth of coarse terminal hair in androgen-sensitive areas: upper cutaneous lip, jawline, shoulders, chest, abdomen, back, thighs. Though its presence is considered predictive of hyperandrogenemia and PCOS in adults, and its prevalence in patients with PCOS is high (estimated at 50-75%) relative to its prevalence in the general population (estimated at 4-11%), the severity of hirsutism correlates poorly with androgen levels (52). Hirsutism is commonly assessed using the modified Ferriman-Gallwey (mFG) instrument, though there are shifting recommendations for determination of hirsutism by mFG score and whether this value should differ between populations due to potential influences of skin type, ethnicity, age, and other factors. Hirsutism is associated with significant quality of life impact and depression, with patient self-ratings best predicting severity compared to clinician assessments (53).

Assessment of dermatological outcomes

One significant practice gap in PCOS is the scarcity of grading tools to measure severity of skin signs especially those that capture responsivity to treatment (51). Another important consideration is the discordance of clinician-based scales with patient-reported self-assessment of clinical presentation and reported quality of life impact for skin signs. Several

studies have reinforced the importance of patient-reported outcomes over clinician ratings in determining the true severity of dermatological outcomes associated with PCOS.

Psychological features

Mental health disorders, though among the least understood complications of PCOS, are increasingly recognized as a significant burden for affected women (54). Research consistently demonstrates a high prevalence of mental health conditions in this population, with depression and anxiety being the most studied. The 2023 International PCOS Guideline cites 80 studies, reporting a striking prevalence of depression and anxiety in up to 80% of women with PCOS, with an odds ratio of 2.5 compared to unaffected women (1,2). Given the extensive research, the PCOS Guideline Clinical Research Roadmap concludes that further prevalence studies are unnecessary unless they focus on underrepresented subgroups, such as specific regional, ethnic, or life-stage populations, including adolescents and women in the perinatal period (55).

Beyond depression and anxiety, emerging evidence highlights a heightened risk of eating disorders and body image disturbances in women with PCOS. The 2023 PCOS Guideline meta-analysis found that the odds of any eating disorder are up to 2.9 times higher in women with PCOS, raising concerns about the potential conflict between standard lifestyle recommendations—such as dietary restrictions or weight-focused interventions — and the needs of those with concurrent eating or body image disorders, as such approaches may worsen psychological distress (4,56). While research on other mental health conditions in PCOS remains limited, large cohort studies suggest elevated risks of borderline personality disorder, bipolar disorder, obsessive-compulsive disorder, and trauma-related disorders (57,58).

The mechanisms linking PCOS to mental health disorders are complex and multifactorial, although a recent genetic analysis found no shared genetic basis or causal relationship between PCOS and mental health disorders (59). Hormonal imbalances, including altered hypothalamic-pituitary-adrenal (HPA) axis stress response, hyperandrogenism (HA), and insulin resistance (IR) interact closely to jointly contribute to mental health disorders (60-62). Women with PCOS exhibit heightened HPA axis reactivity, leading to exaggerated stress responses that disrupt neurotransmitter systems (e.g., serotonin, dopamine) and impair neuroplasticity, fostering depression, anxiety, and other mental health disorders (61,63). Hyperandrogenism further exacerbates HPA axis dysfunction and directly impacts brain regions involved in emotion regulation, such as the amygdala, nucleus accumbens, and prefrontal cortex (64). However, the relationship between androgen levels and mental health disorders is complex with conflicting correlation (60,65). Insulin resistance, another hallmark of PCOS, is associated with increased oxidative stress and inflammation, both of which exacerbate HPA axis dysregulation (66). Additionally, insulin resistance in the brain has been linked to neuroplasticity deficits, particularly in the hippocampus, increasing the risk of cognitive decline and neuropsychiatric disorders (67). A growing body of evidence also supports the association between insulin resistance and depressed mood in women with PCOS (62,67). Moreover, physical symptoms of PCOS, such as obesity, hirsutism, acne, and infertility, often conflict with societal ideals of femininity and beauty, exacerbating psychological distress (67). Adverse childhood experiences (ACEs), including abuse, neglect, and household dysfunction, are more prevalent in women with PCOS and are strongly associated with an increased risk of mental health disorders (57). Together, these intrinsic (hormonal, metabolic) and extrinsic (social, environmental) factors interact synergistically, creating a multifaceted pathway that contributes to the high burden of mental health disorders in women with PCOS.

The healthcare costs associated with mental health disorders in PCOS are substantial, with a recent systematic review estimating that the direct annual costs for the most common

conditions—anxiety, depression, and eating disorders—exceed $4 billion (2021 USD) for the U.S. population alone (68). Despite this significant economic burden, there is a notable lack of research on psychological outcomes in randomized controlled trials (RCTs) for common PCOS treatments, such as combined oral contraceptives (COCP), metformin, antiandrogens, and fertility therapies (1,55). These gaps underscore the urgent need for more research to evaluate the impact of existing and novel treatments on mental health outcomes in women with PCOS, a priority highlighted in the 2023 PCOS Guideline Clinical Research Roadmap to ensure a more holistic approach to their care (1,55).

Conclusion

Epidemiological research has been critical in defining the prevalence, global burden, variation, associated risk factors and natural history of the diverse metabolic, reproductive, dermatological and psychological features of PCOS, it has also been plagued by challenges both inherent in large scale population level studies as well as those unique to PCOS. These include that PCOS is generally neglected in research with inadequate funding compared to the burden and impact of the condition. Other key challenges include a propensity for funding bodies to prioritise randomised controlled trials over critical longitudinal studies. In PCOS the evolution of diagnostic criteria, variable defining of clinical features and concentration of studies in high income regions have contributed to challenges and limited pooling and integration of existing data. Moving forward, application of evidence-based globally endorsed International Guideline Diagnostic criteria, harmonsied definitions and capture of data and greater research including across world regions is vital. These recommendations are captured in the recent International PCOS Research Roadmap that also provides a strategic guide to research priorities in this common condition (69).

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Author contribution statement

AEJ contributed to conceptualisation, writing the manuscript, review and editing of the manuscript. AR, KS, MF, CTT and HT contributed to writing the manuscript, review and editing of the manuscript.

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