Understanding The Influencing Factors in The Onset of PCOS: A Review

Erna Yovi Kurniawati[1]
[1]Midwifery Profession Department, Alma Ata University, Yogyakarta, Indonesia
yovi.raharjanto@gmail.com

ABSTRACT

Polycystic ovary syndrome (PCOS) is an endocrine disorder prevalent in women of reproductive age. This comprehensive review aims to shed light on the various factors that contribute to the onset and progression of PCOS. The analysis includes a thorough exploration of genetic predisposition, environmental influences, and lifestyle factors in the context of their role in the hormonal dysregulation, insulin resistance and ovarian dysfunction associated with PCOS. The complex relationship between these factors and the clinical manifestations of PCOS, including irregular menstrual cycles, hyperandrogenism, and polycystic ovarian morphology, is also discussed. By synthesizing current research findings, this review provides a comprehensive understanding of the various factors that influence the occurrence of PCOS, offering valuable insights for reference in reproductive health education, early detection of PCOS, and development of comprehensive prevention and intervention combinations.

Keyword: *Environmental, Lifestyle, Mental Disorder, Polycystic Ovary Syndrome, Risk Factor*

ABSTRAK

Sindrom ovarium polikistik (PCOS) adalah kelainan endokrin yang lazim terjadi pada wanita usia reproduksi. Tinjauan komprehensif ini bertujuan untuk menjelaskan berbagai faktor yang berkontribusi terhadap timbulnya dan perkembangan PCOS. Analisis ini mencakup eksplorasi menyeluruh terhadap predisposisi genetik, pengaruh lingkungan, dan faktor gaya hidup dalam konteks perannya dalam disregulasi hormon, resistensi insulin, dan disfungsi ovarium yang terkait dengan PCOS. Hubungan yang kompleks antara faktor-faktor ini dan manifestasi klinis PCOS, termasuk siklus menstruasi yang tidak teratur, hiperandrogenisme, dan morfologi ovarium polikistik, juga dibahas. Dengan mensintesis temuan penelitian terkini, tinjauan ini memberikan pemahaman yang komprehensif mengenai berbagai faktor yang memengaruhi terjadinya PCOS, memberikan wawasan yang berharga sebagai referensi dalam pendidikan kesehatan reproduksi, deteksi dini PCOS, dan pengembangan kombinasi pencegahan dan intervensi yang komprehensif.

Kata Kunci: Lingkungan, Gaya Hidup, Gangguan Mental, Sindrom Ovarium Polikistik, Faktor Risiko

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) stands as a significant and prevalent endocrine disorder, presenting a serious challenge to the health and well-being of reproductive-aged women globally (Hoeger et al., 2021). PCOS is characterized by a complex interplay of hormonal imbalances (Gurule et al., 2023), insulin resistance (Purwar & Nagpure, 2022), and ovarian dysfunction, often manifesting as irregular menstrual cycles, hyperandrogenism, and polycystic ovarian morphology (Shorakae et al., 2018). The severity of PCOS extends beyond its reproductive implications, encompassing metabolic (Waniczek et al., 2023), cardiovascular

(Joksimovic Jovic et al., 2021; J. Zhang et al., 2020), and psychological ramifications (Chen et al., 2020; Dubey et al., 2021; Majidzadeh et al., 2023).

Understanding the influencing factors in the onset of PCOS is paramount given its far-reaching impact on women's health. Recognizing the intricate web of genetic(Bhandary et al., 2022), environmental(Sharma et al., 2021), and lifestyle(Lim et al., 2019; B. Zhang et al., 2020) factors contributing to PCOS is crucial for developing effective prevention and management strategies. The prevalence of PCOS is on the rise, and its implications extend beyond fertility concerns (Ignatov & Ortmann, 2020; Mirzohidovna, 2021; Negdel et al., 2021), encompassing long-term health risks such as diabetes (Mustaniemi et al., 2018), cardiovascular diseases (Zhu et al., 2021), and compromised mental well-being (Cheol, 2022; Greenwood et al., 2018).

This review seeks to underscore the seriousness of the PCOS problem by delving into the multifaceted factors that influence its occurrence. By shedding light on the various determinants, ranging from genetic predispositions to lifestyle choices, we aim to emphasize the importance of a comprehensive understanding of PCOS etiology. This knowledge is essential not only for clinicians and researchers but also for empowering individuals to adopt proactive measures in mitigating risk factors and managing the condition effectively. Ultimately, unravelling the complexities of PCOS is instrumental in shaping a more informed and targeted approach toward addressing this critical reproductive health concern.

METHODS

The research articles were sought through databases PubMed, ScienceDirect, and Google Scholar for publications spanning five years (2019-2023) and written in both Indonesian and English. The keywords employed in the article search were aligned with Medical Subject Titles (MeSH), encompassing terms such as "high risk," "risk factor," "PCOS (SOPK)," "polycystic ovary syndrome (sindrom ovarium polikistik)," "obesity," "toxicant," "eating behavior," "lifestyle," "BMI," and "mental disorder," in accordance with the PICOTs framework (Population, Intervention, Comparators, Outcome, Time), as illustrated in Table 1.

Table 1. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	Mus musculus, rats, mice, murine, sheep, human	In vitro
Intervention	Risk factors related to PCOS	Studies irrelevant to PCOS risk factors
Comparators	With or without control group	-
Outcomes	Study that relevant results related to risk factor PCOS	Studies that do not provide sufficient information to be evaluated
Time	2019-2023	< 2019
Study design	Observational and experimental study	-
Language	Indonesian, English	Besides Indonesian and English

Evaluate the quality of risk of bias studies using the Joanna Briggs Critical Appraisal (JBI) instrument (Barker et al., 2023; *JBI Critical Appraisal Tools | JBI*, n.d.) for cohort, case control, cross sectional, Rob 2 for RCT studies (Sterne et al., 2019), and PRISMA (Preferred Reporting Item for Systematic Reviews and Meta-Taken) (Haddaway et al., 2022) guidelines (see figure 1).

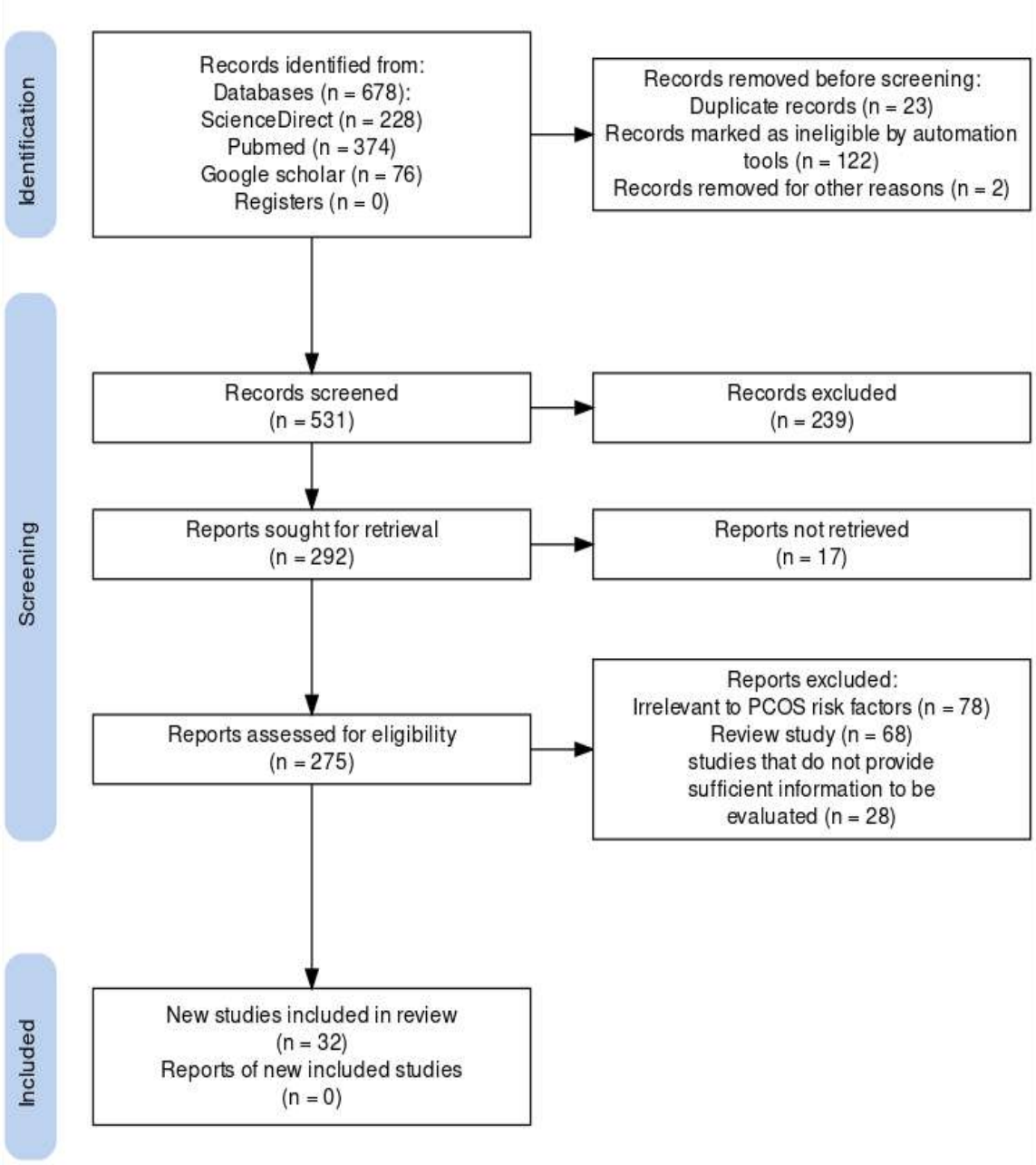

Figure 1. PRISMA flow

The literature obtained from the search results underwent a thorough examination to identify any instances of duplication. After eliminating duplicates, the remaining literature underwent a two-stage screening process. The initial stage involved evaluating the suitability of titles and abstracts against the predetermined inclusion criteria. Subsequently, the selected literature underwent a second round of screening, wherein the correspondence between the journal content and the predetermined inclusion criteria was analyzed. Both reviewers participated in this literature selection process to ensure precision and minimize errors (Haddaway et al., 2022; Higgins et al., 2019).

Table 2. Risk of Bias Analysis Results

Author, Year	Risk of Bias Item Instrument											Risk of bias conclusions
Zhang B, 2020 (B. Zhang et al., 2020)	+	+	+	+	+	+	+	+	+	+	+	Eligible
Greenwood, 2020 (Greenwood et al., 2020)	+	+	+	+	+	+	+	+	+	+	+	Eligible
Jurczewska, 2023 (Jurczewska et al., 2023)	+	+	+	+	+	+	+	+				Eligible
Javed, 2020 (Javed et al., 2020)	+	+	+	+	+		+	+				Eligible
Sharma, 2022 (Sharma et al., 2022)	+	+	+	+	+		+	+				Eligible
Khondker, 2022 (Khondker & Nabila, 2022)	+	+	+	+	+		+	+				Eligible
Lee I, 2020 (I. Lee & Dokras, 2020)	+	+	+	+			+	+				Eligible
Perovic, 2022 (Perovic Blagojevic et al., 2022)	+	+	+	+	+	+	+	+				Eligible
Satyaraddi, 2019 (Satyaraddi et al., 2019)	+	+	+	+			+	+				Eligible
Barrea L, 2021 (Barrea, Muscogiuri, Pugliese, De Alteriis, et al., 2021)	+	+	+	+	+	+	+	+				Eligible
Neubronner, 2021 (Neubronner et al., 2021)	+	+	+	+	+		+	+				Eligible
Abudawood, 2021 (Abudawood et al., 2021)	+	+	+	+	+		+	+				Eligible
Wang W, 2019 (Wang et al., 2019)	+	+	+	+	+	+	+	+				Eligible
Kirmizi D, 2020 (Kirmizi et al., 2020)	+	+	+	+	+		+	+				Eligible
Liang C, 2022 (Liang et al., 2022)	+	+	+	+	+	+	+	+				Eligible
Wahyuni, 2022 (Wahyuni et al., 2022)	+	+	+	+			+	+				Eligible
Guyansyah, 2021 (Guyansyah et al., 2021)	+	+	+	+			+	+				Eligible
Hasan M, 2022 (Hasan et al., 2022)	+	+	+	+	+	+	+	+				Eligible
Cheol J, 2022 (Cheol, 2022)	+	+	+	+	+	+	+	+				Eligible
Almeshari, 2021 (Almeshari et al., 2021)	+	+	+	+	+		+	+				Eligible

Author, Year	Risk of Bias Item Instrument									Risk of bias conclusions
Lin H, 2021 (Lin et al., 2021)	+	+	+	+	+	+	+	+		Eligible
Naz M, 2020 (Naz et al., 2020)	+	+	+	+	+		+	+		Eligible
Dybciak, 2022 (Dybciak et al., 2022)	+	+	+	+	+	+	+	+		Eligible
Damone, 2019 (Damone et al., 2019)	+	+	+	+	+	+	+	+		Eligible
Coban, 2019 (Çoban et al., 2019)	+	+	+	+	+		+	+		Eligible
Basar G, 2020 (Başar Gökcen et al., 2020)	+	+	+	+			+	+		Eligible
Pirotta, 2019 (Pirotta et al., 2019)	+	+	+	+	+	+	+	+		Eligible
Stefanaki, 2023 (Stefanaki et al., 2023)	+	+	+	+			+	+		Eligible
Anand S, 2022 (Anand et al., 2022)	+	+	+	+			+	+		Eligible
Jiskot, 2022 (Jiskoot et al., 2022)	+	+	+	+	+	+				Eligible
Lee J, 2023 (J. Lee et al., 2023)	+	+	+	+	+	+				Eligible

RESULTS

Searching for articles in the three databases using predetermined keywords resulted in 678 articles. The author conducted a duplication check, and 531 articles remained. Furthermore, the author screened 275 articles based on title and abstract. The author conducts screening based on full text and eligibility criteria, leaving 32 articles that will be analyzed. This systematic review is heterogeneous, with 2 articles using RCT methods, 18 cross-sectional articles, 11 case control articles and 2 cohort articles. Provided the final score of the assessment is eligible if it reaches at least 75% meeting the critical assessment criteria, the article will be included for further data synthesis. All articles (n = 32) in the final screening achieved a score equal to and higher than 75% so they were ready for data synthesis.

Table 3. Risk Factor PCOS

Risk Factor		References
Eating behaviour	Eating disorder Food craving	(Anand et al., 2022; Başar Gökcen et al., 2020; Greenwood et al., 2020; Jiskoot et al., 2022; I. Lee & Dokras, 2020; Pirotta et al., 2020; Stefanaki et al., 2023)
Mental Disorder	Emotional disturbance Stress Anxiety Depression Ego resiliency Loneliness	(Almeshari et al., 2021; Anand et al., 2022; Başar Gökcen et al., 2020; Cheol, 2022; Çoban et al., 2019; Damone et al., 2019; Dybciak et al., 2022; Greenwood et al., 2020; Hasan et al., 2022; Javed et al., 2020; I. Lee & Dokras, 2020; Lin et al., 2021; Naz et al., 2020; Pirotta et al., 2019;

Risk Factor		References
		Sharma et al., 2022; Stefanaki et al., 2023)
BMI	Overweight Obesity Visceral fat (VAT)	(Barrea, Muscogiuri, Pugliese, de Alteriis, et al., 2021; Başar Gökcen et al., 2020; Greenwood et al., 2020; Javed et al., 2020; NA & HM, 2020; Neubronner et al., 2021; Perovic Blagojevic et al., 2022; Satyaraddi et al., 2019; Sharma et al., 2022; Stefanaki et al., 2023; Wahyuni et al., 2022)
Environmental toxicants	Agricultural and industrial areas Toxic metal (As, Pb, Ba) Perfluoroalkyl substances (PFASs) As, Cd, Pb, and Hg Decamethylcyclopen-tasiloxane (D5) Plastic tableware	(Abudawood et al., 2021; Guyansyah et al., 2021; Kirmizi et al., 2020; J. Lee et al., 2023; Liang et al., 2022; Wang et al., 2019; B. Zhang et al., 2020)
Family history	Family history	(Javed et al., 2020; NA & HM, 2020; Wahyuni et al., 2022)
Unhealthy lifestyle	Smoking Snoring hypercaloric diet Lack-low of physical activity. Low fibre diet Diet habit. Physical activity Fast-food diet habit	(Alam et al., 2021; Jurczewska et al., 2023; Khondker & Nabila, 2022; NA & HM, 2020; Sharma et al., 2022; Wahyuni et al., 2022; B. Zhang et al., 2020)

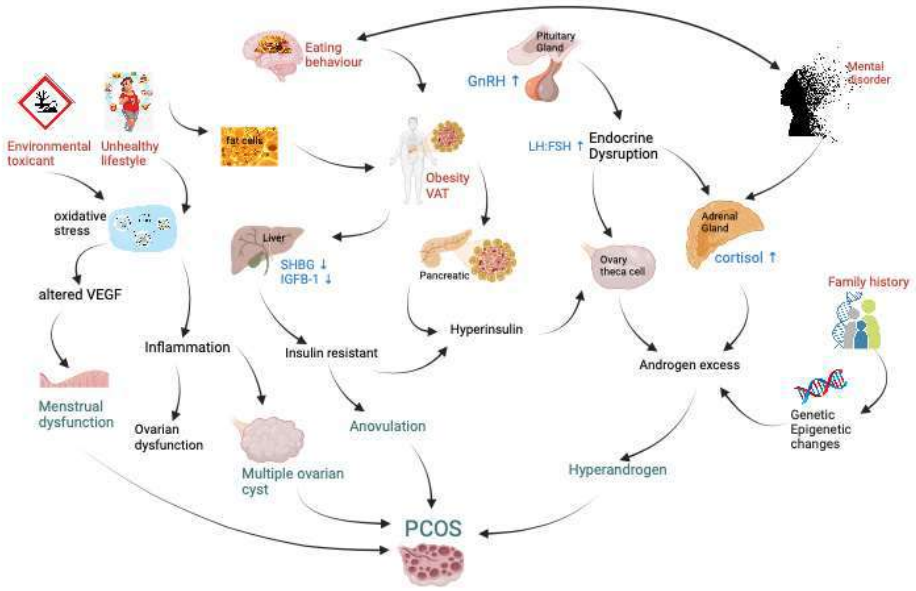

Figure 2. PCOS Risk Factors Mechanism

DISCUSSION

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by hormonal imbalance, reproductive and metabolic dysfunctions, and excess androgen secretion (Chappell et al., 2022). The syndrome's etiology involves multiple genes and pathways, with no single cause accounting for its development. PCOS is prevalent among women of reproductive age, with varying prevalence rates across different regions. The syndrome's pathophysiology has been the subject of extensive research, aiming to understand the molecular processes underlying the disease and identify potential biomarkers and therapeutic targets (Glendining & Campbell, 2023).

Hormonal aspects of PCOS include disruptions in hormone secretion, menstrual dysfunction, hyperandrogenism, and polycystic ovaries (Bhandary et al., 2022). Additionally, environmental factors, including endocrine-disrupting chemicals, maternal smoking, and nutrition, have been associated with the emergence of ovulatory dysfunction through metabolic and epigenetic changes (Bhandary et al., 2022; Kambale et al., 2023; Wawrzkiewicz-Jałowiecka et al., 2020). PCOS is a multifaceted condition influenced by hormonal, genetic, epigenetic, and environmental factors, and understanding these aspects is crucial for developing effective management and treatment strategies for the syndrome (Kambale et al., 2023).

Genetic research has identified candidate genes and loci associated with interruptions in physiological pathways, while epigenetic changes, such as alterations in DNA methylation and non-coding RNA function, have been linked to PCOS phenotypes (Bhandary et al., 2022; Khan et al., 2019). Family history plays a crucial role in determining the risk of developing PCOS, with a significant degree of heritability and environmental factors contributing to PCOS development (Javed et al., 2020; NA & HM, 2020). Genetic factors, including autosomal dominant genes and various candidate genes, have been identified as influential in the pathophysiology of PCOS, affecting insulin signaling, metabolic health, and hormonal balance (Dapas et al., 2019; Khan et al., 2019; Wahyuni et al., 2022).

Environmental factors, such as endocrine-disrupting chemicals (EDCs) and advanced glycation end products (AGEs), play significant roles in the development and exacerbation of PCOS (Bhandary et al., 2022). There are several environmental toxins that can affect biological pathways associated with polycystic ovary syndrome (PCOS) including heavy metals such as copper (Cu), zinc (Zn), manganese (Mn), lead (Pb), selenium (Se), chromium (Cr), cadmium (Cd), nickel (Ni), cobalt (Co), and arsenic (As), as well as exposure to pesticides such as organochlorines (OCPs), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and perfluorooctanoic acid (PFOA) (Liang et al., 2022; Wang et al., 2019; B. Zhang et al., 2020). AGEs, which are proinflammatory molecules, can interact with cell surface receptors and trigger proinflammatory pathways and oxidative stress (Abudawood et al., 2021; Sharma et al., 2021). This can lead to disruptions in hormone secretion, menstrual dysfunction, and hyperandrogenism, all of which are key characteristics of PCOS. Furthermore, AGEs have been shown to play a role in the pathophysiology of PCOS and ovarian cancer (Jozkowiak et al., 2022; Sharma et al., 2021).

The mechanism of environmental toxins in PCOS involves the creation of oxidative stress in the body. Oxidative stress occurs when the balance between the production of free radicals (ROS) and antioxidants is disturbed. Excessive ROS can damage ovarian cells and disrupt hormonal function, which in turn can lead to PCOS (Abudawood et al., 2021; Jozkowiak et al., 2022). Arsenic and pesticides such as PAHs can interact with hormone receptors in the body and disrupt endocrine function. They can mimic or inhibit the action of natural hormones, interfering with hormone metabolism, receptor binding, and steroid synthesis, which can lead to hormonal imbalances that contribute to the development of PCOS(Liang et al., 2022; B. Zhang et al., 2020). Exposure to heavy metals and pesticides can also cause epigenetic changes

in genes associated with PCOS. Epigenetic modifications can affect gene expression and disrupt the function of genes important in hormonal regulation and ovarian development. These epigenetic changes can occur during prenatal or postnatal development and can affect several generations after the initial exposure(Bhandary et al., 2022; Sharma et al., 2021).

The mechanism of obesity as a factor in PCOS involves several complex pathophysiological processes. Obesity can affect hormonal balance and ovarian function, which in turn can trigger the development of PCOS (Mirzohidovna, 2021; Wahyuni et al., 2022). Obesity increases insulin resistance and androgen hormone production, which are key characteristics of PCOS. Insulin resistance can trigger increased production of androgen hormones by the ovaries and adrenal glands, which can then disrupt the menstrual cycle and cause anovulation (Perovic Blagojevic et al., 2022). Obesity can affect the production of reproductive hormones such as estrogen and progesterone, which can affect ovarian function and the menstrual cycle. Furthermore, obesity can also trigger chronic inflammation and disrupt the balance of reproductive hormones, all of which can contribute to the development of PCOS (Stefanaki et al., 2023). In addition, obesity can worsen the symptoms of PCOS, such as hirsutism, menstrual disorders, and infertility. Addressing obesity is therefore important in the management of PCOS, with a focus on weight loss, lifestyle changes, and management of insulin resistance to reduce its negative impact on PCOS progression and symptoms(Long et al., 2022).

Unhealthy habits include fast food consumption, lack of physical activity, and eating disorders (Barrea, Muscogiuri, Pugliese, De Alteriis, et al., 2021). Fast food consumption that is high in refined carbohydrates and saturated fats may increase the risk of insulin resistance, which is a contributing factor for PCOS. In addition, fast food consumption is also associated with an increased risk of obesity, which can worsen insulin resistance and hyperinsulinemia, both associated with PCOS (Stefanaki et al., 2023). Lack of physical activity can lead to accumulation of body fat and contribute to insulin resistance and low-grade inflammation, all of which are associated with PCOS. Low physical activity can increase free fatty acid and triglyceride levels, which can lead to insulin resistance. In women with PCOS, saturated fat in low-density lipoprotein (LDL) can inhibit the action of insulin, resulting in hyperinsulinemia. Insulin resistance reduces insulin sensitivity and may trigger increased androgen production, which is a hallmark of PCOS (Alam et al., 2021; Satyaraddi et al., 2019; Wahyuni et al., 2022). Eating disorders, such as emotional eating tendencies, binge eating disorder and night eating syndrome, are also associated with PCOS (Alam et al., 2021; Başar Gökcen et al., 2020). Eating disorders can be linked to obesity, which in turn can exacerbate insulin resistance and low-grade inflammation associated with PCOS (I. Lee et al., 2017; Pirotta et al., 2019). In addition, eating disorders can also affect hormonal balance and metabolism, all of which contribute to the development of PCOS. Thus, fast food consumption, physical inactivity and eating disorders are all linked to obesity (Khondker & Nabila, 2022; Neubronner et al., 2021), low-grade inflammation, insulin resistance and ultimately the development of PCOS through various complex mechanisms (Alam et al., 2021; Greenwood et al., 2020; Jiskoot et al., 2022; Wahyuni et al., 2022).

The relationship between depression, anxiety, emotional eating (EE), and PCOS is complex and interconnected. Women with PCOS have an increased prevalence of depression and anxiety, with factors such as advanced age, higher BMI values, and hirsutism scores being associated with the increased prevalence of these mental health conditions (Almeshari et al., 2021; Greenwood et al., 2020). Chronic stress caused by negative emotions related to hyperandrogenism, infertility and obesity in women with PCOS can activate the hypothalamic-pituitary-adrenal (HPA) axis and increase cortisol secretion, which in turn suppresses dopamine and serotonin release, leading to mood disturbances and contributing to the development of emotional eating, binge eating disorder and nighttime eating syndrome (Stefanaki et al., 2023). Depression and anxiety can be associated with emotional eating and

obesity which then lead to complications of PCOS (Almeshari et al., 2021; Cheol, 2022; Damone et al., 2019). The complex relationship between mental health, eating behaviors and the development and complications of PCOS involves hormonal, psychological and behavioral factors that contribute to the complex interaction between mental health and PCOS management (Lin et al., 2021).

Overall, addressing obesity, making lifestyle changes such as weight loss, increasing physical activity, and modifying dietary habits, is crucial for managing and preventing the development and exacerbation of PCOS. Understanding the intricate interplay of hormonal, genetic, epigenetic, and environmental factors is essential for developing effective management and treatment strategies for PCOS. By recognizing the multifaceted nature of PCOS, healthcare professionals can tailor interventions to address the various aspects of the syndrome, improving outcomes for individuals with PCOS.

CONCLUSIONS AND RECOMMENDATIONS

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder influenced by a combination of hormonal, genetic, epigenetic, and environmental factors. Intricate interactions between impaired hormone secretion, genetic predisposition, epigenetic modifications, and exposure to environmental toxins such as heavy metals and pesticides contribute to the complex pathophysiology of PCOS. In addition, factors such as obesity and unhealthy habits, including fast food consumption, physical inactivity and eating disorders, further aggravate the condition. Understanding the molecular processes underlying PCOS is essential for identifying potential biomarkers and therapeutic targets. In addition, addressing obesity, making lifestyle modifications, and recognizing the link between mental health and PCOS management are essential for effective interventions. By considering the multifactorial nature of PCOS, healthcare professionals can tailor strategies to better manage and prevent the development and complications of this complex syndrome.

Research limitations in this article include the lack of consistency in the definition and measurement of PCOS symptoms, as well as the lack of control for potential contributing factors such as genetic, environmental, and lifestyle factors. In addition, some studies may have relied on self-reporting which may affect the accuracy of the data. There is also a tendency to focus on specific populations, such as women with diagnosed PCOS, which may result in limited generalizability to the general population. In addition, some studies had small sample sizes, which may limit the statistical power and generalizability of the findings. There is also a need for further research that considers potential factors that have not been fully uncovered, such as the interaction between genetic and environmental factors in the development of PCOS.

REFERENCES

Abudawood, M., Tabassum, H., Alanazi, A. H., Almusallam, F., Aljaser, F., Ali, M. N., Alenzi, N. D., Alanazi, S. T., Alghamdi, M. A., Altoum, G. H., Alzeer, M. A., Alotaibi, M. O., Abudawood, A., Ghneim, H. K., Abdullah, L., & Al-Nuaim, A. (2021). Antioxidant status in relation to heavy metals induced oxidative stress in patients with polycystic ovarian syndrome (PCOS). *Scientific Reports* , *11*(22935), 1–8. https://doi.org/10.1038/s41598-021-02120-6

Alam, F., Tariq, S., Syed, F., & Tariq, S. (2021). Impact Of Eating Habits And Physical Activity On The Fertility Of Females. *Biosight*, *2*(2), 30–39. https://doi.org/10.46568/bios.v2i2.53

Almeshari, W. K., Alsubaie, A. K., Alanazi, R. I., Almalki, Y. A., Masud, N., & Mahmoud, S. H. (2021). Depressive and Anxiety Symptom Assessment in Adults with Polycystic Ovarian Syndrome. *Depression Research and Treatment*, *2021*. https://doi.org/10.1155/2021/6652133

Anand, S., Jahan, N., & Manglani, A. (2022). Eating Behaviour, Sleep Quality, and Emotional Disturbance in women with Poly Cystic Ovary Syndrome (PCOS) Eating Behaviour, Sleep Quality, and Emotional Disturbance in women with Poly Cystic Ovary Syndrome (PCOS). *NeuroQuantology*, *20*(2), 634–639. https://doi.org/10.48047/nq.2022.20.2.NQ22358

Barker, T. H., Stone, J. C., Sears, K., Klugar, M., Leonardi-Bee, J., Tufanaru, C., Aromataris, E., & Munn, Z. (2023). Revising the JBI quantitative critical appraisal tools to improve their applicability: an overview of methods and the development process. *JBI Evidence Synthesis*, *21*(3), 478–493. https://doi.org/10.11124/JBIES-22-00125

Barrea, L., Muscogiuri, G., Pugliese, G., De Alteriis, G., Colao, A., & Savastano, S. (2021). Metabolically Healthy Obesity (MHO) vs. Metabolically Unhealthy Obesity (MUO) Phenotypes in PCOS: Association with Endocrine-Metabolic Profile, Adherence to the Mediterranean Diet, and Body Composition. *Nutrients*, *13*(3925), 1–17. https://doi.org/10.3390/nu13113925

Barrea, L., Muscogiuri, G., Pugliese, G., de Alteriis, G., Colao, A., & Savastano, S. (2021). Metabolically healthy obesity (Mho) vs. metabolically unhealthy obesity (muo) phenotypes in pcos: Association with endocrine-metabolic profile, adherence to the mediterranean diet, and body composition. *Nutrients*, *13*(11). https://doi.org/10.3390/NU13113925/S1

Başar Gökcen, B., Akdevelioğlu, Y., Canan, S., & Bozkurt, N. (2020). Increased risk of eating disorders in women with polycystic ovary syndrome: a case-control study. *Gynecological Endocrinology*, *36*(9), 764–767. https://doi.org/10.1080/09513590.2020.1744554

Bhandary, P., Kumar Shetty, P., Manjeera, L., & Patil, P. (2022). Hormonal, genetic, epigenetic and environmental aspects of polycystic ovarian syndrome. *Gene Reports*, *29*, 101698. https://doi.org/10.1016/j.genrep.2022.101698

Chappell, N. R., Gibbons, W. E., & Blesson, C. S. (2022). Pathology of hyperandrogenemia in the oocyte of polycystic ovary syndrome. *Steroids*, *180*, 108989. https://doi.org/10.1016/J.STEROIDS.2022.108989

Chen, X., Kong, L., Piltonen, T. T., Gissler, M., & Lavebratt, C. (2020). Association of polycystic ovary syndrome or anovulatory infertility with offspring psychiatric and mild neurodevelopmental disorders: a Finnish population-based cohort study. *Human Reproduction*, *35*(10), 2336–2347. https://doi.org/10.1093/HUMREP/DEAA192

Cheol, J. P. (2022). Risk Factors for Depression, Anxiety, and Stress in Patients with Polycystic Ovary Syndrome. *Journal of the Korea Convergence Society*, *13*(3), 337–343. https://doi.org/10.15207/JKCS.2022.13.03.337

Çoban, Ö. G., Tulacı, Ö. D., Adanır, A. S., & Önder, A. (2019). Psychiatric Disorders, Self-Esteem, and Quality of Life in Adolescents with Polycystic Ovary Syndrome. *Journal of Pediatric and Adolescent Gynecology*, *32*(6), 600–604. https://doi.org/10.1016/J.JPAG.2019.07.008

Damone, A. L., Joham, A. E., Loxton, D., Earnest, A., Teede, H. J., & Moran, L. J. (2019). Depression, anxiety and perceived stress in women with and without PCOS: a community-based study. *Psychological Medicine*, *49*(9), 1510–1520. https://doi.org/10.1017/S0033291718002076

Dapas, M., Sisk, R., Legro, R. S., Urbanek, M., Dunaif, A., & Hayes, M. G. (2019). Family-Based Quantitative Trait Meta-Analysis Implicates Rare Noncoding Variants in DENND1A in Polycystic Ovary Syndrome. *Journal of Clinical Endocrinology and Metabolism*, *104*(9), 3835–3850. https://doi.org/10.1210/JC.2018-02496

Dubey, P., Thakur, B., Rodriguez, S., Cox, J., Sanchez, S., Fonseca, A., Reddy, S., Clegg, D., & Dwivedi, A. K. (2021). A systematic review and meta-analysis of the association

between maternal polycystic ovary syndrome and neuropsychiatric disorders in children. *Translational Psychiatry*, *11*(1). https://doi.org/10.1038/s41398-021-01699-8

Dybciak, P., Humeniuk, E., Raczkiewicz, D., Krakowiak, J., Wdowiak, A., & Bojar, I. (2022). Anxiety and Depression in Women with Polycystic Ovary Syndrome. *Medicina 2022, Vol. 58, Page 942*, *58*(7), 942. https://doi.org/10.3390/MEDICINA58070942

Glendining, K. A., & Campbell, R. E. (2023). Recent advances in emerging PCOS therapies. *Current Opinion in Pharmacology*, *68*, 102345. https://doi.org/10.1016/J.COPH.2022.102345

Greenwood, E. A., Pasch, L. A., Cedars, M. I., & Huddleston, H. G. (2020). Obesity and depression are risk factors for future eating disorder-related attitudes and behaviors in women with polycystic ovary syndrome. *Fertility and Sterility*, *113*(5), 1039–1049. https://doi.org/10.1016/J.FERTNSTERT.2020.01.016

Greenwood, E. A., Pasch, L. A., Cedars, M. I., Legro, R. S., Eisenberg, E., & Huddleston, H. G. (2018). Insulin resistance is associated with depression risk in polycystic ovary syndrome. *Fertility and Sterility*, *110*(1), 27–34. https://doi.org/10.1016/j.fertnstert.2018.03.009

Gurule, S., Sustaita-Monroe, J., Padmanabhan, V., & Cardoso, R. (2023). Developmental programming of the neuroendocrine axis by steroid hormones: Insights from the sheep model of PCOS. *Frontiers in Endocrinology*, *14*, 1096187. https://doi.org/10.3389/FENDO.2023.1096187

Guyansyah, A., Wratsangka, R., Dhanardono, D., Ghazali, M. F., Edy, H. J., Widyatama, H. G., Kusumaningrum, D., Tjahyadi, D., & Parwanto, E. (2021). Primary infertility of male and female factors, polycystic ovary syndrome and oligoasthenoteratozoospermia dominate the infertile population in agricultural and industrial areas in Karawang Regency, West Java Province, Indonesia. *Bali Medical Journal*, *10*(1), 167–173. https://doi.org/10.15562/BMJ.V10I1.2281

Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*, *18*(2), e1230. https://doi.org/10.1002/CL2.1230

Hasan, M., Sultana, S., Sohan, M., Parvin, S., Ashrafur Rahman, M., Jamal Hossain, M., Rahman, M. S., & Rabiul Islam, M. (2022). Prevalence and associated risk factors for mental health problems among patients with polycystic ovary syndrome in Bangladesh: A nationwide cross—Sectional study. *PLOS ONE*, *17*(6), e0270102. https://doi.org/10.1371/JOURNAL.PONE.0270102

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). Cochrane handbook for systematic reviews of interventions. *Cochrane Handbook for Systematic Reviews of Interventions*, 1–694. https://doi.org/10.1002/9781119536604

Hoeger, K. M., Dokras, A., & Piltonen, T. (2021). Update on PCOS: Consequences, Challenges, and Guiding Treatment. *Journal of Clinical Endocrinology and Metabolism*, *106*(3), E1071–E1083. https://doi.org/10.1210/CLINEM/DGAA839

Ignatov, A., & Ortmann, O. (2020). Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen. *Cancers 2020, Vol. 12, Page 1766*, *12*(7), 1766. https://doi.org/10.3390/CANCERS12071766

Javed, R., Daud, B., & Jahan, N. (2020). Frequency and Factors of Polycystic Ovarian Syndrome in College Going Females. *Pakistan Journal of Medical & Health Sciences*, *14*(3), 865–868.

JBI Critical Appraisal Tools | JBI. (n.d.). Retrieved January 29, 2024, from https://jbi.global/critical-appraisal-tools

Jiskoot, G., de Loos, A. D., Timman, R., Beerthuizen, A., Laven, J., & Busschbach, J. (2022). Changes in eating behavior through lifestyle treatment in women with polycystic ovary syndrome (PCOS): a randomized controlled trial. *Journal of Eating Disorders*, *10*(1), 1–11. https://doi.org/10.1186/S40337-022-00593-Y/FIGURES/2

Joksimovic Jovic, J., Sretenovic, J., Jovic, N., Rudic, J., Zivkovic, V., Srejovic, I., Mihajlovic, K., Draginic, N., Andjic, M., Milinkovic, M., Milosavljevic, Z., & Jakovljevic, V. (2021). Cardiovascular Properties of the Androgen-Induced PCOS Model in Rats: The Role of Oxidative Stress. *Oxidative Medicine and Cellular Longevity*, *2021*. https://doi.org/10.1155/2021/8862878

Jozkowiak, M., Piotrowska-Kempisty, H., Kobylarek, D., Gorska, N., Mozdziak, P., Kempisty, B., Rachon, D., & Spaczynski, R. Z. (2022). Endocrine Disrupting Chemicals in Polycystic Ovary Syndrome: The Relevant Role of the Theca and Granulosa Cells in the Pathogenesis of the Ovarian Dysfunction. *Cells 2023, Vol. 12, Page 174*, *12*(1), 174. https://doi.org/10.3390/CELLS12010174

Jurczewska, J., Ostrowska, J., Chełchowska, M., Panczyk, M., Rudnicka, E., Kucharski, M., Smolarczyk, R., & Szostak-Węgierek, D. (2023). Physical Activity, Rather Than Diet, Is Linked to Lower Insulin Resistance in PCOS Women—A Case-Control Study. *Nutrients 2023, Vol. 15, Page 2111*, *15*(9), 2111. https://doi.org/10.3390/NU15092111

Kambale, T., Sawaimul, K. D., & Prakash, S. (2023). A Study of Hormonal and Anthropometric Parameters in Polycystic Ovarian Syndrome. *Annals of African Medicine*, *22*(1), 112. https://doi.org/10.4103/AAM.AAM_15_22

Khan, M. J., Ullah, A., Basit, S., Almunawwarrah, A., & Arabia, S. (2019). Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. *The Application of Clinical Genetics*, *12*, 249–260. https://doi.org/10.2147/TACG.S200341

Khondker, L., & Nabila, N. (2022). Comparison of lifestyle in women with Polycystic Ovary Syndrome (PCOS) and healthy women. *The Gulf Journal of Dermatology and Venereology*, *29*(1).

Kirmizi, D. A., Baser, E., Turksoy, V. A., Kara, M., Yalvac, E. S., & Gocmen, A. Y. (2020). Are Heavy Metal Exposure and Trace Element Levels Related to Metabolic and Endocrine Problems in Polycystic Ovary Syndrome? *Biological Trace Element Research*, *198*(1), 77–86. https://doi.org/10.1007/S12011-020-02220-W/METRICS

Lee, I., Cooney, L. G., Saini, S., Smith, M. E., Sammel, M. D., Allison, K. C., & Dokras, A. (2017). Increased risk of disordered eating in polycystic ovary syndrome. *Fertility and Sterility*, *107*(3), 796–802. https://doi.org/10.1016/J.FERTNSTERT.2016.12.014

Lee, I., & Dokras, A. (2020). Mental health and body image in polycystic ovary syndrome. *Current Opinion in Endocrine and Metabolic Research*, *12*, 85–90. https://doi.org/10.1016/J.COEMR.2020.04.004

Lee, J., Kim, K., Park, S.-M., Kwon, J.-S., & Jeung, E.-B. (2023). Effects of Decamethylcyclopentasiloxane on Reproductive Systems in Female Rats. *Toxics*, *11*(4). https://doi.org/10.3390/toxics11040302

Liang, C., Zhang, Z., Cao, Y., Wang, J., Shen, L., Jiang, T., Li, D., Zou, W., Zong, K., Liang, D., Xu, X., Liu, Y., Tao, F., Luo, G., Ji, D., & Cao, Y. (2022). Exposure to multiple toxic metals and polycystic ovary syndrome risk: Endocrine disrupting effect from As, Pb and Ba. *Science of The Total Environment*, *849*, 157780. https://doi.org/10.1016/J.SCITOTENV.2022.157780

Lim, S. S., Hutchison, S. K., Van Ryswyk, E., Norman, R. J., Teede, H. J., & Moran, L. J. (2019). Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*, *2019*(3). https://doi.org/10.1002/14651858.CD007506.pub4

Lin, H., Liu, M., Zhong, D., Ng, E. H. Y., Liu, J., Li, J., Shi, Y., Zhang, C., Wen, X., Mai, Z., Ou, M., & Ma, H. (2021). The Prevalence and Factors Associated With Anxiety-Like and

Depression-Like Behaviors in Women With Polycystic Ovary Syndrome. *Frontiers in Psychiatry*, *12*, 709674. https://doi.org/10.3389/FPSYT.2021.709674/BIBTEX

Long, X., Yang, Q., Qian, J., Yao, H., Yan, R., Cheng, X., Zhang, Q., Gu, C., Gao, F., Wang, H., Zhang, L., & Guo, F. (2022). Obesity modulates cell-cell interactions during ovarian folliculogenesis. *IScience*, *25*(1), 103627. https://doi.org/10.1016/J.ISCI.2021.103627

Majidzadeh, S., Mirghafourvand, M., Farvareshi, M., & Yavarikia, P. (2023). The effect of cognitive behavioral therapy on depression and anxiety of women with polycystic ovary syndrome: a randomized controlled trial. *BMC Psychiatry*, *23*(1), 332. https://doi.org/10.1186/S12888-023-04814-9

Mirzohidovna, H. E. (2021). OBESITY AS A RISK FACTOR FOR RECURRENT POLYCYSTIC OVARY DISEASE. *Asian Journal of Pharmaceutical and Biological Research*, *10*(3). https://doi.org/10.5281/zenodo.5567754

Mustaniemi, S., Vääräsmäki, M., Eriksson, J. G., Gissler, M., Laivuori, H., Ijäs, H., Bloigu, A., Kajantie, E., & Morin-Papunen, L. (2018). Polycystic ovary syndrome and risk factors for gestational diabetes. *Endocrine Connections*, *7*(7), 859. https://doi.org/10.1530/EC-18-0076

NA, I., & HM, S. (2020). Phenotype Characteristics and Risk Factors of Polycystic Ovarian Syndrome among Nursing Students. *La Prensa Medica Argentina*, *106*(3). https://doi.org/10.47275/0032-745x-294

Naz, M. S. G., Tehrani, F. R., Lak, T. B., Mohammadzadeh, F., Nasiri, M., Badr, F. K., & Ozgoli, G. (2020). Quality of life and emotional states of depression, anxiety and stress in adolescents with polycystic ovary syndrome: A cross-sectional study. *Psychology Research and Behavior Management*, *13*, 203–209. https://doi.org/10.2147/PRBM.S241192

Negdel, T., Sengebaljir, D., Munkhbayar, B., Bilegsuren, K., Ganbold, A., Nanjid, K., Readhead, C. W., Erkhembaatar, L.-O., Tuduvdorj, E., Malchinkhuu, M., & Enkhtaivan, O. (2021). Prevalence and Risk factors of Infertility in a Mongolian Population. *Research Square*, 1–17. https://doi.org/10.21203/rs.3.rs-26781/v3

Neubronner, S. A., Indran, I. R., Chan, Y. H., Thu, A. W. P., & Yong, E. L. (2021). Effect of body mass index (BMI) on phenotypic features of polycystic ovary syndrome (PCOS) in Singapore women: a prospective cross-sectional study. *BMC Women's Health*, *21*(1), 1–12. https://doi.org/10.1186/S12905-021-01277-6/TABLES/4

Perovic Blagojevic, I. M., Vekic, J. Z., MacUt, D. P., Ignjatovic, S. D., Miljkovic-Trailovic, M. M., Zeljkovic, A. R., Spasojevic-Kalimanovska, V. V., Bozic-Antic, I. B., Bjekic-Macut, J. D., Kastratovic-Kotlica, B. A., Andric, Z. G., Ilic, D. S., & Kotur-Stevuljevic, J. M. (2022). Overweight and obesity in polycystic ovary syndrome: Association with inflammation, oxidative stress and dyslipidaemia. *British Journal of Nutrition*, *128*(4), 604–612. https://doi.org/10.1017/S0007114521003585

Pirotta, S., Barillaro, M., Brennan, L., Grassi, A., Jeanes, Y. M., Joham, A. E., Kulkarni, J., Couch, L. M., Lim, S. S., & Moran, L. J. (2019). Clinical Medicine Disordered Eating Behaviours and Eating Disorders in Women in Australia with and Without Polycystic Ovary Syndrome: A Cross-Sectional Study. *Journal of Clinical Medicine*, *8*(1682), 1–13. https://doi.org/10.3390/jcm8101682

Pirotta, S., Joham, A., Grieger, J. A., Tay, C. T., Bahri-Khomami, M., Lujan, M., Lim, S. S., & Moran, L. J. (2020). Obesity and the Risk of Infertility, Gestational Diabetes, and Type 2 Diabetes in Polycystic Ovary Syndrome. *Seminars in Reproductive Medicine*, *38*(6), 342–351. https://doi.org/10.1055/S-0041-1726866/ID/JR2000062-20/BIB

Purwar, A., & Nagpure, S. (2022). Insulin Resistance in Polycystic Ovarian Syndrome. *Cureus*, *14*(10), 1–5. https://doi.org/10.7759/CUREUS.30351

Satyaraddi, A., Cherian, K., Kapoor, N., Kunjummen, A., Kamath, M., Thomas, N., & Paul, T. (2019). Body composition, metabolic characteristics, and insulin resistance in obese and nonobese women with polycystic ovary syndrome. *Journal of Human Reproductive Sciences*, *12*(2), 78–84. https://doi.org/10.4103/JHRS.JHRS_2_19

Sharma, P., Bilkhiwal, N., Chaturvedi, P., Kumar, S., & Khetarpal, P. (2021). Potential environmental toxicant exposure, metabolizing gene variants and risk of PCOS-A systematic review. *Reproductive Toxicology*, *103*, 124–132. https://doi.org/10.1016/j.reprotox.2021.06.005

Sharma, P., Kaur, M., Kumar, S., & Khetarpal, P. (2022). A cross-sectional study on prevalence of menstrual problems, lifestyle, mental health, and PCOS awareness among rural and urban population of Punjab, India. *Journal of Psychosomatic Obstetrics & Gynecology*, *43*(3), 349–358. https://doi.org/10.1080/0167482X.2021.1965983

Shorakae, S., Ranasinha, S., Abell, S., Lambert, G., Lambert, E., de Courten, B., & Teede, H. (2018). Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS. *Clinical Endocrinology*, *89*(5), 628–633. https://doi.org/10.1111/CEN.13808

Stefanaki, K., Karagiannakis, D. S., Raftopoulou, M., Psaltopoulou, T., Paschou, S. A., & Ilias, I. (2023). Obesity and hyperandrogenism are implicated with anxiety, depression and food cravings in women with polycystic ovary syndrome. *Endocrine*, *82*(1), 201–208. https://doi.org/10.1007/S12020-023-03436-1/METRICS

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*. https://doi.org/10.1136/BMJ.L4898

Wahyuni, A., Kusumawati, W., Sedah Kirana, K., Dwi Mayayus-tika, C., & Kedokteran dan Kesehatan Indonesia, J. (2022). Family history of PCOS, obesity, low fiber diet, and low physical activity increase the risk of PCOS. *JKKI : Jurnal Kedokteran Dan Kesehatan Indonesia*. https://doi.org/10.20885/JKKI.VOL13.ISS1.ART8

Wang, W., Zhou, W., Wu, S., Liang, F., Li, Y., Zhang, J., Cui, L., Feng, Y., & Wang, Y. (2019). Perfluoroalkyl substances exposure and risk of polycystic ovarian syndrome related infertility in Chinese women. *Environmental Pollution*, *247*, 824–831. https://doi.org/10.1016/J.ENVPOL.2019.01.039

Waniczek, D., Jabczyk, M., Nowak, J., Jagielski, P., Hudzik, B., Kulik-Kupka, K., Włodarczyk, A., Lar, K., & Zubelewicz-Szkodzí Nska, B. (2023). Metabolic Deregulations in Patients with Polycystic Ovary Syndrome. *Metabolites*, *13*(302), 1–10. https://doi.org/10.3390/metabo13020302

Wawrzkiewicz-Jałowiecka, A., Kowalczyk, K., Trybek, P., Jarosz, T., Radosz, P., Setlak, M., & Madej, P. (2020). In Search of New Therapeutics—Molecular Aspects of the PCOS Pathophysiology: Genetics, Hormones, Metabolism and Beyond. *International Journal of Molecular Sciences 2020, Vol. 21, Page 7054*, *21*(19), 7054. https://doi.org/10.3390/IJMS21197054

Zhang, B., Zhang, B., Zhang, B., Zhang, B., Zhou, W., Zhou, W., Zhou, W., Zhou, W., Shi, Y., Shi, Y., Shi, Y., Shi, Y., Zhang, J., Cui, L., Cui, L., Cui, L., Cui, L., & Chen, Z. J. (2020). Lifestyle and environmental contributions to ovulatory dysfunction in women of polycystic ovary syndrome. *BMC Endocrine Disorders*, *20*(1), 1–7. https://doi.org/10.1186/S12902-020-0497-6/TABLES/3

Zhang, J., Xu, J. H., Qu, Q. Q., & Zhong, G. Q. (2020). Risk of Cardiovascular and Cerebrovascular Events in Polycystic Ovarian Syndrome Women: A Meta-Analysis of

Cohort Studies. *Frontiers in Cardiovascular Medicine*, *7*, 552421. https://doi.org/10.3389/FCVM.2020.552421/BIBTEX

Zhu, T., Cui, J., & Goodarzi, M. O. (2021). Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke. *Diabetes*, *70*(2), 627–637. https://doi.org/10.2337/DB20-0800