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Meta Analysis
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Evaluating the Roles of Lifestyle, Genetics, and Menstrual Cycle in Polycystic Ovarian Syndrome: A Meta-Analysis

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ABSTRACT

Background: The WHO in 2023 reports that polycystic ovary syndrome (PCOS) has affected about 8–13% of women of reproductive age. Some studies report that lifestyle, hormones, and genetics are one of the risk factors for PCOS. This study aims to analyze and estimate the magnitude of the effects of obesity, smoking, irregular menstruation, and having a family history of PCOS with the incidence of PCOS in women of childbearing age.
Subjects and Method: Systematic review and meta-analysis studies were conducted according to the PRISMA flowchart and PICO model. Population: women of childbearing age. Intervention: obesity, smoking, irregular periods, and a family history of PCOS. Comparison: Normal BMI, no smoking, regular periods, and no family history of PCOS. Outcome: PCOS. The basic data used involves Google Scholar, PubMed, BMC, ScienceDirect, and Springer Link. The inclusion criteria are full-text articles with observational study design using multivariate analysis that attaches aOR values and is published from 2013-2024. Data analysis using Review Manager 5.3 application.
Results: Five primary studies were used to analyze obesity with PCOS. Women with obesity had 2.49 times the risk of developing PCOS compared to non-obese (OR= 2.49; CI 95%= 1.59 to 3.88; p < 0.001). Five primary studies were used to analyze smoking with PCOS. Women with smoking habits have a risk of developing PCOS 1.42 times compared to nonsmokers (OR= 1.42; CI 95%= 1.04 to 1.95; p= 0.03). Ten primary studies were used to analyze irregular periods with PCOS. Women with irregular periods had a 3.32 times risk of developing PCOS compared to regular periods (OR= 3.32; CI 95%= 2.77 to 3.97; p < 0.001). Eleven primary studies used for analysis had a family history of PCOS with PCOS. Women with a family history of PCOS had a 2.94 times higher risk of having PCOS than no family history of PCOS (OR= 2.94; CI 95%= 2.11 to 4.09; p < 0.001).
Conclusion: Obesity, smoking, irregular periods, and a family history of PCOS increase the risk of PCOS in women of childbearing age.

Keywords: obesity, smoking, menstrual cycle, family history, pcos.

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BACKGROUND

The World Health Organization reports that by 2023, Polycystic Ovary Syndrome (PCOS) will affect about 8–13% of women of reproductive age. Unfortunately, up to 70% of women affected by PCOS go undiagnosed worldwide. PCOS is the most common cause of anovulation and is a major factor in infertility cases. More than just reproductive problems, PCOS is also closely linked to a variety of long-term health problems that affect physical and emotional well-being (Cooney et al., 2018). Women who have PCOS have a higher risk of developing insulin resistance and type 2 diabetes, especially if they are obese (Peeva et al., 2022). In addition, the hormonal imbalances and insulin resistance associated with PCOS increase the risk of developing cardiovascular disease. This is due to inadequate lipid profiles and increased susceptibility to hypertension and atherosclerosis (Krysiak et al., 2023).

In 2016, 39% of adults aged 18 years and over (39% of men and 40% of women) were overweight (WHO, 2021). Research by Rizvi et al. (2023) shows that women with obesity have a greater risk (aOR = 2.34, p<0.05) of developing PCOS. This is related to insulin resistance, a key characteristic of the condition (Makhija et al., 2023). Insulin resistance can lead to hyperandrogenism, irregular periods, and anovulation, all of which are common features of PCOS (Mandate et al., 2021).

Previous primary studies have shown that smoking is significantly correlated with PCOS (aOR = 2.39, p<0.010), whereby smoking increases the risk of ovulatory dysfunction in women with PCOS and can also affect ovarian reserve (Oladipupo et al., 2022; Zhang et al., 2020). Interestingly, the WHO report (2023b) highlights that 7.8% of women worldwide are smokers, with an increasing prevalence in Southeast Asia, especially in Indonesia and the Philippines (Jafari et al., 2021).

Studies by Shan et al. (2015) irregular menstrual cycles are significantly at risk of developing PCOS (aOR = 5.82; p<0.010). Irregular menstruation is not only common in PCOS, but is also often an early indicator of the condition due to its close association with anovulation and hyperandrogenism (Witchel et al., 2019; Hanedan et al., 2022).

A family history of PCOS was identified as another risk factor for developing the condition. Kaur et al. (2022) reported that women with a family history of PCOS are at risk of developing PCOS 16.12 times. Evidence suggests that genetic effects include familial classification of PCOS and increased frequency of symptoms such as hyperandrogenism and type 2 diabetes in close relatives of women with PCOS. According to these results, genetic effects determine the risk of PCOS by about 65% (Bahadori et al., 2016).

Women with PCOS have a higher risk of gestational diabetes mellitus, pregnancy-induced hypertension, placental and membrane abnormalities, fetal death, neonatal complications, and miscarriage (Ni et al., 2022). PCOS is also associated with an increased risk of endometrial cancer due to chronic anovulation and unoffset estrogen exposure (Özay et al., 2020). Based on the description of the impact of PCOS, it is a source of emotional distress for women who have PCOS, so it is not uncommon for PCOS sufferers to also experience higher levels of anxiety and depression (Simon et al., 2023).

This study is expected to estimate the magnitude of the influence of obesity, smoking, irregular menstrual cycles, and having a family history of PCOS on the incidence of PCOS in women of childbearing age.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic review and meta-analysis guided by PRISMA flowcharts. The databases used involve Google Scholar, PubMed, BMC, ScienceDirect, and Springer Link. The keywords used are ("determinant" OR "risk factor") AND "obesity" AND "smoking" AND "irregular menstruation" AND "family history" AND "PCOS" AND ("multivariate" OR "odds ratio").

2. Steps of Meta-Analysis

Meta analysis was carried out in the following 5 steps:

1) Formulate questions in PICO format (Population, Intervention, Comparison, Outcome).
2) Search for primary articles from databases such as Google Scholar, PubMed, BMC, ScienceDirect, and Springer Link.
3) Carry out screening by determining inclusion and exclusion criteria and conducting quality assessments.
4) Extract and analyze data using RevMan 5.3 Software.
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

The authors developed inclusion criteria, namely English-language articles with cross-sectional studies, case-control studies, and cohort studies, published between 2013-2024. The analysis used is a multivariate analysis with an adjusted odds ratio (aOR). The subjects of the study were women of childbearing age aged 15-49 years, and the results analyzed were PCOS.

4. Exclusion Criteria

The exclusion criteria in this study were RCT (randomized controlled trials) studies, quasi-experiments, research protocols, preliminary studies, non-full text articles.

5. Operational Definition of Variable

PCOS is a heterogeneous endocrine disorder characterized by irregular menstruation, hyperandrogenism, and polycystic ovaries, with diagnostic criteria from the NIH, Rotterdam, and Androgen Excess.

Obesity is excessive fat accumulation due to an imbalance between energy intake and energy expenditure over a long period of time with a BMI of 30 kg/m^2.

Smoking is the behavior of people during their entire life smoking cigarettes.

Irregular menstrual cycle is the time of repeated menstruation calculated from the day of the beginning of menstruation to the day of the beginning of menstruation with a distance between these periods of less than 21 days or more than 35 days.

Family History is generally understood as the occurrence of a certain disease condition in one or more family members.

6. Instrument

Primary studies that have been screened will undergo a critical appraisal or review of studies to determine feasibility. The assessment instrument uses the Critical Appraisal Cohort Study, Cross-Sectional Study, and Case-Control Study for Meta-analysis Research published by the Master of Public Health, Sebelas Maret University Surakarta (Murti, 2023).

7. Data Analysis

Article search results are collected with the help of PRISMA diagrams. Main articles that fit the inclusion criteria were analyzed using the RevMan 5.3 application to calculate effect size and study heterogeneity. The results of data processing are represented as [OR, 95% confidence interval, and p value] using the Mantel-Haenszel method for meta-analysis and presented in the form of forest plots and funnel plots.

RESULTS

1. Study characteristics

The baseline data resulted in 2,381 potentially relevant articles. PRISMA's literature

search flowchart and its results are reported in Figure 1 based on selection criteria, a total of 365 articles were identified for further full-text assessment. In the end, 19 full-text articles were included for the meta-analysis with details of 5 cross-sectional studies, 7 case-control studies, 7 cohort studies. Furthermore, in Table 1, Table 2, and Table 3 researchers assess the quality of study articles. Table 4 is a description of the 19 major studies that have been selected and meet the assessment criteria. The articles come from 5 different continents, namely 3 articles from North America, 1 article from South America, 2 articles from Europe, 3 articles from Australia, 10 articles from Asia. The total sample was 486,766 people.

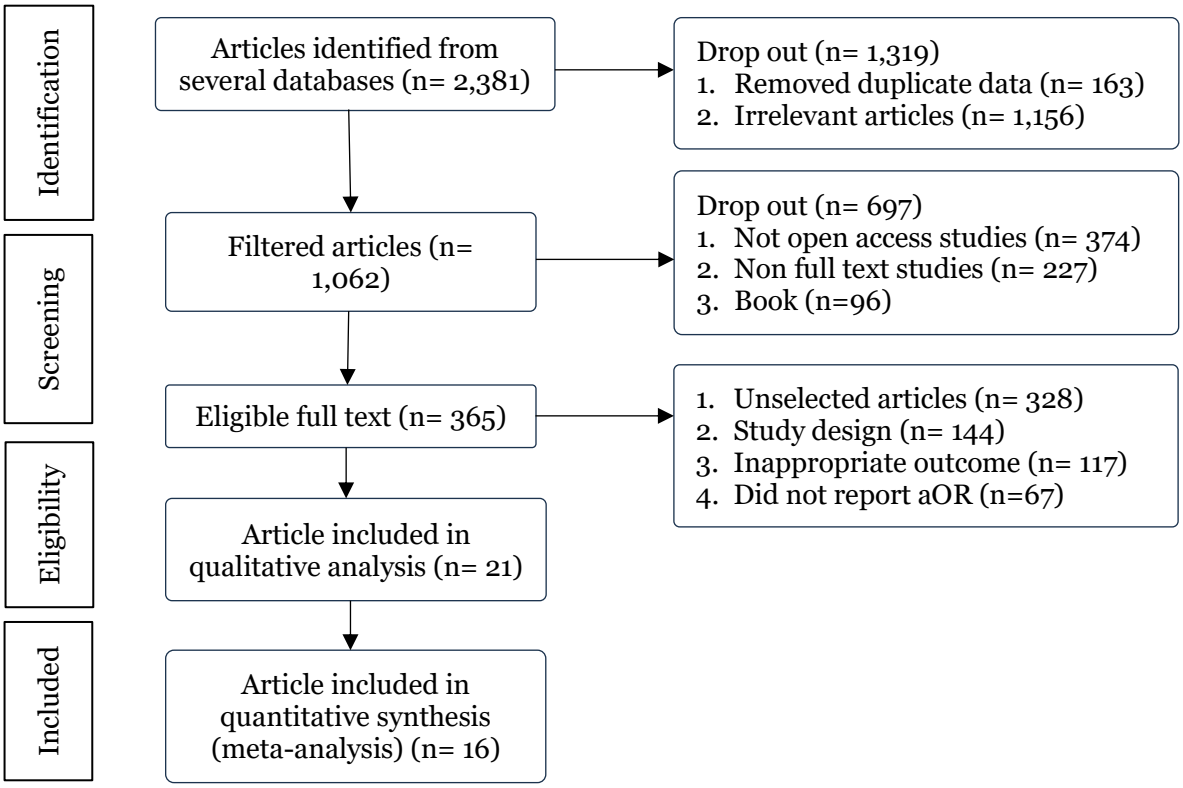

Figure 1. Results of PRISMA flow diagrams

Table 1. Critical appraisal for cohort study of the effect of lifestyle, genetic, and menstrual cycle on PCOS

(Author, Year)	Checklist Question														Total
	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5	6a	6b	7	
Jain et al. (2021a)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Jain et al. (2021b)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Jain et al. (2021c)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Jain et al. (2021d)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Jain et al. (2021e)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Zhang et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Kim et al. (2023)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28

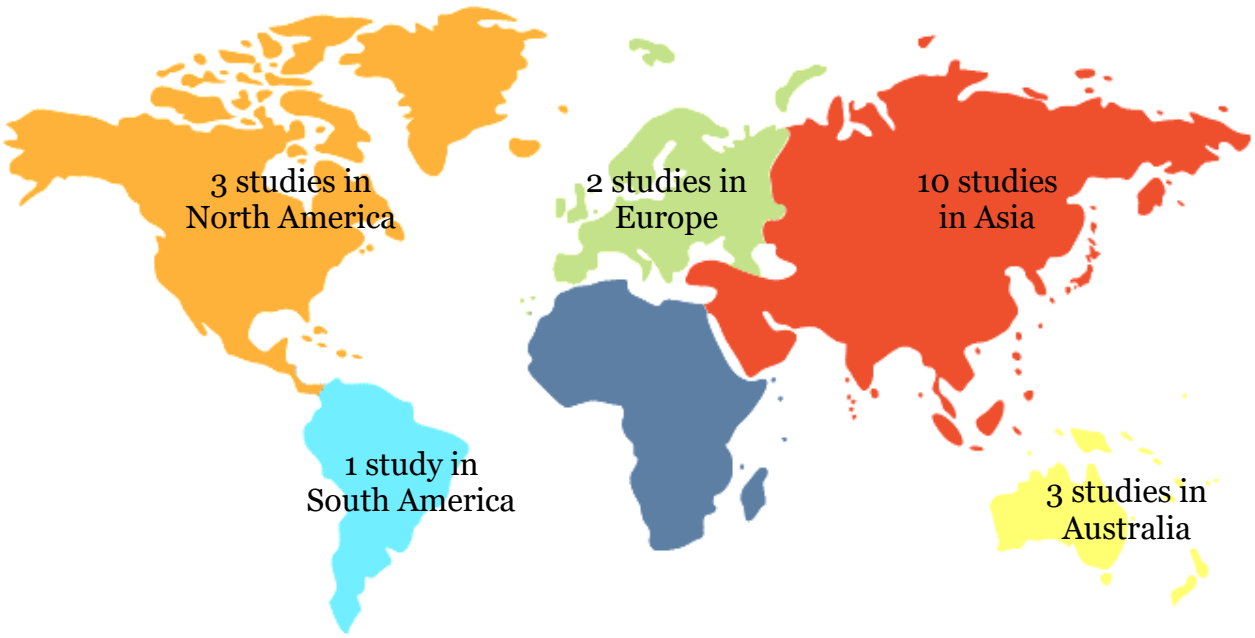

Figure 1. Map of distribution studies on lifestyle, genetic, and menstrual cycle effects on PCOS

Description of the question criteria for cohort studies:

1. Formulation of study questions in the acronym PICO
a. Is the population in the primary study the same as the population in the PICO meta-analysis?
b. Is the operational definition of the intervention, i.e. exposure status in the primary study the same as the definition intended in the meta-analysis?
c. Is the comparator, i.e. non-exposure status used by the primary study the same as the definition intended in the meta-analysis?
d. Are the outcome variables studied in the primary study the same as the definitions intended in the meta-analysis?
2. Methods for choosing a subject of study
a. Was it that at the beginning of the study, the target population and the affordable population had not experienced the outcomes studied?
b. Was the baseline of the study differentiated between exposed groups and unexposed groups?
3. Methods for measuring exposure and outcome variables
a. Were both exposure and outcome variables measured with the same instruments in all primary studies?
b. If variables are measured on a categorical scale, are the cutoffs or categories used the same between primary studies?
4. Design-related bias
a. Is there no possibility of "Loss-to Follow-up Bias" in primary studies?
b. Have primary study researchers made efforts to prevent or overcome such bias?
5. Methods for controlling redundancy

Have primary study researchers done anything to control the effects of confusion?

6. Statistical analysis methods
a. Did the researchers analyze the data in this primary study with a multivariate analysis model?
b. Does the primary study report the effect size or relationship of the results of the multivariate analysis?
7. Conflict of interest

Is there no possibility of a conflict of interest with the sponsor of the study, which causes

bias in concluding the results of the study?
Assessment instructions:

1. Total number of questions = 14 questions.
2. A "Yes" answer to each question gives a score of "2". The answer "Undecided" gives a score of "1". The answer "No" gives a score of "0".
3. Maximum total score = 14 questions x 2 = 28.
4. Total number of minium scores= 14 questions x 0 = 0. So the total score ranges for a primary study between 0 and 28.
5. If the total score of a primary study ≥ 24, then that study can be included in the meta-analysis. If the total score of a primary study < 24, then the study is excluded from the meta-analysis.

Table 1. Critical appraisal for cross-sectional study of the effect of lifestyle, genetic, and menstrual cycle on PCOS

(Author, Year)	Checklist Question													Total
	1a	1b	1c	1d	2a	2b	3a	3b	4	5	6a	6b	7	
Yang et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Tay et al. (2023)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Musmar et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Moran et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Rizvi et al. (2023)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

Description of the question criteria for cross-sectional studies:

1. Formulation of study questions in the acronym PICO

a. Is the population in the primary study the same as the population in the PICO meta-analysis?
b. Is the operational definition of the intervention, i.e. exposure status in the primary study the same as the definition intended in the meta-analysis?
c. Is the comparator, i.e. non-exposure status used by the primary study the same as the definition intended in the meta-analysis?
d. Are the outcome variables studied in the primary study the same as the definitions intended in the meta-analysis?

2. Methods for choosing a subject of study

a. In cross-sectional analytical studies, do researchers randomly select a sample from the population?
b. Alternatively, if in an analytically cross-sectional study the sample is not randomly selected, do researchers select the sample based on outcome status or based on intervention status?

3. Methods for measuring exposure and outcome variables

a. Were both exposure and outcome variables measured with the same instruments in all primary studies?
b. If variables are measured on a categorical scale, are the cutoffs or categories used the same between primary studies?

4. Design-related bias

If the sample is not randomized, have researchers done anything to prevent bias in choosing research subjects?

5. Methods for controlling redundancy

Have primary study researchers made efforts to control the influence of confusion?

6. Statistical analysis methods

a. Did the researchers analyze the data in this primary study with a multivariate analysis model?

b. Does the primary study report the effect size or relationship of the results of the multivariate analysis?

7. Conflict of interest

Is there no possibility of a conflict of interest with the sponsor of the study, which causes bias in concluding the results of the study?

Assessment instructions:

1. Total number of questions = 13 questions.
2. A "Yes" answer to each question gives a score of "2". The answer "Undecided" gives a score of "1". The answer "No" gives a score of "0".
3. Maximum total score = 13 questions x 2 = 26.
4. Total number of minium scores= 13 questions x 0 = 0. So the total score ranges for a primary study between 0 and 26.
5. If the total score of a primary study ≥ 22, then the study can be included in the meta-analysis. If the total score of a primary study < 22, then the study was excluded from the meta-analysis.

Table 2. Critical appraisal for case control study of the effect of lifestyle, genetic, and menstrual cycle on PCOS

Publication (Author and Year)	Checklist Question														Total
	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5	6a	6b	7	
Kaur et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Bedrick et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Zeidan et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Tao et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Azevedo et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Niu et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Shan et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28

Description of the question criteria for case control studies:

1. Formulation of research questions in the acronym PICO

a. Is the population in the primary study the same as the population in the PICO meta-analysis?

b. Is the operational definition of the intervention, i.e. exposure status in the primary study the same as the definition intended in the meta-analysis?

c. Is the comparator, i.e. non-exposure status used by the primary study the same as the definition intended in the meta-analysis?

d. Are the outcome variables studied in the primary study the same as the definitions intended in the meta-analysis?

1. Methods for choosing a subject of study

a. Does the selected affordable population represent the target population?

b. Were case groups and control groups selected at the beginning of the study?

2. Methods for measuring exposure and outcome variables

a. Are both exposure and outcome variables measured by the same instruments, what are all primary studies?

b. If variables are measured on a categorical scale, are the cuttoffs or categories used the same between primary studies?

3. Design-related bias

a. Is there no possibility of recall bias in this primary study?

b. Have researchers made efforts to prevent or address such biases?

4. Methods for controlling redundancy

Have primary study researchers made efforts to control the influence of confusion?

5. Statistical analysis methods
a. Did the researchers analyze the data in this primary study with a multivariate analysis model?
b. Does the primary study report the effect size or relationship of the results of the multivariate analysis?
6. Conflict of interest
Is there no possibility of a conflict of interest with the sponsor of the study, which causes bias in concluding the results of the study?

Assessment instructions:
1. Total number of questions = 14 questions.
2. A "Yes" answer to each question gives a score of "2". The answer "Undecided" gives a score of "1". The answer "No" gives a score of "0".
3. Maximum total score = 14 questions x 2 = 28.
4. Total number of minium scores= 14 questions x 0 = 0. So the total score ranges for a primary study between 0 and 28.
5. If the total score of a primary study ≥ 24, then that study can be included in the meta-analysis. If the total score of a primary study < 24, then the study is excluded from the meta-analysis.

Table 4. Description of the primary studies used in the meta-analysis

Author (Year)	Country (sample) Study Design	Population	Intervention	Comparation	Outcome
Yang et al. (2022)	China (28,739) Cross-Sectional	Women of reproductive age	Obesity	Normal	PCOS
Tay et al. (2023)	Australia (7,966) Cross-Sectional	Women aged 24-30 years old	Obesity	Normal	PCOS
Rizvi et al. (2023)	Pakistan (646) Cross-Sectional	Female undergra-duate students 18 years above	1. Obesity, 2. Irregular menstruation 3. Having a family history of PCOS	1. Normal, 2. Regular menstruation 3. Not having a family history of PCOS	PCOS
Bedrick et al. (2020)	United States (101) Case Control	Women aged 18-50 years old	Obesity	Normal	PCOS
Niu et al. (2020)	China (120) Case Control	Women of reproductive age	1. Obesity 2. Having a family history of PCOS	1. Normal 2. Not having a family history of PCOS	PCOS
Zhang et al. (2020)	China (517) Cohort	Women of reproductive age	Smoking	Not smoking	PCOS
Musmar et al. (2013)	Palestine (137) Cross-Sectional	Women aged 18-24 years old	Smoking	Not smoking	PCOS
Moran et al. (2017)	Australia (7767) Cross-Sectional	Women aged 18-23 years old	Smoking	Not smoking	PCOS
Tao et al. (2021)	Eropa (20,129) Case Control	Women of reproductive age	Smoking	Not smoking	PCOS

Author (Year)	Country (sample) Study Design	Population	Intervention	Comparation	Outcome
Jain et al. (2021a)	US (243,238) Cohort	Women of reproductive age	1. Irregular menstruation 2. Having a family history of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Jain et al. (2021b)	UK (68,325) Cohort	Women of reproductive age	1. Irregular menstruation 2. Having a Family History of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Jain et al. (2021c)	Australia (29,926) Cohort	Women of reproductive age	1. Irregular menstruation 2. Having a Family History of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Jain et al. (2021d)	Philipines (35,131) Cohort	Women of reproductive age	1. Irregular menstruation 2. Having a Family History of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Jain et al. (2021e)	India (40,093) Cohort	Women of reproductive age	1. Irregular menstruation 2. Having a Family History of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Kim et al. (2023)	US (2028) Cohort	Women aged 18-30 years old	Irregular menstruation	Regular menstruation	PCOS
Zeidan et al. (2022)	Baghdad (200) Case Control	Women of reproductive age	1. Regular menstruation 2. Having a Family History of PCOS	1. Irregular menstruation 2. Not having a family history of PCOS	PCOS
Shan et al. (2015)	China (865) Case Control	Women of reproductive age	1. Irregular menstruation 2. Having a Family History of PCOS	1. Regular menstruation 2. Not having a family history of PCOS	PCOS
Kaur et al. (2022)	India (619) Case Control	Women of reproductive age	Having a Family History of PCOS	Not having a family history of PCOS	PCOS
Azevedo et al. (2020)	Brazil (219) Case Control	Outpatient clinic women	Having a Family History of PCOS	Not having a family history of PCOS	PCOS

2. Correlation of obesity with PCOS

Figure 2 presents a forest plot on the effect of obesity on PCOS risk in women of child-bearing age. Women with obesity had 2.49 times the risk of developing PCOS compared to non-obese (OR= 2.49; CI 95%= 1.59 to 3.88; $p < 0.001$).

The forest plot also showed high heterogeneity, estimated effect between studies (I^2= 70%). Thus, calculating the average effect estimation using a random effect model approach.

Figure 3 shows a funnel plot on the estimated distribution of the effects of obesity on PCOS risk. The funnel plot shows that the estimated distribution of effects is more or less balanced to the right and left of the average vertical line. Thus, the funnel plot does not show any publication bias.

Table 3. Adjusted Odds Ratio (aOR) value of the effect of obesity on PCOS

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Rizvi et al. (2023)	2.34	1.27	4.31
Tay et al. (2023)	1.01	0.55	1.85
Yang et al. (2022)	2.77	2.20	3.49
Bedrick et al. (2020)	6.70	2.50	17.96
Niu et al. (2020)	2.97	1.64	5.36

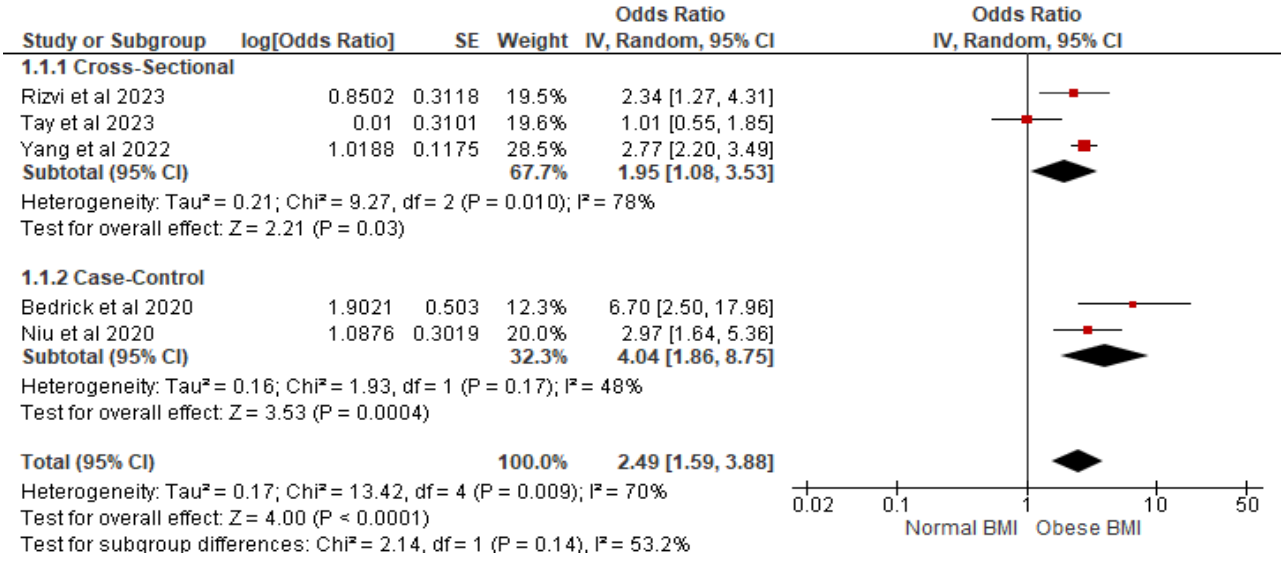

Figure 2. Forest plot of the effects of obesity on PCOS

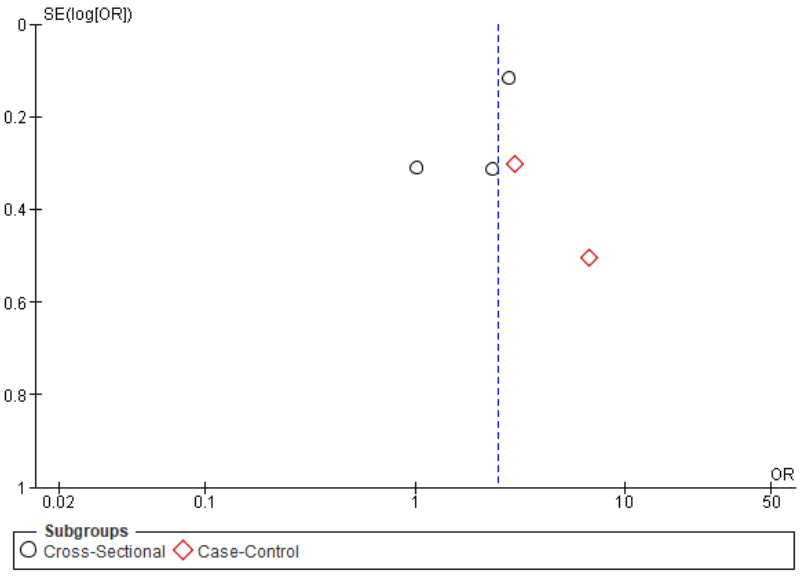

Figure 3. Funnel plot of the effects of obesity on PCOS

3. Correlation of smoking with PCOS

Figure 4 presents a forest plot on the effect of smoking on PCOS risk in women of childbearing age. Women with smoking habits have a risk of developing PCOS 1.42 times compared to nonsmokers (OR= 1.42; CI 95%= 1.04 to 3.89; p= 0.03).

Table 4. Adjusted Odds Ratio (aOR) value of the effect of smoking on PCOS

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Musmar et al. (2013)	1.62	0.20	9.37
Moran et al. (2016)	1.60	1.02	2.51
Tay et al. (2023)	0.90	0.61	1.33
Tao et al. (2021)	1.32	1.06	1.64
Zhang et al. (2020)	2.39	1.47	3.89

The forest plot also showed high heterogeneity, estimated effect between studies (I^2= 60%). Thus, calculating the average effect estimation using a random effect model approach.

Figure 5 shows a funnel plot on the estimated distribution of the effects of smoking on PCOS risk. The funnel plot shows that the distribution of effect estimates is balanced to the right and left of the average vertical line. Thus, the funnel plot does not show any publication bias.

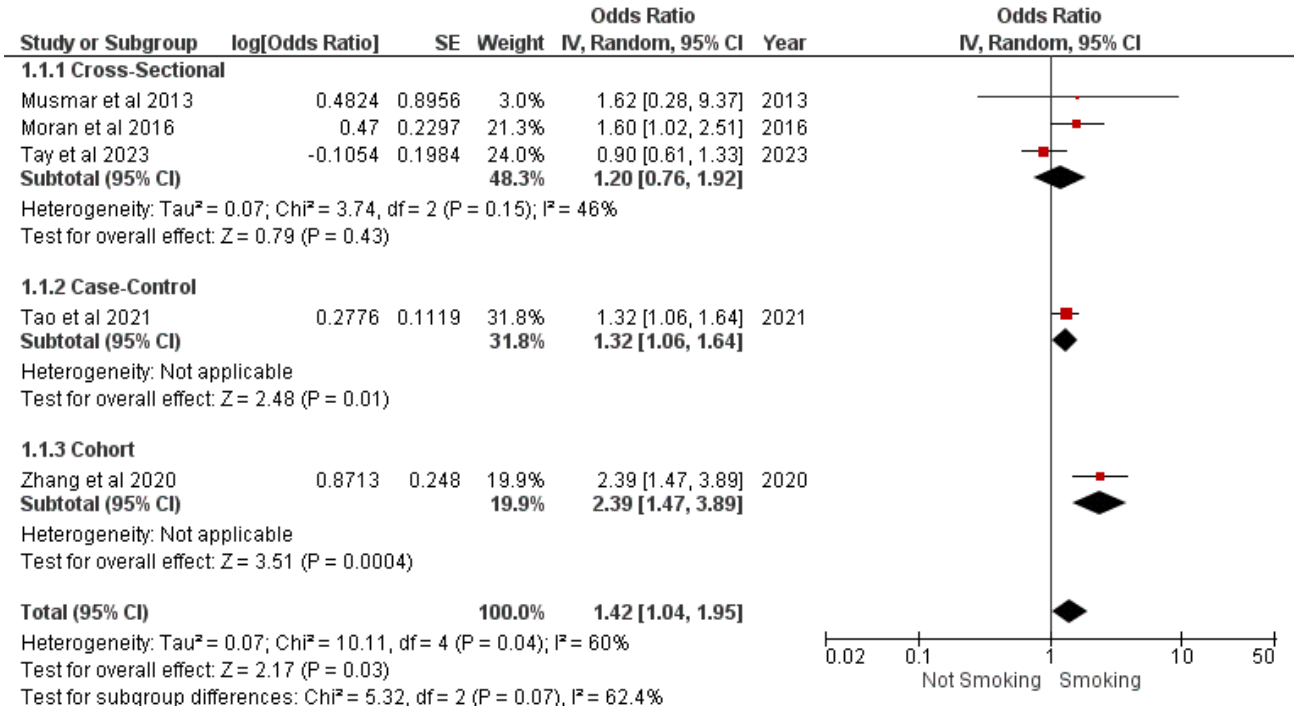

Figure 4. Forest plot of the effects of smoking on PCOS

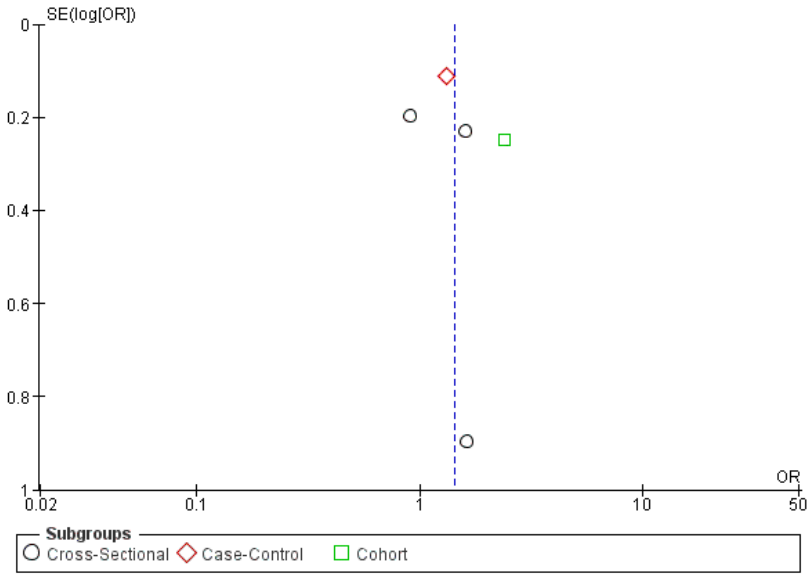

Figure 5. Funnel plot of the effects of smoking on PCOS

4. Correlation of irregular menstruation with PCOS

Figure 6 presents a forest plot of the effect of irregular periods on the risk of PCOS in women of childbearing age. Women with irregular periods were 3.44 times more likely to develop PCOS than those with regular periods, and the effect was statistically significant (OR= 3.44; CI 95%= 2.85 to 4.16; $p < 0.001$).

The forest plot also showed high heterogeneity, estimated effect between studies (I^2= 97%). Thus, calculating the average effect estimation using a random effect model approach. Figure 9 shows a funnel plot on the distribution of estimated effects of family history of PCOS-on-PCOS risk. The funnel plot shows that the estimated distribution of effects is more or less balanced to the right and left of the average vertical line. Thus, the funnel plot does not show any publication bias.

Table 5. Adjusted Odds Ratio (aOR) value of the effect of irregular menstruation on PCOS

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Jain et al. (2021a)	2.92	2.63	3.24
Jain et al. (2021b)	2.41	1.85	7.40
Jain et al. (2021c)	3.39	2.63	4.37
Jain et al. (2021d)	2.99	2.45	3.65
Jain et al. (2021e)	2.76	2.35	3.24
Kim et al. (2023)	3.70	1.85	7.40
Rizvi et al. (2023)	3.70	1.94	7.06
Shan et al. (2015)	5.82	4.42	7.68
Zeidan et al. (2022)	10.31	5.35	19.87

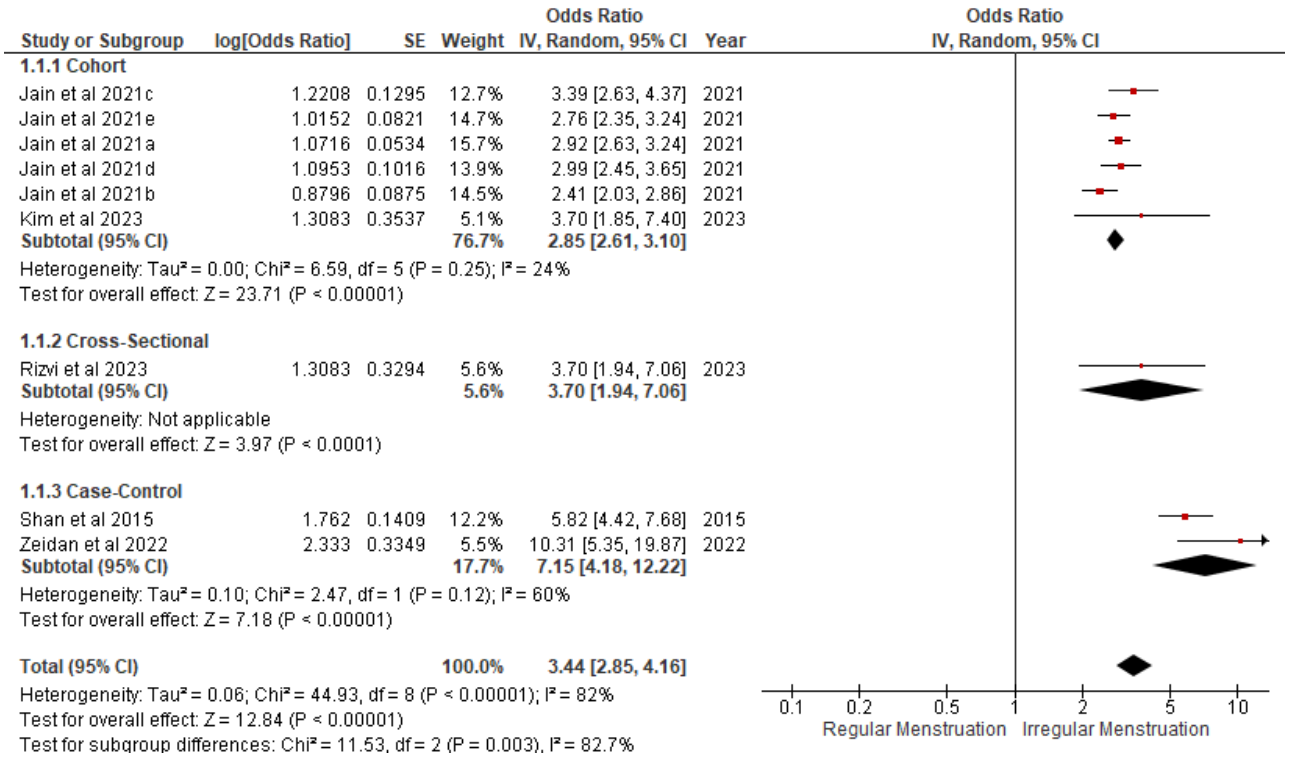

Figure 6. Forest plots of the effects of irregular menstruation on PCOS

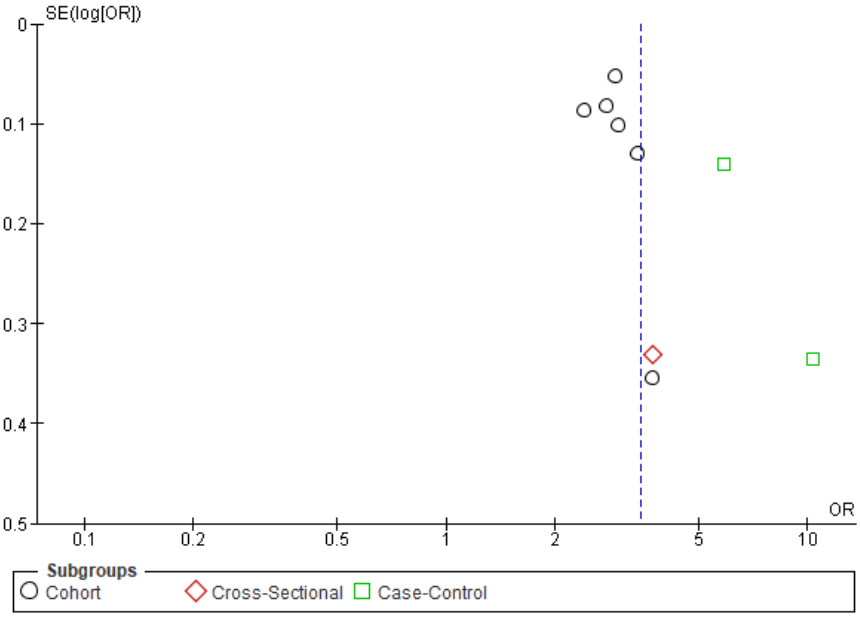

Figure 7. Funnel plot of the effects of irregular menstruation on PCOS

5. Correlation of having a family history of PCOS with PCOS

Figure 8 presents a forest plot on the effect of family history of PCOS-on-PCOS risk in women of childbearing age. Women with a family history of PCOS had a 2.94 times higher risk of having PCOS than no family history of PCOS (OR= 2.94; CI 95%= 2.11 to 4.09; p < 0.001).

Table 6. Adjusted Odds Ratio (aOR) value of the effect of having a family history of PCOS on PCOS

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Jain et al. (2021a)	2.24	1.91	2.63
Jain et al. (2021b)	1.68	1.53	1.84
Jain et al. (2021c)	1.64	1.45	1.85
Jain et al. (2021d)	2.39	2.08	2.75
Jain et al. (2021e)	1.84	1.63	2.08
Niu et al. (2020)	2.38	0.25	22.69
Rizvi et al. (2023)	2.01	1.19	3.39
Shan et al. (2015)	11.95	9.51	15.02
Zeidan et al. (2022)	4.47	1.92	10.41
Azevedo et al. (2020)	2.96	1.54	5.69
Kaur et al. (2022)	16.12	5.76	45.12

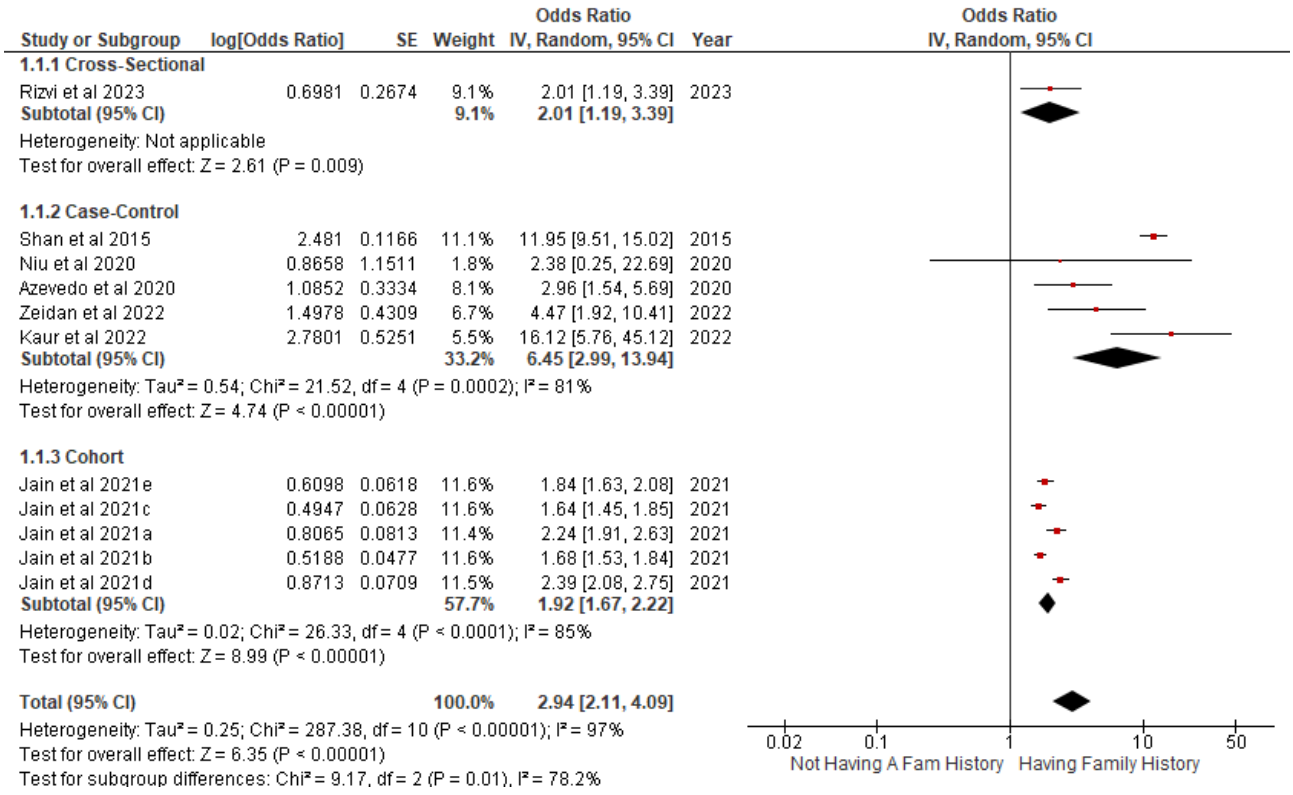

Figure 8. Forest plot of the effects of having a family history of PCOS on PCOS

The forest plot also showed a large heterogeneity of the effect of the study (I^2= 82%). Thus, the calculation of the average effect estimation is done with a random effect model.

Figure 7 shows a funnel plot on the estimated distribution of the effects of irregular periods on PCOS risk. The funnel plot shows that the distribution of effect estimates between studies is more or less balanced to the right and left of the mean vertical line. Thus, the funnel plot does not show any publication bias.

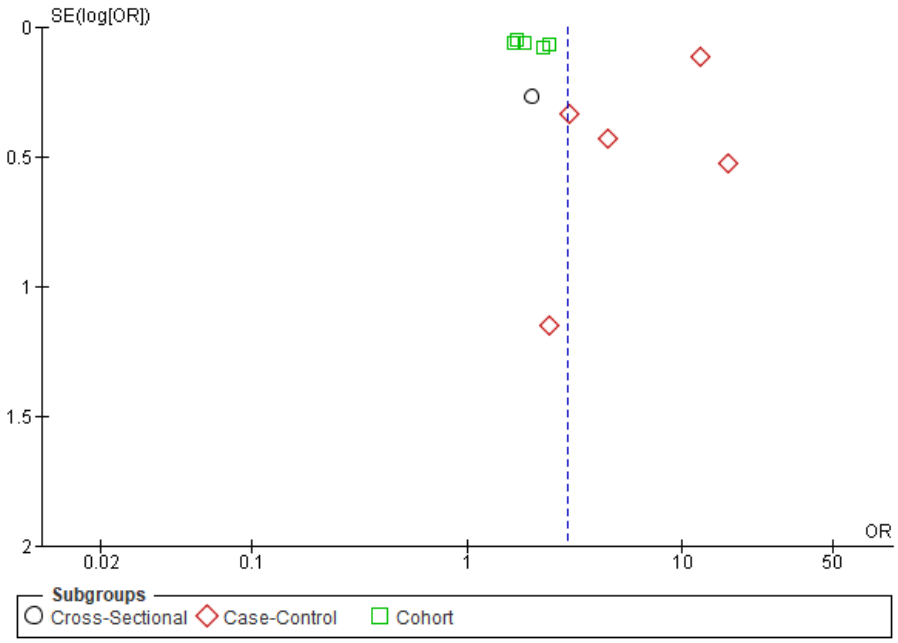

Figure 9. Funnel plot of effects having a family history of PCOS on PCOS

DISCUSSION

1. Obesity with PCOS

There are 5 articles from several countries used to measure the magnitude of the effect of obesity on PCOS. The article consists of 2 study designs, namely 3 cross-sectional studies and 2 case-control studies. Studies have shown a strong link between obesity and PCOS. Data shows that women with obesity have a significantly higher risk of developing PCOS compared to women who are of normal weight.

One study conducted by Sirmans et al. (2013) found that more than 50% of women with PCOS were obese, highlighting the strong correlation between the two conditions. In addition, the effect of obesity on PCOS is not just limited to the risk of developing this syndrome. Excessive body fat can affect hormone levels and insulin resistance, which are key elements of PCOS (Kaur et al., 2022; Makhija et al., 2023).

Insulin resistance can result in excessive production of androgens, male hormones that can interfere with the normal functioning of the ovaries and cause PCOS symptoms, such as irregular periods, infertility, and cyst formation on the ovaries (Hanedan et al., 2022; Peeva et al., 2022; West et al., 2014). Inflammatory factors associated with obesity may also play a role in the pathophysiology of PCOS (Stokkeland et al., 2022). On the other hand, PCOS itself can also play a role in weight gain and obesity. Hormonal imbalances in PCOS make it difficult for women to maintain a healthy weight, and PCOS symptoms can be challenging in managing weight effectively (Witchel et al., 2019). Lifestyle choices such as smoking and diet are also associated with an increased risk of ovulatory dysfunction in women with PCOS (Yang et al., 2022).

2. Smoking with PCOS

There are 5 articles from several countries used to measure the magnitude of the effect of smoking on PCOS. The article consists of 3 study designs, namely 3 cross-sectional studies, 1 case-control study, and 1 cohort study. Studies have shown a strong link

between smoking and PCOS. Data shows that women who smoke have a significantly higher risk of developing PCOS compared to women who don't smoke.

The results of this study are in line with the study of Coffin et al. (2023) found that medical students who experienced PCOS had a previous family history of PCOS, 2.9% of medical students reported the presence of PCOS in their family. Another study also reported that 12.6% of medical students with PCOS had a mother or at least one of their sisters showing similar symptoms (Tahir et al., 2020).

The study of Özay et al. (2020) showed that smoking can affect ovarian stromal blood flow, both in individuals with PCOS and those who are healthy. In PCOS patients and healthy individuals who smoked showed markedly higher pulsation rates and resistance indices in both ovaries compared to nonsmokers. This reduction in ovarian stromal blood flow is associated with the impact of smoking on vascular structure, including increased stiffness, resistance, intima-media thickness, and endothelial injury, all of which contribute to decreased adherence and elasticity.

Not only that, smoking is also associated with increased androgen levels in the blood circulation, as seen from the positive relationship between the number of cigarettes consumed per day and the free androgen index, both in PCOS patients and healthy women (Tao et al., 2021). This indicates that smoking's primary impact on ovarian blood flow may be through its influence on androgen metabolism. Furthermore, smoking is associated with hemodynamic changes, endothelial dysfunction, and increased stiffness in vascular structures, which can result in decreased perfusion in central and peripheral tissues (Oladipupo et al., 2022).

3. Irregular periods with PCOS

There are 10 articles from several countries used to measure the magnitude of the effect of irregular menstruation on PCOS. The article consists of 3 study designs, namely 2 cross-sectional studies, 2 case-control studies, and 6 cohort studies. Studies have shown a strong link between irregular menstruation and PCOS. Data shows that women who have irregular periods have a significantly higher risk of developing PCOS compared to women who menstruate regularly.

A study by West et al. (2014) found that menstrual irregularities at age 16 are associated with an increased risk of PCOS at age 26, suggesting a potential link between menstrual irregularities in adolescence and the development of PCOS later in life. Menstrual irregularities are a striking feature of PCOS, as seen from the duration and cycle, which are very important diagnostic criteria (Hu et al., 2021). This condition of irregularity is closely related to anovulation and hyperandrogenism, two central elements in the pathophysiology of PCOS (Witchel et al., 2019). Women diagnosed with PCOS, particularly those with oligo/amenorrhea, are known to have higher numbers of antral follicles and elevated levels of anti-Müllerian hormone (AMH), confirming a strong correlation between menstrual irregularities and PCOS (Hu et al., 2021).

In addition, menstrual irregularities were also identified as determinants of the presence of PCOS, emphasizing the strong relationship between menstrual irregularities and the condition (Rizvi et al., 2023). Lifestyle factors such as smoking and excessive eating patterns are also associated with an increased risk of ovulatory dysfunction in women with PCOS. This suggests that menstrual irregularities, which are a key feature of PCOS, may be influenced by a variety of lifestyle and environmental factors

(Zhang et al., 2020).

4. Have a family history of PCOS with PCOS

There are 11 articles from several countries used to measure the magnitude of the influence of family history of PCOS on PCOS. The article consists of 3 study designs, namely 1 cross-sectional study, 5 case-control studies, and 5 cohort studies. Studies have shown a strong link between a family history of PCOS and PCOS. Data shows that women who have a family history of PCOS have a significantly higher risk of having PCOS compared to women who do not have a family history of PCOS.

The significant role of genetic factors in explaining and underlying polycystic ovary syndrome (PCOS) cannot be ignored. Studies in this area consistently highlight the hereditary component as an important factor influencing the development and progression of PCOS. As a concrete example, a study conducted by Bogari (2020) shows that the presence of a family history related to type 2 diabetes (T2D) correlates with an increased risk of T2D development in women who have PCOS. This indicates a genetic risk associated with the development of metabolic disorders in PCOS. In addition, the study of genetic polymorphisms that have the potential to predict PCOS provides interesting results. The study of Kaur et al. (2022) showed that genetic variants CYP11B2 and CYP1A1 play a crucial role in enzyme conversion in the steroidogenesis pathway, and disruptions in this pathway can cause hyperandrogenism in women, which is a hallmark of PCOS. Further, the genetic basis of PCOS is also linked to hormonal imbalances, mild inflammation, oxidative stress, and genetic disorders. All of these illustrate the complex genetic influences in the pathogenesis of PCOS (Rakic et al., 2023).

The limitation of this study lies in the limited number of studies that list aOR values. In addition, there are limitations in the number of studies that specifically explore and investigate genetic relationships with PCOS, so in-depth information about the genetic aspects of this condition may not yet be fully available.

In conclusion, the study findings confirm that factors such as obesity, smoking habits, irregular periods, and having a family history of PCOS significantly increase the risk of Polycystic Ovary Syndrome (PCOS) in women of childbearing age.

The implications of these findings point to the need for holistic management and effective health promotion. Obesity was identified as a major risk factor for PCOS, and maintaining a healthy weight through regular exercise and a balanced diet is key in regulating hormone balance as well as reducing the risk of developing PCOS. A focus on healthy food consumption also contributes positively to general well-being and hormonal health. Furthermore, the promotion of regular physical activity is also an important step in the prevention of PCOS, not only helping in weight management but also improving insulin sensitivity which plays a role in the development of the condition. The emphasis on the negative impact of smoking on reproductive health and the integration of smoking cessation support into routine care shows a crucial role in reducing the risk and severity of PCOS. Education about the early signs of PCOS, such as irregular menstrual cycles, is also considered an empowerment step for individuals to get timely medical help, enabling better diagnosis and intervention.

AUTHOR CONTRIBUTION

Dian Ayu Pramukawati as the main researcher chooses topics, searches, collects

study data, and processes data assisted by Rulita Ayu Rachmawati and Normalia Levi Rismawati. Bhisma Murti and Siti Mar'atul Munawaroh analyzed the data and reviewed study documents and articles.

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This study is self-funded.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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