



# Anxiety in polycystic ovary syndrome – a meta-analysis

Ewa Humeniuk<sup>1,A,C-D</sup>, Paweł Dybciak<sup>2,B-D</sup>, Dorota Raczkiewicz<sup>2,C,E-F</sup>, Tomasz Powrózek<sup>3,C</sup>, Teresa Malecka-Massalska<sup>3,E</sup>, Agata Andrzejczyk<sup>4,B</sup>, Krzysztof Suski<sup>2,B</sup>, Iwona Bojar<sup>5,A,F</sup>

<sup>1</sup> Academic Psychological Test Laboratory, Medical University, Lublin, Poland

<sup>2</sup> Department of Medical Statistics, Centre of Postgraduate Medical Education, School of Public Health, Warsaw, Poland

<sup>3</sup> Department of Human Physiology, Medical University, Lublin, Poland

<sup>4</sup> Medical University, Warsaw, Poland

<sup>5</sup> Department of Women's Health, Institute of Rural Health, Lublin, Poland

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation,

D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Humeniuk E, Dybciak P, Raczkiewicz D, Powrózek T, Malecka-Massalska T, Andrzejczyk A, Suski K, Bojar I. Anxiety in polycystic ovary syndrome: a meta-analysis. *Ann Agric Environ Med.* 2025; 190–197. doi: 10.26444/aaem/202444

## Abstract

**Introduction and Objective.** Polycystic ovary syndrome (PCOS) is one of the most common chronic endocrine disorders. One of the serious comorbidity of PCOS are mental disorders including anxiety disorders. The objective of this meta analysis review was to determine the prevalence, the mean level, standardized mean difference and probability of anxiety based on research conducted using the Hospital Anxiety and Depression Scale (HADS-A).

**Materials and Method.** A systematic literature search was conducted using four databases: PubMed, EMBASE, Scopus, ClinicalTrials.gov, and a manual search (Google) for papers written in English published up to October 2023. The meta-analysis was based on 4002 patients obtained from 19 studies that met the inclusion criteria.

**Brief description of the state of knowledge.** The average prevalence of anxiety was found to be 48% (I<sup>2</sup>=97%; p<0.001), whereas the mean HADS anxiety score of PCOS patients was 9.42 (I<sup>2</sup>=95%; p<0.001). Standardized difference in mean anxiety scores – SMD=0.274 (95%, confidence interval – 0.12–0.43, I<sup>2</sup>=18%). The overall probability of anxiety in the group of PCOS patients is about twice higher than in healthy women (RR: 1.91, confidence interval (95% CI [1.52–2.38], I<sup>2</sup>=51%; p=0.08).

**Summary.** The results obtained indicate that women with PCOS may have a significantly increased risk of anxiety compared to those without PCOS, and confirm the need to implement guidelines according to which a woman with PCOS should undergo mental health screening tests, and conduct long-term observation into routine practice.

## Key words

anxiety, meta-analysis, HADS, PCOS

## INTRODUCTION AND OBJECTIVE

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women in their reproductive age. Its prevalence, depending on the diagnostic criteria employed, ranges from 2.2% – 26.7% [1–4]. The most commonly used Rotterdam criteria enable diagnosis of PCOS when two or more of the following symptoms are present: clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, presence of ovarian cysts confirmed by ultrasound examination, and increased AMH levels [5–7]. PCOS is a disorder that can affect many systems and organs and is characterized by a wide range of clinical symptoms [6, 8]. Its most common symptoms are: irregular or absent menstrual cycles and/or infertility [9]; acne vulgaris, androgenetic alopecia, hirsutism or hypertrichosis [10]; dyslipidaemia and markers of endothelial dysfunction [11]; increased insulin level, insulin resistance, type 2 diabetes, increased BMI [12, 13].

The consequences of PCOS go far beyond impairment of the body's biological functions. Based on limited studies, emotional states that are commonly associated with PCOS

include depression and anxiety, as well as such disorders as social phobias, obsessive-compulsive, eating and bipolar disorders, even psychotic episodes have been reported in women with PCOS [14]. Anxiety levels are particularly high in this group of women [15–19]. Recent research and meta-analyses have shown that women who suffer from PCOS present with three to six-fold greater odds ratio of anxiety symptoms, when compared with women who do not suffer from PCOS [15, 20–25].

Elevated levels of anxiety are the most common feature. In asymptomatic women, approximately 25% experience increased anxiety levels at some point in their lives. In the general population, 7.5% present with anxiety related disorders, while in 5–10% anxiety is manifested in various anxiety related syndromes [26]. Anxiety disorders are diagnosed when anxiety interferes with the individual's ability to function efficiently in everyday life, and manifest in panic disorder, phobias and generalized anxiety disorder (GAD) [27, 28].

To provide an explanation for the higher odds ratio of anxiety disorders in women suffering from PCOS remains difficult and its role has not been clearly understood. The results of some studies indicate that hormonal disturbances, particularly increased androgen levels and insulin resistance, may be associated with increased levels of anxiety in women suffering from PCOS [29]. In some women, anovulation, irregular menstruations and fertility difficulties may also

✉ Address for correspondence: Dorota Raczkiewicz, Department of Medical Statistics, Centre of Postgraduate Medical Education, School of Public Health, Warsaw, Poland  
E-mail: dbartos@sgh.waw.pl

Received: 05.07.2024; accepted: 28.02.2025; first published: 25.03.2025

contribute to increased anxiety [5]. Metabolic disorders and increased pro-inflammatory cytokines have also been shown to intensify anxiety symptoms [30]. Due to changes in appearance, such as acne, obesity, excessive hair growth, the syndrome may be related to a negative body image and dissatisfaction with one's appearance, which in itself exacerbates anxiety, and contributes to poorer quality of life and social well-being [23, 31, 32].

Considering these findings and acknowledging the impact of elevated anxiety on both quality of life and coping ability with chronic conditions, it is evident that further exploration of the role of anxiety disorders in women suffering from PCOS is important. However, reports of prevalence and severity of anxiety reported in previous studies have varied significantly, partially on account of the use of different diagnostic tools [25, 33].

The objective of this meta-analysis is to ascertain the following:

- 1) prevalence of anxiety;
- 2) The mean level of anxiety;
- 3) standardized difference in mean scores of anxiety between women suffering from PCOS and women who are asymptomatic;
- 4) probability of anxiety diagnosis based on research utilising the Hospital Anxiety and Depression Scale (HADS-A).

## MATERIALS AND METHOD

Prevalence, mean level and probability of anxiety were analysed based on the Hospital Anxiety and Depression Scale (HADS-A), which serves as a dependable screening tool for identifying clinically significant anxiety and depression in patients attending medical clinics. Furthermore, it effectively measures the severity of mood disorders effectively. The HADS questionnaire consists of 14 questions, seven assessing anxiety (HADS-A subscale) and seven assessing depression (HADS-D subscale). A score of 0–7 on every subscale is seen as normal and scores of 8–10 suggests minor disorders, while a score of 11 potentially indicates the presence of a disorder. HADS has proved to be reliable in identifying anxiety ( $\alpha = 0.83$ ) in a range of validation studies [34].

In a previous study, the current authors reported a meta-analysis on levels of depression utilizing the HADS-D subscale [35], whereas this meta-analysis focuses on anxiety utilizing the HADS-A subscale. For both of these meta-analyses, the same studies were reviewed.

**Search Methodology.** The research adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. A systematic literature search encompassed four resources: PubMed, EMBASE and Scopus, ClinicalTrials.gov, as well as manual searches of English-language studies (via Google) for the periods 2009 and October 2023.

The literature search was performed using applicable search strings, including 'polycystic ovary syndrome', 'PCOS', 'mental disorders', 'anxiety', 'anxiety disorder', and 'HADS'. Additionally, these phrases were utilized in combination with a key word search tool, as in: ('polycystic ovary syndrome', 'PCOS', 'mental disorders', 'anxiety', 'anxiety disorders' and 'HADS'. Moreover, MeSH terms were employed in PubMed, such as 'polycystic ovary syndrome'

(MeSH: ovary syndrome, polycystic', 'syndrome, polycystic ovary', 'polycystic ovary syndrome') and 'anxiety' (MeSH: 'anxiety symptoms', 'symptoms, anxiety') [all boxes]. The research followed PRISMA guidelines available at <http://www.prisma-statement.org> and <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6461330/>.

The study protocol was registered with PROSPERO under Identification No. CDR 42023462618.

**Eligibility.** The following inclusion and exclusion criteria were employed in the systematic review. Inclusion criteria:

- the research encompassed women over 18 years old;
- pre-menopausal women;
- women diagnosed with polycystic ovary syndrome using the criteria established by the National Institute of Health (NIH), the Rotterdam consensus, or other criteria were included [36].
- data on the incidence of anxiety symptoms in the study group could be extracted from the text;
- HADS-A scores could be extracted from the text;
- the study group consisted of at least 30 patients;
- abstracts were considered if they contained all the aforementioned data.

Exclusion criteria:

- review, case report, meta-analysis, or systemic review studies;
- studies not available in English;
- studies recruiting teenagers or women post menopause;
- studies not using HADS to gauge the degree and incidence of mental disorders;
- studies assessing anxiety disorders post treatment;
- studies assessing anxiety disorders only in obese or infertile women, as well as women with hirsutism or other PCOS symptoms'
- studies including women suffering PCOS undergoing treatment or pregnant women.

There were no restrictions on the location of the research. Finding and choosing studies was performed in accordance with the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) scheme:

- Population – Adult and pre-menopausal women with PCOS;
- Intervention – None;
- Comparison – Studies that involved women suffering from PCOS as well as asymptomatic cases (the control group);
- Outcomes – Group size; anxiety measured by HADS-A score; relative risk of anxiety;
- Study design – Case-control, cross-sectional, prospective and retrospective studies written in English.

**Data analysis.** The analysis of data and generation of graphs were conducted using MetaXL (EpiGear) software version 5.4. Cochrane's Q test (Q), as well as the I<sup>2</sup> test, which were supposed to evaluate the heterogeneity or variability in the true effect size estimated across studies. A random effects model was utilized to show heterogeneity; the level of heterogeneity was assessed based on the following criteria: I<sup>2</sup> values of between 0–40% indicate no heterogeneity or rejected heterogeneity, I<sup>2</sup> > 40–70% suggests intermediate heterogeneity, and results of I<sup>2</sup> exceeding 70% indicate high heterogeneity.

The standardized mean difference (SMD; Hedges' g) was used to compare the HADS means between the women suffering PCOS and the women from the control group. SMD of 0.2–0.5 indicates small effects, 0.5–0.8 – medium effects, and >0.8 – large effects. A relative risk (RR) > 1.0 indicates a high collective risk, while an RR of < 1.0 signifies a low collective risk of mental disorder among the groups of women under investigation.

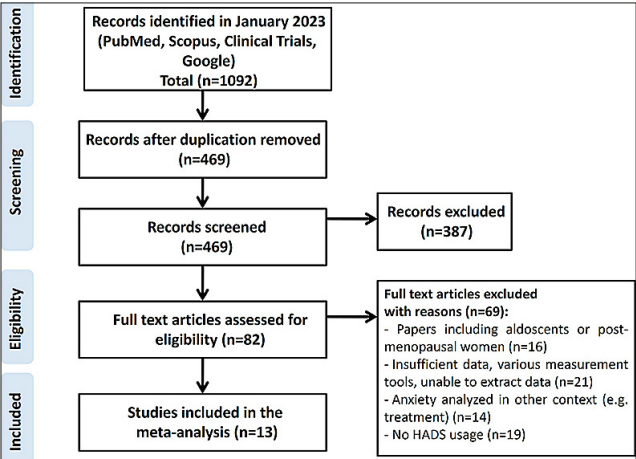
Funnel plots and Luis Furuy-Kanamori index (LFK index) were employed to examine publication bias exists. The LFK index was interpreted as follows: a value below 1 indicates no asymmetry, 1–2 – minor asymmetry, while a value > 2 – major asymmetry.

Level  $p<0.05$  was considered statistically significant in all the analyses.

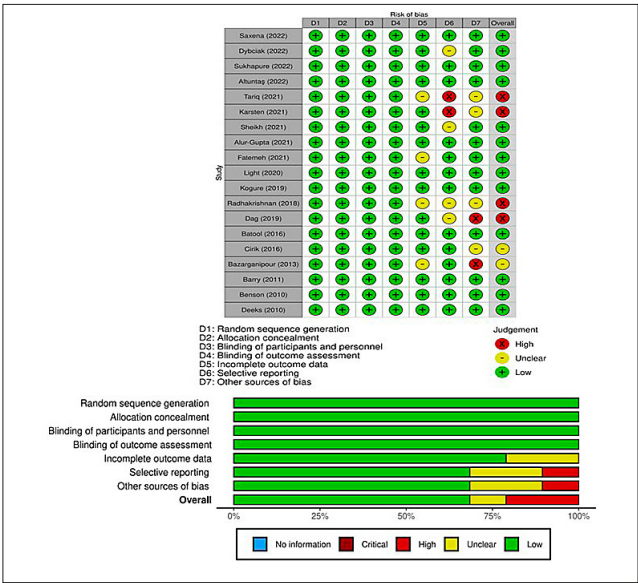
**Search results.** The systematic literature review was concluded on 30 December 2023; the eligibility of article titles, key words, and abstracts were then evaluated. During the initial selection phase, two independent double-blind researchers examined 1,092 studies, identifying, and subsequently eliminating 469 duplicates. Ten ambiguous texts were then deliberated upon, with a consensus being reached (kappa statistics = 0.96). Another 387 studies did not meet the PRISMA criteria, the remaining 82 qualifying reports were then chosen. Of these, 63 studies were eliminated for a variety of reasons, such as involving teenagers or women post menopause (14 studies), insufficient information, or using other measurement tools where it was not possible to obtain the necessary data (total of 19 papers), analysing anxiety in a different framework, such as treatment (13 studies), or employing measurement tools different from the HADS (17 studies). The number of qualifying studies was thus reduced to 19.

Wherever feasible, the following information was taken from each source: diagnostic criteria for PCOS, and whether it was verified by diagnosis or reported by the patient; every feature on which PCOS patients and controls were matched, comparison of demographic data between the groups, location of subject recruitment, total number of patients, and mean age.

The eligible studies provided the following information: primary author, year of publication, country of origin of the study, sample size, prevalence of anxiety, and/or mean HADS-A score. The comprehensive plan employed for identifying, finding, and selecting the literature is illustrated in Figure 1. The same figure is presented in the authors'



**Figure 1.** Flow chart of the search for eligible articles according to PRISMA guidelines [35]



**Figure 2.** Assessment of the risk of bias in studies included in the meta-analysis. (a) reviewers' evaluations of each risk of bias item for each included study; (b) reviewers' assessments of each risk of bias item shown as percentages across all included studies [35]

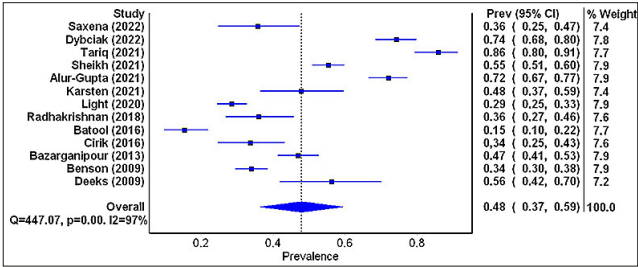
previous meta-analysis relating to depression [35]. The same situation applies to Figure 2.

Figure 2 presents the bias risk evaluation findings for every research project in the meta-analysis, which were performed using the Cochrane Risk of Bias 2 (RoB 2) tool. Concerning the choice of studies, 13 studies were assessed as low risk of bias, while 6 studies were deemed to have a greater risk of bias due to lack of information concerning the study site.

The key aspects of the research studies in the meta-analysis are outlined in Table 1. Thirteen studies were included for the initial phase of the meta-analysis. Each of these studies satisfied the inclusion criteria and provided information on how many patients scored  $\geq 8$  points on the anxiety scale, from a total of 2,903 patients. The included studies originated from six Asian countries, five European countries, one American, and one Australian study. Study group size fluctuated between 33 – 502 patients.

The prevalence of anxiety ranged from 15% – 85.9% (mean 48%). The lowest and highest anxiety rates showed up in two studies from the same country – Pakistan [39,45]. The prevalence of anxiety in selected studies is presented in Table 1. The random effects model showed significant heterogeneity in study outcomes ( $I^2 = 97\%$ ;  $p<0.001$ ) (Fig. 3).

Thirteen research studies were accepted into the following phase of the meta-analysis. These fulfilled the inclusion criteria and possessed information on the mean HADS-A score, totalling 2619 women between the ages of 22.69 – 34.1. One research project did not include a mean age [18] whereas



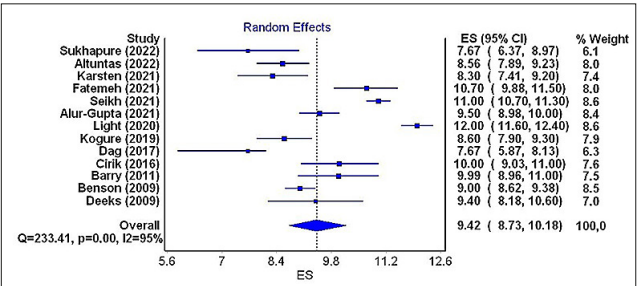
**Figure 3.** Forest plot of the meta-analysed prevalence of anxiety in PCOS patients



**Table 1.** Age, prevalence of anxiety and HADS-A score in PCOS patients

| Study (year)         | Country     | Citation | No. of PCOS patients | PCOS patients age (Mean±SD) | Anxiety (%) (active/cases) | HADS-A score (Mean±SD) |
|----------------------|-------------|----------|----------------------|-----------------------------|----------------------------|------------------------|
| Saxena (2022)/       | India       | [37]     | 70                   | 25.7±7.6                    | 35.7% (25/70)              | -                      |
| Dybciak (2022)       | Poland      | [17]     | 230                  | Min-Max 20-40               | 74.3% (171/230)            | -                      |
| Sukhapure (2022)     | New Zealand | [38]     | 33                   | 29.2±6.8                    | -                          | 7.7±3.8                |
| Altuntaş (2022)      | Turkey      | [6]      | 167                  | 25.9±5.6                    | -                          | 8.6±4.4                |
| Tariq (2021 )        | Pakistan    | [39]     | 135                  | 15-45                       | 85.9% (116/135)            | -                      |
| Karsten (2021 )      | Netherlands | [8]      | 73                   | 34.1±4.1                    | 47.9% (35/73)              | 8.3±3.9                |
| Sheikh (2021)        | UK          | [18]     | 502                  | -                           | 54.4% (278/502)            | 11.0±3.0               |
| Alur-Gupta (2021)    | USA         | [40]     | 272                  | Median 28.9                 | 72% (169/272)              | 9.5±4.4                |
| Fatemeh (2021)       | Iran        | [41]     | 239                  | 30.9±5.5                    | -                          | 10.7±6.5               |
| Light (2020)         | UK          | [42]     | 487                  | 30.8±7.7                    | 28.5% (139/487)            | 12.0±4.2               |
| Kogure (2019)        | Brazil      | [43]     | 120                  | 28.8±5.2                    | -                          | 8.6±3.9                |
| Radhakrishnan (2018) | India       | [13]     | 100                  | 16-36                       | 36.0% (36/100)             | -                      |
| Dag (2019)           | Turkey      | [44]     | 53                   | 22.7±4.5                    | -                          | 7.7±4.2                |
| Batool (2016)        | Pakistan    | [45]     | 137                  | 25.0±8.6                    | 15.3% (21/137)             | -                      |
| Cirik (2016)         | Turkey      | [46]     | 101                  | 24.4±4.2                    | 33.7% (34/101)             | 10.0±5.0               |
| Bazarganipour (2013) | Iran        | [33]     | 300                  | 26.6 ± 4.4                  | 47.0% (141/300)            | -                      |
| Barry (2011)         | UK          | [20]     | 76                   | 28.8±4.8                    | -                          | 10.0±4.6               |
| Benson (2010)        | Germany     | [47]     | 448                  | 29.6±5.5                    | 34% (152/448)              | 9.0±4.1                |
| Deeks (2010)         | Australia   | [16]     | 48                   | 32.5±8.0                    | 56.3% (27/48)              | 9.4±4.3                |

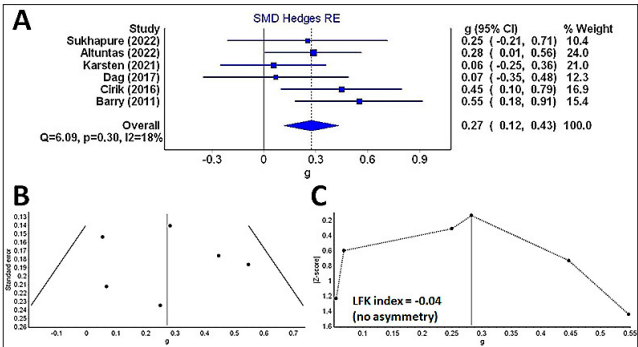
the other project included median age instead of mean age [41]. The mean anxiety score oscillated between 7.67 – 12.0 (9.42, on average). The women from New Zealand and Turkey had the lowest anxiety score (7.67, on average); whereas the women from the United Kingdom had the highest anxiety scores (12.0 and 11.0, on average) similarly to the women from Iran (10.7, on average). Table 1 presents mean HADS-A scores for the women suffering from PCOS. The research results showed high heterogeneity with regard to random effects model ( $I^2 = 95\%$ ;  $p<0.001$ ) (Fig. 4).



**Figure 4.** Forest plot of the meta-analysed mean anxiety scores in PCOS patients

Six studies, including three from Turkey, one from the United Kingdom, one from The Netherlands and one from New Zealand, were taken into consideration for the following stage of the meta-analysis. All of the above-mentioned studies met the inclusion criteria. They comprised data on the mean HADS-A score in the women suffering with PCOS and the women from the control group. The group of patients suffering from PCOS consisted of 503 women, while 350 women belonged to the control group. The women suffering from PCOS were aged between 22.69 – 34.1 years, on average, while the controls were aged 21.34 – 35.12. The lowest standardized mean difference was 0.070, with confidence

interval from -0.35 – 0.48, as seen in research involving 53 Turkish patients [44], and the largest standardized mean difference was 0.55 with confidence interval 0.18 – 0.91 in the group consisting of 76 patients from the United Kingdom [20]. The cumulative standardized mean difference between the mean score of anxiety in the women suffering from PCOS and controls was 0.27 with 95% confidence interval, 0.12 – 0.43 and  $I^2=18\%$ , proving a low overall effects size without heterogeneity (Fig. 5a). The data on the HADS-A scores in both groups and the standardized mean difference (Hedge’s g) is presented in Table 2. A small asymmetry was observed in the funnel plot (Fig. 5b), with LFK score of -0.04 (no asymmetry) confirmed (Fig. 5c). It can be concluded that there was no significant publication bias in the six studies included.



**Figure 5.** (A) Meta-analysis employing a random-effects model to calculate the standardized mean difference (SMD) in HADS-A scores between control and exposed groups. (B) Funnel plot for the SMD in the anxiety meta-analysis. (C) Doi plot and LFK index used to assess publication bias

The next stage of the meta-analysis evaluated anxiety likelihood in women suffering from PCOS (Tab. 3). Five

**Table 2.** Standardized mean difference of the HADS scores for anxiety in PCOS patients and healthy controls

| Study (year)<br>Country         | No. of cases      | Age (years)<br>(Mean±SD) | HADS-A score<br>(Mean±SD) | SMD<br>(Hedge's g) | Citation |
|---------------------------------|-------------------|--------------------------|---------------------------|--------------------|----------|
| Sukhapure (2022)<br>New Zealand | Study group - 33  | 29.24±6.81               | 7.67±3.81                 | 0.250              | [38]     |
|                                 | Control - 41      | 29.29±8.62               | 6.73±3.65                 |                    |          |
| Altuntaş (2022)<br>Turkey       | Study group - 167 | 25.87±5.64               | 8.56±4.42                 | 0.283              | [6]      |
|                                 | Control - 73      | 27.25±5.85               | 7.35±3.87                 |                    |          |
| Karsten (2021)<br>Netherlands   | Study group - 73  | 34.1±4.1                 | 8.3±3.9                   | 0.055              | [8]      |
|                                 | Control - 100     | 35.1±3.7                 | 8.1±3.4                   |                    |          |
| Dag (2017)<br>Turkey            | Study group - 53  | 22.69±4.54               | 7.67±4.2                  | 0.068              | [44]     |
|                                 | Control - 38      | 21.34±2.12               | 7.39±3.88                 |                    |          |
| Cirik (2016)<br>Turkey          | Study group - 101 | 24.44±4.23               | 10±5.0                    | 0.447              | [46]     |
|                                 | Control - 49      | 26.29±5.17               | 8.0±3.0                   |                    |          |
| Barry (2011)<br>UK              | Study group - 76  | 28.8±4.81                | 10±5.0                    | 0.547              | [20]     |
|                                 | Control - 49      | 35.12±4.37               | 8.0±3.0                   |                    |          |

**Table 3.** Prevalence of anxiety in PCOS patients compared to healthy controls

| Study (year) / Country       | POCS (active/cases) | Control(active/cases) | RR [95%CI]       | Citation |
|------------------------------|---------------------|-----------------------|------------------|----------|
| Dybciak (2022) / Poland      | 74.3% (171/230)     | 39.2% (78/199)        | 1.90 [1.57-2.29] | [17]     |
| Tariq (2021) / Pakistan      | 85.9% (116/135)     | 37% (50/135)          | 2.32 [1.84-2.92] | [39]     |
| Karsten (2021) / Netherlands | 47.9% (35/73)       | 37% (37/100)          | 1.30 [0.91-1.83] | [8]      |
| Batool (2016) / Pakistan     | 15% (21/137)        | 8% (11/137)           | 1.91 [0.96-3.81] | [45]     |
| Cirik (2016) / Turkey        | 33.7% (34/101)      | 12.2% (6/49)          | 2.75 [1.24-6.11] | [46]     |

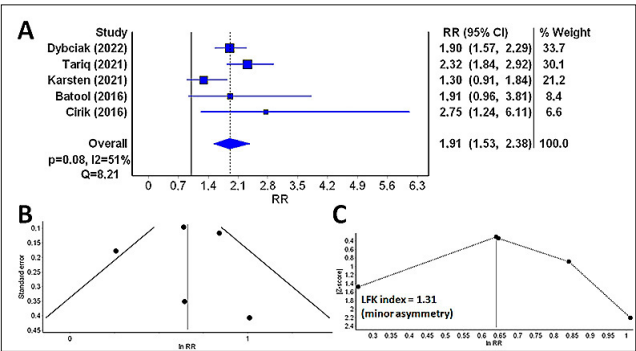
studies met the inclusion criteria. They contained information on the number of women suffering from PCOS and a control group who had anxiety scores of at least eight, resulting in 290 women deemed as suffering from PCOS and 113 women from the control group. Similar weight was observed in all the studies included. The smallest probability of anxiety (RR=1.30 with 95% CI 0.91–1.84) was observed in the study of 35 women from The Netherlands [8]. The highest probability of anxiety (RR=2.75 with 95% CI 1.24–6.11) was found in the study of 34 patients from Turkey [46]. The overall likelihood of anxiety in the women suffering from PCOS was more than double that of controls (RR=1.91 with 95% CI 1.52–2.38 and I2=51%; p=0.08) (Fig. 6a). A small asymmetry was found in the funnel plot (Fig. 6b), and confirmed by the LFK=1.31 (Fig. 6c).

DISCUSSION

The aim of this meta-analysis was to ascertain the prevalence of anxiety, the mean score of anxiety, standardized mean difference, and the likelihood of anxiety, based on research carried out utilizing the Hospital Anxiety and Depression Scale (HADS-A). The meta-analysis involved women suffering from PCOS, gathered from 19 research projects that met the inclusion criteria and originated from several countries (four from the UK, three from Turkey, two from India, two from Iran, two from Pakistan, and one each from Australia, Brazil, Netherlands, New Zealand, Poland, and the USA). The I2 test results indicated considerable heterogeneity for most analyses conducted, using a random effects model. The greatest heterogeneity (I2=97%) was observed in the studies assessing the prevalence of anxiety in PCOS patients, while the lowest (I2=18%) was found in studies calculating the standardized mean difference between women suffering from PCOS and controls.

Based on a meta-analysis of 13 projects (2,903 individuals) researching the incidence of anxiety of ≥ 8 points on the HADS Scale, anxiety ranged from 15% – 85.9%, with a mean of 48% (I2=97%; p<0.001). Both the lowest and the highest prevalence of anxiety and PCOS was observed in the studies conducted in Pakistan [39,45]. Similar results were obtained in two other meta-analyses. The median prevalence of anxiety according to nine studies was 41.9% in the group of women with PCOS, and 8.5% in the control group [23]. Nevertheless, in the meta-analysis by Wang et al. in 2021, the pooled prevalence of anxiety was 37% (95% CI: 14–60%) [24]. A significantly lower prevalence of generalized anxiety disorders, i.e. 20.4%, was demonstrated in four studies meeting the criteria [48].

In a meta-analysis of 13 studies, the mean score of anxiety was observed to range from 7.76 – 12.0 (mean 9.42). The



**Figure 6.** Relative risk (RR). (A) probability of the anxiety incidence in POCS patients. (B) Funnel plot of RR for anxiety meta-analysis. (C) Doi plot and LFK index for the detection of publication bias

highest result was presented by patients from the United Kingdom (12.0 and 11.0) [18,42] and from Iran (10.7) [41], the lowest result was found in the patients from New Zealand and Turkey (7.67) [38,44]. These findings are not applicable to the conclusions reached in preceding meta-analyses because they did not include the same data [15, 22–25].

The cumulative standardized difference between the mean level of anxiety in the group of women suffering from PCOS and the control group in the meta-analysis was  $SMD = 0.27$  (95% CI 0.12–0.43 and  $I^2=18\%$ ), which indicates a small overall effect size without heterogeneity. The lowest standardized mean difference of 0.070 showed up in the study of Turkish women with PCOS [44], and the highest difference of 0.55 in the patients from the United Kingdom [20]. In the previous meta-analyses, the overall effect size was higher ( $SMD = 0.49$ ) [49],  $SMD = 0.49$  [24], ( $SMD = 0.54$ ) [20],  $SMD = 0.63$  [25].

In the meta-analysis based on five qualified studies of similar size (290 patients with PCOS and 113 control subjects), containing data on the number of individuals whose anxiety score was  $\geq 8$ , a cumulative probability of anxiety was calculated. This is almost two-fold higher in the patients with PCOS in comparison with control group ( $RR=1.91$  with 95% CI 1.52–2.38 and  $I^2=51\%$ ;  $p=0.08$ ) with slight asymmetry. The smallest relative risk of anxiety ( $RR=1.30$  with 95%CI 0.91–1.83) was noted in the study of 35 women suffering from PCOS from The Netherlands [8], and the highest ( $RR=2.75$  with 95% CI 1.24–6.11) in the study of 34 patients from Turkey [46].

It is noteworthy that the cumulative standardized difference between the mean anxiety levels in the PCOS group and the control group is relatively small, but the cumulative probability of anxiety is nearly twice as high in patients with PCOS compared to the control group. This discrepancy is likely attributable to the differences in calculation, as the cumulative standardized difference considers all anxiety scores, whereas the cumulative probability is derived exclusively from HADS-A scores  $\geq 8$ .

The likelihood of anxiety disorders was higher in previous meta-analyses when compared with the current research. In the meta-analysis conducted by Brutocao et al., it was almost three-fold higher in the women with PCOS than in the control group ( $OR=2.75$  with 95% CI 2.10–3.60) [15]. Similar results were obtained in another meta-analysis [22]. One other meta-analysis, showed that women suffering from PCOS had almost six-fold higher odds ratio of any anxiety symptoms ( $OR=5.62$  with 95%CI 3.22–9.80, nine studies) and moderate to severe anxiety symptoms ( $OR=6.55$  with 95% CI 2.87–14.93; five studies) [23].

Although a higher prevalence of anxiety in PCOS is evident, the research does not provide the definitive explanation for the causes of the relationship [20, 23, 24, 42]. Results of some research suggest that hormonal imbalance, anovulation, irregular menstrual cycles and infertility are responsible for an increased level of anxiety in women suffering from PCOS [5, 29]. Also, metabolic disorders and an increased level of pro-inflammatory cytokines, as well as changes in the appearance, may intensify anxiety symptoms [23, 30–32].

The strength of this study is its unique inclusion of studies utilizing a singular method for diagnosing depression (the HADS), marking a departure from previous meta-analyses. The authors are not aware of any comprehensive meta-analysis of this kind being carried out previously; earlier

studies relied on diverse diagnostic tools, such as the Beck Depression Inventory (BDI), the 12-item General Health Questionnaire (GHQ-12), or the Depression Anxiety Stress Scale (DASS). This discrepancy might have contributed to the heterogeneity in the results [25, 33]. Moreover, the current meta-analysis incorporated research conducted both with and without control groups, facilitating the determination of anxiety prevalence and mean levels among women with PCOS. Additionally, utilizing research studies with control groups made it possible to determine standardized mean differences and probabilities of depression.

**Limitations of the study.** Every research project used in this meta-analysis was cross-sectional, limiting causal inference regarding the relationship between PCOS diagnosis and depression/anxiety. High heterogeneity among the studies is a primary limitation. Moreover, this study exclusively included published articles, potentially introducing publication bias despite no such statistical observations. Furthermore, factors like infertility, androgen concentrations, body mass index, or length of disease, that can significantly influence mental health, were not consistently studied due to the lack of data availability and other inclusion criteria limitations.

Moreover, as evidenced in the literature, the HADS method may have certain limitations when applied to clinical populations. While these concerns are primarily associated with the assessment of depression, it is important to acknowledge that similar limitations may also affect the evaluation of anxiety [50].

## CONCLUSIONS

The results obtained indicate that women with PCOS may have a significantly increased risk of anxiety compared to those without PCOS, emphasizing the necessity for testing and the ongoing monitoring in this population. These results also support the necessity for integrating guidelines into routine practice, and advocate for mental health screening and long-term follow-up for women with PCOS. The mental health status of these individuals highlights the need for the development of psychological healthcare interventions. Psychoeducation on PCOS is crucial and should be conducted by healthcare professionals as this illness remains poorly understood among both patients and medical practitioners. It is imperative that women with PCOS recognize the mental health risks associated with the condition, and know how to seek professional assistance when needed. Additionally, each consultation should not only focus on the clinical aspects of PCOS, but also note the anxiety symptoms that need to be taken into consideration in order to manage them effectively. Engaging with patients allows for discussion of issues associated with PCOS that pose marital, family, and social challenges, and result in a low quality of life, sexual dysfunctions, and low self-esteem. Furthermore, employing well-established diagnostic tools (e.g. HADS) is essential for accurate diagnosis.

Further studies of the most effective psychosocial interventions for women suffering from PCOS are not only warranted but should be encouraged. Despite using various therapies, such as cognitive behavioural therapy, geared to enhancing mental health and the quality of life in women suffering from PCOS, their effectiveness remains uncertain, highlighting the need for ongoing investigation.



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