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# Mental state and health-related quality of life in patients with polycystic ovary syndrome under metformin therapy – a prospective study

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**ABSTRACT**

PCOS is one of the most prevalent endocrine disorders among women of reproductive age, often involving obesity, insulin resistance, and mental health challenges that reduce health-related quality of life (HRQOL). Although metformin has been shown to improve HRQOL in PCOS patients, it is unclear whether this effect is due to the drug itself or its metabolic benefits. This study included 66 PCOS patients from the University Medical Center Mainz, in two groups: 31 received metformin (M-group) and 35 received alternative or no treatment (C-group). HRQOL and distress were assessed at baseline and after 6 months using the Modified PCOS-Questionnaire (MPCOSQ) and the Hospital Anxiety and Depression Scale (HADS). At baseline, the M-group had significantly worse metabolic markers, including HOMA-IR, waist circumference, Visceral Adiposity Index, and Fatty Liver Index. By follow-up, this group showed greater improvements in these markers. However, both groups improved similarly in HRQOL and distress. Regression analysis revealed that improvements in HOMA-IR and BMI were associated with better HRQOL scores. Group assignment was not a significant predictor. These findings may indicate that improvements in HRQOL and reduced distress are linked to metabolic changes associated with metformin use, underscoring the potential relevance of addressing metabolic health in treatment approaches.

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## Introduction

Polycystic Ovary Syndrome (PCOS) is a complex endocrine-metabolic disorder, affecting approximately 8–18% of women worldwide between the ages of 15 and 44 years [1]. PCOS is a complex condition influenced by multiple factors and can present with a variety of symptom clusters, including obesity, insulin resistance, cardiovascular issues, depression, anxiety, and other disorders [2,3]. Although the pathomechanisms of PCOS are still under investigation and not fully understood, research has shown that metabolic alterations significantly contribute to its development [4]. Insulin resistance and obesity are frequently observed in individuals with PCOS and play a crucial role in both the severity of symptoms and the prognosis of the disorder [5].

The spectrum of symptoms in PCOS patients and their varying severity complicate the standardized assessment of factors influencing health-related quality of life (HRQOL) and mental health. Although the existing studies are difficult to compare due to the heterogeneity of the study populations, research on this subject shows a reduced HRQOL in PCOS patients compared to the general population. This seems to be consistent regardless of the specific tools used to evaluate HRQOL [6]. The same applies to mental health. An Australian longitudinal study found that depression affected up to 27.3% of PCOS patients, compared to 18.8% in the control group, while anxiety and anxiety disorders were present in 50% of cases versus 29.2% in controls [7].

The current 2023 International PCOS Guideline provides a detailed description of the role of pharmacological treatment for the metabolic component of PCOS [8]. If lifestyle changes are unsuccessful, the guideline recommends initiating pharmacological therapy with

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the biguanide metformin. Research has indicated that metformin may promote weight loss by affecting appetite-regulatory pathways in the brain, resulting in reduced food intake. This is particularly significant for women with PCOS, as weight gain and obesity are major concerns [9]. In PCOS patients with metabolic disturbances or obesity, metformin therapy may be started even without prior use of oral contraceptives. Notably, women with a Body Mass Index (BMI) >25 kg/m$^2$ appear to benefit particularly from metformin treatment. However, treatment should be individualized and regularly monitored, as the efficacy of metformin can vary among patients [8]. According to a meta-analysis by Samarasinghe et al. metformin leads to a significant reduction in BMI, fasting glucose, and insulin levels, while having no impact on other metabolic and reproductive outcomes in patients with PCOS [10].

So far, several studies have shown that metformin can lead to improved HRQOL and mental health [11–13]. However, it remains unclear whether the observed improvements in HRQOL and mental health are directly attributable to the medication itself or if they stem from the positive changes in metabolic markers that metformin is known to influence. This ambiguity calls for a more thorough investigation into the specific role that metabolic changes, as a result of metformin therapy, play in improving HRQOL and reducing distress among women with PCOS. This study aims to explore this relationship by assessing both metabolic markers, HRQOL outcomes and mental state in women undergoing metformin treatment.

## Methods

### Study design

This single-center prospective cohort study involved the consecutive enrollment of patients. Each participant underwent a comprehensive assessment at baseline and was scheduled for a follow-up visit 24 weeks after initiating therapy (t1). The study aimed to evaluate treatment efficacy and its impact on metabolic parameters, which were measured both at the time of enrollment (t0) and at the follow-up (t1).

### Inclusion and exclusion criteria

Participants were enrolled from the Fertility Center of the Department of Obstetrics and Gynecology of the University Medical Center Mainz as well as private gynecology practices in Mainz were asked to refer PCOS patients, and announcements were posted on the website of the German PCOS support group and in public places throughout Mainz. The inclusion period for the study spanned 10 months in 2021 and 2022.

Eligible participants could not undergo any PCOS-related therapy or take any metabolic medication at the time of enrollment. If they were on such therapy, it had to be discontinued for 3 months prior to inclusion. The initiation of any new medication during the study period was monitored, and participants were instructed not to start any medication without prior notification and approval from the study team. Additionally, patients actively trying to conceive at the time of the study were excluded. Participants had to be over 18 years old and provide written informed consent to participate.

PCOS diagnosis was confirmed using the criteria from the 2023 International PCOS Guideline [8]. Exclusion criteria included individuals with a history of mental health conditions or significant medical disorders that could interfere with the assessment of variables.

### Diagnostics

At the start of the study, a comprehensive evaluation was conducted, including hormone levels (AMH, androstenedione, dehydroepiandrosterone sulfate, estradiol, follicle-stimulating hormone, testosterone, luteinizing hormone, prolactin, sex hormone-binding globulin, thyroid-stimulating hormone, 17-OH progesterone), liver and kidney values, serum lipids, C-reactive protein (CRP), and an extended 75 g oral glucose tolerance test (OGTT/insulin) to assess metabolism. At t1, hormone levels, clinical chemistry including liver and kidney values, and CRP were measured (except AMH, dehydroepiandrosterone sulfate, androstenedione, 17-OH progesterone, prolactin, oral glucose tolerance test). Each visit included measurements of waist circumference (taken between the last rib and the iliac crest) and body weight and height (measured in kilograms and meters). The World Health Organization defines BMI categories as follows: ≤24.9 kg/m$^2$ as healthy weight, 25–29.9 kg/m$^2$ as overweight, and ≥30 kg/m$^2$ as obesity I and II [14].

### Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the formula:

$$HOMA\text{-}IR = fasting\ insulin\left(mU/L\right) x\ fasting\ glucose\left(nmol/L\right)/22.5$$

A HOMA-IR above 2 was counted as insulin resistance [15].

### Fatty Liver Index (FLI)

The Fatty Liver Index (FLI) assesses the likelihood of a person having hepatic steatosis. Bodogni et al. developed an algorithm based on four parameters—BMI, waist circumference, triglycerides (TG), and gamma-glutamyltransferase (GGT)—to estimate this probability from a range of variables [16].

FLI is calculated as:

$$FLI = e^x / (1 + e^x) \times 100, \text{ where}$$
$$x = 0.953 \times \log_e(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times (\text{waist circumference}) - 15.745,$$

*with TG measured in mmol/l, BMI in kg/m², GGT in U/L, and waist circumference in centimeter.*

The values of FLI vary from 0 to 100. Values of FLI <30 are considered normal, FLI ≥30–59 indicates a low likelihood of hepatic steatosis, and FLI ≥ 60 indicates a high degree of probability of the presence of hepatic steatosis [16].

### Visceral Adiposity Index (VAI)

While BMI is the most often used index in clinical practice for assessing a patient's nutritional status, it does not provide information on the distribution of fat and muscle tissue. The gold standard for evaluating body fat distribution is magnetic resonance imaging (MRI) or computed tomography (CT) [17]. The Visceral Adiposity Index (VAI) offers a reliable and simple alternative for assessing cardiovascular risk [18]. However, a definitive cutoff value for pathological VAI has not yet been established [19,20]. The VAI is calculated using BMI, waist circumference, TG, and high-density lipoprotein cholesterol (HDL), with the formula specific to women used for this calculation [21]:

$$VAI = (\text{waist circumference}(cm)) / (36.58 + (BMI\ x1.89)\ x(TG / 0.81)\ x(1.52 / HDL)$$

### Health-related quality of life

The Polycystic Ovary Syndrome Questionnaire (PCOSQ) was employed to evaluate condition-specific HRQOL. It comprises 26 questions addressing PCOS-related symptom complexes, including emotional well-being, body hair, weight, infertility problems and menstrual problems. Responses are rated on a Likert scale from 1 to 7, with 1 indicating the highest level of impairment [22]. This questionnaire has been expanded with four additional questions on acne, leading to the development of the Modified PCOS-Questionnaire (MPCOSQ), which was used in this study [23].

### Mental state

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [24]. This self-report instrument includes two subscales, each with seven questions dedicated to anxiety and depression. Higher scores reflect greater levels of anxiety or depression. A score of 8 or more on either subscale indicates increased levels of distress. Specifically, scores between 8 and 10 suggest mild anxiety or depression, 11 to 14 indicate moderate anxiety or depression, and 15 to 21 denote severe anxiety or depression [25].

### Hirsutism

To assess hirsutism, patients completed the Ferriman-Gallwey questionnaire. A rating beyond 7 indicates pathological hirsutism [26].

### Therapy

After comprehensive diagnostics, the recommended guideline-based therapy was discussed with the patient through a shared decision-making process. If insulin resistance was present, a metformin therapy was initiated with the patient's consent (M-group). During the study, liver and kidney levels were monitored between study visits to ensure metformin tolerance. The dosage was initially set at 1700 mg daily (850 mg twice daily) but was individually adjusted based on the patient's medical history and profile or if intolerable side effects such as bloating, or diarrhea occurred.

If metformin was not administered, the therapy was selected and implemented according to the patient's individual profile when the patient was included in the study. This included combined oral contraceptives, progestin-only preparations, myo-inositol, or no therapy if there was no indication for medication or if the patient declined treatment (C-group).

## Statistical analysis and ethical considerations

The data were analyzed using descriptive statistics and regression methods, employing IBM SPSS Statistics Version 29. Mean, standard deviation and percentages were used to characterize the participants. Comparisons of means in M- vs. C-group were conducted using the independent t-test, while categorical variables such as PCOS type were analyzed using the $\chi^2$ test.

A multivariate linear regression was used to estimate the association of metabolic markers such as ΔVAI, ΔBMI, Δwaist-circumference, ΔFLI, HOMA-IR and therapy group affiliation (M-/C-group) with the results of the MPCOSQ and HADS subdomains at t1. Confounding variables were selected from a range of clinically plausible factors, including age, ΔFerriman-Gallwey score, partnership status, were identified using causal diagrams and the respective result of the outcome variable at t0. The model was built using a change-in-estimate method, where potential confounders were included in the final multivariate regression model if they changed the regression coefficient (B) by more than 10% [27].

Before including parameters in the multivariate model, they were assessed for potential multicollinearity. Parameters with a Pearson or Spearman correlation coefficient exceeding 0.7 were excluded from simultaneous inclusion in the model. The effects were estimated using the unstandardized regression coefficient B, p-value, and 95% confidence interval (CI).

## Results

A total of 66 patients participated in the study, all of whom had a confirmed diagnosis of PCOS. Among these, 31 patients were indicated for metformin therapy and were included in the M-group. The interval between the start of therapy and the follow-up visit (t1) was 31.1 ± 7.8 weeks for the M-group and 32.1 ± 10.3 weeks for the C-group. The average metformin dosage was 1664.5 ± 254 mg per day. During the therapy, 19.4% of patients experienced persistent side effects after 24 weeks, including abdominal pain (10%), diarrhea (10%), and nausea (7%). No serious side effects were reported, and all serological tests for known liver and kidney toxicity were negative.

The remaining 35 patients did not receive metformin therapy and served as the comparison group for the study (C-group). In this group, 16 patients (46%) used Myo-Inositol, 8 (23%) used a combined oral contraceptive, and 2 (6%) used a progestin-only pill. Additionally, 3 patients (9%) chose a Levonorgestrel intrauterine device, and 6 (17%) did not undergo any medication therapy.

Despite the metabolic differences between the M-group and C-group, both consisted of patients diagnosed with PCOS, and their phenotypes did not differ significantly. All participants were confirmed to be non-diabetic at baseline. Analysis of clinical parameters, including weight, BMI, HOMA-IR, waist circumference, VAI, and FLI, revealed that the M-group was characterized by metabolic disturbances, whereas these features were significantly less pronounced in the C-group. Further details about the study cohort can be found in Table 1.

Participants in both groups were required to attend a second study visit after 24 weeks. The metabolic situation in the M-group improved with metformin treatment, as demonstrated by significant reductions in weight, BMI, and FLI. These changes reflected notable differences in the metabolic parameters of the M-group. Relevant follow-up results are presented in Table 2.

The HRQOL assessment using the MPCOSQ showed that, at baseline (M0 and C0), the M-group had on average lower HRQOL scores, indicating a worse HRQOL compared to the C-group. However, this difference was not statistically significant in any of the MPCOSQ scales between the groups at M0 and C0. Nevertheless, both the M-group and the C-group exhibited a significant improvement in HRQOL across all subdomains and in the total score when comparing the therapy start with t1. There was no significant difference between the M- and C-groups in the delta of improvement (ΔM1-M0; ΔC1-C0); however, the M-group showed a larger delta compared to the C-group (Figure 1).

Regarding mental state, the M-group scored worse on the depression subscale compared to the C-group at baseline. Therapy was associated with a significant improvement in mental health in both groups (Table 3).

No metabolic markers met the change-in-estimate criterion for MPCOSQ-Weight, MPCOSQ-Acne, or HADS-Depression. Some markers did meet the change-in-estimate criterion but did not yield statistically significant results in the multivariate model, including: ΔVAI for MPCOSQ-Emotion; ΔVAI and ΔFLI for MPCOSQ-Infertility; ΔVAI and ΔFLI for MPCOSQ-Total; and ΔVAI for HADS-Anxiety.

For MPCOSQ-Body hair, HOMA-IR met the change-in-estimate criterion, demonstrating a significant association in the model (B −0.23; CI: −0.42, −0.04; $p = 0.02$) with a variance of $R^2$=0.650 and adjusted $R^2$=0.618 in the model. Similarly, for MPCOSQ-Menstrual problems, only ΔBMI met this criterion, showing a significant result (B: −0.20; CI: −0.36,-0.04; $p = 0.02$) with a model variance of $R^2$ = 0.361 and an adjusted $R^2$ = 0.303. In none of the models group affiliation (M-group/C-group) showed a significant result.

## Discussion

In our study, we demonstrated that HRQOL and mental health are significantly associated with key metabolic markers. Initially, there were no significant

**Table 1.** Characteristics of the study population upon enrollment (t0) per group (metformin versus comparison group).

| | Overall t0 | t0 Metformin-Group (M0) | t0 Comparison-Group (C0) | p |
|---|---|---|---|---|
| N | 66 | 31 | 35 | |
| Age (years) Mean ± SD | 26.9 ± 4.1 | 27.2 ± 3.9 | 26.5 ± 4.2 | 0.48 |
| Weight (kg) Mean ± SD | 79.3 ± 21.6 | 89.0 ± 23.4 | 70.7 ± 15.7 | **<0.001** |
| BMI (kg/m$^2$) Mean ± SDHealthy weight BMI 18.5–24.9 | 28.3 ± 7.1<br>29 (43.9%) | 31.9 ± 7.3<br>7 (22.6%) | 25.1 ± 5.1<br>22 (62.9%) | **<0.001** |
| • Overweight BMI 25.0–29.9 | 37 (56.1%) | 24(77.4%) | 13 (37.1%) | |
| • Obesity I BMI 30.0–34.9 | 21 (31.8%) | 17 (54.8%) | 4 (11.4%) | |
| • Obesity II BMI ≥35.0 | 15 (22.7%) | 12 (38.7%) | 3 (8.6%) | |
| PCOS-phenotypeA (hyperandrogenism + ovulatory dysfunction + PCOM) | 45 (68.2%)<br>9 (13.6%) | 20 (64.5%)<br>4 (12.9%) | 25 (71.4%)<br>5 (14.3%) | 0.26 |
| • B (hyperandrogenism + ovulatory dysfunction) | 10 (15.2%) | 7 (22.6%) | 3 (8.6%) | |
| • C (hyperandrogenism + PCOM) | 2 (3.0%) | 0 (0%) | 2 (5.7%) | |
| • D (ovulatory dysfunction + PCOM) | | | | |
| Waist circumference (cm) Mean ± SD | 84.2 ± 16.6 | 92.6 ± 15.4 | 76.7 ± 14.0 | **<0.001** |
| HOMA-IR Mean ± SD | 2.2 ± 1.6 | 3.0 ± 0.6 | 1.5 ± 0.2 | **<0.001** |
| Ferriman-Gallwey-score Mean ± SD< 7 normal | 14.2 ± 6.2 | 15.5 ± 7.8 | 13.1 ± 4.3 | 0.13 |
| • ≥7 pathological hirsutism | 6 (9.1%)<br>60 (90.9%) | 5 (16.1%)<br>26 (83.9%) | 1 (2.9%)<br>34 (97.1%) | |
| Free Androgen Index (FAI) Mean ± SD<5.5 normal | 4.3 ± 2.7<br>47 (71.2%) | 4.8 ± 2.6<br>19 (61.3%) | 3.9 ± 2.6<br>28 (80.0%) | 0.15 |
| • ≥5.5 elevated | 19 (28.8%) | 12 (38.7%) | 7 (20.0%) | |
| Visceral Adiposity Index (VAI) Mean ± SD | 3.4 ± 2.7 | 4.1 ± 2.4 | 2.7 ± 2.7 | **0.049** |
| Fatty Liver Index (FLI) Mean ± SD< 30 no hepatic steatosis | 33.1 ± 34.6<br>39 (37.1%) | 23.4 ± 35.5<br>10 (35.5%) | 14.7 ± 21.1<br>29 (87.9%) | **<0.001** |
| • ≥30 low likelihood of hepatic steatosis | 39 (62.9%) | 19 (65.5%) | 4 (12.1%) | |
| • ≥60 probable hepatic steatosis | 17 (27.4%) | 15 (51.7%) | 2 (6.1%) | |
| PartnershipYes | 36 (54.5%) | 14 (45.2%) | 22 (62.9%) | 0.22 |
| • No | 30 (45.5%) | 17 (54.8%) | 13 (37.1%) | |
| C-reactive protein (CRP) (mg/L) Mean ± SD | 3.5 ± 4.4 | 5.0 ± 5.2 | 2.3 ± 2.8 | **0.03** |
| Anti-Müllerian hormone (AMH) (ng/mL) Mean ± SD | 9.3 ± 5.4 | 8.8 ± 4.5 | 9.8 ± 6.1 | 0.45 |
| LH/FSH ratio Mean ± SD | 1.6 ± 1.1 | 1.3 ± 0.8 | 1.8 ± 1.3 | 0.10 |

BMI: Body Mass Index; C0: comparison group not taking metformin, at t0; FSH: follicle-stimulating hormone; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LH: luteinizing hormone; M0: study group taking metformin, at t0; PCOM: Polycystic Ovary Morphology; PCOS: Polycystic Ovary Syndrome; SD: standard deviation. $p < 0.05$ values are shown in bold.

**Table 2.** Relevant markers at follow-up (t1) in both study groups (M-/-C-group).

| | t1 Metformin-Group (M1) | p (M0-M1) | t1 Comparison-Group (C1) | p (C0-C1) | ΔM1-M0 | ΔC1-C0 | p (ΔM-group vs ΔC-group) |
|---|---|---|---|---|---|---|---|
| Weight (kg) Mean ± SD | 86.7 ± 23.9 | **0.02** | 71.0 ± 16.0 | 0.70 | −2.3 ± 5.3 | 0.28 ± 4.2 | **0.04** |
| BMI (kg/m$^2$) Mean ± SD | 31.1 ± 7.6 | **0.02** | 25.2 ± 5.1 | 0.75 | −0.81 ± 1.9 | 0.08 ± 1.4 | **0.04** |
| Waist circumference (cm) Mean ± SD | 92.4 ± 16.4 | 0.86 | 78.2 ± 13.9 | 0.39 | −0.19 ± 6.1 | 1.5 ± 10.0 | 0.41 |
| Ferriman-Gallwey-Score Mean ± SD | 14.0 ± 8.1 | 0.10 | 12.4 ± 4.7 | 0.19 | −1.5 ± 5.0 | −0.69 ± 3.0 | 0.42 |
| Free Androgen Index (FAI) Mean ± SD | 4.6 ± 2.7 | 0.62 | 3.4 ± 3.3 | 0.32 | −0.21 ± 2.4 | −0.46 ± 2.7 | 0.69 |
| Visceral Adiposity Index (VAI) Mean ± SD | 4.1 ± 2.3 | 0.99 | 3.9 ± 5.5 | 0.24 | −0.00 ± 1.7 | 1.2 ± 5.7 | 0.26 |
| Fatty Liver Index (FLI) Mean ± SD | 50.9 ± 35.1 | 0.15 | 19.2 ± 24.4 | 0.05 | −2.6 ± 9.5 | 4.5 ± 12.3 | **0.01** |
| C-reactive protein (CRP) (mg/L) Mean ± SD | 4.3 ± 5.2 | 0.26 | 2.2 ± 2.8 | 0.83 | −0.67 ± 2.9 | −0.05 ± 1.3 | 0.34 |
| LH/FSH ratio Mean ± SD | 1.6 ± 1.0 | 0.18 | 1.5 ± 1.1 | 0.19 | −0.31 ± 1.2 | −0.30 ± 1.3 | **0.06** |

BMI: Body Mass Index; C0: Comparison group not taking metformin, at t0; C1: Comparison group not taking metformin, at t1; FSH: follicle-stimulating hormone; LH: luteinizing hormone; M0: study group taking metformin, at t0; M1: study group taking metformin, at t1; SD: standard deviation. $p < 0.05$ values are shown in bold.

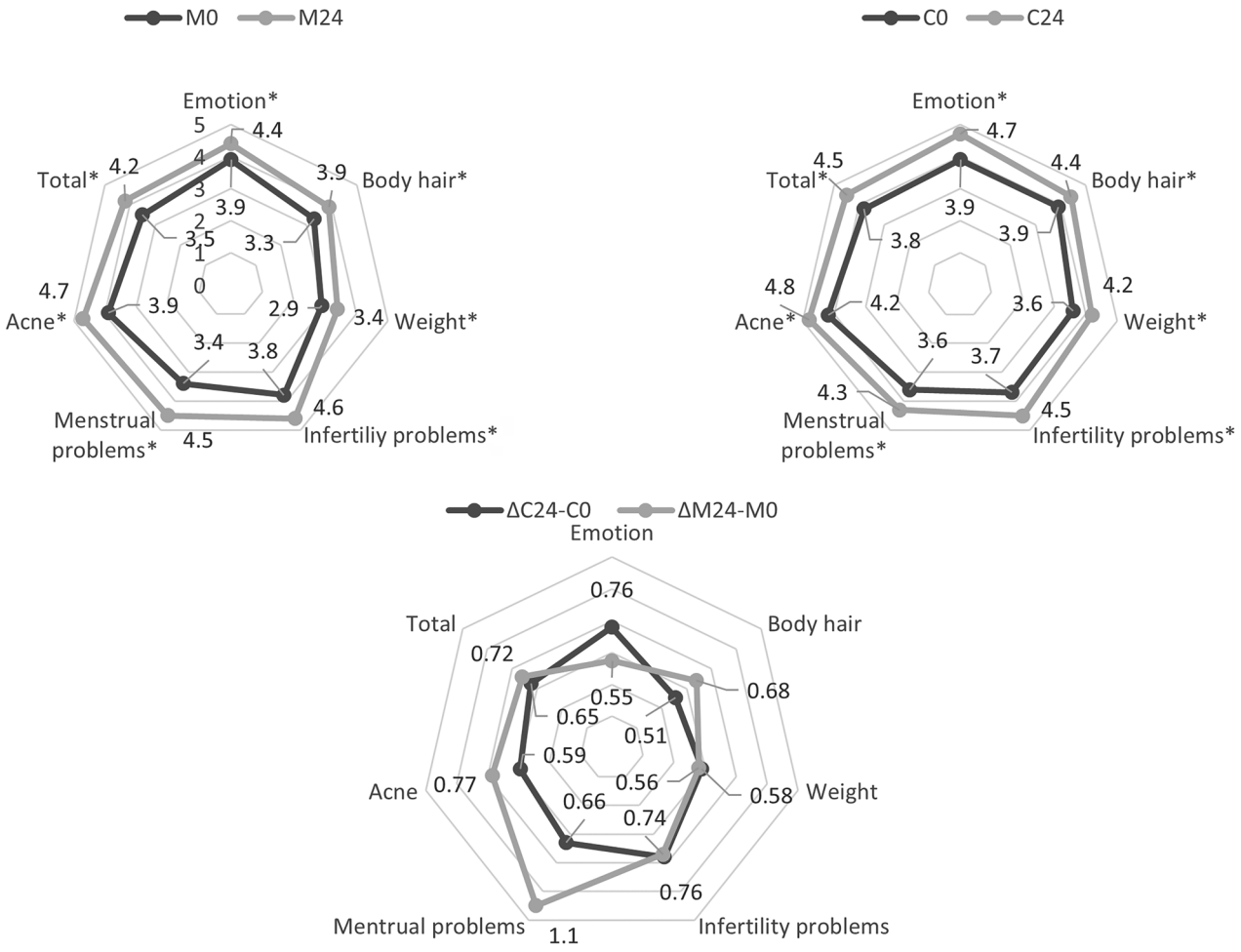


**Figure 1.** Results of the two study collectives (M-group/C-group) at study inclusion and at the follow-up (t1) of the modified PCOS-Questionnaire (MPCOSQ) and its subscales, as well as the Delta of the development. Significant differences between the time points are marked with an asterisk. (C0: Comparison group not taking metformin, at t0; C1: Comparison group not taking metformin, at t1; M0: study group taking metformin, at t0; M1: study group taking metformin, at t1).
Top left plot: Metformin group (M0 vs M24), showing improvements across all symptom categories, including acne, menstrual problems, infertility problems, weight, body hair, emotion, and total score.
Top right plot: Control group (C0 vs C24), with generally smaller changes in symptom scores over time.
Bottom plot: Difference scores between baseline and follow-up (ΔM24-M0 and ΔC24-C0), visualizing the magnitude of change per symptom category.
Asterisks indicate statistically significant differences. Categories include emotion, body hair, weight, infertility problems, menstrual problems, acne, and total score.

differences between the two groups in terms of HRQOL and experienced anxiety. Over the course of the therapy, both groups showed significant improvements in HRQOL and mental health across all MPCOSQ and HADS subscales, with more pronounced benefits in women taking metformin. These results indicated that, despite initial differences in metabolic markers, both interventions may have contributed to better mental and emotional well-being.

In 2006, Hahn et al. demonstrated in a cohort of 64 German PCOS patients that a 6-month metformin therapy was associated with improved HRQOL [12]. Similarly, a study by Huang-Tzou et al. involving 109 Chinese women with PCOS found a clear benefit of metformin on HRQOL as measured by the PCOSQ. However, this study also included PCOS patients trying to conceive, even if they were not undergoing fertility treatment at the time of the study [13].

In contrast, a randomized controlled trial conducted in Denmark by Ravn et al. found no improvement in HRQOL due to metformin therapy, although HRQOL scores in this study remained below those of healthy women in the general population [28,29]. Similarly, Harris-Glocker et al. studied the effect of metformin on HRQOL, but the concurrent implementation of a lifestyle modification program alongside metformin therapy limits the interpretability of these results for metformin alone [30].

In line with these studies, we observed substantial improvements in metabolic markers in the group with PCOS patients taking metformin, while there were no significant changes in the C-group. Melin et al. and

**Table 3.** Results of the two study collectives (M-group/C-group) at study inclusion and at the follow-up (t1) of the hospital anxiety and depression scale (HADS), as well as the Delta of the development.

| HADS | t0 Metformin-Group (M0) | t0 Comparison-Group (C0) | p (M0-C0) | t1 Metformin-Group (M1) | p (M0-M1) | t1 Comparison-Group (C1) | p (C0-C1) | ΔM1-M0 | ΔC1-C0 | p (ΔM-group vs ΔC-group) |
|---|---|---|---|---|---|---|---|---|---|---|
| Anxiety-Subscale Mean ± SD | 9.8 ± 4.6 | 8.4 ± 3.9 | 0.17 | 7.9 ± 4.1 | **0.002** | 7.5 ± 4.1 | **0.04** | −1.9 ± 3.1 | −0.91 ± 2.5 | 0.15 |
| Anxiety > 7 | 19 (61.3%) | 20 (57.1%) | 0.81 | 16 (51.6%) | **0.003** | 16 (45.7%) | **<0.001** | −3 (-9.7%) | −4 (-11.4%) | 0.05 |
| Depression-Subscale Mean ± SD | 8.5 ± 4.1 | 5.8 ± 4.6 | **0.02** | 6.9 ± 3.8 | **0.004** | 4.9 ± 4.4 | **0.01** | −1.6 ± 2.8 | −0.91 ± 1.9 | 0.27 |
| Depression >7 | 19 (61.3%) | 11 (31.4%) | **0.03** | 12 (38.7%) | **0.01** | 10 (28.6%) | **<0.001** | −7 (-22.6%) | −1 (-2.9%) | **0.02** |

C0: Comparison group not taking metformin, at t0; C1: Comparison group not taking metformin, at t1; M0: study group taking metformin, at t0; M1: study group taking metformin, at t1. $p < 0.05$ values are shown in bold.

Samarasinghe et al. reported in their meta-analyses that metformin influenced metabolism in PCOS patients, demonstrating more favorable effects than other insulin sensitizers [9,10]. However, metformin is not the only medication that can be given to PCOS patients and can have an influence on metabolism. Combined oral contraceptives, progestin-only pills, and myo-inositol also affect metabolism in PCOS patients [31,32].

After adjusting for variables in a multivariate model, metformin therapy did not show a significant relationship with any subscale of the MPCOSQ or HADS. Instead, the metabolic markers, such as ΔBMI or HOMA-IR, were significantly associated with improvements. It is important to note, however, that these markers and metformin therapy are inherently linked in PCOS patients, suggesting a possible indirect role of metformin in influencing metabolic changes that may be associated with the observed improvements in HRQOL and mental health.

Overall, women with PCOS have a significantly higher risk of depression and anxiety. A meta-analysis by Cooney et al. found that they were 3.78 times more likely to experience depressive symptoms and 5.62 times more likely to suffer from anxiety disorders than control groups [33]. These findings align with our study, in which both groups exhibited pathological values on the HADS-Anxiety subscale at baseline, while the M-group also showed elevated scores on the HADS-Depression subscale. PCOS management primarily targets its individual components rather than addressing the condition as a whole, with psychotherapy being one approach shown to be effective in managing its psychological aspects [34]. In this context, cognitive behavioral therapy (CBT) can be particularly beneficial, as it helps reduce body image dissatisfaction, anxiety, and depression, making it a viable therapeutic option for PCOS patients [35].

Currently, no specific pharmacological treatment is recommended for anxiety and depression in PCOS. This includes metformin therapy. Research suggests that metformin may have a beneficial effect on depressive symptoms. In a study by AlHussain, PCOS patients in Saudi Arabia were prescribed either metformin combined with lifestyle changes or lifestyle changes alone. The metformin group showed lower odds of having major depression. However, it is important to note that the study did not account for the individual adherence to lifestyle changes compared to the effects of metformin therapy [11]. Given the association between PCOS and mental health disorders, integrating psychological interventions alongside metabolic treatments may provide a more comprehensive approach to improving overall well-being [34].

Consequently, it is particularly relevant for healthcare professionals treating PCOS patients presenting with symptoms of anxiety or depression to know the connection between metformin and mental health: It is essential to consider that successful treatment of psychiatric disorders often requires concurrent management of PCOS, as underlying metabolic and hormonal dysfunctions significantly impact mental health.

In general, the use of metformin in our study appears to be associated with improvements in HRQOL and mental health, possibly mediated by improvements in metabolic parameters. The patients may have experienced some benefit from the therapy.

## Strengths and limitations

This study is the first to investigate the impact of metformin therapy on HRQOL and mental state using the MPCOSQ. Previous research has predominantly utilized general HRQOL questionnaires, such as the Short Form-36 (SF-36), which, unlike the MPCOSQ, do not address the specific issues faced by PCOS patients [8,11,12,23]. Comprehensive diagnostic tests were conducted to ensure accurate identification of individuals with PCOS, which allowed us to attribute the observed effects primarily to the specific characteristics of PCOS rather than to other unrecognized variables. FLI and VAI are not typically included in standard gynecological diagnostic procedures, as they require supplementary laboratory tests, such as lipid profiles. Given the increased lifetime risk of conditions like type 2 diabetes, dyslipidemia, and cardiovascular disease in PCOS patients, it is crucial to place greater emphasis on metabolic health.

Due to the inclusion criteria of this study, PCOS patients with a trying to conceive or those undergoing fertility treatment were excluded. Fertility treatment is a known factor that negatively influences HRQOL and increases the risk of depression and anxiety disorders [36]. Excluding this group enhances the validity of the results by eliminating infertility as a confounding factor, thereby reducing outcome bias.

Moreover, a larger sample size would have enhanced the reliability of our findings. The limited number of participants was largely due to challenges in enrollment. In Germany, women with PCOS who are not pursuing fertility treatment are typically cared for by gynecologists in specialized practices rather than in university clinics, which may have restricted our ability to include more participants.

Our study included only a comparison group, rather than a true control group, which may have limited the generalizability of the findings. The absence of a randomized, placebo-controlled group introduces several sources of bias and potential confounding, making it more difficult to establish causality. Without a true control group, it is also challenging to distinguish the observed effects from natural disease progression, placebo effects, or external influences such as lifestyle changes or concurrent treatments. In addition, potential confounding factors such as diet, physical activity, and access to psychological support were not systematically documented or controlled for, although these factors may independently influence both metabolic outcomes and HRQOL [8]. Future studies might consider addressing these limitations by including a true control group and more systematically accounting for relevant lifestyle and psychosocial variables.

Unfortunately, a control group of BMI-matched individuals without PCOS could not be included, as metformin therapy is generally not indicated for normal-weight individuals without insulin resistance, and thus such patients would not have received the treatment under current guidelines. Furthermore, the intended follow-up period for the patients was six months; however, the actual average follow-up time was 32 weeks. Although this duration was sufficient to observe short-term changes, it does not allow for conclusions about long-term efficacy, safety, or relapse rates. A longer follow-up period would have helped to evaluate the durability of treatment effects, identify late-onset side effects, and better understand the clinical course of the condition under study. Longer-term data might have clarified whether the initial improvements were sustained or transient.

## Conclusion

Metformin therapy may be associated with improvements in HRQOL and reduced distress in PCOS patients, primarily through metabolic improvements rather than direct drug effects. Healthcare professionals treating PCOS patients should be aware of the relationship between metabolism and treatment options for patients experiencing depressive or anxious symptoms.

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## Author contributions

CRediT: **Konstantin Hofmann**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project

administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; **Susanne Singer**: Formal analysis, Validation, Writing – review & editing; **Susanne Theis**: Writing – review & editing; **Anna Dionysopoulou**: Writing – review & editing; **Lina Schiestl**: Writing – review & editing; **Yaman Degirmenci**: Writing – review & editing; **Annette Hasenburg**: Writing – review & editing; **Roxana Schwab**: Writing – review & editing; **Christine Skala**: Writing – review & editing.

## Authors' contributions

Konstantin Hofmann: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing –original draft, writing – review & editing, visualization, project administration; Susanne Singer: validation, formal analysis, writing – review & editing; Susanne Theis: writing – review & editing; Anna Dionysopoulou: writing – review & editing; Lina Schiestl: writing – review & editing; Yaman Degirmenci: writing – review & editing; Annette Hasenburg: writing – review & editing; Roxana Schwab: writing – review & editing; Christine Skala: writing – review & editing.

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Konstantin Hofmann, Susanne Theis, Anna Dionysopoulou, Lina Schiestl, Yaman Degirmenci, Annette Hasenburg, Roxana Schwab and Christine Skala report there are no competing interests to declare. Susanne Singer received honoraria for reviewing papers for the Lilly Quality of Life Award, outside of this study.

## Availability of data and material

The datasets generated and analyzed are available from the corresponding author on reasonable request. Due to privacy and ethical concerns, the data are not publicly available. However, de-identified data supporting the findings of this study can be made available to qualified researchers upon request, subject to approval by the institutional review board.

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