Obesity Exacerbates Irritable Bowel Syndrome-Related Sleep and Psychiatric Disorders in Women With Polycystic Ovary Syndrome

Ping-Huei Tseng¹, Han-Mo Chiu¹, Chia-Hung Tu¹, Ming-Shiang Wu¹,², Hong-Nerng Ho²,³,⁴ and Mei-Jou Chen²,³,⁵*

¹ Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, ² College of Medicine, National Taiwan University, Taipei, Taiwan, ³ Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei, Taiwan, ⁴ Research Center for Cell Therapy and Regeneration Medicine, and College of Medicine, Taipei Medical University, Taipei, Taiwan, ⁵ Livia Shang Yu Wan Chair Professor of Obstetrics and Gynecology, National Taiwan University, Taipei, Taiwan

Background/Objectives: Polycystic ovary syndrome (PCOS) and irritable bowel syndrome (IBS) share similar clinical and psychosocial features. We aimed to investigate the clinical characteristics of IBS in women with PCOS, and its relationship with obesity, metabolic and hormonal profiles, as well as sleep and psychiatric disorders.

Subjects/Methods: This is a cross-sectional case-control study of 431 untreated women with PCOS and 259 healthy volunteers. All participants were assessed with a comprehensive clinical evaluation and two questionnaires: the Athens Insomnia Scale (AIS) and the Brief Symptom Rating Scale (BSRS-5). IBS was defined using the Rome III criteria. Obesity was defined as a BMI ≥30 kg/m². Anthropometric measurements, metabolic and hormonal profiles, and psychosocial morbidities were compared.

Results: Women with PCOS were more likely to have IBS (10.7% vs 5.8%, p=0.029) and obesity (29% vs 4%, p<0.001) than healthy volunteers. Mixed-type IBS (IBS-M) was the most common subtype (74%) among patients with PCOS and IBS. There was a higher prevalence of psychiatric morbidities (total BSRS-5 score ≥10) in women with PCOS than in healthy women (11.4% vs 3.5%, p<0.001). Women with PCOS and IBS were more likely to have sleep difficulties (67.4% vs 30.9%, p<0.001) and psychiatric morbidities (21.7% vs 10.1%, p=0.019) than those without IBS. Anthropometrics, metabolic and hormonal profiles were similar between PCOS women with and without IBS. Among women with PCOS, those with both IBS and obesity had the highest risk of developing sleep difficulties (odds ratio: 5.91; 95% confidence interval: 1.77–19.77) and psychiatric distress (odds ratio: 4.39; 95% confidence interval: 1.26–15.29) than those without.
INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of early reproductive age. It is characterized by chronic anovulation (oligomenorrhea or amenorrhea), clinical or biochemical hyperandrogenism, and the presence of polycystic ovaries (1). Women with PCOS have a higher risk of developing infertility, obesity, insulin resistance, dyslipidemia, hypertension, and metabolic derangement that may lead to subsequent cardiometabolic diseases than women without PCOS (2).

Women with PCOS are also more likely to present with psychological disorders such as depression, anxiety, sexual dysfunction, and psychosocial problems, affecting their health-related quality of life (QOL) (3–5). One study using the Taiwan National Health Insurance Research Database found that the incidence of depressive, anxiety and sleep disorders was higher among patients with PCOS than among those in the comparison cohort (6).

Irritable bowel syndrome (IBS) is characterized by chronic or recurrent abdominal pain or discomfort associated with altered bowel habits in the absence of structural or biochemical abnormalities (7). The prevalence of IBS varies substantially among countries, ethnic populations, and the criteria used to define it. According to the latest meta-analysis, the pooled prevalence of IBS in 53 studies that used the Rome III criteria to diagnose it, from 38 countries and 395 385 participants, is 9.2% (0.4–29.2%) (8). The prevalence of IBS is generally higher in premenopausal women than in men (8). The chronic and relapsing nature of IBS is frequently associated with psychosocial and sleep comorbidities, affecting the patient’s QOL and resulting in frequent hospital visits and increased utilization of healthcare resources (9). Although the pathophysiology of IBS remains unclear, the rapidly increasing incidence in Western countries and Taiwan has been attributed partly to lifestyle changes and increased levels of stress. Even though patients with PCOS and IBS have similar features and risk factors, including young adult women and psychosocial comorbidities, IBS seems to be overlooked in patients with PCOS (10). The related clinical characteristics, such as obesity and metabolic derangement, in this specific population have also been rarely studied with conflicting results (11, 12). Since the respective prevalence rates of PCOS, IBS and obesity are increasing in the Asian population, our primary aim in this study was to investigate the prevalence of IBS, diagnosed using the Rome III criteria, in women with PCOS. In addition, we studied the clinical characteristics, especially the anthropometrics, metabolic and hormonal profiles, of women with PCOS and IBS to clarify the associated risk factors and pathophysiology. Finally, we studied the relationship between IBS, obesity and psychosocial stress and sleep difficulties in women with PCOS.

Conclusion: Women with PCOS have increased IBS, obesity, sleep and psychiatric disturbances. The presence of IBS in PCOS women is associated with sleep and psychiatric disorders. The coexistence of obesity and IBS exacerbates sleep difficulties and psychiatric distress. Screening and management of IBS and obesity might be warranted to improve sleep and psychiatric disturbances in women with PCOS.

Keywords: polycystic ovary syndrome, irritable bowel syndrome, Rome III, obesity, psychiatric morbidity, sleep disorders

MATERIALS AND METHODS

Study Design and Participants

We conducted this case-control study at the National Taiwan University Hospital (NTUH), a tertiary medical center. This study was approved by the institutional ethics committee (No. 201907101RINC). All participants provided their written informed consent before they were enrolled in the study. Consecutive women aged older than or equal to 20 years, with a confirmed diagnosis of PCOS and a chief complaint of irregular menstrual cycles, clinical hyperandrogenism, or both, were eligible for enrolment and were approached by the attending physicians in the reproductive endocrinology clinic. The diagnosis of PCOS was made using the Rotterdam criteria, and the enrolment inclusion and exclusion criteria we used for patients with PCOS have previously been described in detail (13). Briefly, the diagnosis of PCOS required at least two of the following three criteria were met: (1) oligomenorrhea (<8 spontaneous menstrual cycles per year at least 3 years before enrollment) or amenorrhea; (2) biochemical hyperandrogenemia (serum total testosterone level 0.77 ng/ml) and (3) polycystic ovaries (12 follicles [2–9 mm in size] per ovary by transvaginal ultrasonography or an ovarian volume >10 ml per ovary by transabdominal ultrasonography with a distended bladder for virginal women). None of the women had been prescribed medications for their symptoms before enrolment. For the control group, healthy volunteer women who had come to the same institute for a routine health check-up and were older than or equal to 20 years were eligible for enrolment and were invited to participate in this study; the need for healthy volunteers was publicized using advertising messages targeted to the general population. All of the study and control subjects were enrolled after excluding other endocrine, organic and systemic abnormalities, such as hyperprolactinemia, thyroid dysfunction, Cushing’s syndrome, congenital adrenal hyperplasia, an adrenal tumor, an ovarian tumor, autoimmune disease, heart failure, liver cirrhosis, end-stage renal disease,
morbidity that may require psychiatric counselling. 

2. A score ≥ 4, very severe). The total score for all
and related disorders (16). Each item
common psychiatric morbidities such as anxiety, depression,
of insomnia.

A score 6 suggests the presence
acutes. The AIS is a brief self-assessment instrument that consists of
items ranges from 0 to 24. A score
problems; 3, severe problem). The total score for the eight
items: difficulty of sleep induction, awakening during the
first
48.4 ± 10.5, p < 0.001) and larger waist circumference (90.0 ± 14.7
p
77.8 ± 8.5, p = 0.024) than women in the control group. There
was also a higher prevalence of obesity (29% vs 4%, p < 0.001)
and central obesity (73% vs 40%, p < 0.001) in women with PCOS
than in healthy women (Table 1). In the previous three months,
the women with PCOS had more abdominal pain or discomfort
not related to menstruation (p < 0.001) and more hard or lumpy
stool (p < 0.001) than the control group. In the PCOS group, the
overall prevalence of IBS was 10.7%, which was significantly
higher than in the control group (5.8%, p = 0.029). Mixed-type
IBS (IBS-M) was the most common subtype in both
groups (Table 1).

**Comparison of Sleep and Psychological Characteristics Between Patients With PCOS and Healthy Subjects**

Women with PCOS had lower scores than the control group for the AIS items ‘awakening during the night’ and ‘early

**Symptom Evaluation and Diagnosis of IBS**

We assessed participants using a validated symptom
questionnaire and diagnosed IBS using the Rome III criteria. 
Diagnosis is based on the presence of recurrent abdominal pain
or discomfort, at least 3 days/month, for the last three months
with symptom onset for at least six months, combined with at
least two of the following conditions: symptom duration with a
change in the frequency of defecation or form of the stool and
improvement of pain or discomfort following defecation (14).
Participants with IBS were further categorized into four subtypes
according to the predominant stool pattern: diarrhea-
predominant IBS (IBS-D), constipation-predominant IBS (IBS-
C), mixed IBS (IBS-M), and un-subtyped IBS (IBS-U) (14).
awakening’, but higher scores for ‘sleepiness during the day’ (Table 2). These results suggest fewer sleep difficulties during the night but more daytime dysfunction. However, the total AIS scores and the proportion of participants with insomnia (AIS score ≥ 6) did not differ significantly between the groups. The PCOS group had significantly higher scores for three of the BSRS-5 items: ‘feeling easily annoyed or irritated’, ‘feeling depressed’, and ‘feeling inferior to others’ (Table 2). Their total scores were also higher (4.46 ± 3.82 vs 3.49 ± 3.02, p < 0.001), suggesting higher psychosocial stress levels. Additionally, the prevalence of psychiatric morbidity, defined as a total BSRS-5 score of ≥ 10, was higher in the PCOS group (11.4% vs 3.5%, p < 0.001).

Impact of IBS on the Clinical Characteristics of Patients With PCOS
We compared the demographics, metabolic profiles, hormone profiles, and sleep and psychological characteristics of PCOS women with and without IBS (Table 3). Women with PCOS and IBS had higher scores for all eight AIS items and higher total scores. Up to 67.4% of patients with PCOS and IBS had insomnia, which was significantly higher than those without IBS (30.9%, p < 0.001). Patients with PCOS and IBS also had higher scores for all five BSRS-5 items and higher total scores (Table 3). There was a higher prevalence of psychiatric morbidities (21.7% vs 10.1%, p = 0.019) in patients with PCOS and IBS. Other clinical characteristics (anthropometrics and metabolic and hormonal profiles) were similar in the two groups.

Impact of Obesity on the Clinical Characteristics of Patients With PCOS
Because obesity is prevalent in women with PCOS, we compared the clinical characteristics of PCOS women with a BMI ≥ 30 kg/m² and those with a BMI < 30 kg/m² (Table 4). The patients with a BMI ≥ 30 kg/m² were more likely to have metabolic and hormonal derangement. Moreover, these women had higher total scores and scores for multiple items for both the AIS and BSRS-5 instruments, suggesting higher levels of sleep and psychiatric distress in this subgroup. Since both IBS and obesity were associated with more sleep and psychological problems in the participants, we stratified the PCOS group based on both IBS and obesity (Table 5). Women with PCOS, IBS, and obesity had the highest prevalence of insomnia and psychiatric morbidities (69.2% and 30.8%, respectively), followed by those with IBS only and then those with obesity only. Women without IBS or obesity had the lowest prevalence of insomnia and psychiatric morbidities (27.6% and 9.2%, respectively). Among women with PCOS, those with both IBS and obesity had the highest risk of developing sleep

### Table 1

| Characteristics | PCOS | Control | p   |
|----------------|------|---------|-----|
| N              | 431  | 259     |     |
| Age, y         | 25.3 ± 4.9 | 48.4 ± 10.5 | <0.001|
| BMI, kg/m²     | 26.4 ± 6.5 | 23.0 ± 12.6 | <0.001|
| ≤30, n (%)     | 126 (29) | 9 (4)   | <0.001|
| Waist circumference, cm | 90.0 ± 14.7 | 77.8 ± 8.5 | 0.024|
| ≥80, n (%)     | 312 (73) | 102 (49) | <0.001|

| GI symptoms in the last 3 months | PCOS | Control | p   |
|----------------------------------|------|---------|-----|
| Abdominal pain or discomfort not related to menstruation, n (%) |      |         |     |
| Never                            | 162 (38) | 139 (54) | <0.001|
| Less than one day a month        | 59 (14) | 44 (17) |     |
| One day a month                  | 53 (12) | 23 (9)  |     |
| Two to three days a month        | 82 (19) | 33 (13) |     |
| One day a week                   | 27 (6)  | 4 (2)   |     |
| More than one day a week         | 32 (7)  | 11 (4)  |     |
| Every day                        | 16 (4)  | 5 (2)   |     |
| Hard or lumpy stool, n (%)       | 181 (42) | 131 (51) | <0.001|
| Sometimes                        | 189 (44) | 79 (31)  |     |
| Often                            | 34 (8)  | 27 (10) |     |
| Most of the time                 | 20 (5)  | 14 (5)  |     |
| Always                           | 7 (2)   | 8 (3)   |     |
| Loose or watery stool, n (%)     | 174 (40) | 120 (48) | 0.394|
| Sometimes                        | 205 (48) | 110 (43) |     |
| Often                            | 36 (8)  | 17 (7)  |     |
| Most of the time                 | 15 (4)  | 12 (5)  |     |
| Always                           | 1 (0)   | 0 (0)   |     |
| Diagnosis of IBS (Rome III), n (%) | 46 (10.7) | 15 (5.8) | 0.029|
| Constipation-predominant (IBS-C) | 2 (4)  | 1 (7)   |     |
| Diarrhea-predominant (IBS-D)     | 9 (20)  | 1 (7)   |     |
| Mixed (IBS-M)                    | 34 (74) | 13 (87) |     |
| Un-subtyped (IBS-U)              | 1 (2)   | 0 (0)   |     |

- Data are presented as mean ± standard deviation or number (percentage).
- BMI, body mass index; GI, gastrointestinal; IBS, irritable bowel syndrome; PCOS, polycystic ovary syndrome.
- p < 0.05 indicates statistical significance.
The prevalence of IBS in the control group in this study was significantly higher in women than in men (5.4% vs 1.77) and psychiatric distress (OR: 4.39; 95% CI: 1.26–15.29) than those without.

**DISCUSSION**

The main findings of this study are that (1) women with PCOS have a higher prevalence of IBS, as diagnosed using the Rome III criteria, and obesity than healthy controls; (2) women with PCOS and IBS are more likely to have sleep difficulties and psychiatric morbidities; and (3) obesity may increase the impact of IBS to exacerbate sleep and psychiatric disorders in women with PCOS. To our knowledge, this is the first study to report the complex relationship of IBS and obesity in women with PCOS—a population that is increasing continuously—and its relationship with sleep and mental health.

The prevalence of IBS in the control group in this study (5.8%) is consistent with a nationwide questionnaire survey based on the Rome III criteria that was conducted in Taiwan in 2005–2008. The authors of that study reported an overall prevalence of IBS in the general population of 4.4%, and the prevalence was significantly higher in women than in men (5.4% vs 3.4%) (17). Our results are also consistent with two previous studies reporting a higher prevalence of IBS in women with PCOS (11, 12). However, the prevalence of IBS in our study is lower, which may be related to the different diagnostic criteria used (Rome I vs Rome III) and the populations studied. The Rome I criteria did not categorize IBS into subtypes, but using the Rome III criteria we found that mixed-type IBS was the most common subtype in both groups of our study population. This result is consistent with the latest systematic meta-analysis (8). In contrast, IBS-C was found to be the most common subtype in Iranian women with PCOS (12).

Previous studies have consistently shown that IBS is more common in women than in men (8). The prevalence of IBS subtypes varies according to gender and diagnostic criteria used, however. Women are more likely to present with constipation-predominant IBS (OR: 2.38; 95% CI: 1.45–3.92), according to a meta-analysis based on Rome I or II (18). However, IBS-D was the most common subtype in a study based on the Rome IV criteria.

In the present study, we used the Rome III criteria rather than the more recent Rome IV criteria because they remain the most widely used and well-validated diagnostic criteria in the literature. In addition, the Rome IV criteria include ‘abdominal pain’ and exclude ‘abdominal discomfort’, and also include more stringent frequency criteria. The use of the Rome IV criteria has greatly reduced the prevalence of reported IBS, so this system may be less suitable for an epidemiological survey such as this one (8, 19).

Although the exact pathophysiology of IBS remains elusive, previous studies have suggested that sex hormones and gender differences may play pivotal roles in its development (20). Sex hormones may affect peripheral and central regulatory mechanisms involved in the pathophysiology of IBS and thus alter visceral perception and motility, intestinal barrier function, and immune activation of the intestinal mucosa. Sex hormones also directly affect the gut microbiota and the enteric nervous system (20, 21). Menon et al. have shown that the status of estrogen receptor β affects the composition of the gut microbiota of female mice and that these microbiota respond differently to changes in diet complexity (22). Another study utilizing a non-obese diabetic mouse model also shows that the enhancement of testosterone production in pubescent male mice may induce changes in the gut microbiota, which consequently protects against autoimmune disease (23). Several animal studies have

**TABLE 2** | Sleep and psychological characteristics in the PCOS and control groups, based on the Athens Insomnia Scale (AIS) and the Brief Symptom Rating Scale (BSRS-5).

| Characteristics          | PCOS      | Control    | p       |
|--------------------------|-----------|------------|---------|
| n                        | 431       | 259        |         |
| AIS                       |           |            |         |
| Sleep induction           | 0.71 ± 0.85 | 0.68 ± 0.80 | 0.665   |
| Awakening during the night| 0.55 ± 0.69 | 0.95 ± 0.78 | <0.001  |
| Early awakening           | 0.30 ± 0.60 | 0.60 ± 0.75 | <0.001  |
| Total sleep duration      | 0.79 ± 0.75 | 0.86 ± 0.77 | 0.202   |
| Sleep quality             | 0.78 ± 0.92 | 0.88 ± 0.75 | 0.099   |
| Wellbeing during the day   | 0.50 ± 0.66 | 0.49 ± 0.64 | 0.829   |
| Functioning capacity during the day | 0.46 ± 0.67 | 0.39 ± 0.60 | 0.177   |
| Sleepiness during the day  | 0.71 ± 0.70 | 0.49 ± 0.57 | <0.001  |
| Total score               | 4.78 ± 3.97 | 5.17 ± 3.93 | 0.214   |
| Total score ≥ 6, n (%)    | 150 (34.8) | 108 (41.7) | 0.070   |
| BSRS-5                    |           |            |         |
| Feeling nervous           | 0.88 ± 0.87 | 0.80 ± 0.71 | 0.208   |
| Feeling easily annoyed or irritated | 1.04 ± 0.94 | 0.81 ± 0.76 | 0.001   |
| Feeling depressed         | 0.87 ± 0.93 | 0.65 ± 0.80 | 0.002   |
| Feeling inferior to others| 0.87 ± 0.97 | 0.40 ± 0.67 | <0.001  |
| Sleep difficulties        | 0.81 ± 1.04 | 0.89 ± 0.99 | 0.298   |
| Total score               | 4.46 ± 3.82 | 3.49 ± 3.02 | <0.001  |
| Total score ≥ 10, n (%)   | 49 (11.4)  | 9 (3.5)    | <0.001  |

a. PCOS, polycystic ovary syndrome.
b. p < 0.05 indicates statistical significance.
shown that estrogens exert a peripheral effect on smooth muscle contractility via the inhibition of RhoA signaling, cholecystokinin (CCK) and CCK(A) receptor activation (24).

Bowel dysmotility has also been suggested to be an important contributing factor in the development of IBS. Clinical observations have found that women tend to have slower gastrointestinal (GI) transit and are more prone to constipation than men. However, previous studies have obtained contradictory findings regarding the effect of the various sex hormones on GI motility (25–27). A recent study based on female dihydrotestosterone (DHT)-treated PCOS rats found lower maximal colon muscle contractility in response to acetylcholine stimulation in DHT-treated rats than in untreated rats (28). This lower maximal muscle contractility was found to be associated with extracellular calcium levels. This effect occurs partly via a reduction of the responsiveness of acetylcholine and through phosphorylation of 20-kDa regulatory myosin light chain (MLC20) (28). These findings suggest that hyperandrogenism might be involved in bowel dysmotility, resulting in IBS in women with PCOS. However, we did not find any significant differences between the levels of various hormones in PCOS women with or without IBS.

| Characteristics | PCOS with IBS | PCOS without IBS | p |
|-----------------|--------------|-----------------|---|
| n (%)           | 46 (10.7)    | 385 (89.3)      | 0.123 |
| Age, y          | 26.3 ± 4.8   | 25.1 ± 4.9      | 0.701 |
| BMI, kg/m²      | 26.0 ± 6.7   | 26.4 ± 6.5      | 0.878 |
| ≥ 30, n (%)     | 13 (28)      | 113 (29)        | 0.704 |
| Waist circumference, cm | 89.2 ± 15.4 | 90.1 ± 14.6    | 0.630 |
| ≥ 80, n (%)     | 32 (70)      | 280 (73)        | 0.123 |
| Menstrual cycle interval (days) | 154.9 ± 110.6 | 143.8 ± 111.7 | 0.524 |

**Metabolic profile**

- Systolic blood pressure, mmHg: 116.7 ± 14.6 vs. 116.9 ± 13.9, p = 0.934
- Diastolic blood pressure, mmHg: 76.0 ± 10.3 vs. 75.8 ± 11.5, p = 0.895
- Fasting blood glucose, mg/dL: 87.1 ± 7.9 vs. 85.5 ± 12.1, p = 0.382
- Triglycerides, mg/dL: 117.3 ± 82.6 vs. 100.1 ± 59.3, p = 0.176
- Total cholesterol, mg/dL: 184.0 ± 30.6 vs. 189.3 ± 34.1, p = 0.534
- HDL-C, mg/dL: 51.5 ± 11.8 vs. 54.8 ± 24.6, p = 0.361
- LDL-C, mg/dL: 106.8 ± 30.4 vs. 110.6 ± 31.7, p = 0.443
- Uric acid, mg/dL: 5.5 ± 1.3 vs. 5.4 ± 1.2, p = 0.600

**Hormonal profile**

- FSH (mIU/mL): 6.1 ± 1.6 vs. 6.3 ± 2.3, p = 0.611
- LH (mIU/mL): 11.0 ± 4.7 vs. 11.3 ± 6.3, p = 0.769
- E2 (pg/mL): 62.7 ± 40.4 vs. 58.2 ± 66.4, p = 0.659
- P4 (ng/mL): 0.97 ± 1.93 vs. 0.55 ± 1.27, p = 0.155
- Testosterone (ng/mL): 0.67 ± 0.35 vs. 0.61 ± 0.26, p = 0.242
- SHBG (nmol/L): 37.4 ± 25.2 vs. 37.0 ± 21.8, p = 0.932
- FAI (%): 8.7 ± 5.9 vs. 8.3 ± 6.8, p = 0.777
- DHEAS (µg/dL): 299.0 ± 108.2 vs. 266.5 ± 110.2, p = 0.149
- Prolactin (ng/mL): 8.61 ± 3.57 vs. 9.51 ± 5.69, p = 0.298
- TSH (mIU/mL): 1.76 ± 0.67 vs. 1.89 ± 1.07, p = 0.277

**AIS**

- Sleep induction: 1.33 ± 1.06 vs. 0.63 ± 0.79, p < 0.001
- Awakening during the night: 1.02 ± 0.83 vs. 0.49 ± 0.65, p < 0.001
- Early awakening: 0.57 ± 0.81 vs. 0.26 ± 0.57, p = 0.017
- Total sleep duration: 1.07 ± 0.80 vs. 0.75 ± 0.74, p = 0.007
- Sleep quality: 1.26 ± 0.91 vs. 0.72 ± 0.90, p = 0.001
- Wellbeing during the day: 0.91 ± 0.92 vs. 0.45 ± 0.60, p = 0.002
- Functioning capacity during the day: 0.87 ± 0.96 vs. 0.41 ± 0.61, p = 0.003
- Sleepiness during the day: 1.11 ± 0.95 vs. 0.66 ± 0.65, p = 0.003
- Total score: 8.13 ± 5.12 vs. 4.38 ± 3.61, p < 0.001
- Total score ≥ 6, n (%): 31 (67.4) vs. 119 (30.9), p < 0.001

**BSRS-5**

- Feeling nervous: 1.35 ± 1.08 vs. 0.82 ± 0.82, p = 0.002
- Feeling easily annoyed or irritated: 1.46 ± 0.96 vs. 0.99 ± 0.93, p = 0.001
- Feeling depressed: 1.24 ± 1.14 vs. 0.82 ± 0.90, p = 0.004
- Feeling inferior to others: 1.24 ± 1.16 vs. 0.82 ± 0.84, p = 0.006
- Sleep difficulties: 1.59 ± 1.29 vs. 0.72 ± 0.97, p < 0.001
- Total score: 6.87 ± 4.56 vs. 4.17 ± 3.62, p < 0.001
- Total score ≥ 10, n (%): 10 (21.7) vs. 39 (10.1), p = 0.019

The table shows the anthropometrics, laboratory, and sleep and psychological characteristics in PCOS patients with and without IBS. The p values indicate the statistical significance of the differences between the two groups. The table includes various measurements such as BMI, waist circumference, menstrual cycle interval, and various hormones like FSH, LH, E2, P4, Testosterone, FAI, DHEAS, Prolactin, TSH, and metabolic profile parameters like systolic and diastolic blood pressure, fasting blood glucose, triglycerides, and total cholesterol. The sleep and psychological characteristics are assessed using the Athens Insomnia Scale (AIS) and the Brief Symptom Rating Scale (BSRS-5). The p values are calculated using statistical tests such as t-tests and chi-square tests, and the significance level is set at p < 0.05.
### TABLE 4 | Laboratory, sleep, and psychological characteristics of patients with PCOS stratified according to BMI.

| Characteristics | PCOS and BMI ≥ 30 kg/m² | PCOS and BMI < 30 kg/m² | p     |
|----------------|--------------------------|--------------------------|-------|
| n (%)          | 126 (29.2)               | 305 (71.0)               |       |
| **Metabolic profile** |                          |                          |       |
| Systolic blood pressure, mmHg | 127.9 ± 14.8 | 112.4 ± 10.8 | <0.001 |
| Diastolic blood pressure, mmHg | 84.2 ± 12.0 | 72.4 ± 9.2 | <0.001 |
| Fasting blood glucose, mg/dL | 90.9 ± 18.2 | 83.5 ± 6.6 | <0.001 |
| Triglycerides, mg/dL | 142.2 ± 73.1 | 85.4 ± 48.5 | <0.001 |
| Total cholesterol, mg/dL | 192.4 ± 38.2 | 184.7 ± 31.6 | 0.048 |
| HDL-C, mg/dL | 44.9 ± 14.1 | 58.3 ± 25.5 | <0.001 |
| LDL-C, mg/dL | 125.6 ± 33.5 | 103.8 ± 28.4 | <0.001 |
| Uric acid, mg/dL | 6.4 ± 1.2 | 5.1 ± 1.0 | <0.001 |
| **Hormonal profile** |                          |                          |       |
| FSH (mIU/mL) | 6.1 ± 3.2 | 6.4 ± 1.7 | 0.320 |
| LH (mIU/mL) | 8.0 ± 4.8 | 12.6 ± 6.1 | <0.001 |
| E2 pg/mL | 59.9 ± 49.0 | 58.2 ± 69.4 | 0.805 |
| P4 (ng/mL) | 0.56 ± 1.11 | 0.61 ± 1.44 | 0.702 |
| Testosterone (ng/mL) | 0.60 ± 0.27 | 0.62 ± 0.28 | 0.478 |
| SHBG (nmol/L) | 18.8 ± 7.3 | 42.1 ± 22.2 | <0.001 |
| FAI (%) | 13.5 ± 7.8 | 6.9 ± 5.6 | <0.001 |
| DHEAS (µg/dL) | 238.0 ± 116.2 | 279.1 ± 107.2 | 0.017 |
| Prolactin (ng/mL) | 9.61 ± 5.18 | 9.33 ± 5.64 | 0.062 |
| TSH (ng/mL) | 1.17 ± 1.30 | 1.75 ± 0.88 | <0.001 |
| AIS |                          |                          |       |
| Total score | 4.07 ± 3.51 | 5.12 ± 3.77 | 10.92 ± 6.90 | <0.001 |
| TOTAL | 75 (27.6) | 44 (38.9) | 22 (66.7) | 9 (69.2) | <0.001 (for trend) |
| Risk of AIS ≥ 6, OR (95% CI) | 1 | 1.68 (1.06–2.66) | 5.20 (2.41–11.24) | 5.91 (1.77–19.77) | <0.001 (for trend) |
| BSRS-5 |                          |                          |       |
| Total score | 3.85 ± 3.46 | 4.93 ± 3.90 | 6.42 ± 4.04 | 8.00 ± 5.70 | <0.001 |
| TOTAL | 25 (9.2) | 14 (12.4) | 6 (18.2) | 4 (30.8) | 0.009 (for trend) |
| Risk of BSRS-5 ≥ 10, OR (95% CI) | 1 | 1.40 (0.70–2.80) | 2.18 (0.82–5.78) | 4.39 (1.26–15.29) | <0.001 |

a. AIS, Athens Insomnia Scale; BMI, body mass index; BSRS-5, Brief Symptom Rating Scale; DHEAS, dehydroepiandrosterone sulphate; E2, estradiol; FAI, free antigen index; FSH (%) = testosterone (ng/mL) * 3.47 * 100/SHBG (nmol/L); FSH, follicle stimulating hormone; HDL-C, high-density lipoprotein cholesterol; IBS, irritable bowel syndrome; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; P4, progesterone; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding protein; TSH, thyroid stimulating hormone.

b. p < 0.05 indicates statistical significance.

---

### TABLE 5 | Sleep and psychological characteristics of patients with PCOS stratified according to presence of IBS and obesity (BMI ≥ 30 kg/m²).

| Characteristics | IBS (−) BMI < 30 | IBS (−) BMI ≥ 30 | IBS (+) BMI < 30 | IBS (+) BMI ≥ 30 | p     |
|----------------|------------------|------------------|------------------|------------------|-------|
| n (%)          | 272 (63.1)       | 113 (26.2)       | 33 (7.7)         | 13 (3.0)         |       |
| AIS |                          |                  |                  |                  |       |
| Total score | 4.07 ± 3.51 | 5.12 ± 3.77 | 7.03 ± 3.82 | 10.92 ± 6.90 | <0.001 |
| TOTAL | 75 (27.6) | 44 (38.9) | 22 (66.7) | 9 (69.2) | <0.001 (for trend) |
| Risk of AIS ≥ 6, OR (95% CI) | 1 | 1.68 (1.06–2.66) | 5.20 (2.41–11.24) | 5.91 (1.77–19.77) | <0.001 (for trend) |
| BSRS-5 |                          |                  |                  |                  |       |
| Total score | 3.85 ± 3.46 | 4.93 ± 3.90 | 6.42 ± 4.04 | 8.00 ± 5.70 | <0.001 |
| TOTAL | 25 (9.2) | 14 (12.4) | 6 (18.2) | 4 (30.8) | 0.009 (for trend) |
| Risk of BSRS-5 ≥ 10, OR (95% CI) | 1 | 1.40 (0.70–2.80) | 2.18 (0.82–5.78) | 4.39 (1.26–15.29) | <0.001 |

a. AIS, Athens Insomnia Scale; BMI, body mass index; BSRS-5, Brief Symptom Rating Scale; CI, confidence interval; IBS, irritable bowel syndrome; OR, odds ratio; PCOS, polycystic ovary syndrome.

b. The Mantel-Haenszel test was used to test the linear trend for statistical significance.

c. p < 0.05 indicates statistical significance.
that different androgens and their metabolites have different levels of potency, which may explain these results. It is also possible that factors other than the hormones we assayed may contribute to the higher prevalence of IBS in women with PCOS, and this warrants further investigation.

Several studies have highlighted the association between the abundance of gut microbiota and PCOS in humans (29–31). Another study showed that the diversity and composition of gut microbiota in young adults are affected by the combination of sex, sex hormone concentrations, and obesity, and that this has specific consequences in women with PCOS (32). It has also been suggested that the gut microbiota play a key role in modulating the gut–brain interaction and intestinal barrier functioning and, therefore, that they may participate in the pathogenesis of IBS (33). Alteration of the gut microbiome could lead to low-grade inflammation and immune dysfunction in the intestinal mucosa, resulting in changes in intestinal secretion, visceral perception, and intestinal dysmotility in patients with IBS (34). In addition, small intestinal bacterial overgrowth (SIBO), a clinical syndrome featuring an abnormally high number or abnormal type of bacteria in the small intestine, has been associated with the pathophysiology of IBS, and it causes abdominal pain, bloating, diarrhea, steatorrhea, and flatulence (35). Most studies and recent meta-analyses have reported a higher frequency of SIBO among patients with IBS than in controls (36, 37). Therefore, we speculate that gut microbiota dysbiosis in patients with PCOS also contributes to the higher prevalence of IBS in these patients. Further studies to compare the composition of gut microbiota between PCOS women with and without IBS may help to clarify this relationship.

Psychosocial distress is common in both patients with IBS and patients with PCOS, and could also play a bidirectional role in the development of IBS in women with PCOS (6). A recent meta-analysis reported that patients with IBS have more frequent and severe depressive symptoms than healthy controls (38). Further meta-analysis regressions reveal that younger women (the group at most risk for PCOS) have significantly more severe depressive symptoms (38). The close association between psychiatric disorders and IBS has been explained by the ‘gut–brain axis’ hypothesis. Chronic psychological stress has been associated with GI dysmotility, increased intestinal permeability, and visceral hyperalgesia in animal and human studies (39–41). One study demonstrated that corticosterone mediates the chronic psychological-stress-induced increase in intestinal permeability in rats by decreasing the expression of tight junction proteins (39). Depressive symptoms were also found to affect pain thresholds in the alternating IBS subtype (42). Studies based on a nationwide Swedish cohort and hospital admissions found that women with PCOS have an increased risk of depression and anxiety disorders (43, 44). A meta-analysis of 30 cross-sectional studies, representing 3050 patients with PCOS and 3858 controls from 10 different countries, demonstrated a significantly increased risk of moderate and severe depressive and anxiety symptoms in women with PCOS (5). Therefore, PCOS patients are likely to suffer from additional psychiatric distress when they also suffer from troublesome bowel symptoms. In the present study, women with PCOS had a significantly higher prevalence of psychiatric morbidities than healthy volunteers. In addition, women with PCOS and IBS had higher psychiatric distress than patients with PCOS but not IBS. Up to 21.7% of women with PCOS and IBS had moderate psychiatric morbidities. Since IBS symptoms may be relieved by lifestyle modification and pharmacological treatment, further research is required to investigate whether screening and treatment of IBS in women with PCOS may provide psychiatric relief.

Obesity is an important feature of PCOS. Previous studies have found that women with PCOS and IBS had a higher BMI (32.9 ± 2.0 kg/m²) than those with PCOS but no IBS (30.3 ± 1.6 kg/m²) (11). Although our participants with PCOS had a higher BMI than healthy volunteers, the BMI of PCOS women with and without IBS was similar. The BMI of our participants was somewhat lower (26.4 ± 6.5 kg/m²) than in Western studies, suggesting that obesity alone may not play a significant role in the development of IBS in women with PCOS. However, obesity has been associated with increased psychiatric disorders and sleep disturbances in previous studies (45, 46). In one of the aforementioned meta-analyses, women with PCOS and concurrent psychiatric disorders such as depression or anxiety had a higher BMI, suggesting that obesity plays a role in the association between PCOS and psychiatric disorders (5). Similarly, in a community-based sample population, sleep disturbances were almost twice as common in women with PCOS than in women of similar age without PCOS (47). This association was accounted for by body weight and depressive symptoms. This supports our present findings that the women with PCOS and both obesity and IBS had the most severe sleep problems and psychosocial distress.

This study’s strengths include a relatively large sample of women with PCOS and a complete clinical assessment, including anthropometric measurements and hormonal assays, which allowed for a comprehensive subgroup analysis. In addition, we recruited the control group from the general population who attended the routine health check-up. The in-person interviews and physical examination by gynecologist as well as detailed laboratory and imaging studies to exclude any organic lesions which may interfere the manifestations of IBS symptoms and psychosocial comorbidities. However, our study also has several limitations. First, it was designed as a cross-sectional case-control study, and as such it cannot explain the cause–effect relationship between PCOS and IBS. Second, women with PCOS were younger and more obese than the control group, and age and BMI may be confounding factors in interpreting the higher prevalence of IBS in women with PCOS. However, the fact that our study had mostly younger women reflects the real-world situation, and further this aspect is consistent with two similar studies (11, 12). Future studies with age- and BMI-matched controls may help to clarify this important issue. Finally, our study was conducted in an ethnically Chinese population, and it may not be generalizable to other ethnic populations. Further studies to confirm our findings are thus warranted.

CONCLUSIONS

In conclusion, our study shows that women with PCOS have increased IBS, obesity, sleep and psychiatric disturbances. The
presence of IBS in women with PCOS is highly associated with presence of sleep and psychiatric disorders. The coexistence of obesity and IBS exacerbates sleep difficulties and psychiatric distress in women with PCOS. Screening and management of IBS and overweight/obesity might be warranted to improve sleep and psychiatric disturbances in women with PCOS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Taiwan University Hospital (NTUH) Research Ethics Committee (REC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

P-HT, H-MC, C-HT, and M-JC: drafting the manuscript. P-HT, H-MC, and M-JC: study concept and design. P-HT, H-MC, C-HT, and M-JC: statistical analysis. P-HT, M-SW, and M-JC: obtained funding. M-SW, H-MC, and M-JC: study supervision. All authors have given important intellectual content. P-HT and M-JC: statistical analysis. P-HT, H-MC, and C-HT: drafting the manuscript. P-HT, H-MC, C-HT, and M-JC: drafting the manuscript. P-HT, H-MC, C-HT, and M-JC: statistical analysis. P-HT, M-SW, and M-JC: obtained funding. M-SW, H-NH, and M-JC: study supervision. All authors have seen and approved the submission of this version of the manuscript and take full responsibility for the manuscript. All authors have given final approval of the version submitted, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This study was supported by research grants from the National Taiwan University Hospital (NTUH. 106-003411) and the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-002-125-MY3, MOST 105-2325-B-002-041- and MOST 107-2314-B-002-050-). The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

ACKNOWLEDGMENTS

The authors wish to thank the staff of the Eighth Core Lab in the Department of Medical Research of the National Taiwan University Hospital for their technical support during the study. We would also like to thank Uni-edit (www.uni-edit.net) for editing and proofreading this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.779456/full#supplementary-material

REFERENCES

1. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic Ovary Syndrome. Nat Rev Dis Primers (2016) 2:16057. doi: 10.1038/nrdp.2016.57
2. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations From the International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Hum Reprod (2018) 33(9):1602–18. doi: 10.1093/humrep/dey256
3. Sidra S, Tariq MH, Farrukh MJ, Mohsin M. Evaluation of Clinical Manifestations, Health Risks, and Quality of Life Among Women With Polycystic Ovary Syndrome. PloS One (2019) 14(10):e0223329. doi: 10.1371/journal.pone.0223329
4. Dokras A, Stener-Victorin E, Yildiz BO, Li R, Ottey S, Shah D, et al. Androgen Excess- Polycystic Ovary Syndrome Society: Position Statement on Depression, Anxiety, Quality of Life, and Eating Disorders in Polycystic Ovary Syndrome. Fertil Steril (2018) 109(5):888–99. doi: 10.1016/j.fertnstert.2018.01.038
5. Cooney LG, Lee I, Sammel MD, Dokras A. High Prevalence of Moderate and Severe Depressive and Anxiety Symptoms in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Hum Reprod (2017) 32(5):1075–91. doi: 10.1093/humrep/dex044
6. Hung JH, Hu LY, Tsai SJ, Yang AC, Huang MW, Chen PM, et al. Risk of Psychiatric Disorders Following Polycystic Ovary Syndrome: A Nationwide Population-Based Cohort Study. PloS One (2014) 9(5):e97041. doi: 10.1371/journal.pone.0097041
7. Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable Bowel Syndrome. Lancet (2020) 396(10263):1675–88. doi: 10.1016/S0140-6736(20)31548-8
8. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global Prevalence of Irritable Bowel Syndrome According to Rome III or IV Criteria: A Systematic Review and Meta-Analysis. Lancet Gastroenterol Hepatol (2020) 5(10):908–17. doi: 10.1016/S2468-1253(20)30217-X
9. Black CJ, Ford AC. Global Burden of Irritable Bowel Syndrome: Trends, Predictions and Risk Factors. Nat Rev Gastroenterol Hepatol (2020) 17(8):473–86. doi: 10.1038/s41575-020-0286-8
10. Karjula S, Morin-Papunen L, Auvonen J, Ruokonen A, Puukka K, Franks S, et al. Psychological Distress Is More Prevalent in Fertile Age and Premenopausal Women With PCOS Symptoms: 15-Year Follow-Up. J Clin Endocrinol Metab (2017) 102(6):1861–9. doi: 10.1210/jc.2016-3863
11. Mathur R, Ko A, Hwang LJ, Low K, Azziz R, Pimentel M. Polycystic Ovary Syndrome is Associated With an Increased Prevalence of Irritable Bowel Syndrome. Digestive Dis Sci (2010) 55(4):1085–9. doi: 10.1007/s10620-009-0890-5
12. Bazarganipour F, Taghavi SA, Asemi Z, Allan H, Khashavi Z, Safarzadeh T, et al. The Impact of Irritable Bowel Syndrome on Health-Related Quality of Life in Women With Polycystic Ovary Syndrome. Health Qual Life Outcomes (2020) 18(1):226. doi: 10.1186/s12955-020-01428-7
13. Chen MJ, Chen HF, Chen SU, Ho HN, Yang YS, Yang WS. The Relationship Between Follistatin and Chronic Low-Grade Inflammation in Women With IBS in Women With PCOS.
