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Full length article

Sleep disorders and hyperarousal among patients with endometriosis: A case-control survey study

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ABSTRACT

Background: Endometriosis has been associated with sleep disorders, and hyperarousal appears to be involved in their pathogenesis; however, the presence of hyperarousal in the endometriosis population was never investigated.
Methods: We conducted a case-control survey study by sending a questionnaire to all endometriosis patients followed up at our Centers. Controls were recruited among the general population. The questionnaire included demographic information, symptoms and history of endometriosis, the Hyperarousal Scale (H-Scale), the Pittsburgh Sleep Quality Index (PSQI), and the Insomnia Severity Index (ISI).
Results: A total of 847 women completed the questionnaires: 430 (50.8 %) had endometriosis, and 417 (49.2 %) were controls. Endometriosis was associated with higher H-scale score (OR 2.9, 95 % CI 2.4–3.8, p = 0.000), higher PSQI score (OR 4.3, 95 % CI 3.2–5.7, p = 0.000), and higher ISI score (OR 4.6, 95 % CI 3.5–6.1, p = 0.000) in multivariable ordinal logistic regressions analysis. With path analysis, hyperarousal (H-Scale) reported a partial mediating role in the association between endometriosis and sleep disorders. The mediation effect represented 22.3–27.8 % of the entire association between endometriosis and sleep disturbances.
Conclusion: Endometriosis patients complaining sleep disorders may benefit by investigating the presence of hyperarousal given cognitive behavioral therapy was reported effective in improving hyperarousal and associated sleep disorders.

Introduction

Endometriosis is a chronic benign condition affecting 2–10 % of reproductive-age women [1].

Dysmenorrhea, Dyspareunia, chronic pelvic pain, heavy menstrual Bleeding, and infertility are common presenting symptoms, which are known to be associated with the presence of the disease, particularly when two or more of them are present [2,3]. Nevertheless, the impact of endometriosis on affected women extends over gynecological symptoms. A growing body of evidence shows that endometriosis affects the quality of life (QoL) and daily activities [4–6] with higher levels of depression, anxiety, and social dysfunction reported in affected women [7–10].

Among factors affecting QoL, endometriosis has been associated with sleep disorders [11–14]. Sleep disorders in general, particularly the most common insomnia [15] have been demonstrated to significantly impact a wide range of daytime functions with detrimental effects on QoL [16–19].

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This observed association between sleep disorders and endometriosis may represent an opportunity for guiding multidisciplinary interventions and improving patients' wellness. However, understanding the reason for such an association is mandatory. Hyperarousal is defined as a state of increased responsiveness to stimuli deriving from the deregulation of the autonomic nervous system and it consists of one of the psychophysiological measures for fear/anxiety [20]; it has been identified as having a key role in the pathogenesis of insomnia and other sleep disorders [21–23].

When hyperarousal is present and is identified as a cause of poor sleep quality, cognitive behavioral therapy has been reported effective [24]. The Hyperarousal Scale (H-Scale) has been developed to identify patients with high hyperarousal who may benefit from cognitive behavioral therapy to treat sleep disorders [21,25–27]. Nevertheless, the presence of hyperarousal in the endometriosis population and its role as a mediator of the association between endometriosis and sleep disorders has never been investigated.

Given this gap in the literature and the opportunity to identify possible intervention strategies to improve sleep quality in women affected by endometriosis, we conducted a study to explore the prevalence of hyperarousal and sleep disorder in women with endometriosis, investigate the association between endometriosis, hyperarousal, and sleep disorders, and investigate the role of hyperarousal as a mediator of the association between endometriosis and sleep disorders.

Material and methods

Study design and population source

This study is a case-control survey study. We retrieved the complete list of patients affected by endometriosis and followed up at the Gynecological Department of our Centers. All patients were contacted by phone call to inform them about the study, ask for consent for recruitment, and for providing an Controls, recruited among the general population, were to have no current and lifetime symptoms and signs suggestive of endometriosis, and/or other diagnosed gynecological disorders. The exclusion criteria, assessed by specific items, included the presence, at the time of the interview, of psychiatric disorders on drug treatment, history of alcohol or substance addiction, and organic brain disorder or mental retardation. The survey was conducted using an online tool panel for data collection (i.e., Google Forms®) sent within the Italian territory as an invitation to participate in the research that consisted in compiling an unpaid online survey released through social networks (i.e., Facebook® and Instagram®), web advertising, institutional or other professional mailing lists (i.e., University webmail and Linked-In®), and messaging services (i.e., WhatsApp® and Telegram®). The research method avoided incomplete surveys since the online module did not allow to proceed if somewhen one response was left unanswered. Before compiling the survey, participants were provided with written information about the research purposes ("*an investigation on potential correlations among some anxiety components and sleep disorders*") and the confidentiality of the procedure, carried out in total anonymity; the submission of the complete survey was considered informed voluntary consent. Data were collected between January and June 2021.

The design, analysis, interpretation of data, drafting, and revisions conform with the Helsinki Declaration, the Committee eon Publication Ethics (COPE) guidelines, and the "Checklist for Reporting Results of Internet E-surveys" (CROSS) validated by the "Enhancing the quality and transparency of health research" (EQUATOR) network. The data collected through the survey were anonymized, taking into account the observational nature of the study, without personal data that could lead to formal identification, so a formal Institutional Review Board (IRB) approval was not mandatory (Code of Federal Regulation, Title 45, part 46, subpart A, sec. 46.101, available through the Office for Human Research Protections, Rockville, USA, and validated by the American Association for Public Opinion Research, Washington, USA).

Instruments

The online questionnaire retrieved the following demographic information: age, weight, height, fertility state, parity, and history of assisted reproductive techniques. The survey also collected data about symptoms associated with endometriosis and information about previous surgery or pharmacological therapy. For women affected by endometriosis, provided answers were revised and integrated with data retrieved from medical records available at the study centers.

Moreover, the survey included the following instruments:

The hyperarousal Scale (H-Scale) – Italian version, [27,28] a self-report inventory composed of 26 items, was used to assess the hyperarousal behavioral traits on a 4-point likert-type scale coded as following: 0 = not at all; 1 = a little; 2 = quite a bit; 3 = extremely. The scale produces a Total summation Score, with higher scores (max. 78) being representative of higher levels of hyperactivation. In the original publication, a total score of 40 had a sensitivity of 90 % and specificity of 100 % for identifying primary insomnia versus control subjects, but a standardized cut-off point is not available [27,28].

The Pittsburgh sleep quality Index (PSQI), [29] a validated self-report measure of sleep quality in the month before the administration. PSQI is a 19-item questionnaire. Responses are rated on 0–3 likert scales, with 3 indicating the worst condition. Seven domains are present: Subjective sleep Quality, sleep Latency, sleep Duration, habitual sleep Efficiency, sleep Disturbances, use of sleeping Medications, and daytime dysfunction. A total score is obtained by summing the scores of the seven subscales. A PSQI lower than 5 indicates good sleep, while scores equal to or above 5 indicate poor sleep

The Epworth Sleepiness Scale (ESS) [30] is an 8-item self-reported questionnaire. This instrument is an index of daytime somnolence and investigates the possibility of falling asleep during different situations or activities of daily life. A total score ranging from 0 to 24 is calculated as the sum of eight 0–3 likert scale items. Scores between 11 and 24 represent excessive daytime sleepiness (EDS)

The insomnia Severity Index (ISI) [31] is a 7-item scale. It was designed to assess the severity of insomnia, evaluating both difficulties in sleep onset and maintenance and daytime functioning. The severity of insomnia is rated by participants on a 0–4 likert scale, with higher scores representing more severe insomnia. The total score ranged from 0 to 28, and scores above 15 represent clinical insomnia.

Statistical analysis

Patient characteristics, along with the results of the questionnaires included in the study, were summarized using standard descriptive statistics and compared between patients with and without endometriosis. Normal distribution for continuous variables was assessed with the Kolmogorov-Smirnov test for normal distribution. Non-normally and normally distributed variables were analyzed using the Mann–Whitney U and *t*-test, respectively. Categorical variables were analyzed using the Chi-squared test or Fisher's exact test as appropriate. We investigated the association between endometriosis, hyperarousal, and sleep disorders using multivariable analysis based on the type of outcome. In the multivariable analysis, we included variables significantly associated with the outcome in univariate analyses testing the association between demographic, clinical, and endometriosis characteristics and hyperarousal and sleep disorders.

The role of hyperarousal as a mediator of the association between endometriosis and sleep disorders was investigated in two steps. Multivariable analyses, including endometriosis and other factors independently associated with sleep disorders, were conducted with and without hyperarousal. After that, path analysis methods were conducted to confirm and quantify the mediation role of hyperarousal in the association between endometriosis and sleep disorders. A two-tailed p-

value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA /SE 16.1 for Mac (Intel 64-bit) Revision January 21st, 2021. Path analysis was performed using Jamovi Version 2.3.21.0.

Results

A total of 847 women completed the questionnaires and were included in the study. 430 (50,8 %) had endometriosis, and 417 (49,2 %) were controls who did not report symptoms or signs suggestive of endometriosis nor had a history suspect for the disease.

Demographic and clinical characteristics

Patients' demographic characteristics are summarized in Table 1. The mean age was significantly higher among women with endometriosis (35.1 versus 37.0 years, p = 0.006). The frequency of patients with a diagnosis of infertility was higher in the endometriosis group compared to controls (39.3 % (169/430) versus 8.6 % (36/417), p = 0.000), as well as the frequency of women who underwent assisted reproductive technology (ART) (21.6 % (93/480) versus 3.4 % (14/417), p = 0.000). The proportion of women with at least one childbirth was lower in the endometriosis group than in controls; however, the difference was not significant (29.8 % versus 34.5 %, p = 0.138).

Clinical characteristics of women with endometriosis are summarized in Table 2. Three hundred fifty-seven women (83 %) had a surgical diagnosis of endometriosis with histologic confirmation; seventy-three patients (17 %) received a presumptive clinical diagnosis based on symptoms, physical examination, and ultrasound imaging because of absent indication for surgery [32]. According to the American Society for Reproductive Medicine (ASRM) staging system for endometriosis [33], 14.2 % (n = 61) of patients were in stage 1, 15.1 % (n = 65) were in stage 2, 18.1 % (n = 78) were in stage 3, 52.6 % (n = 226) were in stage 4. One hundred seventy-four (48.7 %) patients underwent more than one surgical procedure. Two hundred ninety-five (68.6 %) patients were taking a pharmacological therapy when they filled the survey: 102 (34.6 %) a combined estrogen-progestin oral contraceptives (COC) pill, 154 (52.2) a progestogen-only pill (POP), 20 (6.8 %) a GnRH analog, 11 (3.7 %) a medicated intrauterine device (IUD), six a contraceptive patch (2 %), and 2 (0.7 %) an aromatase inhibitor.

The results of the questionnaires used in the study are listed in Table 3, stratified by endometriosis diagnosis. The median H-Scale Total Score was higher in women with endometriosis compared to controls (45(11) and 39(11), p = 0.000), and the proportion of women who scored equal or above 40 in the H-scale was higher in the endometriosis group (73 % versus 48.2 %, p = 0.000). This difference remained significant even when the score cut-off was lowered to 38, as proposed by Bruno et al. [28]. Endometriosis patients had higher PSQI total scores than non-endometriosis patients (11(9) versus 5(5), p = 0.000). A higher proportion of women with endometriosis scored equal to or above 5 in PSQI than those without endometriosis (90.5 % versus 59.7 %, p = 0.000). The median ESS total score was higher in the endometriosis group. Higher than normal daytime sleepiness was found to be significantly more common in the control group compared to the endometriosis group, while mild and severe excessive daytime sleepiness was more frequent in women with endometriosis compared to controls. No significant difference was found in the proportion of women with moderate excessive daytime sleepiness in cases compared to controls. When the ISI total score was evaluated, women with endometriosis reported a higher median total score compared to women without (13 (9) and 6(8), p = 0.000). Moreover, both subthreshold insomnia and clinical insomnia were significantly more frequent in the endometriosis group than in the control group.

Table 1
Demographic and clinical characteristics of the study population.

Variable	No endometriosis (417, 49.2 %)	Endometriosis (430, 50.8 %)	p	Total (847, 100 %)
Age (y, IQR)	31 (19)	37 (10)	0.000	35 (16)
Age (mean, SD)	35.1 (0.6)	37.0 (0.35)	0.006	36. (0.35)
Weight (Kg, IQR)	59 (13)	59 (15)	0.869	59 (14)
Weight (mean, SD)	60.7 (0.5)	61 (0.6)	0.691	60.8 (0.4)
Height (cm, IQR)	165 (9)	164 (8)	0.241	165 (8)
Height (mean, SD)	163.7 (0.5)	163.7 (0.4)	0.982	163.7 (0.3)
BMI (kg/m2, IQR)	21.8 (4)	21.9 (5)	0.990	21.9 (5)
BMI (mean, SD)	23.4 (12.7)	23 (7.6)	0.532	23.2 (10)
Infertility (N, %)	36 (8.6)	169 (39.3)	0.000	205 (24.2)
Pregnancies (N, IQR)	0 (2)	0 (1)	0.021	0 (1)
Miscarriages (median, IQR)	0 (0)	0 (0)	0.202	0 (0)
One or more miscarriages (N, %)	66 (15.8)	82 (19.1)	0.214	148 (17.5)
Recurrent miscarriages (N, %)	6 (1.4)	9 (2.1)	0.471	15 (1.8)
Childbirth (median, IQR)	0 (1)	0 (1)	0.006	0 (1)
One or more childbirths (N, %)	144 (34.5)	128 (29.8)	0.138	272 (32.1)
ART (N, %)	14 (3.4)	93 (21.6)	0.000	107 (12.6)

y = years; IQR = interquartile range; SD = standard deviation; BMI = Body Mass Index; N = number; ART = assisted reproductive techniques.

Table 2
Clinical characteristics of patients with endometriosis (N = 430).

Stage (median, IQR)	4 (2–4)
Stage I (N, %)	61 (14.2)
Stage II (N, %)	65 (15.1)
Stage III (N, %)	78 (18.1)
Stage IV (N, %)	226 (52.6)
Dysmenorrhea (median, IQR)	8 (7–10)
Chronic Pelvic pain (median, IQR)	6 (4–8)
Dyspareunia (median, IQR)	6 (4–8)
Dysuria (median, IQR)	2 (1–5)
Dyschezia (median, IQR)	5 (1–7)
Hematuria (N, %)	20 (4.6)
Rectal Bleeding (N, %)	112 (26)
Surgery (N, %)	357 (83)
Number of previous surgeries (median, IQR)	1 (1–2)
More than one surgery (N, %)	174 (48.7)
Laparotomy (N, %)	35 (9.8)
Laparoscopy (N, %)	238 (66.7)
Vaginal (N, %)	3 (0.8)
Combined (N, %)	81 (22.7)
Pharmacological Therapy (N, %)	295 (68.6)
COC (N, %)	102 (34.6)
POP (N, %)	154 (52.2)
GnRH analogues (N, %)	20 (6.8)
P-Medicated IUD (N, %)	11 (3.7)
Combined Contraceptive Patch (N, %)	6 (2)
Aromatase Inhibitors (N, %)	2 (0.7)
No Therapy (N, %)	135 (31.4)

y = years; IQR = interquartile range; SD = standard deviation; N = number; ART = assisted reproductive technique; COC = combined oral contraceptive; POP = progesterone only pill; GnRH = gonadotropins releasing hormone; P-Medicated IUD = Progesterone Medicated Intrauterine Device.

Table 3
Scores of Questionnaires used in the study.

Variable	No Endometriosis (417, 49.2 %)	Endometriosis (430, 50.8 %)	p	Tot (847, 100 %)
H-Scale Introspectiveness (Median, IQR)	11 (9–12)	12 (10–14)	0.000	11 (9–13)
H-Scale Reactivity (Median, IQR)	4(3–5)	5(4–6)	0.000	5 (3–6)
H-Scale Extreme responses (Median, IQR)	2(1–5)	4(2–8)	0.000	3 (1–6)
H-Scale TOTAL SCORE (Median, IQR)	39 (33–44)	45 (39–50)	0.000	42 (36–48)
H-Scale score higher than 40 (N, %)	201 (48.2)	314 (73 %)	0.000	515 (60.8)
H-Scale score higher than 38 (N, %)	247 (59.2)	346 (80.5)	0.000	593 (70)
PSQI Total Score	5(3–8)	11(7–16)	0.000	8 (5–13)
PSQI score lower than 5 (N, %)	168 (40.3)	41 (9.5)	0.000	209 (24.7)
PSQI score higher than or equal to 5 (N, %)	249 (59.7)	389 (90.5)	0.000	638 (75.3)
ESS Total Score (Median, IQR)	7(5–10)	9(5–12)	0.001	8 (5–11)
ESS Total score higher than 11 (N, %)	60 (14.4)	111 (25.8)	0.000	171 (20.2)
Lower Normal Daytime Sleepiness (ESS Score 0–5) (N, %)	140 (33.6)	123 (28.6)	0.118	263 (31.5)
Higher Normal Daytime Sleepiness (ESS Score 6–10) (N, %)	189 (45.3)	157 (36.5)	0.009	346 (40.85)
Mild ESS (ESS Score 11–12) (N, %)	45 (10.8)	75 (17.4)	0.006	120 (14.2)
Moderate ESS (ESS Score 13–15) (N, %)	33 (7.9)	49 (11.4)	0.087	82 (9.7)
Severe ESS (ESS Score 16–24) (N, %)	10 (2.4)	26 (6.05)	0.009	36 (4.25)
ISI Total Score (Median, IQR)	6(2–10)	13(8–17)	0.000	9 (4–14)
No clinically significant insomnia (ISI Score 0–7) (N, %)	263 (63.1)	94 (21.9)	0.000	357 (42.2)
Subthreshold insomnia (ISI Score 8–14) (N, %)	113 (27.1)	170 (39.5)	0.000	283 (33.4)
Clinical insomnia (moderate severity) (ISI Score 15–21) (N, %)	38 (9.1)	140 (32.6)	0.000	178 (21)
Clinical insomnia (severe) (ISI Score 22–28) (N, %)	3 (0.7)	26 (6)	0.000	29 (3.4)

IQR = interquartile range; N = number; H-Scale = Hyperarousal Scale; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; ISI = Insomnia Severity Index.

Multivariable and path analyses

Multivariable ordinal logistic regressions confirmed endometriosis as independently associated with a higher median H-Scale total score (OR 2.9, 95 % CI 2.4–3.8, p = 0.000), a higher median PSQI Score (OR 4.3, 95 % CI 3.2–5.7, p = 0.000), a higher median ESS total score (OR 1.5, 95 % CI 1.1–1.9, p = 0.000) and a higher median ISI total score (OR 4.6, 95 % CI 3.5–6.1, p = 0.000) (Table 4). Endometriosis was independently associated with an H-Scale Score higher than 40 (Table 4, **OR 2.8 95** % CI 2.1–3.9, p = 0.000), with a PSQI Score higher than 5 (Table 4, **OR 4.5 95** % CI 2.9–7, p = 0.000), with an ESS score higher than 11 (Table 4, **OR 1.9 95** % CI 1.3–2.9, p = 0.001) and a Severe ISI Score (Table 4, **OR 6.2 95** % CI 1.7–22.4, p = 0.006). Full binary and ordinal multivariable logistic regressions are reported in Supplementary Tables 1-12.

Among other factors included in the multivariable regressions, age was independently associated with a lower median H-Scale Total Score (OR 0.98, 95 % CI 0.97–0.99, p = 0.021), a lower median H-Scale Introspectiveness Score (OR 0.97, 95 % CI 0.96–0.99, p = 0.000), a lower median H-Scale Extreme Responses Score (OR 0.96, 95 % CI 0.95–0.98, p = 0.000), a higher median PSQI Total Score (OR 1.01 95 % CI 1.00–1.03, P=0.017), a higher median ESS Total Score (OR 1.02, 95 % CI 1.00–1.03, p = 0.006) and a higher median ISI Total Score (OR 1.02, 95 % CI 1.01–1.03, p = 0.006) (Table 4). Body mass index (BMI) was independently associated with a higher median H-Scale Extreme Responses Score (OR 1.01, 95 % CI 1.00–1.02, p = 0.021) (Table 4). Finally, infertility was associated with a higher median H-Scale Extreme responses Score (Table 4, **OR 1.4, 95** % CI 1.01–2, p = 0.049). A higher H-Scale Total score was independently associated with a higher PSQI Total Score (OR 1.1, 95 % CI 1.08–1.12, p = 0.000), with a PSQI Score higher than 5 (OR 1.14, 95 % CI 1.10–1.17, p = 0.000), with a higher ESS Total Score (OR 1.11, 95 % CI 1.09–1.12, p = 0.000), with an ESS score higher than 11 (OR 1.02, 95 % CI 1.00–1.04, p = 0.48), with a higher ISI total Score (OR 1.11, 95 % CI 1.09–1.12, p = 0.000) and with a Severe ISI Score (OR 1.08, 95 % CI 1.03–1.13, p = 0.002) (Table 4).

The strength of the association between endometriosis and sleep disorders scores increased when the H-Scale total Score was removed in the above multivariable regressions, with higher Odds ratios (Supplementary Table 13). The path analysis reported a partial mediating role of hyperarousal (H-Scale Total Score) in the association between endometriosis and sleep disorders. The mediation effect represented 22.3–27.8 % of the entire association between endometriosis and sleep disturbances, with the remaining effect of endometriosis on sleep quality regarded as direct (Supplementary Tables 14-16, Figs. 1-3).

In the endometriosis group (Table 5), higher BMI was associated with a higher median H-Scale Score (OR 1.03, 95 % CI 1.01–1.04, p = 0.009), higher median ESS Score (OR 1.02, 95 % CI 1.00–1.04, p = 0.028) and higher median ISI Score (OR 1.02, 95 % CI 1.00–1.04, p = 0.021). Bleeding during defecation was independently associated with a higher median H Scale Score (Table 5, **OR 1.6, 95** % CI 1.1–2.4, p = 0.019) and H-Scale Score higher than 40 (OR1.9, 95 % CI 1.1–3.5, p = 0.028). Patients affected by endometriosis suffering from chronic pelvic pain showed higher odds of having a higher median PSQI score (Table 5, **OR 1.2, 95** % CI 1.05–1.3, p = 0.003). Infertility was independently associated with a median higher H-Scale Reactivity Score (OR 1.5, 95 % CI 1.01–2.1, 0.042). A higher stage (3rd or 4th stage according to ASRM classification) was independently associated with a higher median H-Scale Extreme Responses Score (OR 1.5, 95 % CI 1.01–2.2, p = 0.045) (Table 5). Dysuria was independently associated with a higher median PSQI Score (OR 1.1, 95 % CI 1.04–1.2, p = 0.004), dyspareunia was associated with a higher median ISI Score (OR 1.1, 95 %CI 1.06–1.2, p = 0.001) and a Severe ISI Score (OR 1.5, 95 % CI 1.15–1.95, p = 0.003), and have had a higher number of surgeries was independently associated with a PSQI score higher than 5 (OR 1.6, 95 % CI 1.02–2.5, p = 0.038) (Table 5). A higher median H-Scale Score was associated with higher scores in all questionnaires included in the study. For complete univariate analysis and binary and ordinal multivariable regressions, see Supplementary Tables 17-38.

Discussion

The relationship between hyperarousal and endometriosis in the context of sleep disorders seems to be complex, notably if we assume the hypothesis of a mediating role of hyperarousal. To the best of our knowledge, no studies have explored hyperarousal trait in endometriosis, however, there are research that have observed the contribution of anxiety in these diseases, providing associations between the two

Table 4
Multivariable ordinal logistic regression analysis for factors associated with the Scores of Questionnaires.

	Odds Ratio	[95 % Conf. Interval]		p	Other factors included in the multivariable regression, non-independently associated with questionnaires' scores
H-Scale TOTAL SCORE					
Age	0.9836936	0.9700643	0.9975145	0.021	BMI, Infertility, Parity ≥ 1, ART
Endometriosis	2.920083	2.249939	3.789828	0.000	
H-Scale (Introspectiveness)					
Age	0.9748872	0.9611748	0.9887952	0.000	BMI, Infertility, Parity ≥ 1, ART
Endometriosis	1.943641	1.50288	2.513666	0.000	
H-Scale (Reactivity)					
Endometriosis	2.755272	2.118114	3.584097	0.000	Age, BMI, Infertility, Parity ≥ 1, ART
H-Scale (Extreme Responses)					
Age	0.9637602	0.9500858	0.9776315	0.000	Parity ≥ 1, ART
BMI	1.012331	1.001872	1.0229	0.021	
Infertility	1.420504	1.001716	2.014377	0.049	
Endometriosis	2.270642	1.752354	2.942223	0.000	
H-SCALE score > 40					
Endometriosis	2.845171	2.085929	3.880764	0.000	Age, BMI, Infertility, Parity ≥ 1, ART
PSQI Total Score					
Age	1.017318	1.003061	1.031779	0.017	BMI, Infertility, Parity ≥ 1, ART
Endometriosis	4.290726	3.247742	5.668656	0.000	
H-Scale Total Score	1.102006	1.085712	1.118544	0.000	
PSQI score > 5					
Endometriosis	4.498899	2.889028	7.005847	0.000	Age, BMI, Infertility, Parity ≥ 1, ART
H-Scale Total Score	1.138631	1.109926	1.168077	0.000	
ESS Total Score					
Age	1.020425	1.005921	1.035139	0.006	BMI, Infertility, Parity ≥ 1, ART
Endometriosis	4.604276	3.486702	6.080062	0.000	
H-Scale Total Score	1.107527	1.090948	1.124358	0.000	
ESS>11					
Endometriosis	1.945774	1.323549	2.860519	0.001	Age, BMI, Infertility, Parity ≥ 1, ART
H-Scale Total Score	1.02066	1.000213	1.041525	0.048	
ISI Total Score					
Age	1.020425	1.005921	1.035139	0.006	BMI, Infertility, Parity ≥ 1, ART
Endometriosis	4.604276	3.486702	6.080062	0.000	
H-Scale Total Score	1.107527	1.090948	1.124358	0.000	
Severe ISI					
Endometriosis	6.173209	1.703929	22.36508	0.006	Age, BMI, Infertility, Parity ≥ 1, ART
H-Scale Total Score	1.080783	1.029064	1.135101	0.002	

BMI = Body Mass Index; H-Scale = Hyperarousal Scale; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; ISI = Insomnia Severity Index.

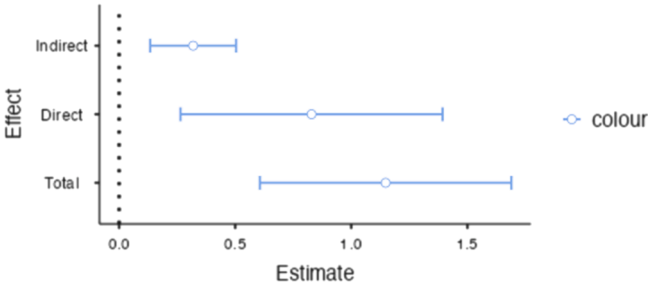

Fig. 1. Estimate Plot: Mediation Effect of Hyperarousal on Epworth Sleepiness Scale; Indirect Effect: mediation of Hyperarousal on Epworth Sleepiness Scale; Direct Effect: effect of endometriosis on Epworth Sleepiness Scale.

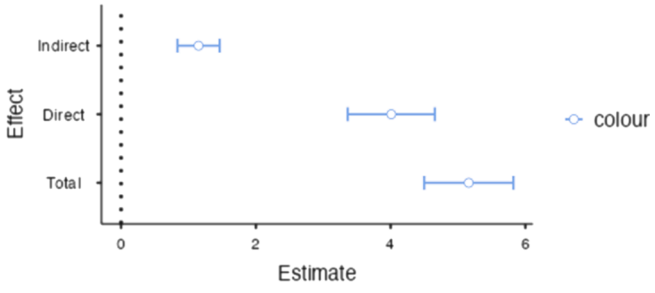

Fig. 2. Estimate Plot: Mediation Effect of Hyperarousal on Pittsburgh Sleep Quality Index; Indirect Effect: mediation of Hyperarousal on Pittsburgh Sleep Quality Index; Direct Effect: effect of endometriosis on Pittsburgh Sleep Quality Index.

conditions with regard to genetic, neuroinflammation and psychopathology [34–36]. Specifically, from a psychopathological perspective, a particular anxious psychological profile seems to be associated with endometriosis, since endometriosis patients show higher psychoticism, introversion and anxiety scores, compared with women without gynecological conditions [37]. Moreover, anxiety negatively affects sleep quality, triggering reduction of total sleep time and/or frequent awakenings, and/or difficulty falling asleep, negatively impacting the global functional activities of endometriosis women.

We observed that endometriosis is associated with poor sleep quality and hyperarousal. Both endometriosis and hyperarousal were independently associated with sleep disorders, and hyperarousal was identified as mediating almost one-quarter of the association between endometriosis and sleep disturbances. Among patients with endometriosis, BMI, bleeding during defecation, and pain-related symptoms (chronic pelvic pain, dysuria, and dyspareunia) were independently associated with poorer sleep quality.

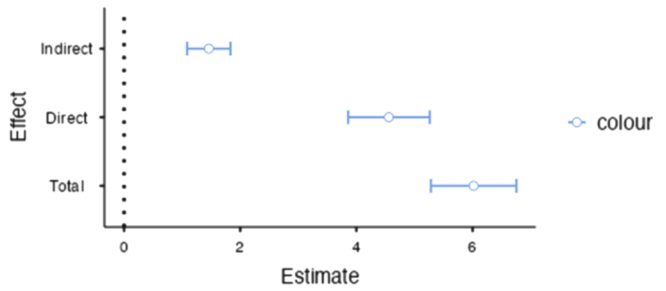

Fig. 3. Estimate Plot: Mediation Effect of Hyperarousal on Insomnia Severity Index; Indirect Effect: mediation of Hyperarousal on Pittsburgh Sleep Quality Index; Direct Effect: effect of endometriosis on Insomnia Severity Index.

Previously published studies reported on the association between endometriosis and poor sleep quality [12–14,38], PSQI [12,13], EPP [12,13], and ISI [13,14] were the most commonly adopted scales to assess sleep disturbances in women with endometriosis, and our results are consistent with previous. Poor sleep quality assessed by PSQI was found in 90.5 % of patients with endometriosis. Women with endometriosis showed a higher prevalence of excessive daytime sleepiness (on EPP) and insomnia (on ISI) than controls. The results of our study also showed that pain-related symptoms such as chronic pelvic pain, dysuria, and dyspareunia are independently associated with significantly higher scores across the tested scales. This is in line with the results of previous studies. Leone Roberti Maggiore et al. used the Italian-validated version of the PSQI [39] the EPP, and the ISI to assess the impact of endometriosis of the posterior cul-de-sac on quality of sleep, average daytime sleepiness, and insomnia in 145 women with a diagnosis of endometriosis compared to controls. The researchers found that endometriosis was associated with a higher prevalence of poor sleep quality, excessive daytime sleepiness, and clinically relevant insomnia compared to controls. Additionally, they found that VAS scores of dyspareunia, dyschezia, and chronic pelvic pain were independent predictors of poor sleep quality in these patients [13]. Facchin et al. compared 123 women with the disease with 123 women without a history of endometriosis and found that women with endometriosis were more likely to experience poorer quality of sleep (assessed by the PSQI) and higher daytime sleepiness (ESS) compared to controls. When women with endometriosis and painful symptoms were compared to those without significant pain, results showed that having pain was significantly associated with poor sleep [12]. De Souza et al. demonstrated that the prevalence of insomnia in women with deep endometriosis was related to pain intensity and duration [14].

Conversely to sleep disorders, this is the first study where the H-scale has been used to evaluate hyperarousal in this group of patients. We found a significantly higher H-Scale score in women with endometriosis than in controls and higher scores in the three scales assessing sleep disorders. This result confirms in patients with endometriosis the same association between hyperarousal and insomnia and other sleep disorders observed in different populations [21–23]. However, the observed association between endometriosis and hyperarousal and the observed mediating role in path analysis support the hypothesis that hyperarousal explains, at least partially, the mechanisms underlining the association between endometriosis and sleep disorders.

The H-Scale was introduced in 1993 by Regestein et al. [25]. It evaluates the hyperarousal trait, which is a state of amplified sensitivity characterized by constant hypervigilance, difficulty in relaxing, increased anger or irritability, reckless or self-destructive behaviors, and increased startle response. High hyperarousal scores correlate with higher general arousal measured by electroencephalogram activity [25], but reduced specific attention, as measured by event-related cortical potentials [21]. The role of hyperarousal in the pathophysiology of insomnia has progressively gained ground [23,40,41]. Indeed, the hyperarousal model of insomnia postulates that acute episodes of insomnia

Table 5
Multivariable ordinal logistic regression analysis for factors associated with the Scores of Questionnaires in the groups of patients with a diagnosis of endometriosis.

	Odds Ratio	[95 % Conf. Interval]		P	Other factors included in the multivariable regression, non-independently associated with scores
H-Scale TOTAL SCORE					
BMI	1.026251	1.006493	1.046398	0.009	Stage (low vs. high), Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Dysuria, Dyschezia
Bleeding during defecation	1.605935	1.079515	2.389061	0.019	
H-Scale (Introspectiveness)					
BMI	1.04	1.01	1.06	0.010	The only factor associated in univariate analysis
H-Scale (Reactivity)					
Infertility	1.46014	1.014657	2.101211	0.042	Age, Stage (low vs. high), Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Dysuria, Dyschezia, Bleeding during defecation, Bleeding during urination, number of previous surgeries
H-Scale (Extreme Responses)					
Stage	1.487857	1.008574	2.194898	0.045	BMI, Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Dysuria, Dyschezia, Bleeding during defecation, Bleeding during urination
H-SCALE score > 40					
Bleeding during defecation	1.931467	1.073977	3.473599	0.028	Stage (low vs. high), Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Dysuria, Dyschezia
PSQI Total Score					
Chronic Pelvic Pain	1.15646	1.051731	1.271617	0.003	Age, BMI, Parity >=1, Stage (low vs. high),
Dysuria	1.132264	1.039342	1.233494	0.004	Dysmenorrhea,
H-Scale Total Score	1.068538	1.04566	1.091915	0.000	Dyspareunia, Dyschezia, Bleeding during Defecation, number of previous surgeries
PSQI score > 5					
Number of surgeries	1.597	1.02543	2.487158	0.038	Chronic Pelvic Pain, Stage (low

(*continued on next page*)

Table 5 (*continued*)

	Odds Ratio	[95 % Conf. Interval]		P	Other factors included in the multivariable regression, non-independently associated with scores
					vs. high), Dysmenorrhea, Dyspareunia, Dysuria, Dyschezia, Surgery
H-Scale Total Score	1.10831	1.060371	1.158415	0.000	
ESS Total Score					
BMI	1.021696	1.002355	1.041411	0.028	Dysmenorrhea
H-Scale Total Score	1.025523	1.004773	1.046701	0.016	
Severe ESS Score					
H-Scale Total Score	1.070477	1.01591	1.127975	0.011	Age, Infertility, Surgery
ISI Total Score					
BMI	1.024265	1.00368	1.045272	0.021	Age, Parity >=1,
Dyspareunia	1.141705	1.058992	1.230879	0.001	Stage (low vs.
H-Scale Total Score	1.084742	1.061285	1.108717	0.000	high), Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Dysuria, Dyschezia, Bleeding during defecation, Surgery
Severe ISI					
Dyspareunia	1.498257	1.151066	1.950169	0.003	Chronic Pelvic Pain, Dysuria, Dyschezia, Bleeding during defecation, number of previous surgeries, H-Scale Total Score

BMI=Body Mass Index; H-Scale = Hyperarousal Scale; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; ISI = Insomnia Severity Index.

triggered by stressors can progress to chronic insomnia in prone individuals with evidence of hyperarousal [22]. Hyperarousal has also been shown to correlate with other dysfunctions such as depression [42], somatization [43], chronic stress [44], distress from interpersonal problems [45] and long-term physical and mental health consequences [46].

Nevertheless, cognitive behavioral therapy has been reported effective when hyperarousal is present and is identified as a cause of poor sleep quality [24]. Given that H-scale completion takes less than 5′ minutes, the investigation of hyperarousal may represent a valuable strategy to identify patients at risk of insomnia and other sleep disturbances among those diagnosed with endometriosis who may benefit from specific treatments.

Evaluating and treating sleep disturbance in patients with endometriosis is essential. Sleep disorders are a common, impactful consequence of chronic pain [47–49]. In turn, sleep deprivation is associated with increased production of inflammatory cytokines [50–52], which are potent modulators of pain cascade [53], resulting in a vicious circle between sleep disturbances and pain symptoms [54–56]. Indeed, poor sleep quality is known to impact pain symptoms in different chronic pain conditions[47], such as fibromyalgia [57], rheumatoid arthritis [58], burn injury [59], and orofacial pain [60].

Endometriosis is an inflammatory disease where inflammation and immune dysfunction are known to play a role in its pathogenesis [61–65]. Different studies provide evidence of the relationship between the highly inflammatory microenvironment of lesions in endometriosis and pain symptoms [66–68]. The association between painful symptoms in endometriosis and poor quality of sleep has a significant impact on patient management as adequate sleep has been reported to improve pain perception in healthy individuals [55] and to improve the long-term prognosis of those with some chronic pain conditions such as tension-type headache, migraine, and chronic musculoskeletal fatigue [47]. On the other hand, targeting pain symptoms in patients with endometriosis may prevent or improve sleep disturbances in these patients.

BMI is another factor reported in the present study implicated in poor sleep quality. Compelling evidence shows the bidirectional relationship between high BMI and poor sleep quality: short sleep duration is associated with weight gain [69–72] and increased BMI is a risk factor for sleep disorders [73–75].

This study also found that the endometriosis stage was not a factor implicated in the association between endometriosis and poor sleep quality. A similar lack of association is also reported between disease stage and pain symptoms [76], which may provide an insight into our results. However, if the disease stage correlates not with the severity of pain is still the subject of debate [77].

The only exception was the association between bleeding with defecation and higher scores on H-scale and PSQI scales. In these patients, associated pain may be a possible explanation, although the association with hyperarousal may identify this factor as a specific mediator in this subgroup of endometriosis patients.

The present study has several strengths. First, we included a high number of patients compared to previous studies. Second, the case-control study design allows the comparisons of variables and outcomes of interest between cases with endometriosis and healthy controls. Thirdly, more than 80 % of patients in the endometriosis group had a histological diagnosis. However, we acknowledge that our study has several limitations. First, the survey was partly conducted during the COVID-19 pandemic; this might have influenced the QOL and quality of sleep of included patients, even if it should affect both groups. Another limitation of the present study was that questionnaires were all administered online.

Conclusion

Endometriosis appears to be associated with poor sleep quality and hyperarousal. Both endometriosis and hyperarousal were independently associated with sleep disorders, and hyperarousal was identified as mediating almost one-quarter of the association between endometriosis and sleep disturbances. Therefore, among patients with endometriosis complaining sleep disorders, the administration of the H-scale to investigate the presence of hyperarousal may have a crucial role in identifying those patients who may benefit more from a multidisciplinary approach given cognitive behavioral therapy was reported effective in improving hyperarousal and associated sleep disorders. Further investigations are needed to confirm the role of hyperarousal and investigate whether cognitive behavioral therapy is effective in patients with endometriosis, along with the search for other mechanisms underlining the association between endometriosis and sleep disorders.

CRediT authorship contribution statement

Fiammetta Iannuzzo: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Simone Garzon:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Cecilia Lazzari:** Investigation,

Writing – original draft. **Irene Porcari:** Investigation, Resources, Writing – original draft. **Mariachiara Bosco:** Data curation, Formal analysis, Investigation, Resources. **Andrea Etrusco:** Data curation, Formal analysis, Investigation, Resources. **Antonio Simone Laganà:** Conceptualization, Supervision, Writing – review & editing. **Stefano Uccella:** Data curation, Formal analysis, Investigation, Resources. **Vito Chiantera:** Data curation, Formal analysis, Investigation, Resources. **Laura Celebre:** Data curation, Formal analysis, Investigation, Resources. **Carmela Mento:** Data curation, Formal analysis, Investigation, Resources. **Maria Rosaria Anna Muscatello:** Conceptualization, Supervision, Writing – review & editing. **Antonio Bruno:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2024.07.031.

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