Sleep disturbances, fatigue, and psychological health in women with endometriosis: a matched pair case-control study

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ABSTRACT

Research question: What are the associations between endometriosis, pelvic pain symptoms, fatigue, and sleep? Psychological health and quality of life (QoL) in endometriosis patients with good vs. bad quality of sleep were also examined.

Design: In this matched pair case-control study, we included 123 consecutive endometriosis patients and 123 women without a history of endometriosis (matched to patients for age and BMI). Endometriosis-related pelvic pain severity was rated on a 0-10 numerical rating scale. Fatigue was measured on a 1-5 Likert scale. Women also completed a set of self-report questionnaires for assessing sleep disturbances (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Insomnia Severity Index), psychological health (Hospital Anxiety and Depression Scale), and QoL (Short Form-12).

Results: Painful endometriosis had an impact on fatigue ($P = 0.006$; $\eta^2_p = 0.041$) and sleep ($P < 0.001$; $\eta^2_p = 0.051$). Women with painful endometriosis reported significantly greater fatigue, poorer quality of sleep, higher daytime sleepiness, and more severe insomnia than women without significant pain symptoms and controls. Poorer quality of sleep among endometriosis patients was associated with greater fatigue ($P < 0.001$; $\eta^2_p = 0.130$), poorer psychological health ($P < 0.001$; $\eta^2_p = 0.135$), and lower quality of life ($P < 0.001$; $\eta^2_p = 0.240$).

Conclusions: Pelvic pain (rather than endometriosis in itself) is associated with fatigue and sleep disturbances, with a detrimental impact of poor sleep on women's psychological health and QoL.

KEYWORDS: endometriosis, fatigue, pelvic pain, psychological health, sleep disturbances.

INTRODUCTION

In women with endometriosis, pelvic pain has negative effects on psychological health, sexuality, intimate relationships, and quality of life (Agarwal et al., 2019; Barbara et al., 2017; Facchin et al., 2017, 2018; Gambadauro et al., 2019; Pluchino et al., 2016). This menstrual cycle-dependent, chronic, inflammatory, systemic disease affects approximately 8-10% of women of reproductive age and may lead to infertility (Acién and Velasco, 2013; Agarwal et al., 2019).

Fatigue is another important symptom of endometriosis. In a study by Surrey et al. (2019), fatigue-related issues were reported at baseline by 54%-74% of women with moderate to severe endometriosis-related pain. In a qualitative study by DiBenedetti et al. (2020), 22 pre-/perimenopausal women with moderate to severe endometriosis-related pain symptoms reported experiencing fatigue, with negative consequences on daily life, physical and social activities, mood and emotions, family and intimate relationships, work and school. In another study by Ramin-Wright et al. (2018), 51% of women with endometriosis (vs. 22% in the control condition) reported frequent fatigue, that was significantly associated with insomnia, depression, pain, and occupational stress. These findings highlight the importance of investigating fatigue and sleep disturbances in women with endometriosis.

In this regard, Leone Roberti Maggiore et al. (2017) found that 145 women with endometriosis of the posterior cul-de-sac, compared with 145 women seeking routine gynecologic consultation, were more likely to report bad sleep quality (65% vs. 15%), excessive daytime sleepiness (23% vs. 13%), and subthreshold or moderate clinical insomnia (29% and 17% vs. 24% and 5%, respectively). In the endometriosis group, women who reported bad sleep quality also showed worse health-related quality of life, and poor sleep was associated with the severity of dysmenorrhea and chronic pelvic pain. Arion et al. (2020) investigated the predictors of sleep quality in 275 women with surgically diagnosed endometriosis and found that worse sleep was associated with poorer quality of life, greater symptoms of depression, and presence of painful bladder syndrome. Endometriosis and pain symptoms were also associated with lower sleep quality

86   in a study of 257 women with the disease compared with 253 women without a history of

87   endometriosis (Nunes et al., 2014).

88   The findings provided by this small body of research are interesting, also considering that

89   sleep disturbances are associated with pain related to chronic diseases other than endometriosis

90   (Finan et al., 2013). However, fatigue and sleep disturbances in women with endometriosis (and

91   especially their associations with pelvic pain, psychological health, and quality of life) remain

92   underexplored.

93   The current study was conducted to provide further insights into this neglected topic. We

94   hypothesized that women with endometriosis, and especially those with moderate to severe pain

95   symptoms, would report greater fatigue and sleep disturbances (poor sleep quality, excessive

96   daytime sleepiness, and insomnia) compared with women without a history of endometriosis. We

97   also hypothesized that endometriosis patients with worse quality of sleep would report greater

98   fatigue, poorer psychological health, and lower quality of life than patients with better sleep quality.

99   **MATERIAL AND METHODS**

100   In this matched pair case-control study, women were recruited from July 2019 to March

101   2020 at a tertiary care endometriosis referral center. We included women aged 18-45 years who

102   were able to understand and speak Italian. Cases were women with a surgical diagnosis of

103   endometriosis in the previous 24 months or with a current clinical diagnosis of endometriosis (as

104   regards to the importance of enhanced use of clinical diagnostic techniques, see Agarwal et al.

105   2019). Controls were women without a previous clinical or surgical diagnosis of endometriosis

106   attending our outpatient clinic for periodical gynecological care, cervical cancer screening program

107   and contraception. In this group, endometriosis was ruled out based on gynecological history,

108   transvaginal ultrasonography, gynecological bimanual examination, and visual inspection of the

109   posterior vaginal fornix. Controls were matched to endometriosis patients for age and body mass

110   index (BMI). Exclusion criteria were: current pregnancy; having children aged < 2 years; night

shifts; diagnosed cardiovascular, respiratory, renal, hepatic, gastrointestinal, and/or psychiatric conditions, including substance abuse.

Sociodemographic and clinical information

Sociodemographic data were collected using a structured interview. Clinical information was retrieved from medical records or directly asked to patients. Women rated endometriosis-related pelvic pain severity (dysmenorrhea, dyspareunia, non-menstrual pelvic pain, and dyschezia) during the past 6 months on a 0-10 numerical rating scale (NRS; 0 = "no pain", 10 = "the worst imaginable pain"), and those who reported a score ≥ 6 for at least one pain symptom were categorized as women with painful endometriosis (vs. women without significant pain symptoms).

Fatigue

All participants were asked to report how often they experienced fatigue (referred to as a feeling of tiredness that could not be relieved by sleep and rest) during the past 6 months on a 5-point Likert scale (1 = "never"; 5 = "very often"). Following the work of Ramin-Wright et al. (2018), fatigue was also categorized as follows: frequent fatigue ("often", "very often"), occasional ("sometimes"), rare ("seldom", "never").

Sleep disturbances

The validated Italian versions of three self-report questionnaires—the Pittsburgh Sleep Quality Index [PSQI] (Buysse et al., 1989; Curcio ET AL., 2013), the Epworth Sleepiness Scale [ESS] (Johns, 1991; Vignatelli et al., 2003) and the Insomnia Severity Index [ISI] (Bastien et al., 2001; Morin, 1993)—were administered to all participants to assess sleep quality, daytime sleepiness, and insomnia, respectively.

The PSQI is a 19-item questionnaire for evaluating sleep quality over the previous month. Responses are rated on 0-3 Likert scales, with 3 indicating the worst condition, and the scores are organized in 7 components (C1: subjective sleep quality; C2: sleep latency; C3: sleep duration; C4: habitual sleep efficiency; C5: sleep disturbances; C6: use of sleep medications; C7: daytime

dysfunction), which can be summed to obtain a global score ranging from 0 to 21 (higher scores reflect worse sleep quality). A PSQI ≤ 5 indicates good sleep, while scores > 5 indicate poor sleep. The ESS consists of 8 items related to different activities and respondents are asked to rate on a 0-3 Likert scale their usual chances to fall asleep during these activities. A global score is calculated as the sum of the 8 items, with values ranging from 0 to 24 (the higher the score, the greater participants' sleep propensity in daily life). Scores between 11 and 24 represent excessive daytime sleepiness (EDS).

The ISI is a 7-item questionnaire that measures insomnia, whose severity is rated by participants on a 0-4 Likert scale (0 = "none"; 4 = "very severe"). The seven individual scores are added up to calculate a total score (values range from 0 to 28, with higher scores representing more severe insomnia). The total score is categorized as follows: 0-7 (no clinically significant insomnia), 8-14 (subthreshold insomnia), 15-21 (clinical insomnia [moderate severity]), 22-28 (clinical insomnia [severe]). In this study, we considered two categories: absence of clinical insomnia (scores between 0 and 14) and presence of clinical insomnia (scores between 15 and 28). In the current study, these three questionnaires had good internal consistency, with Cronbach's alphas ranging from 0.71 for the ESS, to 0.78 for the PSQI and 0.88 for the ISI.

Psychological health and quality of life

The validated Italian version of the Hospital Anxiety and Depression Scale [HADS] (Costantini et al., 1999; Zigmond and Snaith, 1983) was used to examine women's psychological health, focusing on symptoms of anxiety and depression. This 14-item questionnaire, in which responses are scored on a 0-3 scale, comprises two 7-item subscales for the assessment of anxiety (HADS-A) and depression (HADS-D), with scores ranging from 0 to 21, and a global score (HADS-Total, scores between 0 and 42). Higher scores indicate poorer psychological conditions.

Quality of life was measured using the Short Form-12 [SF-12] (Apolone et al., 2001; Gandek et al., 1998) which consists of 12 items assessing the impact of health on people's everyday life. Two

summary measures can be calculated—the physical (PCS-12) and the mental (MCS-12) component

summary scales—with higher scores indicating greater quality of life.

In this study, Cronbach's alpha was 0.76 for the HADS-A, 0.80 for the HADS-D, and 0.87

for the HADS-Total. As regards to the SF-12, Cronbach's alpha was 0.82 for the PCS and 0.84 for

the MCS.

Statistical analyses

Statistical analyses were conducted with SPSS (IBM) version 26. Continuous variables are

reported as mean ± standard deviation, and categorical variables as frequencies. Our analytic

strategy involved three steps. In the first step, descriptive statistics were obtained and the

distribution of continuous variables was examined considering skewness and kurtosis (values of

skewness and kurtosis ranging between -1 and +1 were considered acceptable) (Barbaranelli, 2003;

Marcoulides and Hershberger, 1997). Preliminary analyses (Pearson correlation, independent

samples *t-test*, and univariate analysis of variance, as appropriate) were conducted to examine the

relations between participant characteristics (age, employment status [employed/unemployed],

presence of children [yes/no], BMI, smoking habits), clinical information (form of endometriosis,

hormonal treatment, use of pain killers), and all the dependent variables. In the second step,

independent samples *t-tests* were performed to compare fatigue, quality of sleep (the PSQI total

score), daytime sleepiness, and insomnia severity in women with endometriosis vs. control

participants. Univariate and multivariate analyses of covariance (controlling for the effects of

hormonal treatment) were also performed to compare fatigue and sleep in the study groups,

including women with painful endometriosis and women without significant pain symptoms. Mann-

Whitney U test and Kruskal-Wallis H test were used to further compare quality of sleep

(considering the 7 PSQI components) between the study groups. Chi-squared tests were also

conducted to compare the frequency of fatigue, bad sleep, excessive daytime sleepiness, and clinical

insomnia between all study groups. Pearson or Spearman correlations were used to further examine

186 the association between pain symptoms (dysmenorrhea, dyspareunia, chronic pelvic pain, and

187 dyschezia) and all the dependent variables. In the third step, we compared fatigue, psychological

188 health and quality of life in endometriosis patients with good vs. bad sleep (considering the cut-off

189 of the PSQI) using univariate and multivariate analysis of variance.

190 Findings were considered statistically significant if P was < 0.05. Using the software

191 G*Power (Faul et al., 2007) we calculated that at least 210 participants were necessary to detect a

192 medium effect size ($d = 0.5$) at power 0.95 and $\alpha = 0.05$ when comparing the means of the

193 endometriosis group and the comparison group with independent samples *t-test*.

194 **Ethical approval**

195 Ethical approval was received by the local Ethics Committee (Comitato di Etica Milano

196 Area 2, approval no. 612_2019, approval date 18 June 2019), and all the participants signed a

197 consent form.

198 **RESULTS**

199 **Descriptive statistics and preliminary analyses**

200 Participants were 123 endometriosis patients and 123 women without a history of

201 endometriosis (N = 246). Women's age ranged from 21 to 45 (34.05 ± 6.37), most women were

202 employed (205 [83%]) and did not have children (182 [74%]). Overall, 121 women (49%) were

203 under hormonal treatment. Participant characteristics by study group are extensively presented in

204 Table 1. In the endometriosis group, 62 participants (50%) had ovarian endometrioma and 61 (50%)

205 had deep endometriosis. Fifty-four women (44%) had a surgical diagnosis of endometriosis with

206 histologic verification. Women with painful endometriosis numbered 64 (52%), whereas 59

207 participants (48%) did not have significant pain symptoms. The majority of endometriosis patients

208 (99 [80%]) were under hormonal treatment.

209 The preliminary analyses conducted to explore the relations between participant

210 characteristics, clinical information, and all the dependent variables, revealed that fatigue and sleep

211   did not significantly vary among endometriosis patients using estrogen-progestins vs. progestins vs.

212   no therapy (with *P* values ranging between 0.061 and 0.424). However, considering the whole

213   sample, women who were under hormonal therapy (in general) reported greater fatigue and sleep

214   disturbances than those who were not under therapy (with *Ps* ranging from 0.002 to 0.030), and for

215   this reason the effects of this variable were controlled in the subsequent analyses (see

216   Supplementary Table 1 for further details regarding use of hormonal therapy, fatigue, and sleep).

217   No other significant associations were detected at this stage.

Impact of endometriosis and pelvic pain on fatigue and sleep

219   Complete information regarding fatigue and sleep in all study groups are reported in Table

220   2. Women with endometriosis were more likely to experience frequent fatigue than controls (χ^2 (2)

221    $= 10.767$; $P = 0.005$). Independent samples *t*-tests confirmed that the endometriosis group reported

222   greater fatigue (*t* (244) $= -2.974$; $P = 0.003$), along with poorer quality of sleep (PSQI; *t* (244) $= -$

223   2.916; $P = 0.004$) and higher daytime sleepiness (ESS; *t* (244) $= -2.488$; $P = 0.013$) than the control

224   condition. These two groups did not significantly differ as regards to insomnia severity (ISI; *t* (244)

225    $= -1.787$; $P = 0.075$). However, these differences were no longer significant when we compared

226   fatigue and sleep between the two groups using univariate and multivariate analyses of covariance,

227   controlling for the effects of hormonal treatment.

228   When women with painful endometriosis were compared with endometriosis patients

229   without significant pelvic pain symptoms and control participants, controlling for the effects of

230   hormonal treatment, statistically significant group differences were found related to both fatigue (F

231   [2,242] $= 5.149$; $P = 0.006$; $\eta^2_p = 0.041$) and sleep (F [6,480] $= 4.262$; $P < 0.001$; Wilks $\Lambda = 0.901$;

232    $\eta^2_p = 0.051$). Specifically, the independent variable had an impact on all the sleep dimensions

233   (PSQI: F [2,242] $= 8.724$; $P < 0.001$; $\eta^2_p = 0.067$; ESS: F [2,242] $= 4.420$; $P = 0.013$; $\eta^2_p = 0.035$;

234   ISI: F [2,242] $= 7.152$; $P = 0.001$; $\eta^2_p = 0.056$). Pairwise comparisons revealed that women with

235   painful endometriosis reported poorer outcomes than the other two groups, with the exception of

insomnia severity (i.e., the P value related to the comparison between the painful endometriosis group and the comparison group was 0.245). No significant differences were found between women without significant pain symptoms and controls. When chi-squared tests were conducted to compare the three groups on sleep disturbances considering the cut-offs of each sleep scale, we found that the proportion of women who reported bad sleep quality (χ^2 (2) = 12.117; P = 0.002), excessive daytime sleepiness (χ^2 (2) = 9.028; P = 0.011), and clinical insomnia (χ^2 (2) = 8.209; P = 0.016) significantly differed by condition. The findings also revealed a significant association between condition and frequency of fatigue (χ^2 (4) = 18.159; P = 0.001).

Kruskal-Wallis H test was also used to compare quality of sleep between these three groups, focusing on the 7 components of the PSQI. These analyses showed that there were statistically significant group differences in quality of sleep for almost all the components (C1: H (2) = 12.892; P = 0.002; C2: H (2) = 9.274; P = 0.010; C3: H (2) = 7.208; P = 0.027; C4: H (2) = 6.372; P = 0.041; C5: H (2) = 16.545; P < 0.001; C7: H (2) = 16.678; P < 0.001), except for use of sleep medications (C6: H (2) = 1.239; P = 0.538). Post-hoc analyses revealed that women with painful endometriosis reported poorer outcomes than both women without significant pain symptoms and controls for the majority of the components (with Ps ranging from < 0.001 to 0.033), with the exception of C3 and C4.

We further examined the association between endometriosis-related pelvic pain, fatigue, and sleep using Pearson and Spearman correlations. Results of Pearson correlations indicated that there was a significant positive association between chronic pelvic pain and fatigue (r = 0.352; P < 0.001), quality of sleep (PSQI; r = 0.443; P < 0.001), daytime sleepiness (ESS; r = 0.249; P = 0.005), and insomnia severity (ISI; r = 0.364; P < 0.001). In addition, Spearman correlations revealed that dyschezia was associated with all the dependent variables (fatigue: r_s = 0.234; P = 0.009; PSQI: r_s = 0.403; P < 0.001; ESS: r_s = 0.178; P = 0.049; ISI: r_s = 0.316; P < 0.001).

Psychological health, quality of life, and quality of sleep in the endometriosis group

261   When we compared endometriosis patients with good vs. bad quality of sleep, we found

262   significant group differences related to fatigue (F [1,121] = 18.091; $P < 0.001$; $\eta^2_p = 0.130$), anxiety

263   and depression (F [2,120] = 9.791; $P < 0.001$; Wilks $\Lambda = 0.860$; $\eta^2_p = 0.140$), global psychological

264   health (F [1,121] = 18.900; $P < 0.001$; $\eta^2_p = 0.135$), and quality of life (F [2,120] = 18.972; $P <$

265   0.001; Wilks $\Lambda = 0.760$; $\eta^2_p = 0.240$). In all these analyses, women with bad sleep quality reported

266   significantly poorer outcomes than women with good sleep (see Table 3).

267   **DISCUSSION**

268   The primary aim of this study was to examine fatigue and sleep disturbances in women with

269   endometriosis compared with women without a history of endometriosis, also focusing on the

270   specific role played by pelvic pain symptoms. Our findings revealed that endometriosis (overall)

271   was associated with greater fatigue, poorer sleep quality, and higher daytime sleepiness, which is in

272   line with the evidence provided by the extant literature (Leone et al., 2017; Nunes et al., 2014;

273   Ramin-Wright et al., 2018). However, when we controlled for the effects of hormonal treatment, the

274   group differences were no longer significant.

275   The most important findings of our study are related to the association of pelvic pain with

276   fatigue and sleep disturbances. Compared with both endometriosis patients without significant pain

277   symptoms and controls (and controlling for the effects of hormonal therapy), women with

278   endometriosis-related pain showed worse outcomes on all the dependent variables. No differences

279   were found between endometriosis patients without significant pain symptoms and controls. These

280   findings mirror those of a previous case-control study by Facchin et al. (2015) in which women

281   with painful endometriosis reported worse psychological conditions (greater symptoms of anxiety

282   and depression) and poorer quality of life than endometriosis patients without pelvic pain and

283   controls, while no significant differences were found between endometriosis patients without pelvic

284   pain and control participants.

285   Our analyses also revealed that, in the painful endometriosis group, more than half of the

286   patients (56%) reported frequent fatigue (vs. 34% of women without significant pain symptoms in

287   this study and 45% of endometriosis patients in the study by Ramin-Wright et al. (2018). The

288   frequency of bad sleep quality in our study (67% of patients with pain symptoms) was similar to

289   that reported by Leone Roberti Maggiore et al. (2017) (65%). In addition, we found a significant

290   positive correlation between fatigue, sleep disturbances, and the severity of two types of

291   endometriosis-related pain symptoms: chronic pelvic pain and dyschezia.

292   Our final set of analyses provided further evidence regarding the association between poor

293   sleep quality and fatigue, as previously demonstrated by Ramin-Wright et al. (2018). Our findings

294   also confirmed that endometriosis patients reporting bad sleep have greater symptoms of anxiety

295   and depression, with worse physical and mental quality of life (Arion et al., 2020; Leone et al.,

296   2017). According to the values of $\eta^2{}_p$, the effect size for these analyses was medium-large, which

297   indicates that there is a strong association between sleep disturbances and poorer psychological

298   health and quality of life in women with endometriosis.

299   Overall, our results allowed for identifying a direct association between the presence of

300   moderate to severe pelvic pain symptoms (especially chronic pain and dyschezia), fatigue and sleep

301   disturbances, and corroborated the hypothesis of a vicious circle in which chronic pain, sleep

302   disorders, and psychological symptoms (especially anxiety and depression) intensify each other.

303   Because in our study the mere presence of endometriosis without significant pain symptoms did not

304   lead to poorer sleep and greater fatigue compared with the control group, our findings (including

305   those related to the association between bad sleep and impaired psychological health and quality of

306   life) should not be considered as endometriosis specific. In fact, the vicious circle described above

307   has been also identified in previous studies of people with other painful medical conditions (Cheatle

308   et al., 2016; Finan et al., 2013; Moldofsky, 2001).

309   **Limitations**

Our research presents several limitations. First, in this study—as in any case-control endometriosis study—the choice of the control group represents an important methodological issue. In our study, the control group was composed of women without a previous surgical or clinical diagnosis of endometriosis. However, we are not able to exclude the presence of undiagnosed endometriosis cases among controls, especially women with superficial peritoneal forms of the disease. Under-ascertainment is less likely to occur with deep endometriotic lesions and ovarian endometriomas (Vercellini et al., 2014). In addition, the unintentional inclusion of endometriosis cases in the control group would have led to underestimated (rather than overestimated) group differences. The absence of information regarding pelvic pain severity in control participants should also be considered a study limitation, because we could not investigate fatigue and sleep quality in non-endometriosis women with pain symptoms.

Second, although we controlled for the effects of hormonal therapy in our statistical analyses, this study did not clarify the effects of hormonal treatment on the quality of sleep of women with endometriosis. In this regard, we did not find any statistically significant difference in the quality of sleep of endometriosis patients in relation to the specific type of hormonal treatment (estrogen-progestins vs. progestins). Only a few studies with a very small sample size have tried to evaluate the effect of oral contraceptives use on sleep (Baker, 2001a, 2001b). In these studies, women under hormonal treatment showed a reduction in slow-wave sleep (SWS) compared to non-users in the luteal phase. Third, we did not examine the association between infertility and sleep disorders. There is evidence that stress, sleep dysregulation, and circadian misalignment may be related to infertility (Kloss et al., 2015). Moreover, the sleep measures considered in this study were self-reported and therefore not objective, as also underlined by Arion et al. (2020). In addition, we did not examine the presence of comorbidities, such as fibromyalgia, which is common among women with endometriosis (Shigesi et al., 2019).

Suggestions for future research and clinical practice

Future studies should explore the relation between medical treatment (hormonal therapy and surgical interventions), infertility and IVF, comorbidities, and sleep disorders in women with endometriosis, to identify predictors of sleep problems that are specific to this population. In this regard, our findings suggested that investigating the effects of hormonal therapy on fatigue and sleep quality would be very important, especially in women with severe, painful endometriosis, who are more likely to report fatigue and sleep disorders. Indeed, these associations should be conceptualized as complex (rather than linear) and multifactorial.

Sleep health should be assessed during psychological counselling with women affected by endometriosis. The presence of significant pelvic pain symptoms remains a major clinical problem, also due to its relationship with fatigue and sleep disturbances, which are associated with impaired psychological health and quality of life. In the context of multidisciplinary clinical practice with these patients, helping women find effective personalized strategies to reduce pelvic pain is essential, because the presence of symptoms has a tremendous negative impact on multiple life domains, including sleep.

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453

454   **Table 1.** Participants' characteristics by study group

Variable		Endometriosis group N = 123	Control group N = 123	*P* values
Age (years) (M ± SD)		34.11 ± 6.34	33.99 ± 6.42	0.881
Employment status (N, %)	Employed	105 (85)	100 (81)	0.392
	Unemployed	18 (15)	23 (19)	
Children (N, %)	Yes	29 (24)	35 (28)	0.383
	No	94 (76)	88 (72)	
BMI (Kg/m^2) (M ± SD)		21.57 ± 2.88	21.32 ± 2.74	0.486
Smoking habits (N, %)	Smoker	25 (20%)	25 (20%)	1.00
	Ex-smoker	11 (9%)	11 (9%)	
	Non-smoker	87 (71%)	87 (71%)	
Hormonal therapy (N, %)	Yes	99 (80%)	22 (18%)	<0.001
	No	24 (20%)	101 (82%)	
Type of therapy (N, %)	Oestroprogestins	61 (62%)	21 (95%)	<0.001
	Progestins	38 (38%)	1 (5%)*	
Type of endometriosis (N, %)	Ovarian endometrioma	62 (50%)		
	Deep endometriosis	61 (50%)		
Type of diagnosis (N, %)	Surgical	54 (44%)		
	Clinical	69 (56%)		
Age at diagnosis (M ± SD)		29.03 ± 5.51		
Use of pain killers (N, %)	Yes	55 (45%)		
	No	68 (65%)		
Pelvic pain (M ± SD)	Dysmenorrhea	2.77 ± 3.15		
	Dyspareunia	3.48 ± 2.88		
	Chronic pain	3.02 ± 2.66		
	Dyschezia	1.58 ± 2.34		

455   *Levonorgestrel-releasing intrauterine device

456 **Table 2.** Fatigue and sleep by study group and significant differences

Variable	Endometriosis group N = 123	Women with painful endometriosis N = 64	Women without significant pain symptoms N = 59	Control group N = 123	*P* values*	*P* values**
Fatigue (M ± SD)	3.19 ± 1.07	3.42 ± 1.03	2.93 ± 1.06	2.79 ± 1.03	0.003	0.006
Frequent fatigue (N, %)	56 (46)	36 (56)	20 (34)	32 (26)		
Occasional fatigue (N, %)	38 (31)	18 (28)	20 (34)	46 (37)	0.005	0.001
Rare fatigue (N, %)	29 (24)	10 (16)	19 (32)	45 (37)		
PSQI (M ± SD)	6.68 ± 3.59	7.75 ± 3.59	5.52 ± 3.23	5.45 ± 3.03	0.004	<0.001
(C1) Subjective sleep quality	1.16 ± 0.83	1.37 ± 0.74	0.93 ± 0.87	1.00 ± 0.79	0.112	0.002
(C2) Sleep latency	1.15 ± 0.95	1.36 ± 0.95	0.93 ± 0.92	0.97 ± 0.93	0.121	0.010
(C3) Sleep duration	0.99 ± 0.74	1.14 ± 0.81	0.83 ± 0.62	0.84 ± 0.64	0.103	0.027
(C4) Habitual sleep efficiency	0.71 ± 0.93	0.80 ± 1.03	0.63 ± 0.81	0.43 ± 0.70	0.014	0.041
(C5) Sleep disturbances	1.37 ± 0.53	1.52 ± 0.50	1.22 ± 0.53	1.19 ± 0.54	0.007	<0.001
(C6) Use of sleep medications	0.11 ± 0.51	0.16 ± 0.60	0.07 ± 0.41	0.12 ± 0.50	0.624	0.538
(C7) Daytime dysfunction	0.17 ± 0.86	1.41 ± 0.87	0.91 ± 0.77	0.89 ± 0.66	0.016	<0.001
Bad sleep (N, %)	66 (54)	43 (67)	23 (39)	54 (44)	0.126	0.002
Good sleep (N, %)	57 (46)	21 (33)	36 (61)	69 (56)		
ESS (M ± SD)	8.71 ± 4.20	9.62 ± 4.13	7.73 ± 4.08	7.38 ± 4.20	0.013	0.013
With EDS (N, %)	38 (31)	26 (41)	12 (20)	27 (22)	0.112	0.011
Without EDS (N, %)	85 (69)	38 (59)	47 (80)	96 (78)		
ISI (M ± SD)	8.12 ± 6.10	9.86 ± 5.96	6.24 ± 5.73	6.81 ± 5.36	0.075	0.001
With clinical insomnia (N, %)	19 (15)	15 (23)	4 (7)	14 (11)	0.350	0.016
Without clinical insomnia (N, %)	104 (85)	49 (77)	55 (93)	109 (89)		

457 *P* values related to comparisons between the endometriosis group and the control group

458 ***P* values related to comparisons between women with painful endometriosis, women without significant pain symptoms, and controls

459 PSQI (Pittsburgh Sleep Quality Index)

460 ESS (Epworth Sleepiness Scale)

461 EDS (Excessive Daytime Sleepiness)

462 ISI (Insomnia Severity Index)

Table 3. Fatigue, psychological health and quality of life in endometriosis patients with good vs.

bad quality of sleep

Variable		Good sleep N = 57	Bad sleep N = 66	*P* values
Fatigue (M ± SD)		2.77 ± 1.10	3.54 ± 0.91	< 0.001
	Frequent fatigue (N, %)	17 (30)	39 (59)	
	Occasional fatigue (N, %)	19 (33)	19 (29)	0.001
	Rare fatigue (N, %)	21 (37)	8 (12)	
HADS (M ± SD)	HADS-A	5.96 ± 3.51	8.83 ± 3.76	< 0.001
	HADS-D	5.02 ± 3.41	7.44 ± 3.93	< 0.001
	HADS-Total	10.98 ± 6.31	16.27 ± 7.07	< 0.001
SF-12 (M ± SD)	PCS	51.80 ± 7.13	45.10 ± 10.18	< 0.001
	MCS	44.60 ± 10.52	36.44 ± 10.14	< 0.001

HADS (Hospital Anxiety and Depression Scale)
SF-12 (Short Form-12)
PCS (Physical Component Summary)
MCS (Mental Component Summary)

Supplementary Table 1 Hormonal therapy, fatigue and sleep in the endometriosis group and the control group

Variable	Endometriosis group (N = 123)				Control group* (N = 123)	
	Hormonal treatment (overall) N = 99	Estrogen-progestins N = 61	Progestins N = 38	No hormonal treatment N = 24	Hormonal treatment (overall) N = 22	No hormonal treatment N = 101
Fatigue (M ± SD)	3.24 ± 1.07	3.16 ± 1.14	3.37 ± .94	2.96 ± 1.08	2.82 ± 1.20	2.78 ± .99
Frequent fatigue (N, %)	47 (47.5)	30 (49.2)	17 (44.7)	9 (37.5)	9 (40.9)	23 (22.8)
Occasional fatigue (N, %)	29 (29.3)	14 (22.9)	15 (39.5)	9 (37.5)	4 (18.2)	42 (41.6)
Rare fatigue (N, %)	23 (23.2)	17 (27.9)	6 (15.8)	6 (25)	9 (40.9)	36 (35.6)
PSQI (M ± SD)	6.98 ± 3.67	6.79 ± 3.43	7.29 ± 4.06	5.46 ± 2.98	5.60 ± 3.35	5.41 ± 2.98
(C1) Subjective sleep quality	1.20 ± .82	1.24 ± .83	1.13 ± .81	1.00 ± .88	1.04 ± .78	.99 ± .79
(C2) Sleep latency	1.22 ± .99	1.15 ± .93	1.34 ± 1.10	.87 ± .74	.91 ± .97	.98 ± .93
(C3) Sleep duration	1.03 ± .75	.93 ± .68	1.18 ± .83	.83 ± .70	.95 ± .78	.81 ± .61
(C4) Habitual sleep efficiency	.82 ± .97	.77 ± .99	.89 ± .95	.29 ± .55	.50 ± .74	.41 ± .69
(C5) Sleep disturbances	1.39 ± .53	1.38 ± .49	1.42 ± .60	1.29 ± .55	1.18 ± .59	1.20 ± .53
(C6) Use of sleep medications	.13 ± .56	.13 ± .56	.13 ± .58	.42 ± .20	.23 ± .68	.10 ± .46
(C7) Daytime dysfunction	1.18 ± .87	1.18 ± .83	1.18 ± .95	1.12 ± .80	.77 ± .53	.92 ± .69
Bad sleep (N, %)	56 (56.6)	34 (55.7)	22 (57.9)	10 (41.7)	10 (45.5)	44 (43.6)
Good sleep (N, %)	43 (43.4)	27 (44.3)	16 (42.1)	14 (58.3)	12 (54.5)	57 (56.4)
ESS (M ± SD)	8.84 ± 4.36	8.46 ± 4.03	9.45 ± 4.82	8.21 ± 3.50	7.27 ± 6.35	7.30 ± 4.20
With EDS (N, %)	33 (33.3)	20 (32.8)	13 (34.2)	5 (20.8)	5 (22.7)	22 (21.8)
Without EDS (N, %)	66 (66.7)	41 (67.2)	25 (65.8)	19 (79.2)	17 (77.3)	79 (78.2)
ISI (M ± SD)	8.75 ± 6.21	8.98 ± 6.14	8.37 ± 6.39	5.54 ± 4.94	7.78 ± 4.33	6.71 ± 5.15
With clinical insomnia (N, %)	17 (17.2)	9 (14.8)	8 (21.1)	2 (8.3)	3 (3.6)	11 (10.9)
Without clinical insomnia (N, %)	82 (82.8)	52 (85.2)	30 (78.9)	22 (91.7)	19 (86.4)	90 (89.1)

*In the control group, only 1 participant was using progestins (see Table 1). For this reason, we compared controls who were using hormonal therapy overall vs. those who were not using hormonal therapy.

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