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Increased Pressure Pain Sensitivity in Women With Chronic Pelvic Pain

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Abstract

OBJECTIVE—To determine if women with chronic pelvic pain and variable degrees of endometriosis demonstrate altered pain sensitivity relative to pain-free healthy controls, and whether such differences are related to the presence or severity of endometriosis or comorbid pain syndromes.

METHODS—Four patient subgroups (endometriosis with chronic pelvic pain (n=42), endometriosis with dysmenorrhea (n=15), pain-free endometriosis (n=35), and chronic pelvic pain without endometriosis (n=22)) were each compared to 30 healthy controls in this cross-sectional study. All patients completed validated questionnaires regarding pain symptoms and underwent screening for comorbid pain disorders. Pain sensitivity was assessed by applying discrete pressure stimuli to the thumbnail using a previously validated protocol.

RESULTS—While adjusting for age and education, pain thresholds were lower in all subgroups of women with pelvic pain, relative to healthy controls (all p-values <0.01). There was no difference in pain thresholds when comparing endometriosis patients without pelvic pain to healthy controls (mean difference 0.02 kg/m², 95% confidence interval -0.43, 0.47). The presence and severity of endometriosis and number of comorbid pain syndromes were not associated with a difference in pain thresholds.

CONCLUSION—Women with chronic pelvic pain demonstrate increased pain sensitivity at a nonpelvic site compared to healthy controls, which is independent of the presence or severity of endometriosis or comorbid pain syndromes. These findings support the notion that central pain amplification may play a role in the development of pelvic pain, and may explain why some women with pelvic pain do not respond to therapies aimed at eliminating endometriosis lesions.

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Introduction

Chronic pelvic pain affects 15-20% of reproductive-aged women, creating direct health-care costs of \$2.8 billion annually (1-3). Despite its high prevalence and negative effect, little is known about the pathophysiology underlying the development and persistence of chronic pelvic pain. As with many other chronic pain syndromes, the presence and severity of pelvic pathology, such as endometriosis, do not correlate with symptom burden (4-7). Standard medical and surgical therapies targeting endometriosis lesions are not consistently effective and pain frequently recurs even without visible disease at repeat laparoscopy (8-10). Against this background, endometriosis must be viewed as an important but insufficient risk factor for the development of pelvic pain. Thus, characterization of the underlying mechanisms that lead to chronic pain is necessary to develop targeted treatment strategies for women who are not responsive to traditional therapies for endometriosis and other causes of pelvic pain.

Using various quantitative sensory testing and neuroimaging techniques, central amplification of pain processing has been shown to be an underlying mechanism of persistent pain in many chronic pain syndromes (11-13). Similarly, there is early evidence that central pain amplification may also play an important role in the pathophysiology of chronic pelvic pain. For example, prior studies show heightened pain sensitivity to experimental thermal and mechanical stimuli in women with endometriosis-associated pelvic pain relative to pain-free controls (14-16). However, these smaller studies were not designed to determine whether the presence or severity of endometriosis or comorbid pain syndromes is associated with differences in pain processing. This is important because comorbid pain syndromes, which are highly prevalent in women with pelvic pain, are known to be independently associated with alterations in nociceptive processing and could provide an alternate explanation for observed differences in pain sensitivity in these women. Thus, the aim of this study was to determine if women with pelvic pain and variable degrees of endometriosis demonstrate alterations in pain sensitivity, and whether such differences are related to the presence or severity of endometriosis or comorbid pain syndromes.

Materials and Methods

Between June 2006 and April 2010, women with endometriosis or chronic pelvic pain, and healthy controls were recruited to participate in this observational study. All participants were premenopausal women aged 18-52 years who had not undergone prior hysterectomy or bilateral oophorectomy. Women with endometriosis or chronic pelvic pain were recruited from a tertiary-care endometriosis and pelvic pain referral center, as well as through advertisement to the local community. Pain-free healthy controls were recruited through local advertisements. All participants received \$40 for participating in the study. Approval for this study was obtained from the University of Michigan Institutional Review Board and all participants provided informed, signed consent. A subgroup of these subjects also participated in a previously published study of regional cerebral gray matter differences in women with chronic pelvic pain (17).

Potential participants were screened by phone interview. Those with endometriosis or, chronic pelvic pain were invited to participate if they underwent pelvic surgery within 5 years and reported a history of either surgically confirmed endometriosis or chronic pelvic pain. Controls were pain-free women without symptoms of dysmenorrhea or pelvic pain, and these women had no known history of endometriosis or any other chronic pain syndrome. All potential participants were screened with the M.I.N.I International Neuropsychiatric Interview (18). Those who met criteria for any psychotic disorder were excluded from participating, and potential controls who met criteria for a mood or anxiety

disorder were also excluded. Given the high prevalence of depression and anxiety in persons with chronic pain, endometriosis and chronic pelvic pain participants with comorbid mood or anxiety disorder were included in this study.

Additional exclusion criteria for all participants included severe physical impairment, significant comorbid medical illness that limited physical function, and suicide attempt or substance abuse within 2 years of the study. Women who were pregnant, lactating, or menopausal (defined as no menses for greater than one year unrelated to exogenous hormonal suppression) were also excluded from participation.

For the purpose of these analyses, each participant with endometriosis or chronic pelvic pain was then classified into one of the following four categories based on review of the standardized pelvic pain and menstrual history questionnaire (see below), but blinded to the remainder of the study results: “pain-free” endometriosis ($\oplus\text{Endo}\oslash\text{Pain}$), endometriosis with dysmenorrhea ($\oplus\text{Endo}\oplus\text{dysmenorrhea}$), endometriosis with CPP ($\oplus\text{Endo}\oplus\text{CPP}$), or CPP without endometriosis ($\oslash\text{Endo}\oplus\text{CPP}$). The following criteria were used to define each of these categories: chronic pelvic pain was defined as moderate or severe pelvic pain that was ≥ 4 on a 0-10 numeric rating scale for a duration greater than 6 months that occurred for at least 14 days of each month, not just limited to the time of menstrual bleeding. Dysmenorrhea was defined as 5-13 days of moderate to severe pelvic pain each month, which generally occurred around the time of menses. Dysmenorrhea was identified as its own distinct category because of recent evidence that otherwise healthy women with dysmenorrhea display evidence of central pain amplification (19). Unless otherwise specified, “pelvic pain” refers to women with either chronic pelvic pain or dysmenorrhea. Women with “pain-free” endometriosis were defined as those who reported ≤ 4 days of pelvic pain per month. A summary of case definitions for participant subgroups is illustrated in Table 1. The goal was to recruit controls and each subgroup of endometriosis, chronic pelvic pain, or endometriosis and pelvic pain subgroups in a 1:1 ratio.

All participants completed standardized case report forms to assess their demographics, medical and surgical history, medication use, and menstrual pattern. Using The Complex Medical Symptom Inventory, a standardized, diagnostic tool that uses published criteria for the diagnosis of various chronic pain disorders (20), all participants were formally evaluated for all of the following chronic pain syndromes known to be associated with central nervous system (CNS) pain amplification: fibromyalgia, chronic fatigue syndrome, interstitial cystitis, irritable bowel syndrome, chronic low back pain, chronic migraine headaches, temporomandibular disorder, and vulvodynia. As previously described, potential controls were excluded if they met criteria for any pain syndrome, whereas participants with endometriosis or pelvic pain and comorbid pain syndromes were included in this study.

Participants with endometriosis or pelvic pain completed additional questionnaires to assess the severity, pattern, and characteristics of their pelvic pain and prior treatments for pain. Measurements included numeric ratings (0-10) of pelvic pain severity and unpleasantness during menses and the average number of days with moderate-to-severe pelvic pain each month (0-30 days). Participants provided written release for review of their most recent operative reports. Operative reports were reviewed by one of the authors with significant expertise in the surgical evaluation of endometriosis and other gynecologic disease. This author was blinded to the study results. Most participants received their surgical diagnosis at another medical institution. The operative findings (presence, severity, and location of endometriosis and pelvic adhesive disease) and surgical procedure performed were documented using a standard case report form. When identified, endometriosis was assigned a stage according to the revised American Fertility Society endometriosis scoring system

(21). Surgical biopsy and pathology was documented when available, but not required for participation since pathologic confirmation was not routinely performed in all participants.

Quantitative sensory testing was conducted on all participants using the multiple random staircase method previously described by our group (22, 23). An apparatus that delivers discrete pressure stimuli was used to determine pressure pain sensitivity at the non-dominant thumbnail. Application of calibrated weights to a hydraulic piston produced controlled, repeatable pressure stimuli using water-filled tubing to a second piston with an attached 1 cm² rubber probe. This system was used to present a series of stimuli to the thumbnail in a predictable, “ascending” fashion, beginning at 0.25 kg/cm² and increasing 0.25 - 0.5 kg/cm² increments up to pain tolerance or to a maximum of 10 kg/cm². Perceived pain intensity of each pressure was recorded using the Gracely Box Scale (GBS), a 0-20 numerical descriptor scale used to measure evoked pain intensity (24).

After the ascending series, 36 stimuli were delivered to the thumb at 20-second intervals, using the multiple random staircase method. This method is response-dependent; i.e. it determines the stimulus intensity (kg/cm²) needed to elicit a specific response. This “adaptive” method automatically adjusts the stimulus intensity applied, using each subject’s subjective pain rating and a computer program that randomly switches between 3 different staircase titrations to calculate the pressure intensities required to elicit “faint” pain (0.5 on the GBS), “mild” pain (7.5 on the GBS), and “slightly intense” pain (13.5 on the GBS). The starting points for each staircase are determined from the ascending series. Previous studies have demonstrated that this type of random pressure testing is not influenced by the level of depression or anxiety (“distress”) of an individual (25).

In order to minimize the influence of menstrual cycle variability on study results, all study visits were performed between days 2-10 of the menstrual cycle in women who were not using hormonal contraceptives. All patients were asked to refrain from using opioid analgesia within 48 hours of the study visit. Quantitative sensory testing was performed by a research coordinator blinded to the participant subgroup and the remainder of the survey data.

Sample size determination was based on the primary outcome of differences in pressure pain sensitivity in endometriosis-pelvic pain subgroups relative to healthy controls. Based on a previous study by our group in patients with fibromyalgia (26), we estimated a 1.5 kg/m² difference in pressure to elicit mild pain (standard deviation 2.0) between healthy controls and pelvic pain subgroups. Using a 5-group analysis of variance test, the sample size was calculated to be 20 participants for each category to achieve 90% power and $\alpha=0.05$. Analysis was performed using STATA 12.0 (StataCorp LP, College Station, TX). All continuous variables were evaluated for normality by using the Shapiro-Wilk statistic. Univariate analysis of data included means, medians, ranges, and standard deviations. Comparison of continuous variables between groups was conducted using ANOVA or the Kruskal-Wallis test, as appropriate. Categorical data were compared using Chi-squared test or Fisher’s exact test, as appropriate. Linear regression was used to calculate the mean difference and 95% confidence interval (CI) of pressure required to elicit faint, mild, and slightly intense pain in patient subgroups compared with controls. Based on bivariate analyses, we evaluated age (years), education (<12 years, 12 years, >12 years), and current smoking status as candidate confounders of patient subgroup and pressure pain threshold. Covariates were retained in the final regression model if they changed the effect estimate for the main outcome by 10% when excluded from the model. Age and education status had a modest effect on the main estimate of the main outcome, and were therefore included the final model as covariates.

Results

A total 144 women completed the study between June 1, 2006 and April 31, 2010, including of 30 healthy controls and 114 women with chronic pelvic pain or endometriosis. Among participants with CPP or endometriosis, 35 were classified as endometriosis without pelvic pain ($\oplus\text{Endo}\oslash\text{Pain}$), 15 were endometriosis with dysmenorrhea ($\oplus\text{Endo}\oplus\text{dysmenorrhea}$), 42 were endometriosis with chronic pelvic pain ($\oplus\text{Endo}\oplus\text{CPP}$), and 22 were chronic pelvic pain without endometriosis ($\oslash\text{Endo}\oplus\text{CPP}$).

Characteristics of study participants are summarized in Table 2. There were no significant differences in race, body mass index, number of prior pregnancies, or current use of hormonal contraceptives. On average, $\oplus\text{Endo}\oslash\text{Pain}$ participants were older than the other participant subgroups, and participants with chronic pelvic pain ($\oplus\text{Endo}\oplus\text{CPP}$ and $\oslash\text{Endo}\oplus\text{CPP}$) reported fewer years of education than the non-pelvic pain subgroups. There was no significant difference in the total number of prior abdominal surgeries or the number of surgeries performed for pelvic pain or endometriosis in any of the pelvic pain, endometriosis subgroups. Among women with endometriosis, advanced staged disease (e.g. revised American Fertility Stage III and IV disease) was common and ovarian endometriomas were identified in approximately one third of participants. However, all endometriosis participants had additional peritoneal disease except for three participants (all in the $\oplus\text{Endo}\oslash\text{Pain}$ group) who had ovarian endometriomas without any other pelvic pathology. Most participants with endometriosis had at least partial surgical treatment (ablation or excision) of visible lesions, and only 15.8% had no surgical therapy at all. Among women currently using some form of hormonal contraceptive, all were using either a combined estrogen-progestin method or a progestin-only method. In general, most participants with chronic pelvic pain had clinically severe pelvic pain on most days of the month. Those with dysmenorrhea had a similar intensity of menstrual pain, but experienced pelvic pain for an average of 9 out of 30 days per month.

Significantly lower pressure to the thumbnail was required to induce faint, mild, and slightly intense pain in all pelvic pain subgroups relative to pain-free controls (Table 3). Decreased pressure pain thresholds were identified among all subgroups with pelvic pain, including both chronic pelvic pain and those with dysmenorrhea only. However, there was no difference in pressure pain sensitivity when comparing women with endometriosis to pelvic pain patients without endometriosis (Table 3). Furthermore, among women with chronic pelvic pain, there was no difference in pressure pain sensitivity relative to the presence or severity of endometriosis at the time of the most recent surgery ($P=0.92$, Figure 1), although the power to detect small differences in this study is limited.

The presence of comorbid pain syndromes in participants with endometriosis or chronic pelvic pain was common and identified in approximately 60% of these women (Table 4). Chronic headaches (migraine or tension headaches) and irritable bowel syndrome were the most frequent comorbid pain conditions. Although the presence of one or more comorbid pain conditions was common in the $\oplus\text{Endo}\oslash\text{Pain}$ group, women with pelvic pain (chronic pelvic pain or dysmenorrhea) were more likely to have a comorbid pain condition than endometriosis patients without pain ($p=0.002$). Among all participants with pelvic pain, the presence and number of comorbid pain syndromes was not significantly associated with pressure pain sensitivity ($P=0.77$, Figure 2). Again, the power to detect small differences in this study is limited.

Discussion

Consistent with our hypothesis, women with pelvic pain demonstrate significantly increased pressure pain sensitivity at a non-pelvic site compared to healthy controls. These findings were identified in all subgroups of pelvic pain participants, and did not appear to be related to the presence or severity of endometriosis. While comorbid pain syndromes were commonly identified in participants with pelvic pain, pressure pain thresholds were also unrelated to the presence or number of other pain syndromes. These findings suggest a generalized upregulation of nociceptive processing in patients with pelvic pain, which is not sufficiently explained by endometriosis and is not simply a marker for having another comorbid pain condition.

The strengths of this study include precise phenotyping of pelvic pain subgroups with various combinations of pain severity and pelvic pathology, the prospective collection of detailed data regarding clinical pain, and the systematic assessment of comorbid pain syndromes using standardized criteria. Disease misclassification was limited by surgical confirmation of endometriosis. Furthermore, our sensory testing paradigm, which uses a stimulus delivered to a remote location from the pelvis, has been shown to be minimally influenced by levels of anxiety or depression (25). Moreover, this sensory testing methodology has been shown to be a valid surrogate measure of central pain amplification. For example, previous trials have shown that sensitivity to experimental pressure applied to the thumbnail, a neutral area not associated with clinical symptoms, correlates with clinical pain (23, 27, 28), is a marker of widespread pain throughout the body (29), is associated with augmented brain activity (11, 12) and elevated levels of excitatory neurotransmitters in key pain processing regions of the brain (30).

Our results are consistent with increasing evidence that individuals with various pain syndromes, such as fibromyalgia and vulvodynia have a fundamental problem with pain amplification (11, 12). Relative to pain-free controls, these individuals report increased pain sensitivity and demonstrate increased neuronal activity in regions of the brain associated with pain perception when exposed to stimuli that healthy individuals find innocuous. Given that amplification of CNS pain processing is a common finding across these pain syndromes, these conditions have been referred to as “central pain syndromes.” While the mechanisms contributing to pain likely occur at various levels of the nervous system, the two mechanisms most described in the literature are loss of descending analgesia and central sensitization.

Hyperalgesia to experimental noxious stimuli has been reported in a few earlier studies of women with endometriosis (14-16). However, interpretation and generalizability of the findings are limited due to the small sample size and sparse characterization of the patient population. Unlike these earlier reports, the present study is able to disentangle hyperalgesia from endometriosis, pelvic pain, and comorbid pain disorders by including four patient subgroups with various degrees of pain, pelvic pathology, and comorbid pain disorders.

There are several important limitations of this study. Most importantly, the cross-sectional design of this study precludes our ability to determine whether differences in experimental pain sensitivity are a cause or consequence of the pain experience. Also, the pain testing methods we used cannot identify the specific mechanism of CNS pain amplification or the specific interaction between endometriosis and the peripheral and central nervous system. A minor limitation is possible misclassification bias, as not all healthy controls were surgically explored to exclude the diagnosis of endometriosis. Given a 2-9% estimated prevalence of asymptomatic endometriosis, this may alter the diagnostic category for <3 healthy controls.

In this study, pain-free women with endometriosis did not demonstrate hyperalgesia at the thumbnail and exhibited pressure pain sensitivity similar to healthy controls. This finding may help explain why stage of disease and pain severity does not correlate in women with endometriosis. Perhaps the critical variable defining clinical symptoms is an individual's neural processing, rather than susceptibility to peripheral inflammation from ectopic endometrial implants. Our group has recently reported that women with pain-free endometriosis show an increase in gray matter volume in the periaqueductal gray, a key structure in the antinociceptive pain regulatory system, which was not found in women with chronic pelvic pain (17). These findings suggest that despite having significant pelvic pathology that could act as a source of peripheral nociceptive input, this unique subset of endometriosis patients do not display evidence of central pain amplification. Given these findings, it is tempting to hypothesize that pain-free endometriosis patients experience little if any pain due to adaptive changes in the brain.

In summary, the current study adds to the growing body of literature that suggests that some women with chronic pelvic pain demonstrate evidence of amplification central pain processing. These findings are present in women with no other identifiable pain disorder, and are unrelated to the presence or severity of endometriosis. If chronic pelvic pain is caused in part by central rather than only peripheral factors, this has substantial implications for the evaluation and treatment of women with chronic pelvic pain. For example, it may be that some women will benefit from medical and cognitive therapies aimed at central pain amplification and could avoid repetitive surgeries directed at suppressing or eliminating pelvic structures. Almost certainly, endometriosis and chronic pelvic pain represent highly heterogeneous populations with subgroups that have variable degrees of peripheral and central contributions to pain. Identification of these subgroups may represent a critical step in the development of a personalized, mechanism-based approach that can better guide treatment-decision making for individual patients with chronic pelvic pain.

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Figure 1.

Box- and-whisker plot of pressure pain sensitivity in all participants with pelvic pain according the Revised American Fertility Society endometriosis scoring system. The lower and upper ends of the box indicate the first to third quartile, respectively; the horizontal line indicates the median. Vertical lines (whiskers) indicate the minimum to maximum. Values are adjusted for age and education status, $P=0.92$.

Figure 2.

Box-and-whisker plot of pressure pain sensitivity in all participants with pelvic pain according to the number of additional chronic pain syndromes (CPS). The lower and upper ends of the box indicate the first to third quartile, respectively; the horizontal line indicates the median. Vertical lines (whiskers) indicate the minimum to maximum. Values are adjusted for age and education status, $P=0.53$.

Table 1

Definition of participant subgroups.

	Subgroup abbreviation	Number of days pelvic pain per month (0-30)	Pain intensity with menses (0-10 NRS)	Comorbid pain syndrome*
Healthy controls	HCS	0-4	0-3	None (excluded)
"Pain-free" endometriosis	⊕Endo/∅Pain	0-4	0-10	possible
Endometriosis with dysmenorrhea	⊕Endo⊕dysmenorrhea	5-13	4-10	possible
Endometriosis with chronic pelvic pain	⊕Endo⊕CPP	14-30	4-10	possible
CPP without endometriosis	∅Endo⊕CPP	14-30	4-10	possible

NRS, numeric rating scale

* Comorbid pain syndrome: fibromyalgia, chronic fatigue syndrome, interstitial cystitis, irritable bowel syndrome, chronic low back pain, chronic migraine headaches, temporomandibular disorder, vulvodynia.

Table 2

Characteristics of study participants.

	Healthy controls (n=30)	⊕Endo⊕Pain (n=35)	⊕Endo⊕dysmenorrhea (n=15)	⊕Endo⊕CPP (n=42)	⊕Endo⊕CPP (n=22)	p-value
Age (years)	30.8 ± 8.6	35.5 ± 8.0	31.1 ± 7.8	27.9 ± 7.2	30.8 ± 7.3	<0.001
Race						
White	25 (83.3)	28 (80.0)	12 (80.0)	38 (92.7)	16 (76.2)	0.44
Black	3 (10.0)	1 (2.9)	1 (6.7)	0 (0)	2 (9.5)	
Other	2 (6.7)	6 (17.1)	2 (13.3)	3 (7.3)	3 (14.3)	
Education (years)						
Fewer than 12	0	0	0	2 (5.0)	3 (15.0)	0.04
12 (High school graduate)	0	1 (2.9)	0	3 (7.5)	2 (10.0)	
More than 12	30 (100)	34 (97.1)	15 (100)	35 (87.5)	15 (75.0)	
Current smoker	0	1 (2.9%)	1 (6.7%)	9 (22.5%)	8 (42.1%)	<0.001
Body mass index (kg/m ²)	23.7 (18.8 – 42.8)	25.2 (18.1 – 40.4)	24.8 (20.9 – 42.9)	26.3 (16.6 – 34.6)	24.2 (18.1 – 39.8)	0.88
Gravidity	0 (0 – 4)	0 (0 – 7)	0 (0 – 4)	0 (0 – 3)	1 (0 – 5)	0.25
Parity	0 (0 – 4)	0 (0 – 4)	0 (0 – 3)	0 (0 – 3)	1 (0 – 3)	0.32
Current use of hormonal contraceptive	13 (43.3%)	12 (34.3%)	7 (46.7%)	26 (65.0%)	9 (47.4%)	0.11
Endometriosis stage (rAFS)						
I		7 (20.0)	8 (57.1)	20 (48.7)		
II	n/a	5 (14.3)	0	9 (22.0)	n/a	0.001*
III		13 (37.1)	0	3 (7.3)		
IV		10 (28.6)	6 (42.9)	9 (22.0)		
Number prior surgeries for pelvic pain or endometriosis	0	1 (1 – 5)	1 (1 – 7)	1 (1 – 8)	1 (1 – 3)	0.69
Days of moderate or severe pelvic pain per month (0-30 days)	0	1.7 ± 1.7	8.7 ± 2.8	23.2 ± 6.2	21.5 ± 7.0	<0.001
Menstrual pain						
Severity (0-10)	1.4 ± 1.3	4.6 ± 3.5	6.1 ± 2.5	7.4 ± 2.2	8.5 ± 1.3	<0.001
Unpleasantness (0-10)	1.5 ± 1.5	4.2 ± 3.3	6.0 ± 3.0	7.4 ± 2.3	7.9 ± 2.1	<0.001

rAFS, revised American Fertility Society endometriosis scoring system.

Data are presented as mean ± standard deviation, median (range), or N (%).

* Analysis excludes Healthy Controls and ⊕Endo⊕CPP subgroup.

Table 3

Mean Pressure Pain Thresholds (kg/cm²) at the Nondominant Thumbnail in Patient Subgroups Compared With Various Comparison Groups

Pressure to Elicit Faint Pain		Pressure to Elicit Mild Pain		Pressure to Elicit Slightly Intense Pain	
Pressure	Difference Adjusted Difference*	P	Pressure	Difference Adjusted Difference*	P
Endometriosis and/or pelvic pain subgroups versus healthy controls					
Healthy controls	1.36 ± 1.03	Reference	3.31 ± 2.06	Reference	
⊕Endo/⊘Pain	1.39 ± 1.23	0.89	2.98 ± 1.35	-0.33 (-1.02, 0.35)	0.34
		0.94		-0.42 (-1.13, 0.28)*	0.24
⊕Endo⊕dysmenorrhea	0.92 ± 0.73	0.11	1.94 ± 1.16	-1.30 (-2.17, -0.43)	0.004
		0.12		-1.30 (-2.18, -0.43)*	0.004
⊕Endo⊕CPP	0.67 ± 0.51	0.001	2.23 ± 1.06	-1.08 (-1.73, -0.42)	0.001
		0.002		-1.12 (-1.80, -0.44)*	0.001
⊘Endo⊕CPP	0.79 ± 0.55	0.02	2.26 ± 0.94	-1.05 (-1.82, -0.28)	0.008
		0.04		-1.21 (-2.05, -0.38)*	0.005
Pelvic pain versus pain-free endometriosis[†]					
Pain-free	1.39 ± 1.23	Reference	2.98 ± 1.35	Reference	
With pelvic pain	0.75 ± 0.56	<0.001	2.20 ± 1.03	-0.78 (-1.24, -0.32)	0.001
		0.003		-0.63 (-1.12, -0.14)*	0.012
Endometriosis versus nonendometriosis[‡]					
No endometriosis	0.79 ± 0.55	Reference	2.26 ± 0.94	Reference	
With endometriosis	0.99 ± 0.93	0.35	2.48 ± 1.24	0.22 (-0.34, 0.78)	0.43
		0.45		0.33 (-0.25, 0.91)*	0.26

⊕Endo/⊘Pain, "pain-free" endometriosis; ⊕Endo⊕Dysmenorrhea, endometriosis with dysmenorrhea; ⊕Endo⊕CPP, endometriosis with chronic pelvic pain; ⊘Endo⊕CPP, chronic pelvic pain without endometriosis.

Data are mean ± standard deviation or mean difference (95 % Confidence Interval) unless otherwise specified.

* Adjusted for age and education status.

[†] Patients with pelvic pain (⊕Endo⊕dysmenorrhea, ⊕Endo⊕CPP, and ⊘Endo/⊘Pain) compared with pain-free endometriosis (⊕Endo/⊘Pain).

[‡] Patients with endometriosis (⊕Endo/⊘Pain, ⊕Endo⊕dysmenorrhea, and ⊕Endo⊕CPP), compared with chronic pelvic pain without endometriosis (⊘Endo⊕CPP).

Table 4
Comorbid Chronic Pain Syndromes in Participants With Endometriosis or Chronic Pelvic Pain

	⊕Endo/⊕Pain (n=35)	⊕Endo/⊕Dysmenorrhea (n=15)*	⊕Endo/⊕CPP (n=42)*	⊕Endo/⊕CPP (n=22)*	P
Fibromyalgia	0 (0)	1 (7.7)	2 (5.0)	3 (16.7)	0.10
Chronic fatigue syndrome	1 (2.9)	1 (7.7)	4 (10.0)	6 (28.6)	0.03
Irritable bowel syndrome	4 (11.4)	3 (23.1)	10 (25.0)	4 (19.1)	0.50
Migraine headaches	5 (14.7)	6 (46.2)	17 (42.5)	10 (50.0)	0.02
Recurrent tension headaches	8 (23.5)	7 (53.9)	15 (37.5)	9 (45.0)	0.19
Temporomandibular joint disorder	1 (2.9)	4 (30.8)	3 (7.7)	3 (15.8)	0.03
Interstitial cystitis	0	0	6 (15.4)	3 (16.7)	0.03
Vulvodynia	0	0	4 (10.0)	4 (19.1)	0.04
1 or more chronic pain syndromes	14 (40.0)	9 (60.0)	31 (75.6)	15 (71.4)	0.01

⊕Endo/⊕Pain, “pain-free” endometriosis; ⊕Endo/⊕Dysmenorrhea, endometriosis with dysmenorrhea; ⊕Endo/⊕CPP, endometriosis with chronic pelvic pain; ⊕Endo/⊕CPP, chronic pelvic pain without endometriosis.

Data are n (%) unless otherwise specified.

* Denominators vary as a result of missing data