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Central Sensitization Inventory in endometriosis

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Corresponding Author:	Paul Yong University of British Columbia Vancouver, CANADA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of British Columbia
Corresponding Author's Secondary Institution:	
First Author:	Natasha L Orr, MSc
First Author Secondary Information:	
Order of Authors:	Natasha L Orr, MSc
	Kate J Wahl, MSc
	Michelle Lisonek, BSc
	Angela Joannou, BSc
	Heather Noga, MA
	Arianne Albert, PhD
	Mohamed A Bedaiwy, MD, PhD
	Christina Williams, MD
	Catherine Allaire, MDCM
	Paul J Yong, MD, PhD
Additional Information:	
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Abstract

A key clinical problem is identifying the endometriosis patient whose pain is complicated by central nervous system sensitization, where conventional gynecologic treatment (e.g. hormonal therapy or surgery) may not completely alleviate the pain. The Central Sensitization Inventory (CSI) is a questionnaire previously validated in the chronic pain population. The objective of this study was an exploratory proof-of-concept to identify a CSI cut-off in the endometriosis population to discriminate between individuals with significant central contributors (identified by central sensitivity syndromes (CSS)) to their pain compared to those without. We analyzed a prospective data registry at a tertiary referral center for endometriosis, and included subjects aged 18-50 years with endometriosis who were newly or re-referred to the center in 2018. The study sample consisted of 335 subjects with a mean age of 36.0±7.0 years. An increasing number of CSS was significantly correlated with dysmenorrhea, deep dyspareunia, dyschezia, and chronic pelvic pain scores (p's<.001) and with the CSI score (0-100) (r=.731, p<.001). ROC analysis indicated that a CSI cut-off of 40 had sensitivity 78% (95% CI: 72.7% - 84.6%) and specificity 80% (95% CI: 70.3% - 84.5%) for identifying an endometriosis patient with ≥ 3 CSS. In the group with CSI≥40, 18% retrospectively self-reported pain non-responsive to hormonal therapy and 40% self-reported daily pain, compared to 6% and 20% in the CSI<40 group (p=.003 and .002, respectively). In conclusion, a CSI ≥ 40 may be a practical tool to help identify endometriosis patients with pain contributors related to central nervous system sensitization.

Title Page

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ii. **Authors**: Ms. Natasha L. ORR, MSc[1-2]; Ms. Kate J. WAHL, MSc[1-2]; Ms. Michelle LISONEK, BSc [2]; Ms. Angela JOANNOU, BSc[2]; Mrs. Heather NOGA, MA[3]; Dr. Arianne ALBERT, PhD[3]; Dr. Mohamed A. BEDAIWY, MD, PhD[1-3]; Dr. Christina WILLIAMS, MD[1-2]; Dr. Catherine ALLAIRE, MDCM[1-3]; Dr. Paul J. YONG, MD, PhD[1-3].

iii. **Affiliations**: [1]Department of Obstetrics and Gynecology, University of British Columbia; [2]BC Women's Center for Pelvic Pain and Endometriosis; [3]Women's Health Research Institute, Vancouver, Canada.

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v. **Corresponding author**: Dr. Paul Yong, BC Women's Center for Pelvic Pain and Endometriosis, F2 – 4500 Oak Street, Vancouver, British Columbia, Canada V6H 3N1, Work: 604-875-2534, Fax: 604-875-2569, Email: Paul.Yong@vch.ca

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Introduction

Endometriosis affects 10% of females and is characterized by ectopic endometrial-like tissue and pelvic pain [19]. Anatomic disease burden (Stage) is only marginally corelated with symptoms, but other peripheral modulators include nociceptive, inflammatory, and/or local neuropathic mechanisms related to disease-specific factors such as local invasion and neurogenesis [24,34]. However, pain is not always relieved after treating peripheral factors via conventional gynecologic therapy. For example, 18-27% of endometriosis patients reported combined hormonal contraceptives to be ineffective [59], while surgical excision/ablation of endometriosis lesions is associated with a 20% non-response rate [1]. Similarly, pain can recur even in patients undergoing hysterectomy [13,35]. Central changes may be the explanation for non-response or pain recurrence after conventional gynecologic management of endometriosis, identified by the co-existence of central sensitivity syndromes and other pelvic pain-related comorbidities (CSS) related to underlying central sensitization [3,12,24,45,57].

Central sensitization is characterized by excitability of the central nociceptive system resulting in hypersensitivity to sensory inputs [7,57]. Several lines of evidence support central sensitization in some individuals with endometriosis, ranging from quantitative sensory testing (QST) and MRI studies [4,5,7,20]. Central sensitization may account for the overlapping CSS that can co-exist in a patient with endometriosis, which can contribute to pain in addition to peripheral factors [15,23,58]. It should also be emphasized that central and peripheral contributors to pain

have been proposed to occur along a continuum [15,23,58], and can even occur simultaneously in the same patient [39], rather than being mutually exclusive. Thus any given patient with endometriosis may have a multifactorial pathophysiology with a mix of peripheral and central pain generators.

This leads to a key clinical problem in the practical identification of the patient with endometriosis whose pain has a significant central component with associated CSS, and who may require other treatments in addition to conventional endometriosis medical and surgical therapies. The Central Sensitization Inventory (CSI) has been validated to differentiate between centrally sensitized and non-sensitized patients in the chronic pain literature [33,36], being higher in pain populations compared to controls [2,30,52], with excellent internal consistency, good test-retest reliability, and high construct validity [11,30,33,36,37]. In chronic pain populations, a cut-off of ≥40 on the CSI identified patients with CSS compared to controls [36].

We hypothesize that the CSI can also be applied to the endometriosis population to identify patients with evidence of central sensitization, and therefore, the objective of this exploratory proof-of-concept study is to identify a CSI cut-off in the endometriosis population to identify individuals with CSS and thus significant central contribution to their pain. The first aim was to assess the interrelatedness of CSS in endometriosis patients, in order to provide evidence that these CSS are related to an underlying etiology (central sensitization) [36]. The second aim was to determine whether CSS are associated with endometriosis-associated pain scores to demonstrate their clinical significance, and whether CSS are associated with CSI scores to support the CSI as a tool to assess for CSS. Then, the third aim was to establish a clinically

relevant CSI cut-off for the endometriosis population using a receiver operating characteristic (ROC) analysis, in order to identify those with 3 or more CSS (i.e. endometriosis patients with CSS contributors to their pain). The fourth aim was to assess the convergent validity of the determined CSI cut-off by using selected questions from the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect)[53].

Materials and Methods

Participants

We analyzed cross-sectional baseline data from a prospective patient registry, the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC, ClinicalTrials.gov #NCT02911090) [62], at a tertiary referral center for pelvic pain and endometriosis. These baseline data include patient reported questionnaires and clinician reported data from the index consultation visit. Patient reported questionnaires are: 1) The Endometriosis Phenome and Biobanking Harmonisation (EPHect) clinical questionnaire (see https://endometriosisfoundation.org/ephect/#2); 2) In-house questionnaires including pain scores (11-point numeric rating scale); 3) Diagnostic criteria for irritable bowel syndrome and painful bladder syndrome; 4) Standardized psychological questionnaires. Clinician reported data are: 1) Chart review, e.g. for endometriosis surgical history (whether surgery was previous performed, and if so, whether there was a visual and/or histopathological diagnosis of endometriosis); 2) Physical exam and point of care ultrasound findings: this includes abdominal wall pain via the Carnett test and pelvic floor myalgia via palpation for levator ani tenderness; 3) Clinical impression, diagnoses, and treatment plan based on the patient questionnaires and clinician reported data. Variables in the EPPIC registry have been described in detail previously [62], and the specific variables of interest in this study are defined below under Measures. The majority of the baseline variables are mandatory to

complete as they are part of clinical care. Incomplete appearing data relates to the specifics of the question and may not relate to the participants (i.e. severity of pain question is only completed by people who said they experience pain on the previous question).

The CSI and the EPHect questionnaire of the World Endometriosis Research Foundation (WERF) [53] were incorporated into the registry in January 2018. The first 163 subjects were included in our pilot study on using the CSI to characterize deep dyspareunia (i.e. pelvic pain provoked by deep penetration during sexual activity) [40]. In this study, we divided our endometriosis sample into people with high deep dyspareunia (5-10 score) and bladder and/or pelvic floor tenderness (myofascial pelvic pain syndrome); high deep dyspareunia and no bladder and/or pelvic floor tenderness; and no/low deep dyspareunia (0-4 score). We found that people with high deep dyspareunia and bladder and/or pelvic floor tenderness had the highest CSI score, compared to both the high deep dyspareunia and no bladder and/or pelvic floor tenderness group and the no/low deep dyspareunia group (51.3±16.9 vs. 39.4±17.2 vs. 30.9±15.4). These findings suggested that the group with high severity of deep dyspareunia and myofascial pelvic pain syndrome may have a central component to their pain.

The present study cohort was assembled from the population within the registry meeting the following criteria. Inclusion criteria: a) age 18-50 years; b) endometriosis based on a previous surgical diagnosis of endometriosis (visual only or visual and histopathological confirmed, typically concurrent with treatment by ablation or excision), or current endometrioma on ultrasound, or current deep infiltrating nodule on palpation or ultrasound; c) new or re-referral to the center between January 1, 2018 and December 31, 2018; and d) who prospectively

consented to inclusion in the data registry. Exclusion criteria: a) post-menopausal; b) never sexually active so that we could evaluate dyspareunia as an outcome; and c) missing pelvic examination or the CSI (Figure 1). The study was approved by the University of British Columbia's Children's and Women's Research Ethics Board.

Measures

Part A of the CSI was collected from the EPPIC registry and included 25 patient-response questions, each rated from 0-4 (never, rarely, sometimes, often, always) for a total possible score of 100. The questions assess downstream symptoms associated with central sensitization [38] including feeling pain all over the body, headaches, muscle tension, and stress.

The following 10 CSS were also collected from the EPPIC registry: 1) fibromyalgia (self-report); 2) chronic fatigue syndrome (self-report); 3) migraines (self-report); 4) irritable bowel syndrome (IBS) diagnosed using the Rome III criteria [17,32]; 5) painful bladder syndrome (PBS) diagnosed using criteria from the American Urological Association [21] or the International Continence Society [54]; 6) abdominal wall pain (positive Carnett test) typically due to myofascial trigger points [50,62]; 7) myofascial pelvic pain syndrome diagnosed by digital palpation on pelvic exam for tenderness of the pelvic floor (levator ani) and/or the anterior vaginal wall (bladder base) [61]; 8) moderate depressive symptoms measured on the Patient Health Questionnaire (PHQ-9; cut-off $\geq$10) [31]; 9) moderate anxiety symptoms measured on the Generalized Anxiety Disorder (GAD-7; cut-off $\geq$10) [48]; 10) catastrophizing measured on the Pain Catastrophizing Scale (PCS; 75th centile cut-off $\geq$30) [51]. Factors 1-5 are regarded as central sensitivity syndromes [63], while factors 6-10 are other pelvic pain-related

comorbidities diagnosed on physical examination or validated questionnaires that are also thought to be related to underlying central sensitization [3,60,61,62] and which we have found to be important for pelvic pain severity at baseline and after 1 year of follow-up [3,60]. These 10 factors are conceptualized in terms of provoked vs. non-provoked and regional vs. non-regional vs. psychometric in Table 1.

The EPPIC registry includes demographic and clinical variables, as well as questions about different types of pelvic pain: dysmenorrhea, deep dyspareunia, dyschezia, chronic pelvic pain and back pain reported on an 11-point numeric rating scale (0-10; 0=no pain and 10=worst pain imaginable). The registry also includes the pain section of the EPHect Clinical Minimum questionnaire, which was developed to standardize research data collection between international groups and facilitate detailed description of endometriosis-associated pain [53]. The pain section includes 14 questions on dysmenorrhea, 12 questions on dyspareunia, and 14 questions on pelvic/lower abdominal pain (http://endometriosisfoundation.org/WERF-EPHect-Clinical-Questionnaire-Minimum-2014v1.pdf) [53].

Analysis approach

For the first aim, we examined the correlations between the CSS in order to support a common etiology such as central sensitization. To do so, the interrelatedness of the 10 CSS was assessed using the chi-square based correlation, phi (φ) [26,49].

For the second aim, we assessed the clinical implications of the CSS by testing for correlations between the number of CSS (0 to 10 conditions), with severities of different pelvic pain types

(rated 0-10), using Spearman's rank correlation. The William's T test was used to statistically compare the correlations for the different pelvic pain types [16]. In addition, we determined whether the CSI could be a proxy for the number of CSS, by correlating the raw CSI scores (0-100) and the number of CSS using Spearman's rank correlation.

After establishing the above, for the third aim we established a clinically relevant cut-off of the CSI using ROC analysis, which can be used by a gynecologist or other clinician to identify an endometriosis patient with evidence of central sensitization (i.e. multiple CSS). Specifically, ROC analysis was carried out between the CSI and thresholds for number of CSS (1 or more, 2 or more, or 3 or more CSS). The area under the ROC curve (AUC) was used to measure the ability of the CSI to discriminate, for example, endometriosis patients with 3 or more CSS and endometriosis patients with 0-2 CSS (higher AUC=higher accuracy). Sensitivity and specificity were determined at different CSI cut-off points on the curve [64], and we chose a CSI cut-off point that maximized sensitivity and specificity (requiring a minimum of 75%) [36]. The positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were also calculated [44].

For the fourth aim, the convergent validity of the determined CSI cut-off was studied, by comparing it to selected questions from section C of the EPHect questionnaire. Of particular interest were the EPHect questions on younger age at onset of pain, daily pain, and pain non-responsive to hormonal therapy, which are expected to be characteristics of pain related to central sensitization (rather than peripheral factors related to the endometriosis lesions themselves). Significant associations ($p<.05$) were identified on bivariate analysis: t-test or

Mann-Whitney test for non-normality (continuous variables) or Chi-square/Fisher's test (categorical variables).

Statistics and preliminary results

Means are shown ± one standard deviation. Significance was $p<.05$. IBM SPSS Statistics 24 used for the analysis and missing variables were excluded. The R statistics package cocor web interface (http://comparingcorrelations.org/) was used to compare the correlation coefficients. Using data from our pilot study (n = 163) on the CSI and deep dyspareunia [40], we found that the CSI score was significantly higher among women with myofascial pelvic pain syndrome (47.9 ± 18.4 vs 35.4 ± 16.7, $p<.001$).

Results

Study sample

This study included 335 participants with endometriosis (Figure 1) with a mean age of 36±7.0 years. Sample demographics included: 37.3% (125/335) parous, 67.2% (225/335) partnered, and 69% (231/335) Caucasian. Other sample characteristics are shown in Table 1. About half (52.8%) had a previous surgical and histological diagnosis of endometriosis (177/335), 29.6% had a previous surgical diagnosis without histology (99/335), and the remaining 17.6% did not have previous surgery but had a deep infiltrating nodule or ovarian endometrioma cyst diagnosed at the initial visit at the center (59/335). For prior therapy, 15% (51/335) reported never trying hormones (for either pain or contraception), and only 4% (15/335) reported no prior hormones or surgery.

The mean CSI score in the sample was 41.5±18.9 (range=0-88). For the CSI in this sample, Cronbach's alpha was = 0.93, suggesting excellent internal consistency.

We investigated 10 CSS from the registry (in order of prevalence) (Table 1): IBS (57.0%), PBS (52.5%), depression (42.1%), myofascial pelvic pain syndrome (41.2%), pain catastrophizing (32.8%), migraines (31.6%), abdominal wall pain (25.1%), anxiety (22.4%), fibromyalgia (5.7%), and chronic fatigue syndrome (2.7%). Thirty (9%) subjects had no CSS, while 305 (91%) people had one or more CSS, 244 (73%) people had two or more CSS, and 193 (58%) people had three or more CSS. See Figure 2 for the distribution of the number of CSS per patient.

Interrelationship between central sensitivity syndromes and other pelvic pain-related comorbidities

The interrelationship between the 10 CSS was examined by phi (φ) correlations (Table 2). Depression, anxiety, and pain catastrophizing correlated moderately with each other, with the strongest correlation being between depression and anxiety (φ=.485, p<.001). Myofascial pelvic pain syndrome, abdominal wall pain, IBS, and PBS were all significantly correlated with one another, although to a milder degree than the psychological factors. Fibromyalgia and chronic fatigue syndrome were only significantly correlated with each other and with migraines, likely due to their low prevalence in the sample. With the exception of fibromyalgia and chronic fatigue syndrome, each condition was significantly related to a minimum of 5 other conditions.

Number of central sensitivity syndromes and other pelvic pain-related diagnoses is correlated with pain scores and with the CSI

As shown in Table 3 and Figure 3, there was a significant correlation between an increasing number of CSS and increasing pain scores: a mild correlation with dysmenorrhea (r=.204, p<.001), and moderate correlations with deep dyspareunia (r=.424, p<.001), dyschezia (r=.455, p<.001), chronic pelvic pain (r=.428, p<.001), and back pain (r=.413, p<.001). Interestingly, dysmenorrhea had a significantly smaller correlation coefficient compared to deep dyspareunia (t=-3.55, df=332, p=.0004), dyschezia (t=-4.31, df=332, p<.001), chronic pelvic pain (t=-3.46, df=332, p=.0006), and back pain (t=-3.33, df=332, p=.001) (Table 3). There were no significant differences in the magnitude of the correlation coefficients between deep dyspareunia, dyschezia, chronic pelvic pain, and back pain (Table 3).

In addition, an increasing number of CSS was also significantly and strongly correlated with an increasing score on the CSI (0-100) (r=.731, p<.001), as shown in Figure 4. When broken down by conceptualization of CSS (Table 1), we observed the following correlations with CSI: Non-regional CSS (r = 0.41), Regional CSS (r = 0.49), Psychometric CSS (r = 0.64), Non-provoked CSS (r = 0.71), Provoked CSS (r = 0.49), Provoked functional CSS (r = 0.44), Provoked non-functional CSS (r = 0.31) (all p <.001).

Establishing a ROC for CSI

To identify a clinically significant cut-off of the CSI for this endometriosis sample, a ROC analysis was performed with the number of CSS. We explored the following thresholds for the number of CSS: a) ≥ 1 or more CSS (vs 0 CSS); b) ≥ 2 or more CSS (vs. 0-1 CSS); and c) ≥ 3 or more CSS (vs. 0-2 CSS). The ROC curve for 1 or more, 2 or more, and 3 or more CSS is shown

in Supplementary Figure 1 (a, b, and c, respectively). We focused on the threshold of ≥ 3 CSS (Table 4), as this patient sample is more likely to have underlying central sensitization. Results for ≥ 1 or ≥ 2 thresholds are shown in Supplementary Tables 1 and 2, respectively.

For a threshold of ≥ 3 CSS, the AUC and standard error for the CSI was .858±.020. Based on the ROC curve (Table 4), a CSI cut-off of ≥ 40 was found to have a sensitivity of 78% (95% CI: 72.7% - 84.6%) and specificity or 80% (95% CI: 70.3% - 84.5%) for identifying an endometriosis patient with ≥ 3 CSS. The PPV was 83.2% (95% CI: 78.2% - 87.2%), the NPV was 73.5% (95% CI: 67.5% - 78.8%), the PLR was 3.6 (95% CI: 2.6 – 5.0), and the NLR was .27 (95% CI: .20 - .35).

Convergent validity of the CSI cut-off

In this sample, 45% (151/335) of participants had a low (< 40) CSI score and 55% (184/335) had a high (≥ 40) CSI score. Demographic variables by group (CSI ≥ 40 vs CSI <40) are shown in Supplementary Table 3. A CSI ≥ 40 was significantly associated with more severe dysmenorrhea, deep dyspareunia, dyschezia, chronic pelvic pain, and back pain scores (Table 5), and when the pain scores were dichotomized (< 5 vs. ≥ 5), a CSI ≥ 40 had odds ratios ranging from 2.28 to 4.81 (Table 5).

To explore the convergent validity of the determined CSI cut-off of 40, we studied the association between the CSI ≥ 40 and select questions from the EPHect questionnaire (Table 5). In the dysmenorrhea section of EPHect, the group with high CSI scores (≥40) were significantly younger (16±6 years) when they started experiencing period pain, compared to the low CSI

(<40) group (18±8 years, p=.005). The correlation between CSI and duration of pain (calculated by subtracting age when they started experiencing period pain from the age when they completed the baseline questionnaire) was explored, but no significant relationship was found (data not shown). Additionally, the high CSI group (≥40) experienced more severe pelvic pain during their last period (p<.001), more severe pelvic pain during their period when it was at its worst in the last 12 months (p<.001), and more severe pelvic pain during their period at its worst ever in their life (p=.001). In the dyspareunia section, the high CSI group (≥40) experienced more pelvic pain during intercourse or in the 24 hours following vaginal sexual intercourse and felt more pain deep inside the vagina, compared to the low CSI (<40) group (both p's<.001). In the pelvic pain section, more severe pelvic pain at its worst in the last 3 months and during lifetime was found in the high CSI (≥40) group, compared to the low CSI (<40) group (p<.001 and p=.005, respectively). There was a higher proportion of the patients with high CSI (≥40) who, in the last 3 months and ever in their life, took hormones but did not experience alleviation of pelvic pain compared to the low CSI (<40) group (18.5% vs. 6.3%, p=.003 and 25.0% vs. 12.7%, p=.008). It should be noted that these questions were with respect to pelvic pain in general, rather than just pelvic pain with periods (dysmenorrhea). Additionally, a greater proportion of the high CSI (≥40) group experienced daily pain in the last 3 months, compared to the low CSI (<40) group (40.3% vs 20.0%, p<.001). The complete WERF EPHect pain section C questionnaire associations are shown in Supplementary Table 4 with corrections for multiple comparisons.

Discussion

The objective of this exploratory proof-of-concept study was to evaluate the CSI as a practical clinical tool to identify endometriosis patients whose pain has a central component with central

sensitivity syndromes and pelvic pain-related comorbidities (CSS), compared to other endometriosis patients with pain primarily related to peripheral disease-specific factors.

The number of CSS was significantly correlated with pelvic pain severity scores. Interestingly, the number of CSS had a smaller correlation with dysmenorrhea (r = 0.20), compared to deep dyspareunia, dyschezia, chronic pelvic pain, and back pain (r = 0.41-0.46). Dysmenorrhea (menstrual cramps) is considered the cardinal symptom of endometriosis [19,42] and may be more likely due to direct effects of the endometriosis lesions or of the uterus itself, and thus may have less a component of central sensitization. Alternatively, almost all subjects in the sample had dysmenorrhea ≥ 5/10, and this reduction in variance may account for the lower correlation coefficient. However, there remained a small correlation between dysmenorrhea and the number CSS, which may be in line with previous studies (mostly of primary dysmenorrhea, unrelated to endometriosis) noting some degree of central sensitization using QST (e.g., pain pressure thresholds) and functional MRI [22,41,46,55]. In addition, the number of CSS was highly correlated with the CSI score (r = 0.731). Similar observations have been shown in the chronic pain literature where the CSI correlated with number of CSS [36,37,43].

We performed an AUC ROC analysis and found that a CSI cut-off of ≥ 40 identified endometriosis patients with ≥ 3 CSS with sensitivity of 78% and specificity 80%. This indicates that 78% of the ≥ 3 CSS group were correctly identified by a CSI ≥ 40, while 80% of the 0-2 group were correctly identified by a CSI < 40. Interestingly, in the chronic pain population, a CSI cut-off of ≥ 40 was also found to have similar sensitivity (81%) and specificity (75%) at identifying an individual with one or more CSS [36]. A key difference is that this previous study

compared a chronic pain population to normal controls; however, in our current study, the comparison group was endometriosis patients with pain symptoms, but with 0-2 CSS, where pain may be more likely directly due to the peripheral endometriosis lesions themselves.

The EPHect questionnaire provided detailed description of dysmenorrhea, dyspareunia, and general pelvic/lower abdominal pain. Supporting the convergent validity of the chosen CSI cut-off, the CSI $\geq$ 40 was significantly associated with more severe pain and also had an earlier onset of pain, were more likely to experience daily pain, and more often had pain non-responsive to hormonal therapy. An earlier pain onset may be a risk factor for future development of central sensitization [9,12,25,27,63]. Development of a chronic pain syndrome related to central sensitization would also be more likely to account for daily pain, compared to pain primarily due to endometriosis lesions which tends to be cyclical with the menstrual cycle. Furthermore, once central sensitization has developed, a patient may be less likely to experience complete pain resolution with hormonal therapy that targets the endometriosis lesions but not central pain [10,56,58,59].

Given the rates of non-response after conventional gynecologic management of endometriosis [1,13,35], an important clinical problem in the management of endometriosis is identifying those with a central component to their pain, as opposed to pain primarily due to peripheral factors. Patients in this cohort came from a tertiary referral center where a comprehensive pain assessment was performed. However, this type of assessment may not be widely available for community gynecologists, and thus the CSI may be a triage tool to identify centrally sensitized patients with endometriosis. In patients with CSI $\geq$ 40, we hypothesize that repeated

conventional gynecologic therapy (hormonal or surgical) may not be effective enough by themselves, and a multidisciplinary care program addressing central pain should be considered such as pain education, pelvic floor physiotherapy, counselling/psychotherapy, as well as pharmaceutical or interventional treatments for chronic pain [3]. While such a multidisciplinary approach may be important with CSI ≥ 40, this does not discount that conventional therapy may play a partial but important role. For example, hormonal suppression may still be required for suppression of cyclical exacerbations in pain. There is also some evidence that surgical therapy for endometriosis may reduce markers of central sensitization [14,18], by removing the original peripheral nociceptive source. Future research is needed to clarify how best to manage patients with endometriosis and central sensitization, with unanswered questions including the timing of interventions (e.g. multidisciplinary care before or after surgery) and whether there might even be scenarios where central sensitization has become autonomous from the periphery [57] and where treatment should be focused on multidisciplinary chronic pain management. Consideration should also be given to referring patients with high CSI to a tertiary referral center to address these questions (Figure 5). However, more research is needed on the role of multidisciplinary tertiary centers in treating pain when endometriosis is complicated by central sensitization, preferably with suitable control arms. The CSI may also serve as a tool for clinicians to help counsel patients with endometriosis of the multifactorial nature of their pain.

Strengths of this study include the use of a prospective registry, the EPHect questionnaire for detailed pain characterization, standardized criteria for IBS and PBS, the incorporation of physical examination findings, and validated questionnaires for psychological variables. Another strength is that participants had a rigorous diagnosis of endometriosis (history of

surgically-confirmed endometriosis or a current ovarian endometrioma or deep infiltrating nodule on ultrasound or physical exam). For limitations, there is a need to externally validate these findings in the community setting where the CSI would be important in the triaging of endometriosis patients. In addition, while we found a CSI ≥ 40 to be associated with a history of non-response to previous hormonal therapy, the EPHect questionnaire does not contain a question about non-response to previous surgical therapy. The self-reported questions ask participants to recall previous pain scores which introduce recall bias, specifically for the dysmenorrhea scores of people who do not have regular periods (i.e. if the person only has a period every 3 months, their "last period" dysmenorrhea score may be recalled from 3 months ago, compared to a person who has a period each month). It should be noted that QST or brain MRI, as objective measures of central nervous system changes [5,6,28,29,47], were not performed in this study due in part to the challenge of performing these tests in a large sample (n > 300). We included subjects with different methods of endometriosis diagnosis, who were not all prospectively taken to surgery, and thus who may have variable anatomic loads of disease. Another limitation of this study is that we are unable to tease apart to what degree the endometriosis-associated pain scores are related to each type of CSS. Our conceptual model is that CSS are related to a common etiology of central sensitization, however we acknowledge that there may be alternative explanations such as myofascial pain arising from biomechanical changes. Lastly, this paper did not explore causal pathways but only correlations and thus the results may be interpreted in either direction (e.g., people with high CSI have higher pain, or people who have higher pain scores report higher CSI scores).

In future research, we plan to determine whether the baseline CSI prospectively predicts poorer treatment response to conventional hormonal or surgical therapy, with adequate sensitivity and specificity, in people with endometriosis from our registry. The CSI has previously been found to predict post-operative outcomes in patients who underwent spinal fusion [8]. Ultimately, the CSI could be combined with other baseline features on history and examination, in order to create a predictive tool for clinicians to counsel endometriosis patients about the signs of central sensitization and their implications for response to conventional hormonal suppression/surgery alone.

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Figure Legends

Figure 1. Study population.

Figure 2. Distribution of the number of central sensitivity syndromes and other pelvic pain-related comorbidities. These include: fibromyalgia; chronic fatigue; migraines; irritable bowel syndrome; painful bladder syndrome; abdominal wall pain (positive Carnett test) typically due to myofascial trigger points; myofascial pelvic pain diagnosed by digital palpation on pelvic exam for tenderness of the pelvic floor (levator ani) and/or the anterior vaginal wall (bladder base); moderate depression (PHQ-9 $\geq$ 10); moderate anxiety (GAD-7 $\geq$ 10); pain catastrophizing (Pain Catastrophizing Scale $\geq 75^{th}$ centile cut-off $\geq$ 30).

Figure 3. Association between endometriosis-associated pain scores with the number of central sensitivity syndromes and other pelvic pain-related comorbidities. Spearman correlation coefficients: a) dysmenorrhea (r=.204, p<.001); b) deep dyspareunia (r=.424, p<.001); c) dyschezia (r=.455, p<.001); d) chronic pelvic pain (r=.428, p<.001); and e) back pain (r=.413, p<.001).

Figure 4. Association between the CSI and the number of central sensitivity syndromes and other pelvic pain-related comorbidities. Spearman's correlation r=.731, p<.001.

Figure 5. CSI as a tool to triage patients.

Summary

A Central Sensitization Inventory cut-off of 40 had good sensitivity and specificity for identifying ≥3 central sensitivity syndromes and other pelvic pain-related comorbidities in endometriosis.

Figure 1

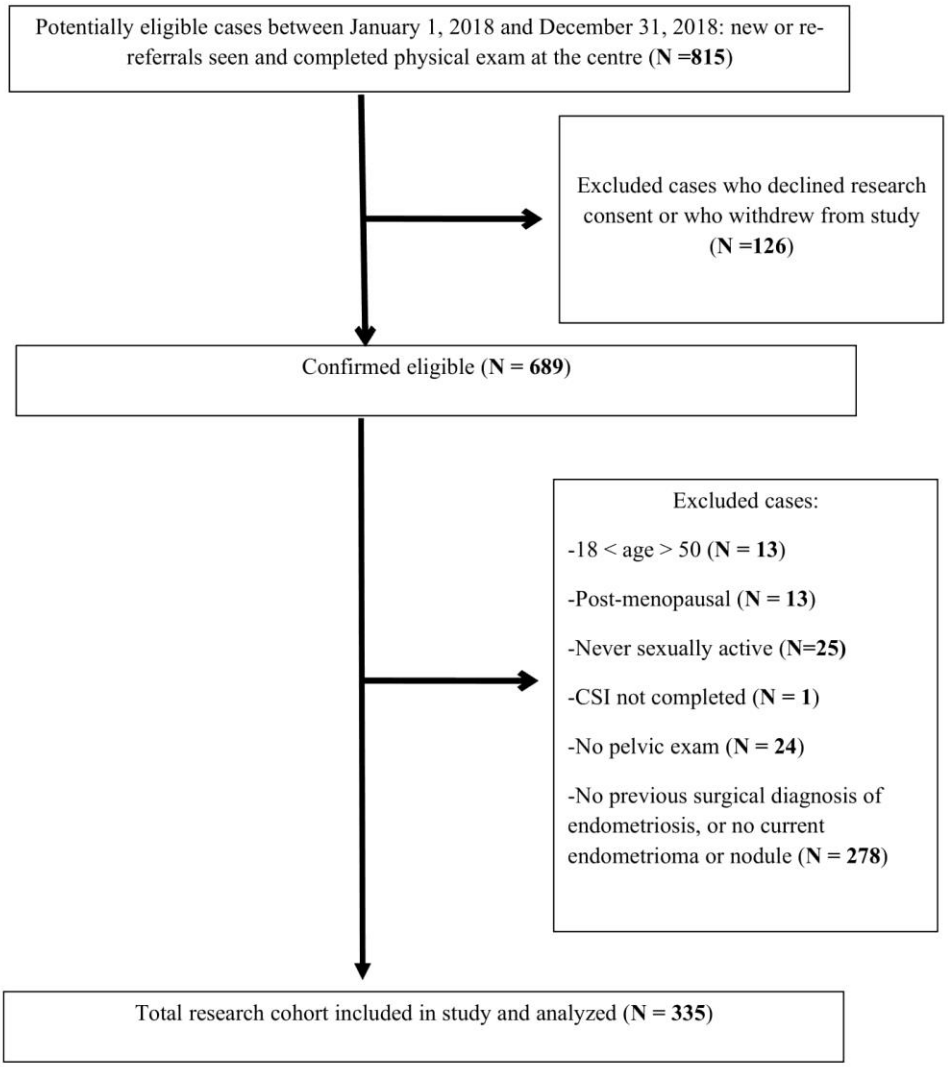
Potentially eligible cases between January 1, 2018 and December 31, 2018: new or re-referrals seen and completed physical exam at the centre (N =815)
Excluded cases who declined research consent or who withdrew from study (N =126)
Confirmed eligible (N = 689)
Excluded cases:
-18 < age > 50 (N = 13)
-Post-menopausal (N = 13)
-Never sexually active (N=25)
-CSI not completed (N = 1)
-No pelvic exam (N = 24)
-No previous surgical diagnosis of endometriosis, or no current endometrioma or nodule (N = 278)
Total research cohort included in study and analyzed (N = 335)

Figure 2

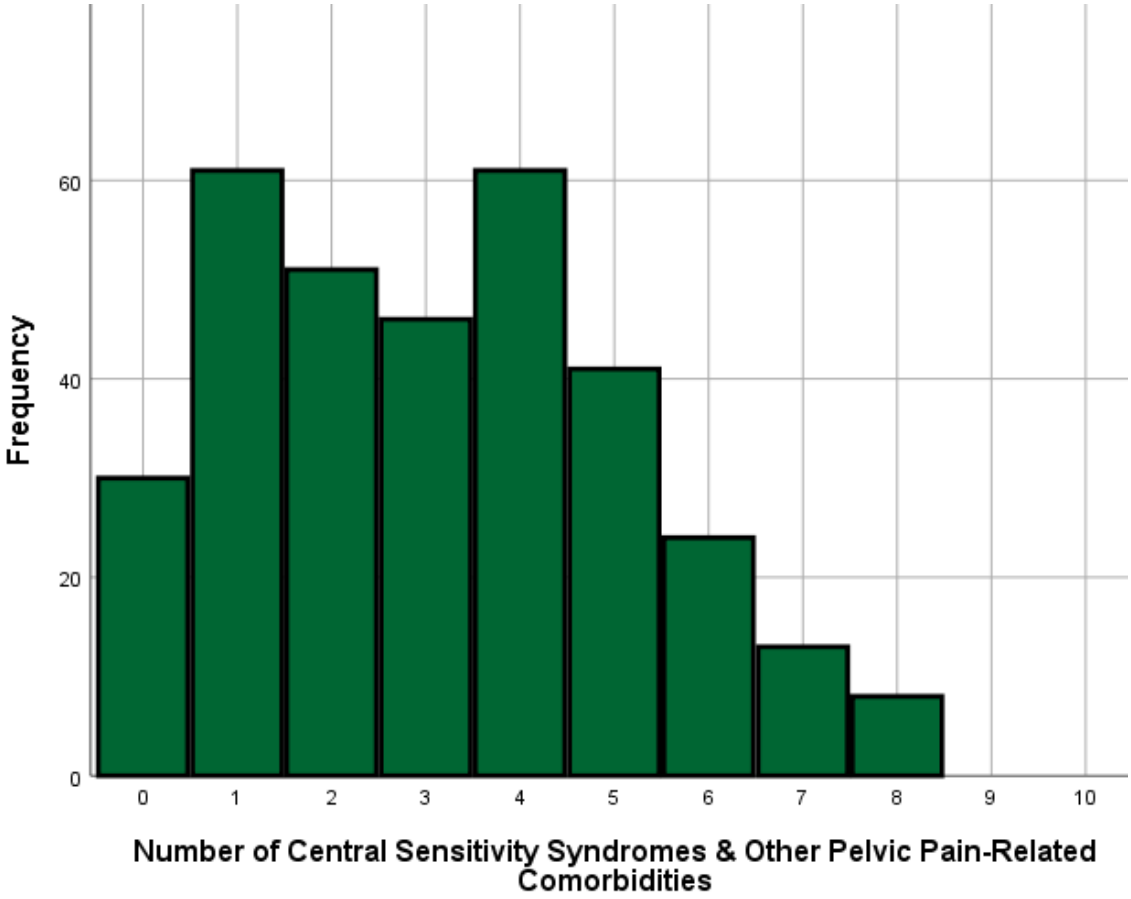
Frequency
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Number of Central Sensitivity Syndromes & Other Pelvic Pain-Related Comorbidities

Figure 3

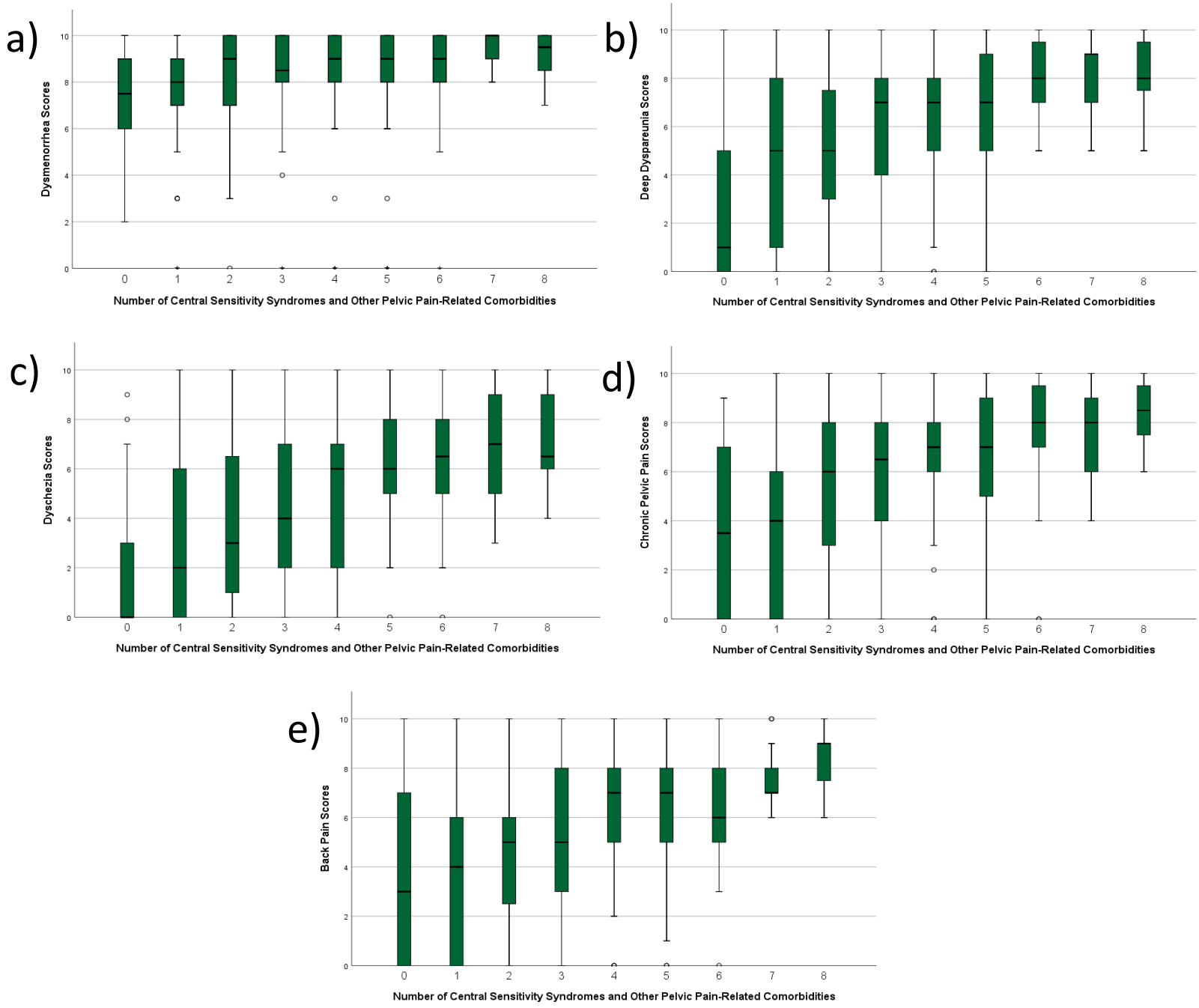
a)
Dysmenorrhea Scores
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities
b)
Deep Dyspareunia Scores
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities
c)
Dyschezia Scores
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities
d)
Chronic Pelvic Pain Scores
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities
e)
Back Pain Scores
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities

Figure 4

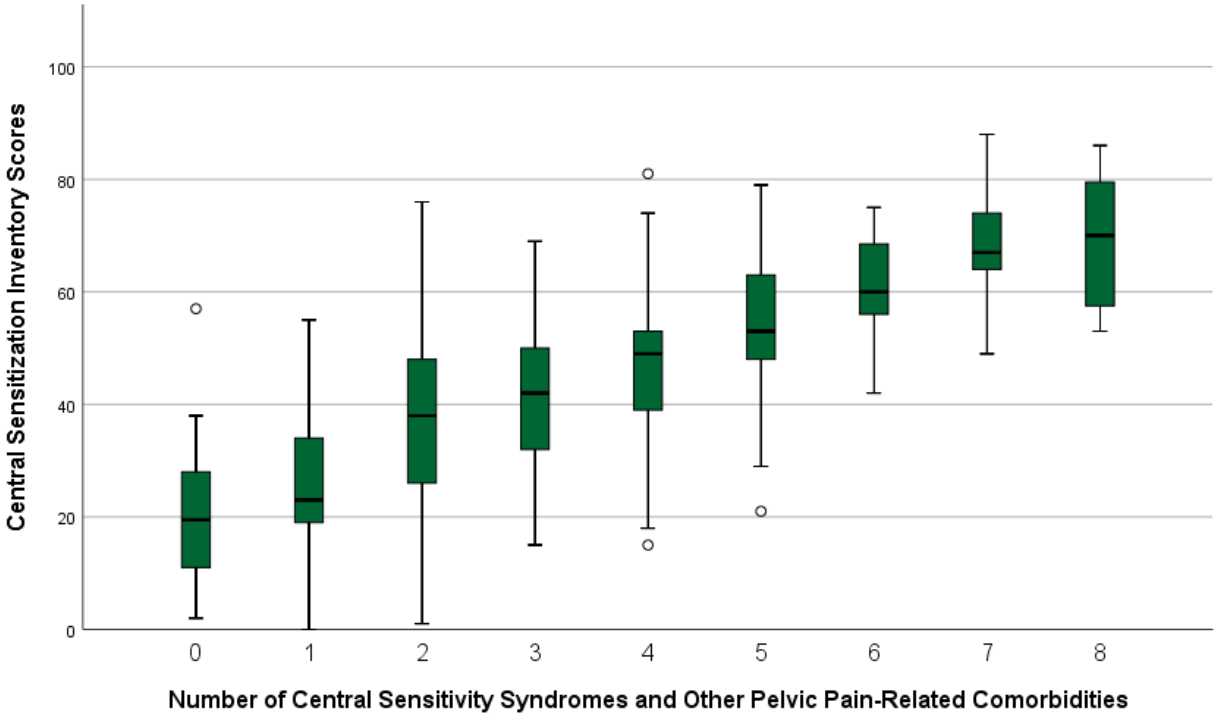
Central Sensitization Inventory Scores
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
Number of Central Sensitivity Syndromes and Other Pelvic Pain-Related Comorbidities

Figure 5

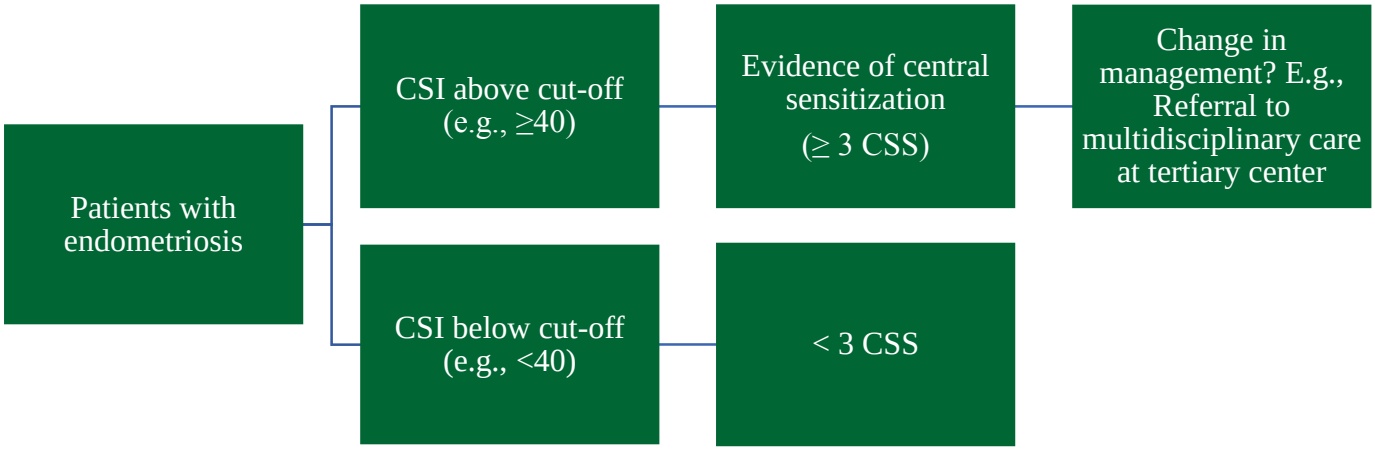
Patients with endometriosis
CSI above cut-off (e.g., ≥40)
Evidence of central sensitization (≥ 3 CSS)
Change in management? E.g., Referral to multidisciplinary care at tertiary center
CSI below cut-off (e.g., <40)
< 3 CSS

Table 1. Sample characteristics.

	Sample (n=335)			
Characteristic	**Frequency**	**Criteria**	**Regional (pelvic) vs. non-regional (non-pelvic) vs. psychometric**	**Provoked (functional or non-functional) vs. non-provoked**
Central sensitivity syndromes and other pelvic pain-related comorbidities				
Fibromyalgia		Self-report	Non-regional	Non-provoked
Yes	5.7% (19)			
No	94.3% (316)			
Chronic fatigue syndrome		Self-report	Non-regional	Non-provoked
Yes	2.7% (9)			
No	97.3% (326)			

Migraine Yes No	 31.6% (106) 68.4% (229)	Self-report	Non-regional	Non-provoked
Irritable bowel syndrome Yes No	 57.0% (191) 43.0% (144)	Rome III	Regional	Provoked, functional
Painful bladder syndrome Yes No	 52.5% (176) 47.5% (159)	AUA or ICS	Regional	Provoked, functional
Abdominal wall pain Yes (Carnett test positive) Negative (Carnett test negative)	 25.1% (84) 74.9% (251)	Carnett test	Regional	Provoked, non-functional
Myofascial pelvic pain Yes (tender anterior vaginal wall or pelvic floor)	 41.2% (138)	Levator ani or anterior vaginal wall tenderness	Regional	Provoked, non-functional

No (non-tender anterior vaginal wall or pelvic floor)	58.8% (197)			
Moderate depression; PHQ-9 ≥ 10		PHQ-9 ≥10	Psychometric	Non-provoked
<10	57.9% (194)			
≥10	42.1% (141)			
Moderate anxiety; GAD-7 ≥ 10		GAD-7 ≥10	Psychometric	Non-provoked
<10	77.6% (260)			
≥10	22.4% (75)			
Pain Catastrophizing Scale ≥ 75th centile; PCS ≥ 30		PCS ≥ 30	Psychometric	Non-provoked
<30	67.2% (225)			
≥30	32.8% (110)			
Demographics				
Age, years	36.0±7.0	Self-report	--	--
Sexual Orientation		Self-report	--	--
Heterosexual	86% (288)			

Other	14% (47)			
Hormone use (ever) Yes No	 85.7% (287) 14.3% (48)	Self-report	--	--
Endometriosis diagnosis Previous surgical/histological diagnosis Previous surgical diagnosis without histology No previous surgery, but current deep infiltrating nodule or ovarian endometrioma on exam/ultrasound	 52.8% (177) 29.6% (99) 17.6% (59)	Self-report	--	--
Ethnicity Caucasian Other	 69% (231) 31% (104)	Self-report	--	--
Education		Self-report	--	--

College or more	87.5% (293)			
High school or below	12.5% (42)			
Parity		Self-report	--	--
Parous	37.3% (125)			
Nulliparous	62.7% (210)			
BMI		Self-report	--	--
Underweight (<18.5)	3.0% (10)			
Healthy (18.5-24.9)	49.3% (165)			
Overweight (25-29.9)	26.9% (90)			
Obese (≥30)	19.7% (66)			
Missing	1.2% (4)			
Partnered (married or common-law)		Self-report	--	--
Yes	67.2% (225)			
No	32.8% (110)			
Currently Working		Self-report	--	--
Yes	69.0% (231)			

No	20.6% (69)			
Missing	10.4% (35)			

Table 2. Interrelated correlations within central sensitivity syndromes and other pelvic pain-related comorbidities.

	PHQ	GAD	PCS	Myo	Car	IBS	PBS	Fibro	CFS	Mig
PHQ	-	-	-	-	-	-	-	-	-	-
GAD	**.485****	-	-	-	-	-	-	-	-	-
PCS	**.331****	**.326****	-	-	-	-	-	-	-	-
Myo	**.257****	**.132***	.099	-	-	-	-	-	-	-
Car	**.190****	**.135***	**.109***	**.313****	-	-	-	-	-	-
IBS	**.239****	**.163***	**.119***	**.237****	.015	-	-	-	-	-
PBS	**.169***	**.138***	**.206****	**.176****	.040	**.237***	-	-	-	-
Fibro	.078	.023	.048	-.022	.096	-.048	.026	-	-	-
CFS	.083	-.001	-.077	.048	-.054	-.005	.084	**.279****	-	-
Mig	**.213****	.097	.044	**.148***	**.184****	.046	**.120***	**.166***	**.165***	-

Abbreviations: PHQ, depression; GAD, anxiety; PCS, pain catastrophizing; Myo, Myofascial pelvic pain syndrome; Car, Carnett (abdominal wall pain); IBS, irritable bowel syndrome; PBS, painful bladder syndrome/interstitial cystitis; Fibro, fibromyalgia; CFS, chronic fatigue syndrome; Mig, migraine. Phi (φ) correlation coefficients listed. * indicates $p \leq .05$, ** indicates $p \leq .001$.

Table 3. Correlation between endometriosis-associated pain scores and number of central sensitivity syndromes and other pelvic pain-related comorbidities.

Factor	N Total	Spearman r	P value
Dysmenorrhea*	335	.204	**<.001**
Deep Dyspareunia	335	.424	**<.001**
Dyschezia	335	.455	**<.001**
Chronic Pelvic Pain	335	.428	**<.001**
Back Pain	335	.413	**<.001**

*Dysmenorrhea question asked whether the patient ever had period cramps in their lifetime.

William's T comparison of correlation coefficients found that the dysmenorrhea correlation with number of central sensitivity syndromes and other pelvic pain-related comorbidities was significantly different than the correlations for deep dyspareunia (t=-3.55, df=332, p=.0004), dyschezia (t=-4.31, df=332, p<.001), chronic pelvic pain (t=-3.46, df=332, p=.0006), and back pain (t=-3.33, df=332, p=.001).

Table 4. ROC analysis for CSI cut off to identify 3 or more central sensitivity syndromes and other pelvic pain-related comorbidities.

Cut off scores	Sensitivity	Specificity
36.5	82.4%	72.5%
37.5	81.9%	72.5%
38.5	81.9%	77.5%
39.5	79.3%	78.2%
40.5	77.2%	81.7%
41.5	75.1%	83.1%
42.5	74.1%	83.1%

Table 5

Table 5. Validation: Bivariate associations between endometriosis-associated pain scores and the CSI cut off ≥ 40

Factor	N total	CSI low <40	CSI high ≥40	P value	OR
In house questions					
Dysmenorrhea	335	7.61±2.55	8.43±1.97	**.002**	
Deep Dyspareunia	335	4.47±3.33	6.67±2.48	**<.001**	
Dyschezia	335	3.48±3.22	5.35±2.96	**<.001**	
Chronic Pelvic Pain	335	4.83±3.26	6.49±2.83	**<.001**	
Back Pain	335	4.28±3.18	6.12±2.68	**<.001**	
Dysmenorrhea	335			**.013**	**2.98**
0-4		69% (18)	31% (8)		
5-10		43% (133)	57% (176)		
Deep Dyspareunia	335			**<.001**	**4.81**
0-4		70% (76)	30% (32)		
5-10		33% (75)	67% (152)		
Dyschezia	335			**<.001**	**2.69**
0-4		57% (94)	43% (70)		
5-10		33% (57)	67% (114)		
Chronic Pelvic Pain	335			**.001**	**2.28**
0-4		59% (62)	41% (43)		
5-10		39% (89)	61% (141)		
Back Pain	335			**<.001**	**3.67**

0-4 5-10		66% (75) 34% (76)	34% (39) 66% (145)		
WERF EPHect questions					
Dysmenorrhea					
At what age did you start having period pain?	317	18.1±7.8	15.9±5.9	**.005**	
Please rate how severe your pelvic pain was at its worst during your last period.	299	6.6±2.5	7.7±2.0	**<.001**	
Please rate how severe your pelvic pain during your period was at its worst in the last 12 months.	271	7.0±2.7	8.4±1.6	**<.001**	
Please rate how severe your pelvic pain during your period was when it was at its worst in your life.	317	8.6±1.7	9.1±1.5	**.001**	
Dyspareunia					
Have you ever had pelvic pain during intercourse or in the 24 hours following vaginal sexual intercourse/penetration?	303			**<.001**	

Yes		62.6% (82)	91.9% (158)		
No		37.4% (49)	8.1% (14)		
When you last had vaginal intercourse/penetration, where did you feel the pain? (Deep inside the vagina)	335			**<.001**	
Yes		23.8% (36)	47.8% (88)		
No		76.2% (115)	52.2% (96)		
Pelvic Pain					
Approximately how long in total did you have this pain for <u>in the last 3 months</u>?	209			**<.001**	
Less than one day a month		10.0% (8)	3.9% (5)		
One day a month		3.8% (3)	1.6% (2)		
Two to three days a month		30.0% (24)	14.0% (18)		
One day a week		5.0% (4)	4.6% (6)		
More than one day a week		31.2% (25)	35.6% (46)		
Daily pain		20.0% (16)	40.3% (52)		
Have you taken any hormones, but pain was not	299			**.003**	

alleviated, in the last 3 months? Yes No (excluding those who did not take any medication to alleviate pain)		6.3% (8) 93.7% (118)	18.5% (32) 81.5% (141)		
Please rate how severe your pelvic pain was at its worst in the last 3 months.	209	6.3±2.3	7.4±2.2	**<.001**	
Please rate how severe your pelvic/lower abdominal pain was when it was at its worst in your life.	253	7.7±2.3	8.5±1.8	**.005**	
During the time in your life when your pelvic/lower abdominal pain was at its worst, were you taking any hormones, but pain was not alleviated? Yes No	302	12.7% (17) 87.3% (117)	25% (42) 75% (126)	**.008**	

(excluding those who did not take any medication to alleviate pain)					