

A systematic review and meta-analysis of the Endometriosis and Mental-Health Sequelae; The ELEMI Project

Women's Health
Volume 17: 1–16
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DOI: 10.1177/17455065211019717
journals.sagepub.com/home/whe


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Abstract

Background: It is important to evaluate sequelae for complex chronic health conditions such as endometriosis and mental health disorders. Endometriosis impacts 1 in 10 women. Mental health outcomes can be a primary determinant in many physical health conditions although this is an area not well researched particularly in women's health. This has been problematic for endometriosis patients in particular, who report mental health issues as well as other key comorbidities such as chronic pelvic pain and infertility. This could be partly due to the complexities associated with comprehensively exploring overlaps between physical and mental health disorders in the presence of multiple comorbidities and their potential mechanistic relationship.

Methods: In this evidence synthesis, a systematic methodology and mixed-methods approaches were used to synthesize both qualitative and quantitative data to examine the prevalence of the overlapping sequelae between endometriosis and psychiatric symptoms and disorders. As part of this, an evidence synthesis protocol was developed which included a systematic review protocol that was published on PROSPERO (CRD42020181495). The aim was to identify and evaluate mental health reported outcomes and prevalence of symptoms and psychiatric disorders associated with endometriosis.

Findings: A total of 34 papers were included in the systematic review and 15 were included in the meta-analysis. Anxiety and depression symptoms were the most commonly reported mental health outcomes while a pooled analysis also revealed high prevalence of chronic pelvic pain and dyspareunia.

Interpretation: It is evident that small-scale cross-sectional studies have been conducted in a variety of settings to determine mental health outcomes among endometriosis patients. Further research is required to comprehensively evaluate the mental health sequelae with endometriosis.

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Keywords

adenomyosis, BAME, chronic pelvic pain, dysmenorrhea, dyspareunia, endometriosis, mental health, women's health, women's mental health

Date received: 24 March 2021; revised: 4 May 2021; accepted: 5 May 2021

Research in context

Evidence before this study

Research into exploring the mental health sequelae in endometriosis is limited. Therefore, to our knowledge, this is the first evidence synthesis conducted to determine the prevalence of the endometriosis, mental health (MH) and associated presentations, including chronic pelvic pain. The evidence demonstrated limited data around MH outcomes. Most published systematic reviews and meta-analysis, as well as research studies in relation to endometriosis, report MH outcomes either in isolation or as a generic quality of life feature, but did not focus on the sequelae. Previous studies did not estimate the proportion of cases that may be affected or their relevance to Black, Asian and Minority Ethnic populations.

Added value of this study

This study is composed of a comprehensive evidence synthesis which includes a narrative and meta-analysis conducted using a systematic approach to report the prevalence of the endometriosis and MH sequelae.

Implications of the available evidence

This review demonstrates a complex relationship between MH and endometriosis. To evaluate this disease sequelae comprehensive research is required. Additionally, race and ethnicity specific information is required to better evaluate cultural adaptations that may be required for example to improve patient reported outcomes as this study detected the paucity of this data. This evidence should support the development of new healthcare policies to diagnose and manage patients more holistically.

Introduction

Endometriosis is defined by the presence of endometrium-like tissue outside the uterine cavity and can lead to complex outcomes such as dysmenorrhea, chronic pelvic pain (CPP), sexual dysfunction and subfertility. Women with endometriosis suffer from a range of symptoms although the most complex of these are frequently associated with mental health (MH)-related distress and psychiatric comorbidities. Consequential psychosocial factors and a range of pelvic pain disorders frequently exacerbate the patient's experience of endometriosis and associated MH symptoms. Cross-sectional studies have shown exacerbated MH distress due to alterations of body image, loss, hopelessness, alexithymia and worthlessness as a result of endometriosis.¹ Aerts et al.¹ summarized the detrimental psychological impact and adjustments made by women with endometriosis, including heightened pain-related experiences and levels of distress.

One of the theories of the pathogenesis in endometriosis is Sampson's transplantation theory,^{2,3} where retrograde

motion of endometrial cells via the fallopian tubes into the pelvic cavity during menstruation. During this process, endometrial tissue implants on the peritoneal surface. This theory is further evidenced where increases in endometriosis incidence among women with Mullerian Duct anomalies indicate an obstructed flow increases the possibility of retrograde menstruation. This is also supported by the frequent, lengthy and heavy menstruation common in endometriosis, which further increases the exposure of the pelvic cavity to develop endometriosis. However, contradictions to this theory have been published, as some epidemiological data indicate that only 0.5%–5% of women with retrograde menstruation appear to develop endometriosis.⁴

The diagnosis and management of endometriosis is complicated by multiple factors, including issues around the pathophysiology of the disease, staging, severity and treatment responses, as well as limitations in current clinical and surgical management. However, the most severe and common comorbidities are pelvic pain, infertility and MH issues. As a result of this, further complications may arise in its long-term management as a result of MH

symptomatology and psychiatric comorbidities that may compromise the social relationships of these patients. CPP is a key clinical feature of endometriosis which may exacerbate depression and anxiety, and these, in turn, may exacerbate CPP. In addition to these complex symptoms, these patients are also at high risk of comorbidities such as inflammatory bowel disease, adenomyosis, fibromyalgia and autoimmune diseases.⁵ Endometriosis is further influenced by ovarian hormone fluctuations and dynamic inflammatory changes in the ‘ectopically’ located endometriotic tissues, that can lead to changes in the temporal pattern of any pain and a wide range of symptoms that can be challenging to manage. As a result, these issues can have a negative impact on all aspects of a woman’s life and her wellbeing and may have wider implications for ongoing management.

The latest epidemiological data from the UK suggest 1 in 10 women may have endometriosis although the international prevalence remains unclear⁶ as comprehensive global endometriosis and mental health research is lacking. Although, even with further epidemiological study, given endometriosis comprises of subclinical courses and is frequently subject to misdiagnoses and delayed diagnosis, affirming prevalence with ‘real-world’ data could be challenging.

The relationship between endometriosis and MH issues have been reported differently across a variety of studies. In addition, the perception of CPP or pain disorders such as dyspareunia, their reporting and impact on MH symptoms remain complex to evaluate, although there is some evidence to suggest they could lead to the development of mood disorders.^{7,8} Laganà et al.⁷ demonstrated an association between psychiatric disorders such as depression, somatization and anxiety among endometriosis patients. Given the presentation of endometriosis, it is very likely to adversely affect women’s MH, although theories around the pathophysiology and mechanism remain under-researched and unclear.⁹ The long-term consequences of restricted preoperative psychosocial evaluations and the lack of ongoing psychological support after surgery could be far reaching. Similarly, delayed or under diagnosed endometriosis could cause MH issues. Therefore, the overall quality of life of women with endometriosis is at risk and it has been reported that the potential for increased incidence in depression may be significant.¹⁰

Current published research indicates a strong link between mental and physical health,¹¹ although most chronic conditions are not well evaluated holistically. As per guidelines from the American Society for Reproductive Medicine, it is argued that women with endometriosis require lifelong personalized management plans.¹² However, similar guidelines are not available globally. In order to achieve such recommendations, further knowledge of the prevalence of the MH sequelae would be required.

Methods

An evidence synthesis protocol was developed as part of a systematic methodology. As part of this evidence synthesis, a systematic review was conducted to evaluate the current knowledge gap around MH outcomes within endometriosis patients, to help develop evidence based clinical guidelines and inform the design and conduct of future research. There are many different types of evidence synthesis methodologies that could be used, although these are mostly non-standardized and non-specific to research associated with sequelae where a primary and secondary health condition is evaluated. Therefore, we developed a multi-analysis method. The systematic review protocol was developed in accordance with the International Prospective Register of Systematic Reviews (PROSPERO) on the 15 July 2020 (CRD42020181495) with an eligibility criteria that is relevant to the clinical research question.

Research question/aims

The primary aim was to determine the prevalence of the MH sequelae in endometriosis (symptoms and/or psychiatric disorders), including any indirect covariates.

Data extraction

The search strategy comprised of the use of multiple MeSH and key terms such as *Mental Health, Depression, Anxiety, Mental Health and Endometriosis, Biopolar, Psychological disorders, Psychological distress, Post-Traumatic-Stress-Disorder (PTSD), Psychosis, Mental wellbeing and Mood disorders*. A snowball method was applied using these MeSH and key terms to identify any other relevant studies from within citation lists. Grey literature was reviewed to better evaluate patient reported outcomes although these were not included in the paper due to the lack of peer review available. Multiple databases were used, including PubMed, PROSPERO, EMBASE, ProQuest, BIOSIS, Science direct, Ovid MEDLINE and ClinicalTrials.gov. Variables of any MH symptomatology and/or psychiatric comorbidity were used as part of the inclusion/exclusion criteria for this study. Studies that reported both MH outcomes as a primary endpoint and any associated pain which demonstrated psychological distress were included. All randomized controlled trials (RCTs) and non-RCTs published in English between the 1 November 1995 and 30 November 2020 were included.

Multiple analysis methods were completed on the final systematically gathered dataset. Studies that may be excluded from the meta-analysis were analysed narratively. The data collection was completed using Endnote. An independent reviewer was used to evaluate the initial dataset as well as the final analysis (Table 1).

Table 1. Systematically included studies.

Author	Age	Clinical presentation	Sample	Medication	MH Outcomes	Pain outcomes	Other findings	Eligibility
Garry et al. (2000)	Not given	Pelvic pain Dyspareunia	57	Not applicable	Mental Health	Pelvic Pain Dysmenorrhoea Dyspareunia	Fertility Quality of Life	Included
Simoens et al. (2012)	36.1 (15–67)	Depression Anxiety	909	Not applicable	Depression Anxiety		Healthcare costs Costs of productivity loss Total costs Quality-adjusted life years	Excluded
Kumar et al. (2011)	30.3 (19–44)	Pelvic pain	39	Not applicable	Bipolar I Disorder Bipolar II disorder Bipolar disorder Panic Disorder Major Depressive Disorder Quality of Life	Pelvic Pain	Life satisfaction	Included
Aubry et al. (2017)	18–52	Pain Dysmenorrhoea Pelvic pain	216	Use of Painkillers	Quality of Life	Pain Intensity Intensity of Dysmenorrhoea Intensity of Pelvic Pain Frequency of Painful defecation Frequency of dyspareunia Daily Pain Intensity Daily Pain Frequency	Fertility	Excluded
Hansen et al. (2013)	Not given	Pain	1361	Not applicable	Anxiety Depression Quality of Life		Low Mood	Excluded
Friedl et al. (2015)	Patients: 33.4 Control: 29.6 (18–44)		62	Not applicable	General mental health		Anxiety Depression	Excluded
Fourquet et al. (2011)	33.2 (18–52)	Pelvic pain Dysmenorrhoea Dyspareunia Depression Anxiety	193	Not applicable			General physical health	Excluded
Sepulcri et al. (2009)	34.6 (19–48)		104	Not applicable	Degree of Depression Degree of Anxiety Depression–None Depression–Mild Depression–Moderate Depression–Severe Anxiety–None Anxiety–Minor Anxiety–Major			Excluded
Soliman et al. (2017)	34.3	Pelvic pain Dyspareunia	1269	Not applicable	Control and Powerlessness Emotional Well-being Social Support Self-image	Pain	Low mood, anxiety	Excluded

(Continued)

Table 1. (Continued)

Author	Age	Clinical presentation	Sample	Medication	MH Outcomes	Pain outcomes	Other findings	Eligibility
Youseflu et al. (2020)	Case group: 31.01, Control group: 29.35		156	Isoflavones Genistein Daidzein Formononetin Glycitein Lignans Secoisolaricresinol Pinoresinol Laricresinol Matairesinol Coumestrol Phytoestrogens Not applicable	Physical-Psychosocial Psychological Social		Diet	Excluded
Moradi et al. (2019)	(16–58)		423	Not applicable			Physical Sexual Fertility Employment Educational Lifestyle Duration of infertility	Excluded
Gao et al. (2020)	Not specified (Born between 1973–1990 from age 14 to 2016)		173,650	Not applicable	Depressive, Anxiety and Stress-related Disorders Attention-Deficit Hyperactivity Disorder Personality Disorder		Duration of infertility	Excluded
Matalliotakis et al. (2008)	34.4	Pelvic pain, dysmenorrhea, and dyspareunia	735	Not applicable		Pelvic Pain Duration of infertility Dysmenorrhoea Dyspareunia		Included
Matalliotakis et al. (2017)	18.3 (13–21)		55	Not applicable			Endometriosis and congenital malformations Dry Eye Syndrome	Excluded
Chen et al. (2015)	Not given		10439	Not applicable	Major depression Depressive Disorders Anxiety			Excluded
Carey et al. (2014)	36.4	Pelvic pain	79	Not applicable	Mental Health Depression (Normal/Borderline) Depression (Mild/Moderate/Severe) Mood Disorder	Dyspareunia	Physical Health Menses	Included
Smorgick et al. (2013)	17.8		138	Not applicable		Pelvic Pain Pain or burning during urination Pain with bowel movements Pain with sexual intercourse Pain with physical activity		Included
Kumar et al. (2010)	16–40	Chronic pelvic pain	200	Not applicable				Excluded
Roth et al. (2011)	32.1	Endometriosis	138	Not applicable	Chronic Pain Depression Affective Disorder	Pain Pain Disability		Excluded

(Continued)

Table 1. (Continued)

Author	Age	Clinical presentation	Sample	Medication	MH Outcomes	Pain outcomes	Other findings	Eligibility
Eriksen et al. (2007)	33.1 (with pain) 36.7 (without pain)		63	Not applicable	Depression Rational coping Emotional coping Detached coping Avoidant coping Anxiety Emotional control	Pain Severity	Coping	Excluded
Lorençatto et al. (2006)	Not given		100	Not applicable	Mild depression Moderate/severe Depression			Excluded
Low et al. (1993)	Not given		81	Not applicable	Depression Psychoticism Extroversion Neuroticism Lie State anxiety Trait anxiety	Total pain Score	Marital state General Health	Excluded
Lewis et al. (1989)	Not given		16	Not applicable	Depression Bipolar-mixed Bipolar-manic			Excluded
Laganà et al. (2015)	Not given		166	Not applicable	Somatization Depression Phobic anxiety Obsessive-compulsive Symptoms Anxiety Hostility Paranoid ideation		Somatization, anxiety, depression, ocd	Excluded
De Graaff et al. (2016)	Not given		243	Not applicable	Chronic pain Sexual anxiety and discomfort Anxiety Depression	Dysmenorrhoea	Sexual Function Wellbeing Fertility, depression, anxiety scores, dyspareunia	Included
Waller and Shaw (1995)	Not given	Control group—patients admitted for sterilization and found to have a normal pelvis Group 2—patients complaining of infertility who were found to have minimal or mild endometriosis Group 3—patients found to have minimal or mild endometriosis complaining of one or more of the following: dysmenorrhea, dyspareunia, or pelvic pain Group 4—patients with pelvic pain symptoms with no obvious pathology at laparoscopy	49	Not applicable	State anxiety Trait anxiety Depression		Women undergoing sterilization (Group 1) were slightly older; this represents un-avoidable bias due to the selection of patients for the operation.	Excluded

(Continued)

Table 1. (Continued)

Author	Age	Clinical presentation	Sample	Medication	MH Outcomes	Pain outcomes	Other findings	Eligibility
Facchin et al. (2015)	(20–40)	Pelvic pain	171	Not applicable	Quality of life Mental health Anxiety Depression	Dysmenorrhea Dyspareunia Pelvic pain Dyschezia		Excluded
Bergqvist and Theorell (2001)	(18–46)		48	Group 1—received nafarelin 200 ug IN twice daily plus placebo tablets twice daily Group 2—three MPA tablets twice daily together with placebo nasal spray twice daily.	Anxiety–depression	Dysmenorrhoea Dyspareunia Pelvic Pain Pelvic Tenderness	Spotting Induration Disturbed Sleep	Excluded
Cavaggioni et al. (2014)	With endometriosis: 36 ± 7.6 Control: 34.9 ± 10.1	Non-menstrual pelvic pain, Dysmenorrhoea, Dyspareunia	80	Not applicable	Psychotic disorder Mood disorders Anxiety disorders Somatoform disorders Eating disorders Alexithymia Depression Anxiety Psychosocial stress	Dysmenorrhoea Dyspareunia Non menstrual pelvic pain		Included
Laganà et al. (2017)	Not given			Not applicable		Chronic pelvic pain	Poor quality of life	Excluded
Vitale et al. (2016)	Not given			Not applicable			Migraine, fertility, depression, anxiety	Excluded
Fleming et al. (2018)	Not given			Not applicable			Psychiatric disorders	Excluded
Chen et al. (2020)	Not given		35,664	Not applicable	Bipolar disorder		Bipolar disorder	Excluded

MH: mental health.

Quality assessment

All studies identified within this review were cross-sectional studies. As such, it was important to assess the risk of bias, reliability of the analysis and validity of the evaluation conducted. The Newcastle-Ottawa Scale (NOS) was used to conduct this assessment. NOS allows 9 points of risk bias assessment associated with the study group, comparability within the groups based on outcomes as well as exposure and outcomes (Table 2).

Table 2. Newcastle-Ottawa Scale (NOS).

Author	NOS score
Garry (2000)	***** (5)
Simoens et al. (2012)	***** (6)
Kumar et al. (2011)	***** (6)
Aubry et al. (2017)	***** (6)
Hansen et al. (2013)	***** (5)
Friedl et al. (2015)	***** (7)
Fourquet et al. (2011)	***** (5)
Sepulcri et al. (2009)	***** (5)
Soliman et al. (2017)	***** (6)
Youseflu et al. (2020)	***** (6)
Maryam et al.	***** (6)
Gao et al.	***** (7)
Matalliotakis et al.	***** (6)
Matalliotakis et al.	***** (5)
Chen et al.	***** (7)
Carey et al.	***** (6)
Smorgick et al.	***** (7)
Roth et al.	***** (6)
Eriksen et al.	***** (5)
Lorençatto et al.	***** (5)
Low et al.	***** (6)
Lewis et al.	***** (5)
Laganà et al.	***** (5)
De Graaff et al.	***** (5)
Waller and Shaw	***** (6)
Bergqvist and Theorell	***** (6)
Cavaggioni et al.	***** (7)
Vitale and Laganà	-
Fleming et al.	-
Chen et al.	***** (6)
González-Echevarría AM et al.	***** (5)
Mathias et al.	***** (4)
Randolph ME et al.	***** (6)
Stratton P et al.	***** (6)

NOS: Newcastle-Ottawa Scale.

*Quality of the included cross-sectional studies was measured using the modified Newcastle-Ottawa Measurement Scale specific for cross-sectional studies.

We rated the quality of the studies (good, fair and poor) by allocating each domain with stars in this manner:

- A good quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes.
- A fair quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes.
- A poor quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain in line with the NOS guidelines.

An independent reviewer appraised the risk of bias and methodological quality in accordance to the NOS that has validity for use in cohort studies and the adapted version by Modesti and colleagues (2016) was used for cross-sectional studies. An eight item scale with three quality parameters of (1) selection, (2) comparability and (3) outcome. The quality of the studies were rated (good, fair and poor) by allocating each domain with stars in this manner:

- A **Good** quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes.
- A **Fair** quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes.
- A **Poor** quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain.

Data synthesis

For prevalence estimation, summary statistics were extracted from studies that reported MH outcomes in women with endometriosis or chronic pain or CPP. These statistics were either prevalence or mean (standard deviation (SD) or median and interquartile range (IQR). Estimates for studies that reported median and IQR were converted to mean and SD. For studies that did not report prevalence rates but reported only mean (SD) or median (IQR) we employed Monte Carlo simulations to estimate the proportion of the outcome based on appropriate cut-off points for the tool used to measure the outcome (a score of 19 for BDI and 8 for HADS).¹³⁻¹⁵ We assumed normality of the distribution when mean (SD) were reported or the data were symmetrical.

Estimate pooled prevalence were calculated for anxiety and depression, CPP, and dyspareunia for which purpose we used a random-effects model. We also used a random effect model to compute pooled estimate of mean score of CPP measured using SF-MPQ and compute prevalence ratios of anxiety and depression. We used the I^2 statistic to assess heterogeneity between the studies for which the cut-off values for degree of heterogeneity were – 25% for low, 50% for moderate, and 75% for high.¹⁶ To investigate sources of heterogeneity we conducted sensitivity analyses for outcomes that had sufficient sample size for these analyses. These included estimate of prevalence of depression by excluding a lone study where participants were enrolled from primary care and another analysis that included only cross-sectional studies. We were able to assess potential publication bias through visualization of funnel plot and Egger's test for only depression since it was the only outcome with ≥ 10 studies. Analysis was conducted using STATA 14.0.

A total of 34 cross-sectional studies were finalized for the systematic review, although 12 were included into the meta-analysis. The 12 studies reported depression, anxiety, CPP,

dyspareunia and dysmenorrhea. The remaining studies were reviewed as part of the thematic and narrative analysis.

Meta-analysis

Anxiety. The prevalence for anxiety symptoms was found to be 31.8% (95% CI: 26.5% - 37.1%) (Figure 2(a)). We were able to pool five studies to compute prevalence ratios. The prevalence of anxiety symptoms was 2.8 times higher among women who had endometriosis compared to women without endometriosis (Figure 3(a)). A prospective cohort study that was not included in the meta-analysis¹⁷ reported 44% increased risk for anxiety for women with endometriosis compared to women without endometriosis. The same study reported a hazard ratio of 1.39 (95%CI: 1.14, 1.71) for anxiety among women with endometriosis who were < 40 years of age and 1.53 (95%CI: 1.15, 2.04) for women who were ≥ 40 years of age.

Depression

We found the prevalence of depressive symptoms among women with endometriosis to be 28.9% (95% CI: 8.6%–49.2%) (Figure 2(b)). When we included only the studies that used the Beck Depression Inventory (BDI) to assess depressive symptoms we did not find the results to be materially different from the overall estimate (prevalence: 24.8%, 95% CI: 10.1%–39.4%) (Supplemental Figure 1). Analysis conducted after excluding a study that enrolled patients from primary care instead of tertiary care/women’s clinics/university hospital/gynaecological clinics resulted in little change to the prevalence estimate (Supplemental Figure 2). However, meta-analysis of only cross-sectional studies resulted in a lower prevalence compared to the overall estimate (22.0% vs 28.9%) (Supplemental Figure 3). Meta-analysis of three studies did not reveal strong evidence of higher prevalence of

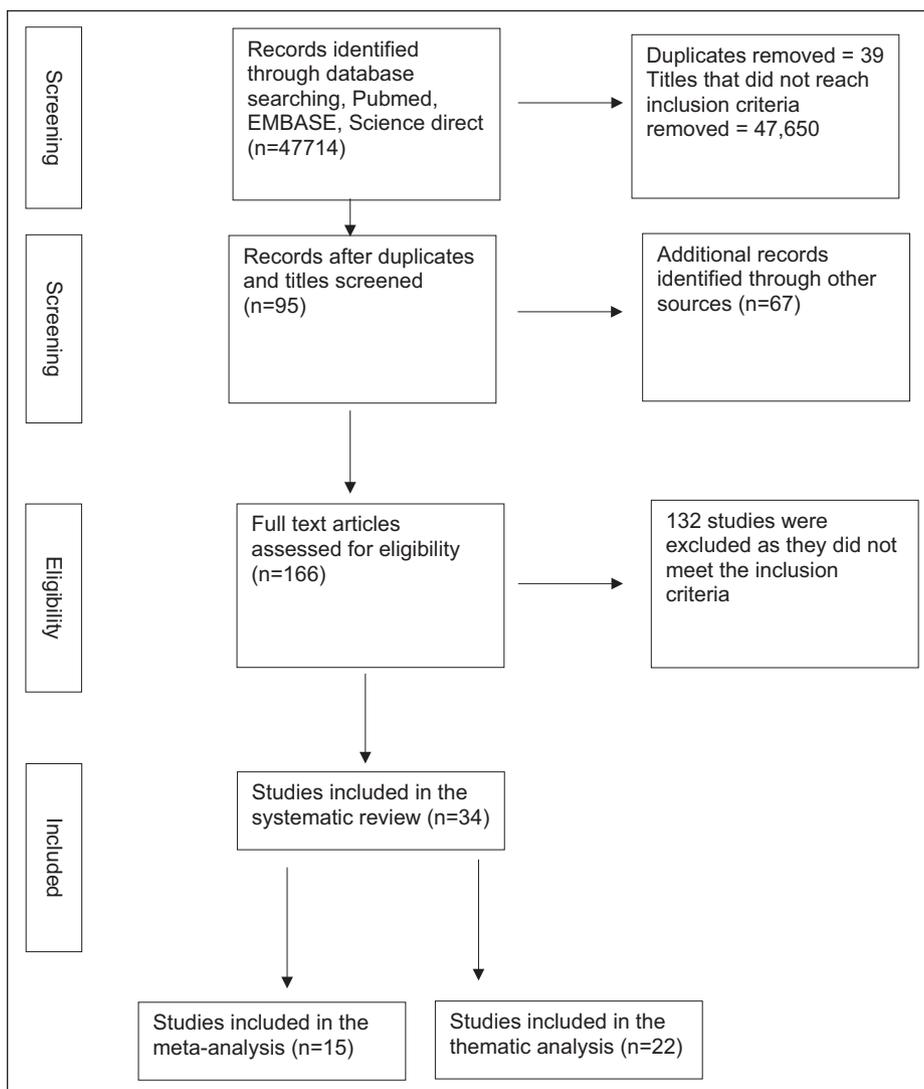


Figure 1. PRISMA chart.

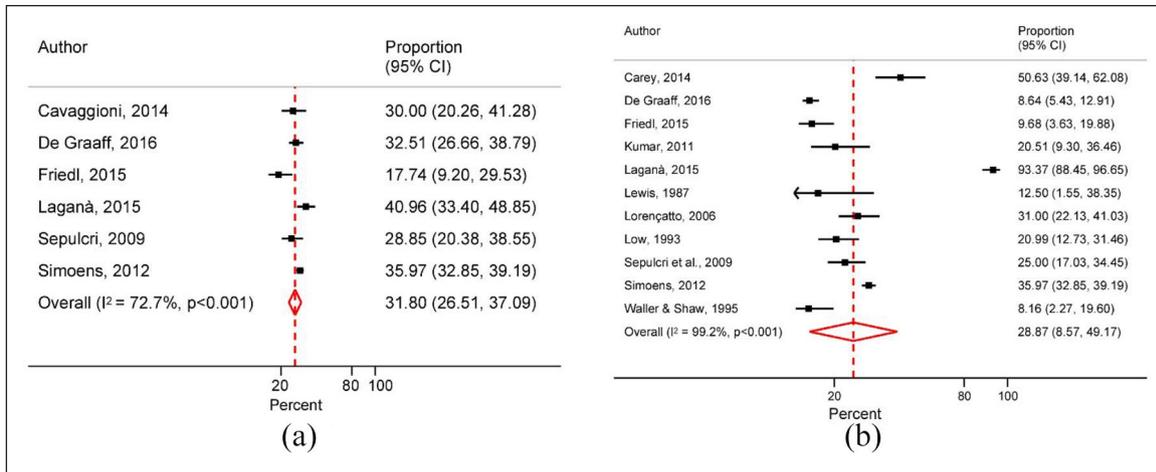


Figure 2. Forest plot of pooled prevalence of (a) anxiety among women with endometriosis, (b) depression among women with endometriosis.

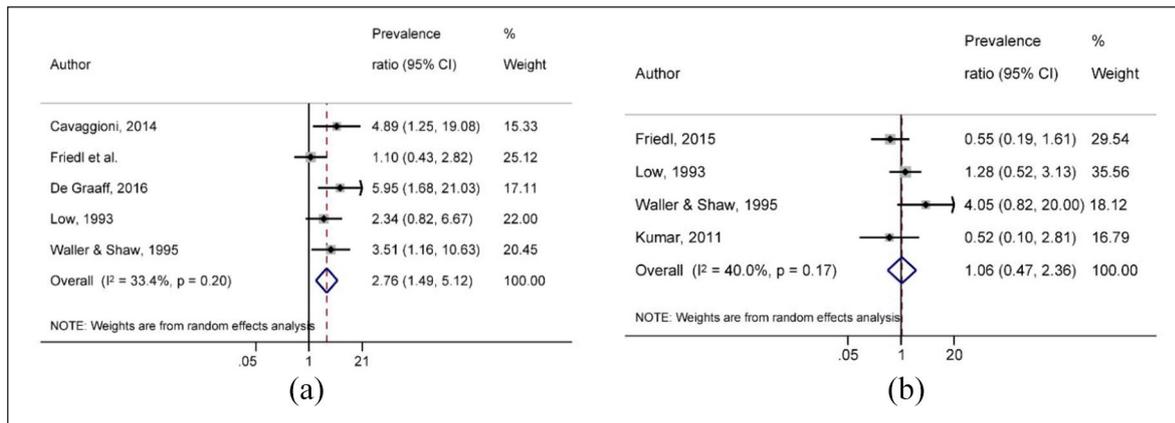


Figure 3. Forest plot of prevalence odds ratio of (a) anxiety among women with endometriosis compared to women without endometriosis, (b) depression among women with endometriosis compared to women without endometriosis.

depression among women with endometriosis compared to women without endometriosis (Figure 3(b)).

Other outcomes

The pooled prevalence for CPP was high at 57.2% (95% CI: 7.0%–107.4%) (Figure 4(a)). We found the pooled estimate of mean SF-MPQ for chronic pain to be 13.09 (95% CI: 7.13–19.05) (Supplemental Figure 4). The other outcome for which we were able to compute prevalence was dyspareunia which was found to be high too at 54.9% (95% CI: 43.9%–65.9%) (Figure 4(b)). Six studies that reported anxiety among BAME women with endometriosis were identified, therefore it was not possible to complete a meta-analysis.

Studies that were excluded from the meta-analysis were still part of the systematic review and therefore were used as part of the thematic and narrative analysis included within the discussion.

Publication bias

Funnel plot suggested evidence for publication bias with a tendency for studies with low prevalence rates for depression to be not published (Supplemental Figure 5). However, the p-value for Egger’s test for funnel asymmetry was found to be 0.50 suggesting insufficient evidence to test for publication bias, probably due to low power (only 11 studies included) to detect such a bias.

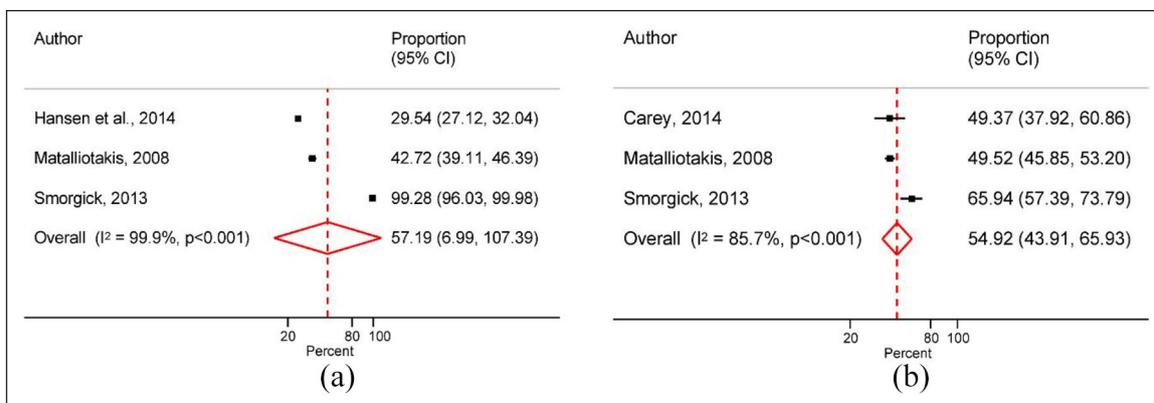


Figure 4. Forest plot of pooled prevalence of (a) chronic pelvic pain among women with endometriosis, (b) dyspareunia among women with endometriosis.

Narrative analysis

The translation of analytical and descriptive themes are important to facilitate transparency of reporting qualitative and quantitative data. Based on all 34 papers identified systematically, anxiety, depression, CPP and dyspareunia were identified as recurring themes reported by all the studies. In addition, a range of other non-standardized variables were identified as demonstrated in Table 3. However, the data were unclear regarding the prevalence of symptoms versus clinical diagnoses, which hinders a full assessment of the short, medium and long-term implications for patients and healthcare systems. The identification of CPP and dyspareunia in particular purports further impact on patients' MH, as highlighted by Till et al.¹⁸ Women with

CPP are reported to have significant rates of psychological disorders in comparison to those without CPP.¹⁸ Bryant et al.¹⁹ further reported that in their outpatient clinics for CPP, over 50% of patients had moderate to severe anxiety while over 25% had moderate to severe depression. Symptoms such as anxiety and depression may share a symbiotic relationship which may be exacerbated among endometriosis women that use opioids due to CPP. Generalized anxiety disorder (GAD) has been found to be more common in patients with CPP or any type of pain disorder or symptomatology associated with a primary condition such as endometriosis. Bryant et al.¹⁹ reported patients with CPP demonstrate 30%–73% with anxiety which is 3 to 7 times higher in comparison to the general population which is around 12%.²⁰

Table 3. Demonstration of mental health themes identified within the systematically identified dataset.

Themes	Population Group
	Endometriosis Patients
Depression	+++++
Anxiety	+++++
Pelvic pain	+++++
Pain	+++++
Dysmenorrhoea	+++++
Dyspareunia	+++++
Mental health	+++++
Bipolar I disorder	++
Bipolar II disorder	++
Bipolar disorder	++
Major depressive disorder	++
Control and powerlessness	++
Well-being	++
Physical health	++
Sexual function	++
Mood disorder	++
Psychotic disorder	++

(continued)

Table 3. (continued)

Themes	Population Group
	Endometriosis Patients
Somatization	++
Panic disorder	+
Life satisfaction	+
Quality of life	+
Disturbed sleep	+
Induration	+
Pelvic tenderness	+
General physical health	+
Social support	+
Obsessive-compulsive symptoms	+
Spottings	+
Sexual anxiety	+
Self-image	+
Hostility	+
Paranoid ideation	+
Drug use	+
Psychological	+
Social	+
Fertility	+
Employment	+
Education	+
Lifestyle	+
Attention-deficit hyperactivity disorder	+
Personality disorder	+
Duration of infertility	+
Congenital malformations	+
Dry eye syndrome	+
Menses	+
Affective disorder	+
Pain disability	+
Coping styles	+
Marital status	+
General health	+
Eating disorder	+

GAD causes pervasive worries which can be coupled with muscle tension or fatigue that impact other endometriosis symptoms.

Dyspareunia is a key feature of sexual pain disorders and CPP. It is also a cardinal feature of endometriosis,²¹ and is connected with various other gynaecological conditions such as infertility. However, this meta-analysis has demonstrated that despite a high prevalence of CPP, the assessment tools used in most trials are inadequate and its association with dyspareunia is unclear. Furthermore, while it is agreed most endometriosis patients may have 'deep dyspareunia', it is challenging to confirm this clinically. Self-administered measures of pain (e.g. the McGill Pain Questionnaire²²) and its impact on sexual function (e.g. Female Sexual Function Index,²³ Female Sexual Distress Scale²⁴), and psychological (e.g. Beck Depression

Inventory-II,²⁵ Beck Anxiety Inventory²⁶) and relationship adjustment (e.g. Dyadic Adjustment Scale,²⁷ the Locke-Wallace Marital Adjustment Test²⁸) are some of the tools that have been used. These assessment questionnaires are often nonspecific for CPP. There is scant evidence that the current assessment tools provide meaningful clinical results in patients suffering from CPP as a consequence of endometriosis. The pain assessment tools are not universally used for CPP suffers and this can be attributed to lack of evidence and a clear guidance for its use.

Surgically diagnosed endometriosis patients may have a better probability of confirming symptomatology of dyspareunia. Inadequate assessments could be one reason for the current difficulties in identifying and managing these symptoms, that could lead to psychological distress which could further impact physical and mental wellbeing.

This in turn could make the provision of the clinical care of CPP cumbersome. The EUA guidelines on management of persistent CPP after appropriate medical treatment recommends an approach focussed on managing pain, via integrated medical and psychological care. Patients with pelvic pain differ substantially in the extent they will volunteer information about emotional and behavioural aspects of pain.²⁹ One way to address this would be to introduce a tool for early assessment of pain and any associated psychosocial impact, that incorporates long-term monitoring that could support clinical management.

A total of 17 papers reported the impact of endometriosis on generalized quality of life (QoL) using the Short Form Health Survey-36 and 12 (SF36 and SF 12) and also using assessments specific to endometriosis (Endometriosis Health Profile-30 and EHP-30 and EHP-5). These studies (which were not included in the meta-analysis) demonstrated a reduction in QoL,^{29–34} with a few patients reporting their experience to be ‘worse than death’.³⁵ However, these QoL assessments were not conducted in conjunction with any MH assessments.

Discussion

In order to better characterize the MH sequelae of endometriosis, it is equally important to understand the pathogenesis of the disease which is driven by an oestrogen dependency and its association with the central feature, CPP. Sensitisation to pain varies across women with the disease, which may alter their behaviour due to changes within the electrophysiology of the brain. Li et al.³⁶ tested their theory of endometriosis and change in the electrophysiology and found a number of genes were involved with pain, locomotion and anxiety. They concluded that endometriosis associated pain sensitisation, depression and anxiety all altered the electrophysiology of the brain.³⁶ Furthermore, Tokushige et al.³⁷ demonstrated that nerve fibres within the functional layer of the endometrium and ectopic endometriosis lesions were nociceptive within clinical studies. Thus, nascent endometriosis specific neuropathological involvement could have a wider effect on neuronal behaviour within the central neural system (CNS) and influence pain sensitisation among patients, and it could be argued that this may impact the electrophysiology of the brain further.³⁸ In addition, in CPP associated with endometriosis, endometriotic lesions elicit increases in prostaglandin, cytokine and growth factor concentrations inducing a unique neural and vascular implantation process via neuroangiogenesis.³⁸ Overall, these mechanisms appear to be complex in nature and remain unclear. In addition to this, further evidence of the CNS involvement has been reported by Agarwal and Subramanian³⁹ including two cases of cerebral endometriosis with cystic masses in the cerebellar vermis. As a result of these factors, there are potential neuropsychiatric

mechanisms to consider. All this only emphasizes the need to better characterize and understand the MH sequelae among endometriosis patients. To do this, comprehensive assessment tools maybe required to better characterize and report MH symptoms and clinical features through patient reported outcomes.

Four of the 34 studies identified used a validated, clinical diagnostic assessment to diagnose psychiatric disorders. Kumar et al.⁴⁰ described 37% of the endometriosis group and 50% of the pelvic pain group having a familial history of mood disorders although, they were not taking any GnRH agonist treatments. Pharmacological, surgical or psychosocial interventions and potential associations were not identified within these studies.⁴¹

To fully explore QoL among endometriosis patients, the mechanistic nature and role of MH difficulties should be explored in the first instance. Current QoL data are probably not reflective of the *true* individual disease burden in the short, medium or long-term. QoL data should also be used to develop suitable health economic models (HEMs) for endometriosis and its associated comorbidities. Without this, it is not feasible to evaluate the true health and social care cost of endometriosis and its relevance to the MH sequelae shared with endometriosis. Thus, there still remains a significant gap in understanding the actual cost implications of MH symptoms in endometriosis on clinical services. Research into this area appears to be absent although, some studies have attempted to evaluate HEMs for endometriosis using estimated costs, despite the lack of comprehensive prevalence data.

Use of qualitative or quantitative methods alone may not suffice to inform the knowledge and practice based requirements in endometriosis, because of the complex characteristics demonstrated among this population of patients. This is also apparent in grey literature.

In this meta-analysis, majority of the data were on prevalence, although the sample sizes were limited, preventing any sub-group analysis being conducted on age groups, ethnicity and geographical location. Most studies did not report these aspects, therefore, a sub-group analysis was not conducted. In addition to this, a compute odds ratio was conducted despite a small number of studies, that indicated insufficient evidence within the literature to identify the effects of endometriosis on MH in the short, medium and long-term. This further reinforces the need for comprehensive clinical research to be conducted that would enable the results to be generalized to the wider population.

Across most studies, a recurring theme is patients’ experiences of pain, dyspareunia, irregular bleeding and infertility. While endometriosis is associated with infertility, QoL of patients could be impacted in a number of ways including their psychological wellbeing. Most papers report on both severe and progressive pain during menstruation and in pre- and post-menstruation phases. Symptomatology

such as fatigue, tiredness, sleep disturbances, bowel and bladder symptoms have been reported. As a result of these symptoms, there is also a reported impact on a woman's mental wellbeing, and women frequently experience and report depression and anxiety. Empirical research also suggests an exacerbation of MH symptoms due to a delayed diagnosis and the heightened experiences of severe symptoms that remained clinically undermanaged. Prolonged low-dose hormonal contraception or progestogens, offered as first-line treatment, may in turn aggravate the risk of MH problems.⁴²

There was also a theme that indicated endometriosis impacted intimate relationships. This has been suggested to be between 33.5% and 71%,^{29,43} largely as a result of CPP and dyspareunia. Bernuit et al.²⁹ across-country study indicated 24–25% women within their endometriosis population experienced dyspareunia. However, the precise MH impact of this and the possible association with symptoms such as low mood was unreported. It is further evident that the impact of endometriosis on women's partners remains unexplored and requires further research.^{44,45}

A distinctive feature reported by researchers and patients alike within these papers is CPP. As a result of endometriosis-associated pain, women may have reduced physical functioning that may affect mobility long-term, as well increase their risk for other health conditions such as diabetes. Simoens et al.³⁵ reported between 16% and 61%⁴³ of women with endometriosis reported challenges with daily activities, including self-care. However, based on these studies, it is unclear if the reported deterioration and ongoing difficulties with MH is as a direct result of the decline in activities or other underlying disorders. Interestingly, Nnoaham et al.⁴⁶ demonstrated a considerable reduction in physical health among endometriosis patients in comparison to the rest of the population.

Based on this evidence, it appears endometriosis patients have significant MH symptoms such as depression and anxiety, although the relative clinical significance within a generalisable population remains unclear. In order to provide optimal care to endometriosis patients, MH difficulties need to be taken into account by clinical teams, and based on this evidence, it is unlikely a uniform holistic approach is currently being used, or at least reported by all global healthcare systems. As a result of this, a wider evaluation of the MH sequelae of endometriosis is required.

Limitations

The primary limitations of this review is the small number of studies included in the meta-analysis. This evidence synthesis is based on cross-sectional studies only. Cross-sectional data often lacks directionality and provides no insight into mechanistic associations or causal effects between endometriosis and MH issues. Furthermore, poor quality data was a concern, as was the lack of psychiatric diagnostic data, and

some studies were excluded on this basis. There was moderate-to-high heterogeneity for the studies included in the overall prevalence estimates of anxiety ($I^2=73\%$) and depression ($I^2=99\%$). We could not, however, thoroughly investigate sources of heterogeneity due the limited number of studies included in the analysis (especially for CPP and dyspareunia prevalence estimate). Another limitation is that, the results of the meta-analysis should be interpreted with caution given that it is based on small number of studies for each outcome, but this also throws light on the fact that there is a gap in the literature on MH disorders in women with endometriosis.

Discussion

This paper highlights the prevalence of MH sequelae in endometriosis. But a key finding of the review is that the pain and MH assessments used have considerable variability, and lack specificity. As a result, this could contribute to a significant knowledge and practice gap.

Most studies describe stress-related disorders, eating disorders, attention deficit hyperactivity disorders and personality disorders as being common among women with endometriosis and some even suggest familial liability, although the mechanistic causation requires to be investigated further as the generalizability of this data remains poor.

Overall, psychiatric comorbidities remain unreported and unsubstantiated with the exception of a study reporting reduced psychological functioning and QoL as a result of MH difficulties,⁴¹ when the authors reported that 56.4% of women with endometriosis fulfilled the clinical criteria for psychiatric disorders.

While we acknowledge pain and MH disorders are complex conditions independently, they appear to share an overlapping sequelae with endometriosis. However, the pathophysiology of this construct remains to be seen. It is important that future research conducted should comprise of larger sample sizes that could be generalisable to the wider population, as well as psychiatric diagnostic assessments. In order to evaluate, diagnose and treat endometriosis in a holistic manner, it is vital to understand the applicability of existing instruments and whether these could be harmonized even when varied methods and settings use these. Finally, the MH burden associated with endometriosis and its associated pain disorders should be determined to improve clinical practices.

Conclusion

This SR demonstrated that the most common type of MH symptoms and psychiatric comorbidities reported in patients with endometriosis are anxiety and depression. However, there were a large proportion of studies with poor study designs and small sample sizes, therefore, these outcomes may not be reflective of the wider

population. These studies also failed to differentiate MH symptoms from psychiatric disorders. Overall, the prevalence of psychiatric comorbidities among the endometriosis populations remains significantly unresearched. Interim clinical plans to address these disturbances remain inconclusive due to the lack of association data from epidemiological studies between CPP, endometriosis and MH issues. This paper also demonstrates that the current literature is insufficient to establish either a unidirectional and/or a bidirectional causality between endometriosis and MH problems. It is vital to acknowledge the importance of conducting comprehensive and statistically significant research to further the understanding of the association of endometriosis and MH issues. This would further the management of this complex, and life long, multifaceted condition.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

References

1. Aerts L, Grangier L, Streuli I, et al. Psychosocial impact of endometriosis: from co-morbidity to intervention. *Best Pract Res Clin Obstet Gynaecol* 2018; 50: 2–10.
2. Koninckx PR, Ussia A, Adamyan L, et al. Pathogenesis of endometriosis: the genetic/epigenetic theory. *Fertil Steril* 2019; 111(2): 327–340.
3. Sampson JA. Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. *Am J Pathol* 1927; 3: 93–110.
4. Halme J, Hammond MG, Hulka JF, et al. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 1984; 64(2): 151–154.
5. Ballard KD, Seaman HE, de Vries CS, et al. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study – part 1. *BJOG* 2008; 115(11): 1382–1391.
6. Mowers EL, Lim CS, Skinner B, et al. Prevalence of endometriosis during abdominal or laparoscopic hysterectomy for chronic pelvic pain. *Obstet Gynecol* 2016; 127: 1045–1053.
7. Laganà AS, La Rosa V, Petrosino B, et al. Comment on ‘risk of developing major depression and anxiety disorders among women with endometriosis: a longitudinal follow-up study’. *J Affect Disord* 2017; 208: 672–673.
8. Cavaggioni G, Lia C, Resta S, et al. Are mood and anxiety disorders and alexithymia associated with endometriosis? A preliminary study. *Biomed Res Int* 2014; 2014: 786830.
9. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Res*. Epub ahead of print 23 April 2019. DOI: 10.12688/f1000research.14817.1.
10. Warzecha D, Szymusik I, Wielgos M, et al. The impact of endometriosis on the quality of life and the incidence of depression – a cohort study. *Int J Environ Res Public Health* 2020; 17(10): 3641.
11. Ohrnberger J, Fichera E and Sutton M. The relationship between physical and mental health: a mediation analysis. *Soc Sci Med* 2017; 195: 42–49.
12. Bodenheimer T, Lorig K, Holman H, et al. Patient self-management of chronic disease in primary care. *JAMA* 2002; 288(19): 2469–2475.
13. Low WY, Edelmann RJ and Sutton C. A psychological profile of endometriosis patients in comparison to patients with pelvic pain of other origins. *J Psychosom Res* 1993; 37(2): 111–116.
14. De Graaff AA, Van Lankveld J, Smits LJ, et al. Dyspareunia and depressive symptoms are associated with impaired sexual functioning in women with endometriosis, whereas sexual functioning in their male partners is not affected. *Hum Reprod* 2016; 31(11): 2577–2586.
15. Waller KG and Shaw RW. Endometriosis, pelvic pain, and psychological functioning. *Fertil Steril* 1995; 63(4): 796–800.
16. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557–560.
17. Chen LC, Hsu JW, Huang KL, et al. Risk of developing major depression and anxiety disorders among women with endometriosis: a longitudinal follow-up study. *J Affect Disord* 2016; 190: 282–285.
18. Till SR, As-Sanie S and Schrepf A. Psychology of chronic pelvic pain: prevalence, neurobiological vulnerabilities, and treatment. *Clin Obstet Gynecol* 2019; 62(1): 22–36.
19. Bryant C, Cockburn R, Plante AF, et al. The psychological profile of women presenting to a multidisciplinary clinic for chronic pelvic pain: high levels of psychological dysfunction and implications for practice. *J Pain Res* 2016; 9: 1049–1056.
20. Romão AP, Gorayeb R, Romão GS, et al. High levels of anxiety and depression have a negative effect on quality of life of women with chronic pelvic pain. *Int J Clin Pract* 2009; 63(5): 707–711.
21. Wahl KJ, Orr NL, Lisonek M, et al. Deep dyspareunia, superficial dyspareunia, and infertility concerns among women with endometriosis: a cross-sectional study. *Sex Med* 2020; 8(2): 274–281.
22. Melzack R and Katz J. The McGill pain questionnaire: appraisal and current status. In: Turk DC and Melzack R (eds) *Handbook of pain assessment*. 2nd ed. New York: Guilford Press, 2001, pp. 35–52.
23. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; 26(2): 191–208.

24. Derogatis LR, Rosen R, Leiblum S, et al. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002; 28(4): 317–330.
25. Beck AT, Steer RA and Brown GK. *Beck depression inventory manual*. 2nd ed. San Antonio, TX: Psychological Corporation, 1996.
26. Beck AT and Steer RA. *Beck anxiety inventory*. San Antonio, TX: Psychological Corporation, 1990.
27. Spanier GB. Measuring dyadic adjustment: new scales for assessing the quality of marriage and similar dyads. *J Marriage Family* 1976; 38: 15–28.
28. Hawkins JL. The Locke marital adjustment test and social desirability. *J Marriage Family* 1966; 28(2): 193–195.
29. Bernuit D, Ebert AD, Halis G, et al. Female perspectives on endometriosis: findings from the uterine bleeding and pain women's research study. *J Endometr Pelvic Pain Disord* 2011; 3(2): 73–85.
30. Marques A, Bahamondes L, Aldrighi JM, et al. Quality of life in Brazilian women with endometriosis assessed through a medical outcome questionnaire. *J Reprod Med* 2004; 49(2): 115–120.
31. Petrelluzzi KF, Garcia MC, Petta CA, et al. Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. *Stress* 2008; 11(5): 390–397.
32. Siedentopf F, Tariverdian N, Rücke M, et al. Immune status, psychosocial distress and reduced quality of life in infertile patients with endometriosis. *Am J Reprod Immunol* 2008; 60(5): 449–461.
33. Tripoli TM, Sato H, Sartori MG, et al. Evaluation of quality of life and sexual satisfaction in women suffering from chronic pelvic pain with or without endometriosis. *J Sex Med* 2011; 8(2): 497–503.
34. Chene G, Jaffeux P, Lasnier C, et al. Quality of life of women with endometriosis: comparison between epiphenomenon and severe disease. *J Endometr Pelvic Pain Disord* 2012; 4(2): 77–84.
35. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod* 2012; 27(5): 1292–1299.
36. Li T, Mamillapalli R, Ding S, et al. Endometriosis alters brain electrophysiology, gene expression and increases pain sensitization, anxiety, and depression in female mice. *Biol Reprod* 2018; 99(2): 349–359.
37. Tokushige N, Markham R, Russell P, et al. Different types of small nerve fibers in eutopic endometrium and myometrium in women with endometriosis. *Fertil Steril* 2007; 88(4): 795–803.
38. Asante A and Taylor RN. Endometriosis: the role of neuroangiogenesis. *Annu Rev Physiol* 2011; 73: 163–182.
39. Agarwal N and Subramanian A. Endometriosis – morphology, clinical presentations and molecular pathology. *J Lab Physicians* 2010; 2(1): 1–9.
40. Kumar A, Gupta V and Maurya A. Mental health and quality of life of chronic pelvic pain and endometriosis patients. *J Project Psychol Mental Health* 2010; 17(2): 153–157.
41. Pope CJ, Sharma V, Sharma S, et al. A systematic review of the association between psychiatric disturbances and endometriosis. *J Obstet Gynaecol Can* 2015; 37(11): 1006–1015.
42. Skovlund CW, Mørch LS, Kessing LV, et al. Association of hormonal contraception with depression. *JAMA Psychiatry* 2016; 73(11): 1154–1162.
43. Fourquet J, Báez L, Figueroa M, et al. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. *Fertil Steril* 2011; 96(1): 107–112.
44. Hudson N, Law C, Culley L, et al. Conducting dyadic, relational research about endometriosis: a reflexive account of methods, ethics and data analysis. *Health* 2020; 24(1): 79–93.
45. Culley L, Law C, Hudson N, et al. A qualitative study of the impact of endometriosis on male partners. *Hum Reprod* 2017; 32(8): 1667–1673.
46. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011; 96(2): 366–373.