

## **A Systematic Review of the Endometriosis and Mental Health sequelae; The ELEMI Project**

Gayathri Delanerolle<sup>1</sup>, Rema Ramakrishnan<sup>7</sup>, Dharani Hapangama<sup>2</sup>, Ashish Shetty<sup>3</sup>, Martin Hirsh<sup>3</sup>, Molola Oyewole<sup>3</sup>, <sup>4</sup>Peter Phiri, <sup>5</sup>Kathryn Elliot, <sup>6</sup>Trusha Kotari, <sup>1</sup>Natasha Sandle, <sup>1</sup>Nyla Haque, <sup>8</sup>Lee Lim, <sup>10</sup>Nicola Pluchino, <sup>11</sup>Martin Silem, <sup>12/15</sup>Jian Qing Shi, <sup>13</sup>Beck O'Hara, <sup>13</sup>M. Louise Hull, <sup>14</sup>Kingshuk Majumder, <sup>16</sup>Vanessa Rayment

### *Affiliations*

<sup>1</sup>University of Oxford, Oxford Brain Health Clinical Trials Unit,

<sup>2</sup>University of Liverpool

<sup>3</sup>University College London Hospitals NHS Foundation Trust

<sup>3</sup>University College London

<sup>5</sup>Southern Health NHS Foundation Trust

<sup>6</sup>Liverpool Women's NHS Foundation

<sup>4</sup>University of Southampton, Primary Care, Population Sciences and Medical Education Division

<sup>7</sup>University of Oxford, Nuffield Department of Women's and Reproductive Health

<sup>8</sup>University of Oxford Health NHS Foundation Trust

<sup>13</sup>University of Adelaide, Robinson Institute

<sup>14</sup>University of Manchester NHS Foundation Trust

<sup>10</sup>Division of Gynaecology and Obstetrics, University Hospital of Geneva

<sup>11</sup>University Medical Center Freiburg

<sup>12</sup>Southern University of Science and Technology

<sup>15</sup>Allen Turin Institute

<sup>16</sup>Department of Psychiatry, University of Oxford

**Correspondence to:** [vanessa.rayment@psych.ox.ac.uk](mailto:vanessa.rayment@psych.ox.ac.uk)

## Abstract

**Background:** Mental Health can be a primary determinant in many physical health conditions although this area is not well researched in women's health. In this systematic review, we evaluate the prevalence and sequential relationship between endometriosis and mental health symptomatologies and psychiatric comorbidities, based on the evidence available. Endometriosis is a complex yet common gynaecological disease impacting 1 in 10 women and is a result of the presence of ectopic proliferating endometrial tissue. Endometriosis can present with severe symptoms of dyspareunia, chronic pelvic pain (CPP), menstrual irregularities and infertility, to name a few. Thus, the relationship between these symptoms and psychological and social effects may be complex to evaluate.

**Methods:** The systematic review protocol was published on PROSPERO (CRD42020181495) prior to the data collection and analysis. The aim was to identify and evaluate mental health reported outcomes including symptomatologies or any psychiatric disorders associated with endometriosis alongside of the prevalence.

**Findings:** A total of 28 papers were included in the systematic review and 17 in the metanalysis. Anxiety and depression symptoms were the mostly commonly reported mental health outcomes whilst a pooled analysis also revealed high prevalence of CPP and dyspareunia.

**Interpretation:**

**Funding:**

## Introduction

Women's health is a complex and vital healthcare composite to manage effective long-term wellbeing. As most women's physical health conditions have a mental health (MH) impact, combining the diagnoses and treatments to provide a holistic approach could optimise clinical care, thereby maximising patient benefit and experience. The issue of multimorbidity has been examined in other areas (Sheehy et al., 2006; Theis et al., 2007; Livermore et al., 2010; Naylor et al., 2012) and has identified how multi-faceted diseases can be managed. This is an important concept for the sustainable development of MH services in such conditions. However, Gynaecology and MH care services globally mostly function independently of each other. This is further reflected in published global healthcare reports, such as those from the World Health Organisation (WHO). For example, the WHO reports that mental illness is a significant morbidity with rapidly

### Research in context

#### *Evidence before this study*

Research into exploring the endometriosis and mental health sequelae is limited. Whilst there have been some cross-sectional studies conducted globally, these have had small sample sizes thus, making statistical significance negligible when compared to the prevalence rates and the generalisability to the wider population. Furthermore, MH is considered as a research priority as reported by The Endometriosis Priority Setting Partnership (PSP) that used James Lind Alliance's priority setting guidelines and reported these in Lancet (2017). Furthermore, NICE guidelines currently stipulate the psychological complexities associated with this cohort of patients is of concern although, there is no diagnosis or treatment standards provided.

#### *Added value of this study*

This systematic review includes an evidence synthesis of the aetiology, pathophysiology and current published literature that shows a sequelae between endometriosis and MH. Previous reviews a combined approach for indicating prevalence data between endometriosis and MH as well as it's association with current pain instruments used within this population of patients.

#### *Implications of the available evidence*

This review demonstrates a complex relationship between mental health and endometriosis that requires comprehensive research to be conducted to explore the mental health disorder prevalence and associations

increasing prevalence rates globally. Depressive disorders account for around 41.9% of dysfunctions amongst women and thus are a leading mental health condition (WHO, 2020). However, these reports do not indicate if these women have any other physical conditions which may have a causal effect. Anxiety, depression and psychological distress are said to be rising at alarming rates as a result of many factors (WHO, 2020), and any association with comorbidities remains unclear. The WHO 2020 global disability burden reports show unipolar depression has doubled in term of its burden amongst women (WHO, 2020). Yet, minimal research is available to clinically develop the required services and interventions to address these issues.

Additionally, there maybe added complexities around communication and engagement between women and healthcare professionals that could attribute to non-disclosure of psychological and/or emotional distress. This could lead to gender biases in the treatment of women. Couple these factors with complex clinical conditions such as endometriosis, and the global MH burden for women may increase further, at undetermined rates. Despite this, currently, the WHO and many other health care organisations lack comprehensive systems and methods to report prevalence data pertaining to multimorbidity conditions and their MH sequelae.

In order to further evaluate this issue, high quality and generalisable research is required to understand the MH sequelae of chronic long-term conditions such as endometriosis, to demonstrate the knowledge and clinical practice gaps that require addressing. Thus we conducted a multi-faceted evidence synthesis using a systematic review and meta-analysis to identify and report on the epidemiological, aetiological and pathophysiology of endometriosis and its MH sequelae.

## **Evidence synthesis:**

### *Epidemiology and burden of disease*

Identification of MH disorders and pathways for their clinical care are explored within the UK via National Institute of Care and Excellence (NICE), with an aim to improve diagnosis and treatments. According to NICE, the most common MH disorders in the general population are depression and anxiety disorders. The prevalence data varies, although the Quality and Outcomes Framework indicated over 4.5 million people were diagnosed with depressive disorders in 2017/2018 alone. This equates to 10% of all adults registered with UK GPs in comparison to the 6% in 2012/2013. However, it is unclear the number of women with endometriosis that have been diagnosed with depressive illness or other MH conditions in the UK. In contrast to this, the global MH burden currently resides at over 700 million. Thus, a global solution to this health issue could be an effective way to manage the current population of patients and the medium to long-term burden of disease. In line with this, the WHO introduced a comprehensive MH action plan (2013-2020) to better direct and support MH initiatives, in order to recognise and improve MH healthcare services (WHO, 2013; Saxena et al 2013; WHO, 2008). Some of the targets from these discussions indicated the need for strengthening information systems and increasing the evidence base, as well as research around MH to better integrate these systems into routine care. This was further advocated by various international reports, including the Global Burden of Disease (2017) that highlighted 792 million people live with MH disorders globally. Whilst these reports and recognition are

vital for clinical researchers, clinicians and patients, prevalence data for multi-morbid conditions such as endometriosis and the sequelae shared with MH remains unresolved. This is concerning given that, current data indicates endometriosis affects 176 million women globally (De Graff et al 2013). Furthermore, De Graff and colleagues report over 50% of women with endometriosis report a negative impact of the disease on their personal relationships (De Graff et al 2013). Delayed diagnoses is a significant factor in the delay in diagnosis of the disease that on average takes 7-8 years. The UK National Institute for Health and Care Excellence (NICE) guidelines stipulates that delays in diagnosis of endometriosis can affect quality of life and result in disease progression (NICE, 2018). The subsequent progression of endometriosis beyond the initial diagnosis remains a controversial issue with a hitherto unknown natural history of the disease (Tempest et al 2020). Consequently, there is a dearth of reliable evidence to suggest earlier medical intervention may affect the long-term clinical outcomes of endometriosis, since the available treatments are neither universally acceptable or curative. Endometriosis is also a heterogeneous condition, and even surgical excision doesn't completely or consistently relieve the commonly experienced pelvic pain, and this adds to the difficulties of identifying the prevalence of MH symptoms and disorders. For women who are trying to conceive naturally, apart from simple analgesics, there are no suitable treatments available to alleviate CPP and dyspareunia. Thus, the consequent cost of endometriosis to the women, their families, health services, the economy and society can be significant.

### *Aetiology of Endometriosis*

Endometriosis is defined by the presence of endometrium-like tissue outside the uterine cavity and comprises of complex symptomatology such as, dysmenorrhea, CPP, sexual dysfunction, and subfertility. A widely accepted theory of pathogenesis is Sampson's transplantation theory (Koninckx et al 2018; Sampson et al 1927), 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 amongst women with Mullerian Duct anomalies indicate an obstructed flow increases the possibility of retrograde menstruation. This is also purported by patient reported outcomes of frequent and heavy menstruation with an unusually lengthy duration, thus, further increasing the exposure of the pelvic cavity to develop endometriosis. However, contradictions to this theory have been published, where epidemiological data also indicates that where only 0.5-5% of women with retrograde menstruation appear to develop endometriosis (Halme et al 1984).

Therefore, theories still require more robust evidence to explain the reasons for the presence of endometriosis within other areas such as the pleurae, central nervous system and even the prostate. Rock and colleagues (1992) proposed haematogenous spread, peritoneal mesothelium metaplasia or embryonic rests as plausible explanations for development of endometriosis. In recent years, it has been hypothesised that a degree of genetic susceptibility may lead to increased disease prevalence in first-degree relatives of women with endometriosis, based on data from the Oxford Endometriosis Gene (OXEGENE) study (Kennedy et al 1998). A composite theory that includes all of the above features may be a more suitable explanation, as immunogenic factors are also associated with the development and spread of endometriosis, based on analysis of peritoneal fluid that shows disproportionate levels of cytokines, interleukins, prostanooids and growth factors (Sourial et al 2014).

### *Pathophysiology of Endometriosis*

The diagnosis, management and treatment of endometriosis is complicated by multiple factors, including issues around the development of the disease, staging, severity and treatment responses, as well as the 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, as with any multimorbidity condition, further complications may arise in its long-term management as a result of MH symptomatology and comorbidities. Furthermore, these symptoms may compromise the social relationships of these patients. CPP is one of the most common chronic pain problems experienced by women, which may certainly be compounded by MH sequelae. In addition to these complex symptoms, these patients are also at high risk of comorbidities such as inflammatory bowel disease, adenomyosis, fibromyalgia and other autoimmune diseases. 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.

### *Pathophysiology and relevance to Mental Health*

Current published research indicates a strong link between mental and physical health (Ohenberger et al 2017), although most chronic conditions are not well evaluated sequentially. To complicate the field further, despite numerous theories being proposed (Souriel et al 2014), both the pathogenesis and pathophysiology of endometriosis are poorly understood, and there is no correlation between the severity of symptoms and surgically assessed disease, in location, content and subtype. All of these features of endometriosis are likely to adversely affect women's mental health although, theories around the pathophysiology of this sequelae also remain under-researched and unclear. The long-term consequences of lack of any preoperative psychosocial evaluations, lack of ongoing psychological support could be far reaching.

As a result of these factors, a suitable hypothesis was developed with a systematic review protocol, in order to identify the MH sequelae of endometriosis based on existing published data.

## **Systematic review**

### *Methods*

A systematic review protocol was developed and published on PROSPERO (CRD42020181495) with a specific inclusion and exclusion criteria to identify endometriosis (with or without pain) studies that reported MH outcomes amongst women of reproductive age. Both interventional and non-interventional randomised controlled clinical trials, quasi-experimental and all other study types were included into the review. The review focused on a timeline dating back to 1987 until the 30<sup>th</sup> of August 2020<sup>1</sup>. The exclusion criteria focused on studies that did not report on MH outcomes.

The definition of MH outcomes for the purpose of this review includes any diagnosed and/or treated disorders or symptoms such as depression or anxiety. Studies with health-related quality of life (QoL) or self-efficacy were also part of the inclusion criteria, if there were MH specific patient reported outcomes that indicated psychosocial factors.

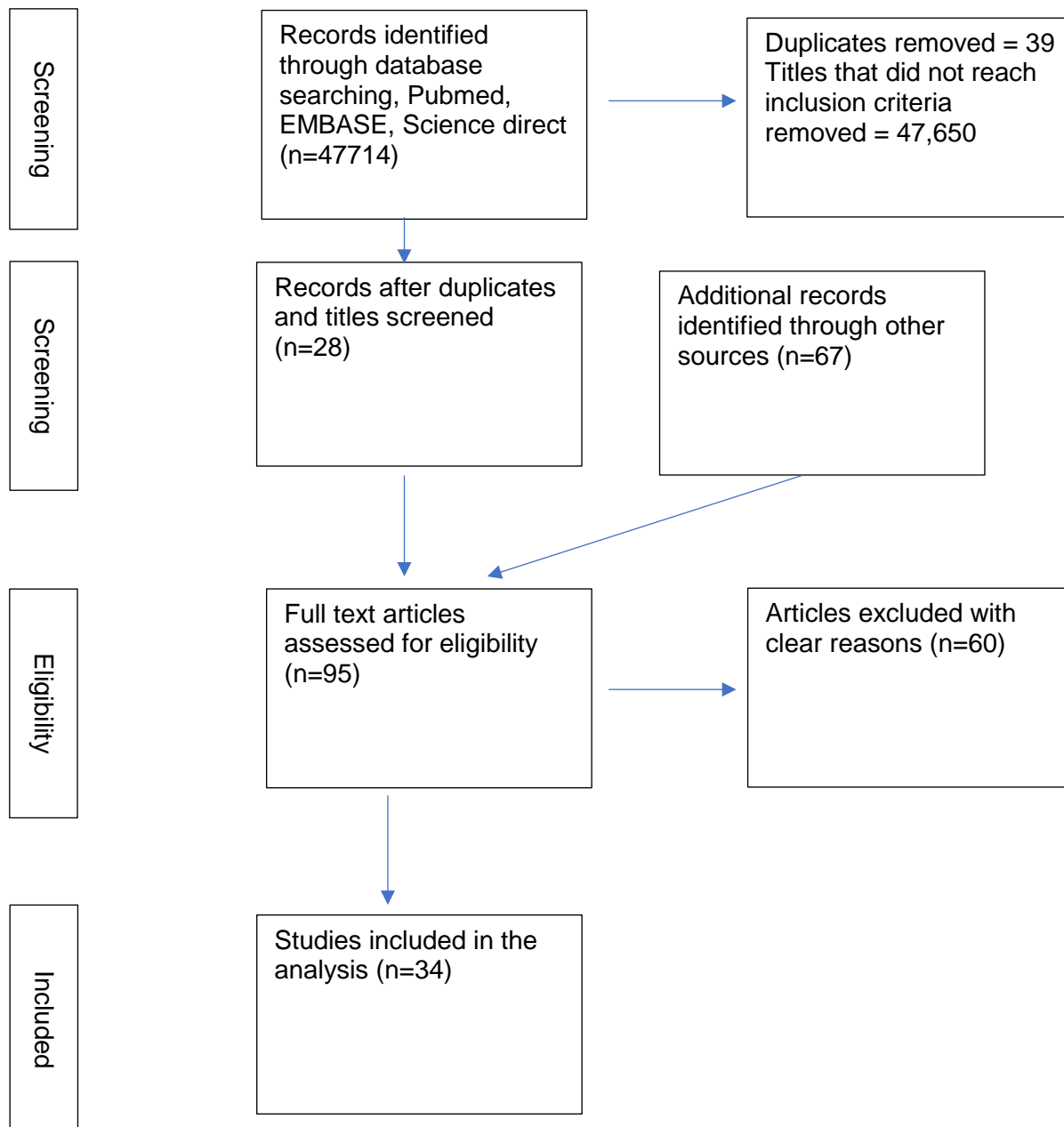
### *Search strategy*

In order to conduct the search strategy, key words and phrases were developed to apply to electronic databases of Ovid Embase, Ovid EDLINE, Cochrane Gynaecology and Fertility Group, Science Direct, BIOSIS, EBSCO and Cochrane Central Register of Controlled Trials. All papers listed as having endometriosis as the primary condition, with any MH conditions reported as an underlying issue, and vice versa (PROSPERO, 2020). All publications identified were restricted to English as the primary language. Relevant articles were then finalised as per the inclusion criteria.

### *Data extraction and synthesis*

Two authors screened the study titles, abstracts and references to ensure the inclusion and exclusion criteria was met prior to listing these within the SR. A total of 34 studies were selected and their full texts were reviewed to ensure the eligibility criteria was met. A data extraction was created specifically highlighting characteristics of the study and patient reported outcomes, in addition to overall study specific outcome measures, main findings and any interventions used. This data was then examined by the SR statistician for further refinement to ensure the quality of the evidence was assessed prior to completing the analysis.

### Study and data collection



## Results

A total of 34 cross-sectional studies were identified, of which 28 were included into the SR. Out of 28 studies included in the SR, 17 were included in the meta-analysis (anxiety: 6, chronic pelvic pain: 3, depression: 11, and dyspareunia: 3).

No	Author	Age	Clinical presentation	Sample	Medication	MH Outcomes	Pain outcomes	Outcome Assessment Tools	Other findings
1	(Garry.et al 2000)	Not given	Pelvic pain Dyspareunia	57	Not Applicable	Mental Health	Pelvic Pain Dysmenorrhoea Dyspareunia	SF12 - Mental component Modified Redwine and Perex questionnaire	Fertility Quality of Life
2	(Kumar et al., 2011)	30.3 (19-44)	Pelvic pain	39	Not Applicable	Biopolar I Disorder Biopolar II disorder Biopolar disorder Panic Disorder Major Depressive Disorder	Pelvic Pain	DSM-IV SF-MPQ FPS LSQ	Life satisfaction
3	(Matalliotakis et., al 2008)	34.4	Pelvic pain, dysmenorrhea, and dyspareunia	735	Not Applicable		Pelvic Pain Duration of infertility Dysmenorrhoea Dyspareunia	Medical records	
4	(Carey et al., 2014)	36.4	Pelvic pain	79	Not Applicable	Mental Health Depression (Normal/Borderline) Depression (Mild/Moderate/Severe)	Dyspareunia	SF-MPQ BDI	Physical Health Menses
5	(Smorgick et al., 2013)	17.8		138	Not Applicable	Mood Disorder	Pelvic Pain Pain or burning during urination Pain with bowel movements Pain with sexual intercourse Pain with physical activity	Medical Records	
6	(De Graaff et al., 2016)	Not given		243	Not Applicable	Chronic Pain Sexual Anxiety and discomfort Anxiety Depression	Dysmenorrhoea	FSFI SF-12 PCS SSCS HADS	Sexual Function Wellbeing Fertility, depression, anxiety scores, dyspareunia
7	(Cavaggioni et al., 2014)	With Endometriosis: 36±7.6 Control: 34.9 ± 10.1	Non-menstrual pelvic pain, Dysmenorrhea, Dyspareunia	80	Not Applicable	Psychotic Disorder Mood Disorders Anxiety Disorders Somatoform Disorders Eating Disorders Alexithymia	Dysmenorrhoea Dyspareunia Non Menstrual fPelvic Pain	SCL-90-R DSM IV-TR SCID-I cv SCL-90-R TAS-20	



## ***Statistical analysis***

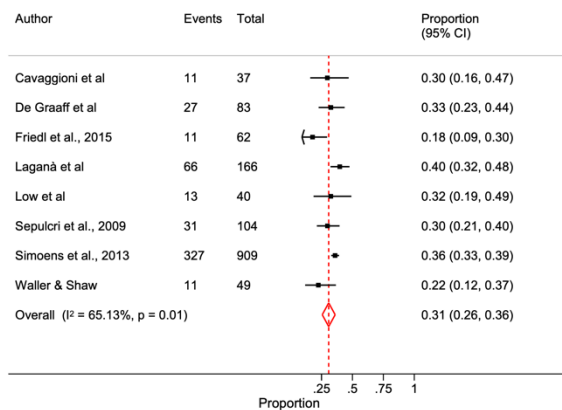
Summary statistics were extracted from studies that reported mental health outcomes in women with endometriosis or chronic pain. These statistics were either prevalence or mean (standard deviation [SD]) or median and interquartile range (IQR). Estimates for studies that reported median and IQR were converted to mean and standard deviation. 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. We assumed normality of the distribution when mean (SD) were reported or the data were symmetrical. The total sample size for this SR is 4266 with 1564 attributed for anxiety followed by 2234, 1848 and 952 for CPP, depression and dyspareunia respectively.

Estimate pooled prevalence were calculated for anxiety, depression, chronic pelvic pain 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 chronic pelvic pain 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 (citation: Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60). 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 visualisation of funnel plot and Egger's test for only depression since it was the only outcome with sufficient number of studies. Analysis were conducted using STATA 14.0.

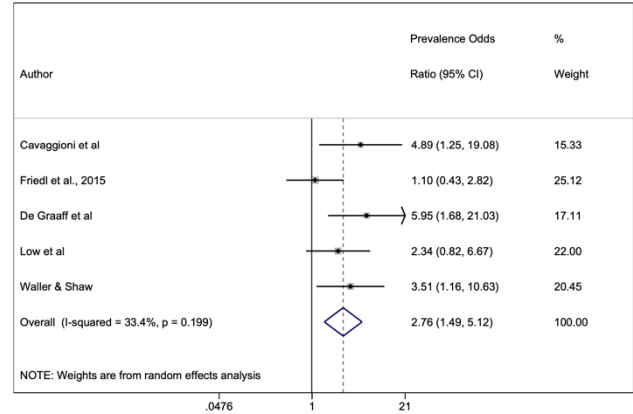
### ***Anxiety***

The pooled prevalence estimate was found to be 31.8% (95% CI: 26.5% - 37.1%). (Figure) We were able to pool three studies to compute prevalence ratios. The prevalence of anxiety symptoms were 2.5 times higher among women who had endometriosis compared to women without endometriosis. A prospective cohort study that was not included in the meta-analysis (insert citation: Chen, 2016) 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.

Forest plot of pooled prevalence estimate of anxiety among women with endometriosis

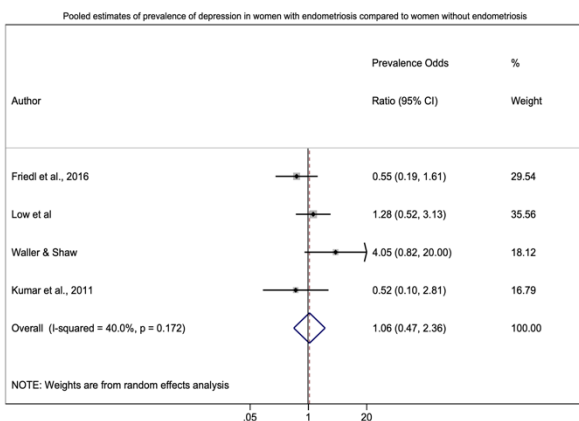


Pooled estimates of prevalence of anxiety in women with endometriosis compared to women without endometriosis

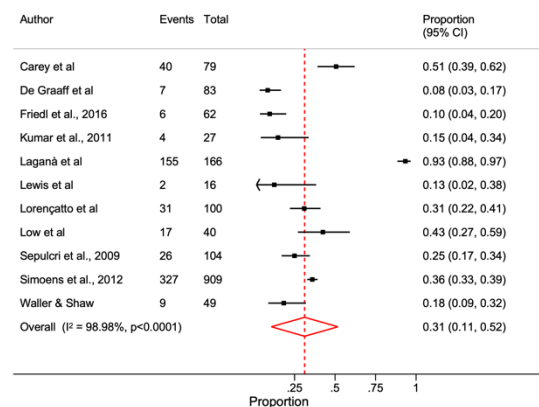


## Depression

We found the pooled estimate for depressive symptoms among women with endometriosis to be 28.9% (95%CI: 8.6%-49.2%) (Figure). 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%) (Figure). Sensitivity analysis conducted after excluding a study that enrolled patients from primary care instead of tertiary care/women's clinic/university hospital/gynaecological clinic resulted in little change to the prevalence estimate. However, meta-analysis of only cross-sectional studies resulted in a lower prevalence compared to the overall estimate (22.0% vs 28.9%) (Figure). However, meta-analysis of three studies did not reveal strong evidence of higher prevalence of depression among women with endometriosis compared to women without endometriosis (Figure).

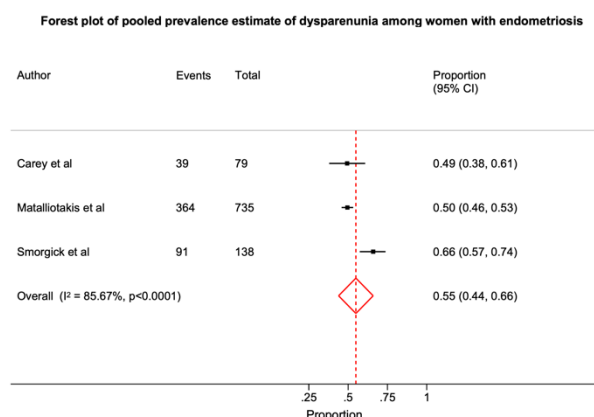


Forest plot of pooled prevalence estimate of depression among women with endometriosis



## Other outcomes

The pooled prevalence estimate for CPP was high at 57.2% (95%CI: 7.0%, 107.4%) (Figure). We found the pooled estimate of mean SF-MPQ for chronic pain to be 13.09 (95%CI: 7.13, 19.05) (Figure). The other outcome for which we were able to compute prevalence was dyspareunia which was found to be high (prevalence: 54.9%, 95%CI: 43.9%, 65.9%) (Figure).



### *Publication bias*

Funnel plot suggested evidence for publication bias with a tendency for studies with low prevalence rates for depression to be not published (Figure). 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.

### *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.

### ***Thematic and narrative analysis***

#### *Mental Health*

Based on the 3 variables identified (i.e. depression and anxiety), the evidence does not indicate if the reported MH outcomes are reported symptoms, disorders or confirmed diagnoses. Thus, whilst this SR has identified patient reported MH outcomes, their clinical significance remains unclear. Overall, there is negligible evidence to indicate adequate reporting of the MH needs within the endometriosis population based on the pooled studies. 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 holistic approach is being used, or at least reported. As a result of this, a wider evaluation of the MH sequelae of endometriosis is required.

In order to better characterise 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 and colleagues (2017) 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 (Li et al 2017). Furthermore, Tokushige (2007) et al 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) (Asante, et al 2011) and influence pain sensitisation amongst patients, and it could be argued that this may impact the electrophysiology of the brain further. Additionally, 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 (Asante et al 2011). So overall, these mechanisms appear to be complex in nature. In addition to this, further evidence of the CNS involvement has been reported by Agarwal and colleagues (2010) 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 emphasises the need to better characterise and understand the MH sequelae amongst endometriosis patients. To do this, comprehensive assessment tools maybe required to better characterise and report MH symptoms and clinical features through patient reported outcomes.

Additionally, to better develop rationalised approaches using logic models, MH issues contribute to evaluations of Quality of Life (QoL) in a binary manner. To fully explore QoL amongst endometriosis patients, the mechanistic nature and role of MH difficulties should be further explored. Current QoL data is probably not reflective of the *true* individual disease burden in the short, medium or long-term, and thus is less indicative of the *true* impact to endometriosis on women.

QoL data should also be used to develop suitable health-economic-models (HEM) for endometriosis and associated comorbidities. Without this, it is not feasible to evaluate the true health and social care cost as a result of endometriosis and MH sequelae globally or regionally. 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 because of the complex characteristics demonstrated amongst this population of patients. This is also apparent in grey literature. In this meta-analysis, the majority of the data was on prevalence although, the sample sizes were limited, preventing any sub-group analysis being conducted on age groups, ethnicity and geographical location. Therefore, only a compute pooled estimate of prevalence was reported. 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 generalised to the wider population.

## *Pain*

Dyspareunia is a feature of sexual pain disorders. It is also a cardinal feature of endometriosis (Kate et al 2020), thus leads to 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, whilst 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 Questionnaire [96]) and its impact on sexual function (e.g., Female Sexual Function Index [97], Female Sexual Distress Scale [98]), and psychological (e.g., Beck Depression Inventory-II [99], Beck Anxiety Inventory [100]) and relationship adjustment (e.g., Dyadic Adjustment Scale [101], the Locke-Wallace Marital Adjustment Test [102]) 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 sufferers and this can be attributed to lack of evidence and a clear guidance for its use.

Indeed, surgically diagnosed endometriosis patients may have a better probability of obtaining confirmed diagnosis of dyspareunia. Inadequate assessments could be one reason for the current difficulties in managing these symptoms, that could ultimately lead to psychological distress impacting a patient's 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. One way to address this would be to introduce a tool for early assessment of pain and any associated psychosocial impact with long-term monitoring that could significantly support patients and clinicians alike.

## *Mental health difficulties as a result of Endometriosis*

Across most studies, a recurring theme is patients' experiences of pain, dyspareunia, irregular bleeding and infertility. 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. However, 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 (Skovlund et al 2016).

There was also a theme that indicates endometriosis impacted intimate relationships. This has been suggested to be between 33.5% and 71% (Bernuit et al 2011; Fourquet et al 2011), largely as a result of CPP and dyspareunia. Bernuit and colleagues' (2011) 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 (Hudson et al 2018; Culley et al 2017)

Furthermore, due to the mental and physical health impact of endometriosis, studies indicate changes in psychosocial behaviours. A total of 17 papers reported the impact of endometriosis on general 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 demonstrated a reduction in QoL (Marques *et al.*, 2004; Petrelluzzi *et al.*, 2008; Siedentopf *et al.*, 2008; Bernuit *et al.*, 2011; Tripoli *et al.*, 2011; Chene *et al.*, 2012) with a few patients reporting their experience to be "worse than death" (Simoens et al 2012).

A distinctive feature reported by researchers and patients alike within these papers is pain which is consistent with a negative connotation when managing MH. 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 (2012) reported between 16-61% (Fourquet et al., 2011) 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 and colleagues (2011) demonstrated a considerable reduction in physical health amongst endometriosis patients in comparison to the rest of the population.

## **Limitations**

The primary limitation of this review is the inclusion of cross-sectional study data 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, and some studies were excluded on this basis.

## **Discussion**

Women with endometriosis suffer from a range of symptoms although the most complex symptomatology is frequently associated with mental health-related distress and psychiatric comorbidities. Psychosocial factors and a range of pelvic pain disorders frequently exacerbate the patient's experience of endometriosis and associated MH symptoms. Furthermore, cross sectional studies have shown exacerbated MH distress due to alterations of body image, loss, hopelessness, alexithymia and worthlessness (Aerts, 2018). Pluchino and colleagues (Aerts, 2018) discussed the detrimental psychological impact and adjustments made by women with endometriosis and heightened pain-related experiences and levels of distress.

Four of the 34 studies identified used a clinical diagnostic assessment to diagnose psychiatric disorders. These samples examined age ranges from adolescence to the mid-life, whilst Kumar and colleagues demonstrated characteristics of the patients. Kumar and colleagues described that familial mood disorders were identified amongst 37% of the endometriosis

sample and 50% of the pelvic group. Neither of these groups were receiving any GnRH treatments, thus, causation of psychological distress may be independent of any reported drug side effects (Pope et al 2015). Kumar et al 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 (Pope et al 2015).

A key finding of our review is that the pain instruments used have considerable variability, in terms of the questions included as well as scores provided to calculate the burden of symptoms. It is unclear, based on these findings, if patients were diagnosed with a pain condition, with the exception of a few studies that reported the specifics around such diagnoses. Whilst we acknowledge pain is a complex condition to evaluate, diagnose and treat, to understand the applicability of the scores requires common denominators between the instruments which are currently lacking. Therefore, the mental health burden associated with pain in this instance cannot be determined. Furthermore, the lack of confirmed endometriosis cases with pain and the subsequent relationship with mental health is based largely on study reported outcomes, rather than via a comprehensive association or dissipation paradigm analysis

## **Conclusion**

This SR shows that the most common type of MH symptoms and psychiatric comorbidities reported in patients with endometriosis are anxiety and depressive disorders. There are a large proportion of studies with poor study designs and small sample size, which therefore may not be reflective of the wider endometriosis population. These studies also fail to differentiate MH symptoms from psychiatric disorders. Overall, psychiatric comorbidities remain unreported and unsubstantiated with the exception of the study reported by Fleming et al (2020) that suggested reduced psychological functioning and QoL as a result of mental health difficulties. In fact, the authors reported that 56.4% of women with endometriosis fulfilled the clinical criteria for psychiatric disorders. However, the risk of psychiatric comorbidities amongst the endometriosis populations remain significantly unresearched. Interim clinical plans to address these disturbances remain inconclusive due to the lack of association data between CPP, endometriosis and mental health issues. This paper also demonstrates that the current literature is insufficient to establish either a unidirectional or a bidirectional causality between endometriosis and mental health problems. The more precisely a patient can describe her pain in terms of time, location, triggering and relieving factors, the higher the likelihood that surgical or medical treatments will help, but it is also likely that pain presentation is influenced by mental health symptoms. Most studies describe stress-related disorders, eating disorders, attention deficit hyperactivity disorders and personality disorders as being common amongst women with endometriosis and may even suggest familial liability, although the mechanistic causation requires to be investigated further as the generalisability of this data remains poor. It is important to acknowledge the importance of conducting comprehensive and statistically significant research to further the understanding of the association of endometriosis and MH conditions. This would further treatment for women with endometriosis using a multidisciplinary approach, which could provide improved management for this complex, multifaceted condition.

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