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Depression, Anxiety, and Correlating Factors in Endometriosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Endometriosis stage is not directly related to the burden of symptoms, and recurrence of symptoms occurs frequently. It is suggested that symptoms are associated with psychological distress, as in depression and anxiety disorders. Our aim was to explore the strength of the associations between endometriosis and depression or anxiety and to review correlating factors.

Materials and Methods: A literature search was carried out using the electronic databases Embase, PubMed, Web-of-science, and PsycINFO. Search terms related to depression, anxiety, and endometriosis were combined resulting in 1,837 records. Articles were included when describing an association between patients with endometriosis and symptoms of depression or anxiety assessed by validated tools, structured psychiatric interviews, or a documented diagnosis. With 47 articles a systematic qualitative review was performed. Seventeen studies were eligible for meta-analysis.

Results: Endometriosis patients experienced significantly more symptoms of depression (standardized mean difference [SMD] of 0.71 (95% confidence interval [CI] 0.36–1.06)) and anxiety (SMD 0.60 (95% CI 0.35–0.84)) compared with healthy controls, but no differences were found comparing endometriosis patients with other chronic pelvic pain patients (SMD −0.01 [95% CI −0.17 to 0.15] for depression and SMD −0.02 [95% CI −0.22 to 0.18] for anxiety). Besides the effect of pain, other correlating factors included age, quality of life, quality of sleep, fatigue, sexual function, gastrointestinal symptoms, comorbidity, self-esteem, emotional self-efficacy, coping style, social adjustment, pain imagery, and pain sensitization.

Conclusion: This systematic review supports the assumption that symptoms of depression and anxiety occur frequently in endometriosis patients and are related to chronic pain. Correlating factors should further be investigated.

Keywords: anxiety, depression, endometriosis, pain, psychosomatic symptoms

Introduction

Endometriosis is defined as an estrogen-dependent condition with the presence of endometrium-like tissue outside the uterus.[1] The prevalence has been estimated between 2% and 10% in women of reproductive age and up to 50% in women with chronic pelvic pain (CPP) or fertility problems.[2,3] A combination of retrograde menstruation, defective immune clearance, and changes in the peritoneal environment that stimulate cell growth is the most widely

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accepted explanation concerning pathogenic mechanisms.[4] Dysmenorrhea, CPP, dyspareunia, fatigue/weariness, and infertility are the leading symptoms,[5–7] and the nonspecific presentation of these symptoms often causes a delay concerning diagnosis.[8–10] The stage of the disease, pelvic pain, infertility, and a higher number of years since diagnosis are associated with higher economic burden to society, as symptoms affect physical, mental, sexual, and social well-being, in addition to work productivity.[11–13] Furthermore, the anatomical stage of endometriosis is not directly related to the burden of symptoms[14] and recurrence of symptoms after surgical or medical interventions occurs frequently.[15] It is suggested that the perception of symptoms may be associated with psychological distress and related affective conditions, such as depression and anxiety disorders.[16,17] Depression and anxiety disorders are classified by the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V) psychiatric diagnostic criteria,[18] and the global prevalence ranges from 4.5% to 7% and 5.5% to 6% respectively in women of reproductive age.[19] A relationship between depression, anxiety, and endometriosis has been described from 1979 onward.[20] Demographic characteristics, social and disease-specific factors may predict psychological ill-health in endometriosis patients and could therefore lead to potential prediction models for the risk of developing depression or anxiety disorders in these patients.

This systematic review aims to give an overview of what is known about the association between endometriosis and symptoms of depression or anxiety regarding its strength and direction and to further examine which factors are associated. In addition, this review may help to elucidate the importance of psychological and psychiatric screening and to evaluate which patients are vulnerable to developing depression or anxiety disorders. This is important for clinical practice since the presence of anxiety and depression may influence the perception of symptoms, prognosis, compliance with treatment, and quality of life.[21]

Materials and Methods

This systematic review was registered in PROSPERO (CRD42018106983) and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22,23]

In- and exclusion criteria

Full-length original articles meeting the following criteria were included:

- Including patients with suspected endometriosis corroborated by physical examination and imaging techniques and/or proven by laparoscopy;
- Using a validated multi-item scale or structured diagnostic interview for the assessment of depressive symptoms and/or anxiety, or a registered diagnosis of depression or anxiety disorder (DSM or International Classification of Diseases [ICD] code)*.
- Reporting an association between endometriosis and depression and/or anxiety;
- Peer-reviewed journal articles published in English.

Animal studies, reviews, abstracts, and expert opinions were excluded.

*DSM or ICD codes for depression or anxiety disorder are given by a professional and therefore most likely (in the past) followed by a structured diagnostic interview.

Literature search

A systematic literature search was performed in PubMed, Embase, PsychInfo, and Web of Science until the 16th of June 2020. All studies that were published by that date were included. The detailed query is listed in the Supplementary Appendix Table SA1. Search terms used were related to endometriosis, depression, and anxiety. First, duplicates were removed. Three reviewers (E.B., J.M., and M.P.) independently reviewed titles and abstracts, and selected articles were reviewed on full text. Disagreements were handled by discussion and a third opinion (L.V.).

Risk of bias assessment

Assessing the risk of bias, the Newcastle–Ottawa quality assessment scale for cohort studies and case–control studies was used[24] as advised by The Cochrane Reviewers' Handbook.[25] In studies not including a control group, the checklist for reporting case series as published by Kempen was used.[26]

Data selection and analysis

Articles were screened on reporting an association between endometriosis and depressive or anxiety symptoms. Furthermore, factors correlated with or contributing to this association were listed. Data from studies using validated outcome measures and reporting a mean and standard deviation (SD) concerning depression or anxiety scores in endometriosis patients compared with a control group were pooled. Women of reproductive age without a diagnosis of endometriosis or pelvic pain were considered as healthy controls. Women with CPP syndromes without a diagnosis of endometriosis were considered as CPP patient controls. The corresponding author was contacted if a mean and/or SD was not provided in the article, and additional data were added to pooling. Values were not included when not following a normal distribution. A random-effects meta-analysis was carried out using STATA version 14 Software. Because of the heterogeneity in assessment tools, a standardized mean difference (SMD) with a 95% confidence interval (CI) was calculated. The heterogeneity was tested through I^2 tests with a significance level of 5%. An I^2 of >50% was considered as significant heterogeneity. In this case, a sub-analysis was performed. Mean age (and SD) of cases and controls are provided to assess comparability.

Results

Selection process

The database search initially identified 1,837 records. After removal of duplicates and adding articles from reference lists, 1,289 remained for screening on title and abstract. A total of 127 articles were assessed on full text. A consensus was obtained in 90%, the remaining 10% were handled by discussion and a third opinion. Finally, 47 articles were included and a systematic qualitative review was performed.[20,27–72] Due to

variations in study design, lack of control groups, different methods of outcome measuring and due to missing data, only 17 articles were eligible for data-pooling and meta-analysis.[20,28,29,35,38,43,46,51,54–56,59–61,66,67] Figure 1 shows a flowchart of the literature review process.

Study characteristics

An overview of the included articles, study design, sample size, population characteristics, measurement tools, results, and factors correlated to anxiety and depression in endometriosis patients is listed in the Supplementary Appendix Table SA2.[20,27–72] We have included 41 studies with a cross-sectional design, three longitudinal cohort studies, and three retrospective cohort studies. Most studies (52%) originated from Europe, 26% from the United States of America or Canada, 15% from South and Central America. The remaining articles (7%) originated from Asia, Africa, or Oceania. Eleven of the included studies were published in the current year 2020.

Quality assessment

An overview concerning the risk of bias ascertained for each article is listed in the Supplementary Appendix Table SA3. Overall, biases were mostly caused by study design (not including a healthy control group) and patient selection as most studies included women in tertiary referral centers. Most case series lacked the description of a hypothesis or did not discuss the biological plausibility of the hypothesis in the light of reports' observations.[26] Cohort studies and case–control studies, as assessed by the Newcastle-Ottawa scale,[25] most frequently used hospital controls instead of community controls, and missing data were poorly reported.

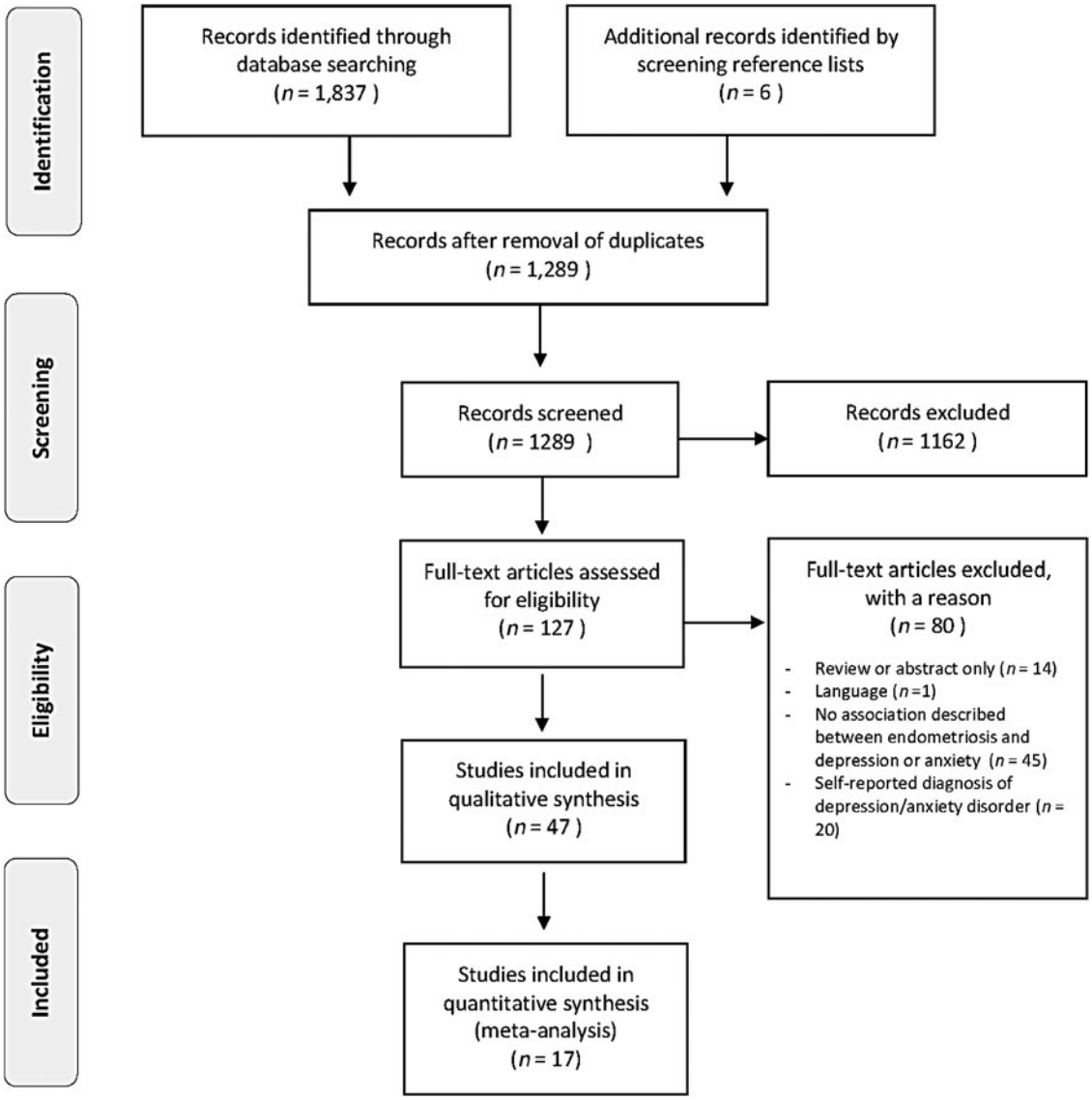

FIG. 1. Flowchart of selection process according to the PRISMA guidelines, 2009.[23] PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Assessment tools

Forty studies included in this systematic review used a self-reporting validated outcome measurement tool and two studies performed a structured diagnostic interview for reporting either depressive or anxiety symptoms or both. Five studies reported depression or anxiety disorders based on medical records (ICD-9 diagnoses). Various outcome measures were used, of which the details are listed in Supplementary Appendix Table SA4.[73–92] In 83% of studies, assessment tools with adequate or good reliability and validity were used (Cronbach's alpha >0.8 and correlation coefficient >0.60 respectively). With regard to the assessment of depressive symptoms, the Hospital Anxiety and Depression Scale (HADS) or Becks Depression Inventory were most frequently used (28% and 26% of studies respectively).[75,82] Concerning the assessment of anxiety symptoms, the most commonly used tools were the HADS (28%) or the State-Trait Anxiety Inventory (STAI, 13%).[82,91] Assessment of anxiety symptoms included the evaluation of either general, state, trait, and/or phobic anxiety. Instruments developed for the global assessment of anxiety focus on the assessment of mood, cognition and behavior, whereas tools for assessing phobic anxiety more often include somatic symptoms of anxiety.[93] State anxiety questionnaires evaluate anxiety as a current emotional state, whereas trait anxiety questionnaires evaluate individual differences in anxiety as a personality trait.[94]

Study subjects

A total of 1,933,846 subjects were reviewed, including 154,725 endometriosis patients, 1,778,317 healthy controls, 418 CPP patients, in whom endometriosis was ruled out by laparoscopy, and 386 infertile women without endometriosis. Of 47 included studies, 32 studies (68%) specifically included only endometriosis patients with a surgical diagnosis of endometriosis. For the comparison of patient groups, different types of methods were used. Twenty-one studies investigated anxiety and depression symptoms in endometriosis patients without including a control group[27,33,34,36,37,39–42,45,47,49,50,52,57,58,62,64,65,68,69,71,72] and were, therefore, not eligible for the meta-analysis. Twenty-six studies compared endometriosis patients with a group of pain-free healthy controls (community or hospital controls),[30,32,35,38,39,46,51,55] CPP patients without endometriosis,[29,48,54,59,66] infertile patients without endometriosis,[60,63] or a combination of pain and pain-free patient control groups.[20,28,43,44,53,56,61,67,70] Healthy pain-free controls were most frequently hospital controls (75%). However, some studies used community controls or medical staff and students as a (non-patient) healthy control group (15%). In 5% of studies the type of control group was unclear or mixed (hospital and community controls). Four studies compared endometriosis patients with pain symptoms with pain-free endometriosis patients.[28,34,35,47] Two studies compared endometriosis patients with and without infertility.[58,61]

Depression

Depending on the outcome measure that was used, depressive symptoms occurred in 10%–86% of patients with endometriosis. Symptoms were reported to be mild in 13%–68% and moderate to severe in 2%–64% of patients. In comparison, depressive symptoms occurred in 7%–19% of healthy controls in the included studies. Chen et al. reported an increased risk of developing major depression (hazard ratio [HR]: 1.56, 95% CI 1.24–1.97) and any depressive disorder (HR: 1.44, 95% CI 1.25–1.65) for women with endometriosis compared with healthy controls.[31]

Most case–control studies reported that symptoms of depression occurred significantly more often in endometriosis patients compared with healthy controls[20,28,30–32,35,39,43,46,51,61,65,67] but not compared with CPP patients without endometriosis.[20,29,43,48,53,54,56,59,61,66] On the contrary, four studies did not find a higher depression rate in endometriosis patients compared with healthy controls.[38,44,56,70] Two studies found no difference in depression symptoms in pain-free endometriosis patients compared with healthy controls.[28,35] Stratton et al. found a higher rate for depression in CPP patients compared with endometriosis patients.[67]

Figure 2A shows pooled data including 11 studies comparing 513 endometriosis patients with 600 healthy controls. Meta-analysis reveals a significantly higher symptom score for depression in patients with endometriosis (SMD 0.71 [95% CI 0.36–1.06]). The I^2 value of 83.7% shows high and significant heterogeneity, which was most likely caused by the variety in definitions of healthy controls. A sub-analysis including seven studies with solely hospital controls, without infertility, reveals an SMD of 0.75 (95% CI 0.54–0.96) with a low and nonsignificant I^2 of 27.8% (Fig. 3A). Figure 2C shows pooled data including 11 studies comparing 284 endometriosis patients with 407 CPP patients without endometriosis. Meta-analysis shows no significant difference in depression scores between the two groups (SMD −0.01 [95% CI −0.17 to 0.15]). The I^2-test reveals heterogeneity of 0%. The mean scores and SD of age and results on validated outcome questionnaires per study are shown in Tables 1 and 2.

Anxiety

Depending on the outcome measurement, anxiety occurred in 10%–79% of patients with endometriosis. Symptoms of anxiety were reported to be mild in 22%–79% and moderate/severe in 23%–64% of patients. In comparison, anxiety occurred in 6%–14% of healthy controls in the studies included. Chen et al. reported an increased risk for women with endometriosis of developing anxiety disorders (HR: 1.44, 95% CI 1.22–1.70) compared with healthy controls.[31]

Twelve studies reported higher anxiety scores (including state, trait, and phobic anxiety) in endometriosis patients compared with healthy controls.[20,28,31,32,35,39,43,44,46,51,65,67] In nine studies no differences in anxiety scores were found between endometriosis patients and CPP patients.[20,29,43,44,54,56,59,61,66] Furthermore, four studies did not report any difference between endometriosis patients and healthy controls concerning anxiety scores.[30,38,56,61] Quiñones et al. reported higher trait anxiety in endometriosis patients compared with healthy controls, but no difference concerning state anxiety. Two studies reported a controversial difference in anxiety scores between endometriosis patients and CPP patients without endometriosis.[48,67]

Figure 2B shows pooled data including 12 studies comparing 544 endometriosis patients with 636 healthy controls.

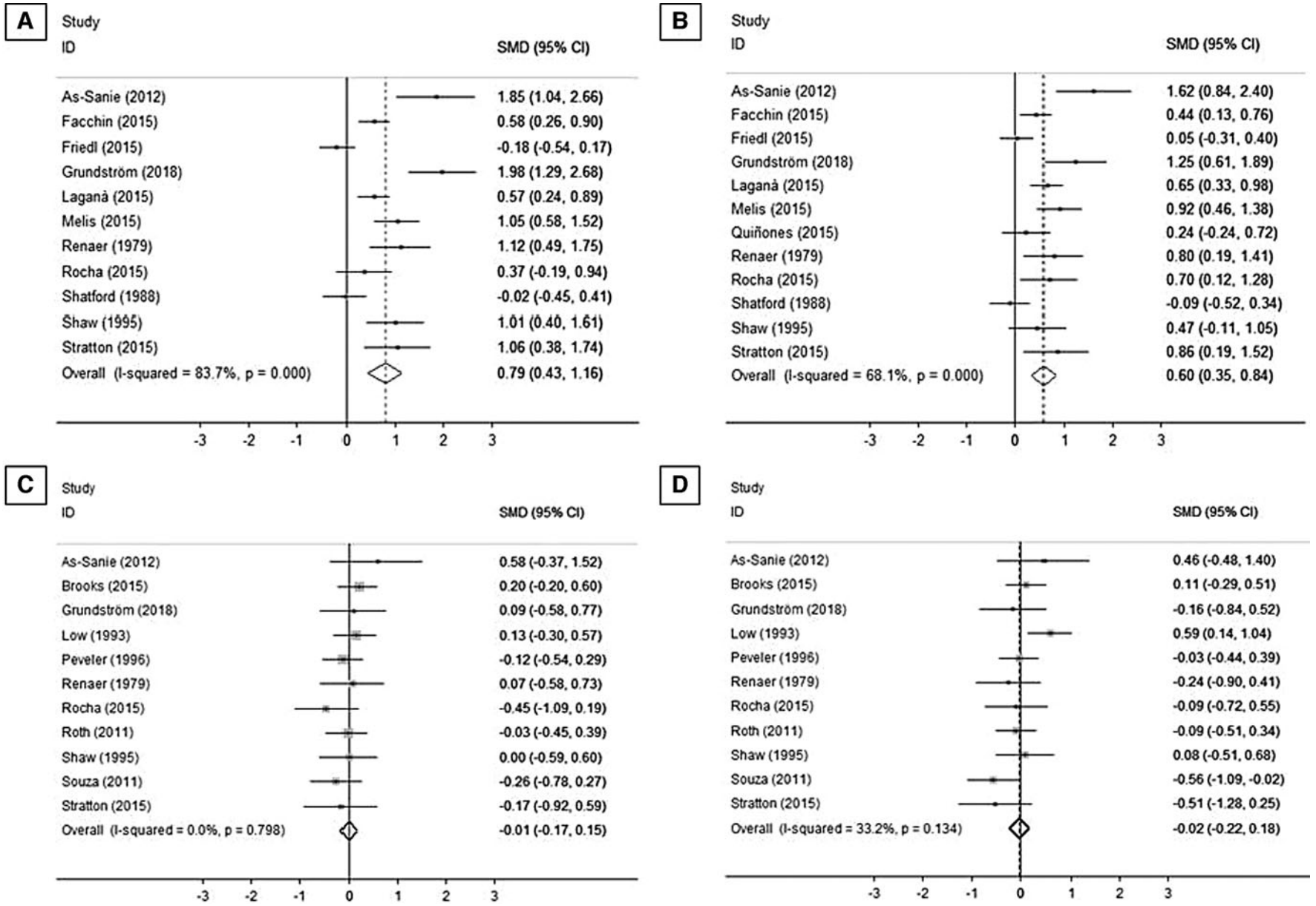

FIG. 2. Forest plot showing SMDs in depression and anxiety scores within studies. These plots show the pooled SMD (*large diamond shape*) and I^2 resulting from the meta-analysis. **(A)** Depression scores comparing endometriosis patients with healthy controls. **(B)** Anxiety scores comparing endometriosis patients with healthy controls. **(C)** Depression scores comparing endometriosis patients with CPP patients without endometriosis. **(D)** Anxiety scores comparing endometriosis patients with CPP without endometriosis. CPP, chronic pelvic pain; SMD, standardized mean difference.

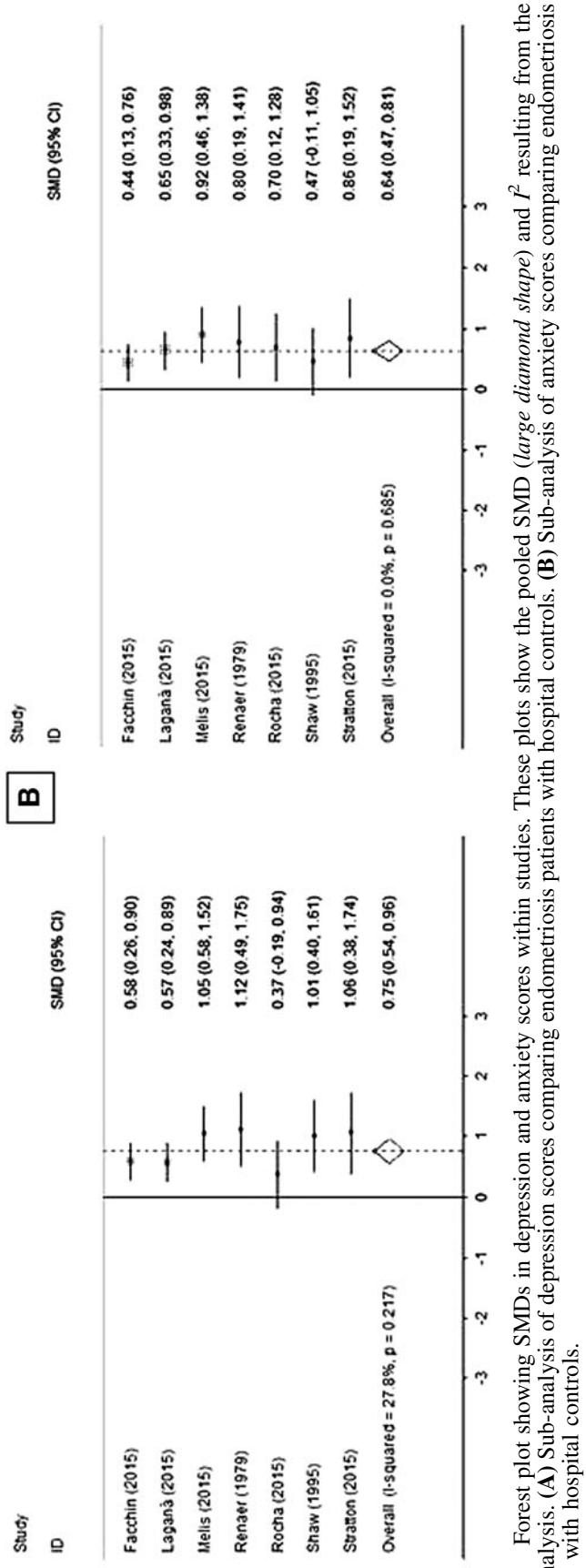

FIG. 3. Forest plot showing SMDs in depression and anxiety scores within studies. These plots show the pooled SMD (*large diamond shape*) and I^2 resulting from the meta-analysis. **(A)** Sub-analysis of depression scores comparing endometriosis patients with hospital controls. **(B)** Sub-analysis of anxiety scores comparing endometriosis patients with hospital controls.

Meta-analysis reveals significantly higher anxiety scores in patients with endometriosis (SMD 0.60 [95% CI 0.35–0.84]). The I^2 value of 68.1% shows high and significant heterogeneity. The sub-analysis including seven studies with solely hospital controls without infertility reveals an SMD of 0.64 (95% CI 0.47–0.81) with an I^2 of 0% (Fig. 3B). Figure 2D shows pooled data including 11 studies comparing 284 endometriosis patients with 407 CPP patients without endometriosis. Meta-analysis reveals no significant difference in anxiety scores between these groups (SMD −0.02 [95% CI −0.22 to 0.18]). In this meta-analysis, the state anxiety score (but not the trait anxiety score) is used when the STAI questionnaire was assessed.

Correlating factors with depression and anxiety in endometriosis patients

The role of endometriosis-related pain and the association with depression and anxiety was the most commonly described factor. Facchin et al. reported an increase of 9.6% in depression and a 10.6% increase in anxiety symptoms in the case of endometriosis-related predictors (hormonal treatment, surgical interventions, infertility, time from diagnosis, and pain severity).[36] Four out of five studies comparing endometriosis patients with pain with pain-free endometriosis patients found significantly higher rates of depression, up to 86% in the pain-group.[28,35,47,61] As-Sanie et al. and Facchin et al. also found significant differences in anxiety scores between these groups. However, Eriksen et al. reported no significant correlation between the degree of pain and depression or anxiety scores.[34] There was no consensus on the association concerning type of pain (CPP, dysmenorrhea, and dyspareunia).

Infertility was the second most investigated factor that was hypothesized to contribute to depression or anxiety in endometriosis patients. However, comparison of infertile with fertile endometriosis patients[58] or with infertile patients without endometriosis[60,61] did not show any significant difference in depression or anxiety symptoms. In addition, Shaw et al. described that in women with endometriosis-related pain, depression occurred more frequently (23.5%) compared with endometriosis patients with infertility (13%).[61]

Studies, investigating other factors than pain or infertility, reported that higher scores of depression or anxiety in endometriosis patients were correlated to poorer quality of sleep,[27] fatigue,[52] poorer quality of life,[32,49,50,52] gastrointestinal symptoms,[69] lower self-esteem,[36] lower emotional self-efficacy,[36] lower sexual functioning,[32,51] dysfunction on social adjustment,[54] pain imagery,[42] and clinical signs of pain sensitization.[67] Also, it was reported that patients who used positive coping strategies experienced fewer depressive symptoms.[33,34] Furthermore, it was described that depression and anxiety occurred more frequently in patients with advanced age,[38,62] lower cortisol levels,[55] metabolic syndrome,[31] and comorbid pain syndromes,[64] and, the presence of depression and anxiety was independently associated with increased costs.[45]

No correlation was found between depression or anxiety and endometriosis stage,[30,62] being childless,[37] experiencing no pain relief after surgery,[41] or oral contraceptive therapy.[71] Correlations of anxiety and depression in endometriosis patients concerning the time of diagnosis were described contradictorily.[36,62,68]

Table 1. Characteristics and Mean Scores of Studies in the Meta-Analysis Comparing Endometriosis Patients to Healthy Controls

	Sample size		Age (mean, SD)		Depression score (mean, SD)			Anxiety score (mean, SD)		
Study	E	Co	E	Co	E	Co	PROM	E	Co	PROM
As-Sanie et al.[28]	17	17	26.1±1.5	25.9±1.6	12.5±7.2	2.4±2.8	CES-D	18.3±4.5	12.5±2.3	STPI
Facchin et al.[35]	110	61	32.9±2.3	27.9±4.4	7.7±2.2	6.5±3.5	HADS	5.9±2.2	4.7±3.1	HADS
Friedl et al.[38]	62	61	33.4±5.4	29.6±7.3	5.9±4.5	5.7±3.1	HADS	3.4±3.8	4.2±4.3	HADS
Grundström et al.[43]	13	55	26.2±6.4	30.2±5.6	8.1±4.6	2.3±2.4	HADS	9.4±5.4	4.6±3.4	HADS
Laganà et al.[46]	166	48	36.0±6.0	38.4±12.8	59.3±12.8	52.0±13.0	SDS	58.2±11.5	50.5±12.9	SAS
Melis et al.[51]	41	40	31.5±6.4	30.4±5.1	14.3±11.9	4.7±4.7	BDI	17.0±13.0	7.4±6.9	BAI
Quiñones et al.[55]	31	36	29.1±1.2	31.7±2.4	—	—	—	2.2±0.8	2.0±0.6	STAI
Renaer et al.[20]	22	23	—	—	61.8±11.0	50.5±9.3	MMPI	52.2±9.0	44.9±9.3	MMPI
Rocha et al.[56]	24	25	32.9±9.0	35.4±6.7	9.6±5.0	6.4±4.1	HADS	8.3±4.6	6.5±5.0	HADS
Shatford et al.[60]	23	212	32		4.5±4.2	4.6±6.3	BDI	33.0±9.2	33.9±10.8	STAI
Shaw and Waller.[61]	17	38	30.9±7.5	35.0±4.9	11.2±6.6	5.7±4.8	BDI	43.1±14.5	37.5±10.6	STAI
Stratton et al.[67]	18	20	32.1±8.0	35.4±8.8	32.4±16.9	14.4±17.1	DHP	36.6±17.7	19.9±21.0	DHP

BAI, Beck Anxiety Inventory; BDI, Becks Depression Inventory; CES-D, Center for epidemiological studies-Depression; Co, healthy controls; DHP, Duke Health Profile; E, endometriosis patients; HADS, Hospital Anxiety and Depression Scale; MMPI, Minnesota Multiphasic Personality Inventory; PROM, Patient Reported Outcome Measure; SAS, Self-Rating Anxiety Scale; SD, standard deviation; SDS, Self-Rating Depression Scale; STAI, State-Trait Anxiety Inventory; STPI, State-Trait Personality Inventory.

Discussion

Main findings

This systematic review gives an overview of the literature concerning the association between endometriosis and symptoms of depression and anxiety and the factors that are correlated to this association. A total of 47 articles comprising 1,933,846 subjects were reviewed. Data from 17 studies using validated outcome measures were pooled for a random-effects meta-analysis comparing 677 endometriosis patients with 636 healthy controls and 407 CPP patients without endometriosis. Reviewed articles showed a prevalence of 10%–86% for depression and 10%–79% for anxiety, whereas the global prevalence of depressive and anxiety disorders in women of reproductive age ranges from 4.5% to 7% and 5.5% to 6% respectively.[19] Derived from the pooled data, the SMDs in anxiety and depression scores are significantly higher in studies of endometriosis patients compared with healthy controls but not in comparison to CPP patients. Hence, this elevated prevalence seems to be not specific for endometriosis but is comparable to women with other conditions representing CPP. This systematic review included mostly studies with a cross-sectional design and does not allow for analysis of causal inference. Nevertheless, two studies with a longitudinal design showed an elevated likelihood of developing depression and anxiety disorders in endometriosis.[31,39] In addition, women with a previously diagnosed depression or anxiety disorder were more likely to be later diagnosed with endometriosis.[31,39] Regrettably, the authors did not evaluate the impact of endometriosis-related factors such as pain on the risk of the affective disorders.

The majority of cross-sectional studies investigating pain as a dependent factor reported a positive association between pain intensity and scores for depressive symptoms and anxiety. This is a well-known phenomenon in pain being part of functional psychosomatic syndromes.[102] In endometriosis

Table 2. Characteristics and Mean Scores of Studies in the Meta-Analysis Comparing Endometriosis Patients to Patients with Chronic Pelvic Pain Without Endometriosis

	Sample size		Age (mean, SD)		Depression score (mean, SD)			Anxiety score (mean, SD)		
Study	E	CPP	E	CPP	E	CPP	PROM	E	CPP	PROM
As-Sanie et al.[28]	17	6	26.1±1.5	24.2±1.9	12.5±7.2	8.8±2.6	CES-D	18.3±4.5	16.3±3.9	STPI
Brooks et al.[29]	31	110	33.3±13.0		6.0±6.5	4.6±7.0	DASS21	5.0±5.8	4.5±4.4	DASS21
Grundström et al.[43]	13	24	26.2±6.4	26.6±5.7	8.1±4.6	7.7±4.2	HADS	9.4±5.4	10.1±3.7	HADS
Low et al.[48]	40	41	30.0±7.7	35.5±9.2	14.4±8.2	13.3±8.2	BDI	45.8±12.1	38.2±13.6	STAI
Peveler et al.[54]	40	51	32.2±6.3	30.6±7.7	0.75±0.83	0.84±0.67	BSI	0.9±0.8	0.88±0.7	BSI
Renaer et al.[20]	22	15	—	—	61.8±11.0	60.9±13.9	MMPI	52.2±9.0	54.5±10.0	MMPI
Rocha et al.[56]	24	16	32.9±9.0	32.7±7.8	8.3±4.6	10.8±6.7	HADS	9.6±5.0	10.1±6.9	HADS
Roth et al.[59]	30	78	32.1±9.5		15.9±12.1	16.2±9.7	BDI	0.84±0.7	0.90±0.7	BSI
Shaw and Waller[61]	17	30	30.9±7.5	30.6±7.6	11.2±6.6	11.2±7.6	BDI	43.1±14.5	42.1±10.2	STAI
Souza et al.66	32	25	36.1±7.8	40.6±8.6	15.6±8.2	17.5±6.1	BDI	26.6±10.2	32.4±10.5	HARS
Stratton et al.[67]	18	11	32.1±8.0	35.9±9.3	32.4±16.9	35.0±13.5	DHP	36.6±17.7	45.0±13.7	DHP

BSI, Brief Symptom Inventory; CPP, chronic pelvic pain; DASS21, Depression Anxiety Stress Scale; HARS, Hamilton Anxiety Rating Scale.

studies, however, there was no consensus on the relation between the type of pain (CPP, dysmenorrhea, dyspareunia), and affective symptoms. Facchin et al. were the first to test the ''disease-focused hypothesis'' and the ''pain-focused hypothesis'' in endometriosis by comparing asymptomatic endometriosis patients, endometriosis patients with pelvic pain, and healthy pain-free controls. Their findings offered the conclusion that painless endometriosis does not necessarily involve psychological pain or discomfort. However, the researchers did not control for the effect of diagnostic and demographic factors. Other studies suggest that factors correlated to affective symptoms in endometriosis patients include age, quality of life, quality of sleep, fatigue, sexual function, gastrointestinal symptoms, comorbidity, self-esteem, emotional self-efficacy, coping style, social adjustment, pain imagery, and pain sensitization. This indicates that different factors are involved in symptom burden and treatment refractoriness in women suffering from endometriosis. As in other complex patients, these aspects remain frequently undetected, which could lead to misdiagnosis and puzzled treatment pathways.[103,104] However, whether effective endometriosis treatment would have a significant impact on depression/anxiety symptoms, and vice versa, is unknown.

Strengths, limitations, and interpretation

In addition to earlier published reviews concerning the association between endometriosis and psychological problems,[21,95] the current review specifically provides an up to date overview on both depressive and anxiety symptoms in these patients. Furthermore, we provided information concerning factors that correlate with depression and anxiety symptoms in endometriosis. Reporting these correlations is important to recognize vulnerable patients in clinical practice. Since research demonstrated the reliability of nonsurgical diagnosis of endometriosis, we also included studies including patients with a clinical diagnosis of endometriosis, which made it possible to generate a large number of studies. In contrast to Gambadauro et al., our review excluded studies with self-reported diagnoses of depression and studies using nonstandardized assessment methods, to limit the risk of overreporting. The current meta-analysis included solely studies using standardized outcome measurements to limit heterogeneity in results. The overall SMD of studies comparing endometriosis patients with CPP patients without endometriosis showed an I^2 of 0% ($p = 0.798$) for depression scores and an I^2 of 33.2% ($p = 0.134$) for anxiety scores, which means that the heterogeneity between these studies was low and nonsignificant. Nevertheless, heterogeneity between studies comparing endometriosis patients with healthy controls was significant: I^2 84.6% ($p < 0.001$) for depression scores and I^2 68.1% ($p < 0.001$) for anxiety scores. This was most likely caused by a variety of definitions of healthy controls, which makes it difficult to compare and generalize the study outcomes. A sub-analysis including solely studies using painless and noninfertile ''hospital patient controls'' as a healthy control group, showed low and nonsignificant heterogeneity. However, heterogeneity might be primarily related to the inclusion of pain symptoms in the definition of study populations or to other characteristics, such as age (As-Sanie et al. investigated a relatively young population). In that regard, the inclusion of non-surgically diagnosed endometriosis patients could also explain heterogeneity. Hence, the strategies of research groups and their assessment tools need to be standardized to produce robust and reliable results for meta-analyses. A sub-analysis including only studies using the HADS as outcome measurement, did not change outcome nor improved I^2 results. Furthermore, this review has some other limitations. First, including articles written in English only limits the number of included studies. Risks of bias were mostly caused by study design and patient selection as most studies included women in tertiary referral centers. This could have led to an over-presentation of symptoms compared to patients in the general population. Inclusion of studies without a control group has the potential to create bias. This is evidenced by the very broad prevalence percentages in the cross-sectional studies. Furthermore, whether described associations end up in the published literature is very likely to be determined by publication and small study bias. Although validated, the assessment tools used are predominantly self-assessment questionnaires, which give an indication of a depressive or anxious state but does not provide a valid diagnosis. Furthermore, 17% of studies used assessment tools with poor reliability/validity. Studies using reported ICD-9 diagnoses given by professionals could have led to underreporting of depressive and anxiety complaints as those might have not received an official diagnosis. Another important limitation is the variation in types of anxiety disorders that were pooled in the meta-analysis. Screening tools for anxiety disorders usually provide lower sensitivity and specificity than tools for depressive disorders, as anxiety disorders have more heterogeneous symptoms (state, trait, or phobic anxiety).[93]

Implications for further research and treatment

There is a need to understand the consequences of affective symptoms on pain amplification or pain reduction during endometriosis treatment to improve clinical outcome. CPP reduction alone does not automatically reduce depressive symptoms and this assumption produces delays concerning psychosomatic care.[96,97] On the other hand, improvements in depression, anxiety, and pain catastrophizing can influence pain perception[98] and, therefore, improve quality of life along with sexual and social functioning, which in turn may reduce societal relevant health care costs.[8,13] Hence, an integrated and patient-centered approach to medical, psychological, and sexual issues is suggested.[51,105] Integration of care is deemed necessary at the hospital level and between hospital and primary care, and a multicomponent strategy should include efforts to combat stigmatization concerning psychiatric comorbidity.[99] With regard to symptom formation (or in other words how symptoms impact on symptoms as in pain sensitization), the experience sampling method (ESM) might be able to unravel how affective complaints and pain are related over time/during treatment.[106] ESM is an ecological momentary assessment tool, which could help to provide information on symptoms in the context of daily life including psychological symptoms and sexuality,[107] to overcome the limitations of current retrospective questionnaires.[100]

Conclusion

This systematic review supports the assumption that symptoms of depression and anxiety in endometriosis patients are

predominantly related to chronic pain. Anxiety and depression may influence pain perception in endometriosis, and currently there is no consensus which condition comes first. A broad spectrum of correlating factors should be investigated further. Besides medical endometriosis treatment and behavioral pain management, the improvement of emotion regulation skills could be another treatment goal in endometriosis patients.[101]

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Authors' Contributions

All those designated as authors meet all four criteria for authorship: substantial contributions to the conception or design of the work; the acquisition, analysis, interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material

Supplementary Appendix Table SA1
Supplementary Appendix Table SA2
Supplementary Appendix Table SA3
Supplementary Appendix Table SA4

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