Depressive symptoms among women with endometriosis: a systematic review and meta-analysis

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OBJECTIVE: To evaluate whether endometriosis is associated with depressive symptoms, and whether the association is modulated by pelvic pain.

DATA SOURCES: PubMed, Embase, PsychINFO, and the Cochrane Library, were systematically searched through September 2017.

STUDY ELIGIBILITY CRITERIA: The following eligibility criteria applied: full-text original article; quantitative data about depressive symptoms or depression; comparison of women with and without endometriosis, or women with endometriosis with and without pelvic pain. Articles reporting duplicated data were excluded.

STUDY APPRAISAL AND SYNTHESIS METHODS: Two reviewers selected and reviewed the studies. Disagreements were resolved through discussion or a third opinion. Qualitative synthesis was performed through tabulation and assessment using a modified version of the Newcastle−Ottawa Scale. Effect sizes were pooled through meta-analysis, and moderator analyses were performed to identify potential confounders with several variables: region of the sample, method of ascertainment of endometriosis, method of measurement of depression, year of publication, and quality score.

RESULTS: A meta-analysis of 24 studies (99,614 women) showed higher levels of depression among women with endometriosis compared to controls (standardized mean difference [SMD], 0.22, 95% confidence interval [CI], 0.13−0.32). The heterogeneity in this analysis ($I^2 = 68\%$) was not explained by any of the moderating variables. When only healthy controls were considered, a larger endometriosis-depression effect was found (11 studies, SMD, 0.49; 95% CI, 0.24−0.73; $I^2 = 69\%$). Endometriosis patients reporting pelvic pain had significantly higher levels of depression compared to those without pain (4 studies; SMD, 1.01; 95% CI, 0.71−1.31; $I^2 = 0\%$). No significant difference was found between women with pelvic pain and endometriosis and those with pelvic pain but without endometriosis (11 studies, SMD, −0.11; 95% CI, −0.25 to 0.04; $I^2 = 0\%$).

CONCLUSION: The association between endometriosis and depressive symptoms is largely determined by chronic pain but may also be modulated by individual and context vulnerabilities. Awareness of the complex relationship between endometriosis and depressive symptoms informs tailored care and patient-centered research outcomes.

Key words: chronic pelvic pain, depression, endometriosis, mental health, meta-analysis, patient-centered care, reproductive health, systematic review

Introduction

Endometriosis is a chronic condition defined by ectopic endometrial-like tissue and is thought to affect 10% of reproductive-aged women.[1] This complex disorder is characterized by clinical manifestations such as pain and subfertility, which deeply influence the physical, mental, and social well-being of affected women.[2−6] Chronic pelvic pain, in particular, is the most common symptom of endometriosis and determines lower quality of life as well as increased costs related to health care and loss of productivity.[2,7]

Depressive symptoms are also common, and 11−15% of people worldwide are estimated to suffer from major depression at any time in their life.[8,9] Depression is significantly more common among women and among individuals with chronic pain.[10,11] An association between endometriosis and depression may therefore be reasonably assumed and its relevance is not limited to the expected downstream effects on well-being and quality of life. Comorbid depression hinders or complicates some of the possible treatment strategies,[12,13] and is associated with increased health loss and health care costs for endometriosis patients.[14]

It could therefore be useful to early detect depressive symptoms among women with endometriosis through screening and/or identification of high-risk groups, although existing quantitative evidence is relatively scarce and conflicting. The risk of psychiatric disturbances among women with endometriosis was highlighted by a systematic review of studies published through 2014, although quantitative data pooled from 3 studies failed to show a significantly higher frequency of a clinical diagnosis of depressive disorders among women with

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AJOG at a Glance

Why was this study conducted?

- Endometriosis is expected to have mental health manifestations, although research and guidelines largely focus on its physical symptoms.
- Recently, interest toward patient-centered care and outcomes in endometriosis has emerged.
- However, despite the potential magnitude of the association between endometriosis and depression, evidence from individual studies is conflicting, and no robust quantitative synthesis of literature data is available.

Key findings

- This comprehensive synthesis of scientific literature published during the last 30 years shows that the association between endometriosis and depressive symptoms is largely determined by chronic pain but may also be modulated by individual and context vulnerabilities.

What does this add to what is known?

- Awareness of the complex relationship between endometriosis and depressive symptoms informs tailored care and patient-centered research outcomes.

endometriosis compared to controls.[15] One possible explanation for such findings is that traditional psychiatric diagnoses are pragmatically based on categorizations that fail to capture the dimensional nature of depression and the relevance of subthreshold symptoms.[9,16,17] Furthermore, inconsistent findings may be related to the heterogeneous clinical presentation of endometriosis.[2]

In this context, efforts to improve the current fragmented understanding should acknowledge and address both the dimensional nature of depression and the clinical heterogeneity of endometriosis. The aim of this systematic review was to study the association between endometriosis and depressive symptoms through meta-analysis of controlled studies. The main objective was to evaluate whether endometriosis is associated with depressive symptoms. Secondary objectives were to evaluate whether depressive symptoms are more common among women with endometriosis-related pelvic pain compared to women with endometriosis but without pelvic pain and women with pelvic pain but without endometriosis.

Materials and Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18] was followed as a methodological and reporting framework. Structured literature searches were conducted in English across several databases, including PubMed, Embase, PsychINFO, and the Cochrane Library, with no start date and through September 2017. The search strategy was developed around the main concepts "depression" and "endometriosis" and was based on relevant free text terms (eg, depression; depressive; endometriosis). Thin word variants, wildcards and, where available, controlled vocabulary (eg, MeSH terms) were tested and kept when appropriate (Appendix A).

Study selection

Records obtained from the database searches were imported into a local reference manager. Duplicates were removed, and all records were screened by title and abstract. Full texts of the items identified by title/abstract screening were obtained and thoroughly evaluated for eligibility by 2 authors independently. Articles were selected for review according to the following predefined inclusion criteria: being a full-text original article; reporting quantitative observational data about depressive symptoms or depression; and comparing women with and without endometriosis, or women with endometriosis with and without pelvic pain. Articles were excluded if they reported duplicated data.

Data management

For all included papers, data regarding the following variables were collected: clinical and demographic characteristics of the study population; number of women with and without endometriosis (including subgroups); method of ascertainment and exclusion of endometriosis; and method of evaluation of depressive symptoms. When available, quantitative measurements of the main outcome "depressive symptoms" were extracted, with means and standard deviations of symptom scales/scores as first choice. In absence of such data, quantitative data about the prevalence of above-the-cutoff depressive symptoms scores, self-reported depression or of a clinical diagnosis of depressive disorder were collected.

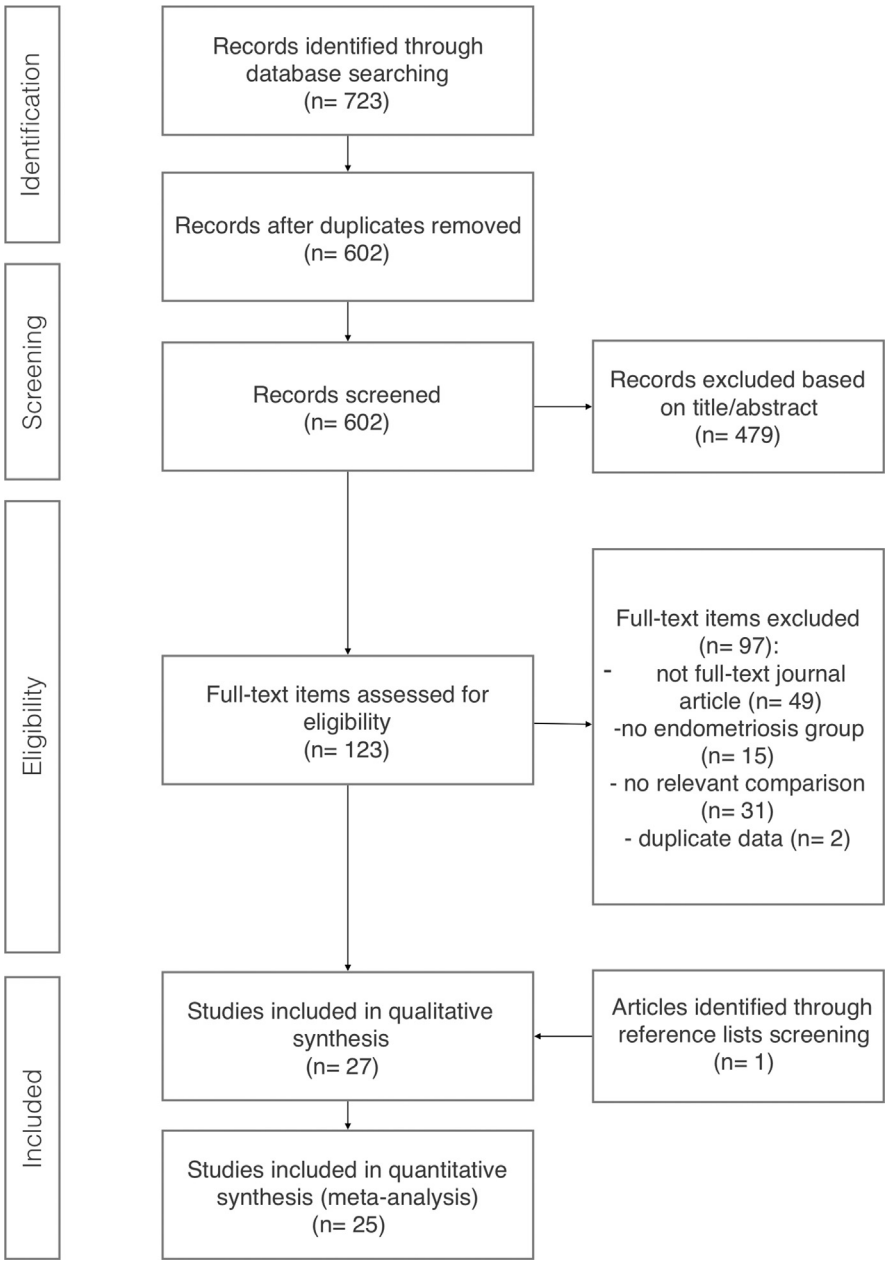
The above mentioned data were identified and extracted from the reports by hand and desktop-search engines to improve accuracy. Further attempts to obtain relevant but unavailable quantitative data were made by contacting the corresponding authors. A dedicated data extraction form was developed and piloted on an online office productivity suite,[19] and a resulting digital spreadsheet was used as the main database.

Synthesis of results

Two reviewers screened, selected, and reviewed the studies. In case of disagreement, consensus either was reached through discussion or the opinion of a third researcher was obtained. A qualitative synthesis of the studies was performed through tabulation, and a quality assessment was based on ad hoc and/or general criteria listed in a quality assessment form (eg, a modified Newcastle−Ottawa Scale) that was designed for this study (Appendix B).

Quantitative data from comparative studies were tabulated on a spreadsheet. Because depressive symptoms are most often measured as continuous data (ie, scores) and with different available scales, the standardized mean difference (SMD) was used as effect size.[20] SMDs and corresponding 95% confidence intervals (CI) were obtained directly from the reported means and standard deviations of depressive symptoms scores,

FIGURE 1
Study flowchart



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or calculated from 2 × 2 frequency tables when only categorical data regarding dichotomous variables were available.[20,21] The effect sizes were then pooled through meta-analysis to investigate the following hypotheses: (1) Women with endometriosis have higher depressive symptoms compared to women without endometriosis; (2) women with endometriosis and pelvic pain have higher depressive symptoms compared to women with endometriosis but without pain; and (3) women with endometriosis and pelvic pain have higher depressive symptoms than women with pelvic pain but no endometriosis. The meta-analyses were performed using Review Manager v5.3.5 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark), with the inverse variance method and a random effects model. Heterogeneity was assessed by I^2 statistics. Moderator analyses were carried out to identify potential confounders with the following variables: region of the sample (defined as Europe, North America, and other), method of ascertainment of endometriosis (surgical vs other), method of measurement of depression (validated psychometric scales vs other), year of publication (continuous), and quality assessment score (continuous).

Study registration

This study was registered as CRD42018086399 in the PROSPERO database (University of York, UK; http://www.crd.york.ac.uk/PROSPERO/).

Results

Selection and characteristics of the studies

A total of 723 records were identified through the systematic database searches (Figure 1). After duplicates removal, 601 items were screened by title and abstract, 127 items were assessed in full text, and 26 items were eventually selected. One additional item was identified through reference lists screening. Therefore, a total of 27 studies were included in this systematic review;[22–48] their general characteristics and main relevant findings are presented in Table 1.

Most of the articles were published during the last decade, and 80% originated from either Europe (50%) or North America (32%). Only 2 studies had a longitudinal registry-based design,[42,48] whereas the majority reported cross-sectional findings. The median number of subjects per study was 100, and ranged from 39 to 75,140 (total N = 99,736).

The definition of endometriosis was established within the study in 85% of the cases and based on a surgical (and/or imaging in 2 cases) diagnosis,[23–30,32–41,43–47] whereas 3 studies included women with previous registered diagnosis,[22,42,48] and in 1 study[31] no details were available. In 12 of 25 studies including women without endometriosis, the latter was ruled out

TABLE 1
Studies included in the systematic review

Study	Subjects	Endometriosis, n	Non-endometriosis, n	Diagnosis of endometriosis	Exclusion of endometriosis	Evaluation of depressive symptoms	Relevant findings
Shatford et al, 1988 (Canada)[22]	Subfertility by endometriosis or other factor	23	212 tubal 50 idiopathic 15 male 48 multiple	Registered diagnosis	Unknown	Questionnaire (BDI)	No significant differences in depressive symptoms scores among groups
Walker et al, 1989 (USA)[23]	Laparoscopy for pelvic pain, subfertility, or sterilization	14	55	Surgical	Surgical	Clinical interview	No significant difference in prevalence of current or lifetime depression
Low et al, 1993 (UK)[24]	Laparoscopy for pelvic pain (with/without subfertility)	40	41	Surgical	Surgical	Questionnaire (BDI)	No significant difference in depressive symptom scores
Waller and Shaw 1995 (UK)[25]	Laparoscopy for pelvic pain, subfertility, or sterilization	31 no pain 18 pain (all minimal–mild)	30 pelvic pain 38 sterilization	Surgical	Surgical	Questionnaire (BDI)	Women with pain have higher depressive symptoms scores, regardless of endometriosis
Peveler et al, 1996 (UK)[26]	Laparoscopy for pelvic pain	40	51	Surgical	Surgical	Questionnaire (BSI)	No significant difference in depressive symptom scores
Lorençatto et al, 2006 (Brazil)[27]	Endometriosis with/without pain	50 no pain 50 pain		Surgical	Not applicable	Questionnaire (BDI)	BDI $\geq$12 more prevalent among women with pain
Tietjen et al, 2007 (USA)[28]	Migraine with/without endometriosis and age-matched controls[a]	36 with migraine	127 with migraine 104 without migraine	Surgical, self-reported	No surgical diagnosis, self-reported	Self-reported diagnosis	Similar prevalence of depression among women with migraine with and without endometriosis
Eriksen et al, 2008 (Denmark)[29]	Laparoscopic diagnosis of endometriosis	20 no pain 44 pain		Surgical	Not applicable	Questionnaire (BDI)	No significant difference in BDI scores; no correlation between pain intensity and BDI scores
Siedentopf et al, 2008 (Germany)[30]	Laparoscopy for subfertility	19 minimal–mild 7 moderate–severe	17	Surgical	Surgical	Questionnaire (CES-D)	Higher CES-D scores among women with moderate-severe endometriosis
Kumar et al, 2010 (India)[31]	Pelvic pain with/without endometriosis, and healthy controls	100	100 healthy 100 pelvic pain	Unknown	Unknown	Questionnaire (Asha–Deep Depression Scale)	Significant differences in scores among the three groups (cpp scoring highest and controls lowest)
Baron et al, 2011 (Malta)[32]	Laparoscopy for pelvic pain and/or subfertility	23	34	Surgical	Surgical	Self-reported symptom	Higher frequency of depressive symptoms in endometriosis group

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(continued)

TABLE 1
Studies included in the systematic review *(continued)*

Study	Subjects	Endometriosis, n	Non-endometriosis, n	Diagnosis of endometriosis	Exclusion of endometriosis	Evaluation of depressive symptoms	Relevant findings
Kumar et al, 2011 (Canada)[33]	Pelvic pain with/without endometriosis	27	12	Surgical	Surgical	Clinical interview	No significant difference in prevalence of major depression, but higher prevalence of bipolar disorder in the endometriosis group.
Roth et al, 2011 (USA)[34]	Pelvic pain and endometriosis, myofascial pain, or pelvic adhesions	30	70 myofascial pain 38 pelvic adhesions	Surgical	Surgical for adhesions	Questionnaire (BDI)	No significant difference in BDI score across the groups
Souza et al, 2011 (Brazil)[35]	Pelvic pain with/without endometriosis	32	25	Surgical	Surgical	Questionnaire (BDI)	No significant difference in BDI score between groups or between pain level groups
As-Sanie et al, 2012 (USA)[36]	Endometriosis with/without pelvic pain, pelvic pain without endometriosis, or healthy controls	17 pain 15 no pain	43 healthy 6 pain	Surgical	Surgical for pain	Questionnaire (CES-D)	Women with pain, regardless of endometriosis, have higher scores than controls. Women with endometriosis and pain higher scores than those without pain.
Issa et al, 2012 (UK)[37]	Laparoscopy for pain or sterilization, or IBS diagnosis	20 minimal–mild 20 moderate–severe	20 sterilization 20 pain 20 IBS	Surgical	Surgical for sterilization and pain	Questionnaire (HADS-d)	No significant difference in HADS-d scores across the groups
Hansen et al, 2013 (Denmark)[38]	Women in employment with/without endometriosis	487	583	Surgical or MR	No diagnosis	Self-reported symptom	Higher prevalence of depressive symptoms in women with endometriosis
Cavaggioni et al, 2014 (Italy)[39]	Endometriosis and healthy controls	37	43	Surgical	Clinical with ultrasound	Questionnaire (SCL90) and clinical interview	Higher prevalence of above cut-off depressive symptoms SCL 90 among endometriosis
Facchin et al 2015 (Italy)[40]	Endometriosis and healthy controls	78 pain 32 no pain	61	Surgical	Clinical	Questionnaire (HADS-d)	Higher HADS-d scores for endometriosis and pain, particularly if non menstrual-pelvic pain
Friedl et al, 2015 (Austria)[41]	Endometriosis and student sample without	62	61	Surgical	Self-report	Questionnaire (HADS-d)	No significant difference in HADS-d scores between women with/without endometriosis

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TABLE 1
Studies included in the systematic review *(continued)*

Study	Subjects	Endometriosis, n	Non-endometriosis, n	Diagnosis of endometriosis	Exclusion of endometriosis	Evaluation of depressive symptoms	Relevant findings
Fuldeore et al, 2015 (USA)[42]	Insured women with endometriosis, and age–region-matched controls	37,570	37,570	Registered diagnosis	No diagnosis	Registered diagnosis	Higher frequency of depression 1 year before endometriosis diagnosis compared to controls
Laganá et al, 2015 (Italy)[43]	Monolateral adnexal disease (endometriosis or other)	166	48	Surgical	Surgical	Questionnaire (SCL-90-R, SDS)	Higher prevalence of above–cut-off depressive symptoms among women with endometrioma
Melis et al, 2015 (Italy)[44]	Deep endometriosis and healthy controls	41	40	Surgical	Clinical, no pain	Questionnaire (BDI)	Higher BDI scores in endometriosis; depression negatively correlated with sexual functioning
Rocha et al, 2015 (Brazil)[45]	Endometriosis or myofascial pain, and healthy controls	24 (moderate or severe)	25 healthy 16 myofascial pain	Surgical	Clinical	Questionnaire (HADS-d)	No significant difference in HADS-d scores and above the cutoff prevalence across the groups
Stratton et al, 2015 (USA)[46]	Pelvic pain with/without endometriosis and healthy controls	18 (10 minimal–mild, 8 moderate–severe)	20 healthy 11 pain	Surgical	Clinical, no symptoms	Questionnaire (Duke Health Profile)	Significant score differences across the groups (cpp highest, control lowest). Association between high depressive scores and sensitization.
De Graaff et al, 2016 (Netherlands)[47]	Women with endometriosis in a sexual relationship and healthy controls requesting contraception	83	40	Surgical or US/MR	Unknown	Questionnaire (HADS-d)	Higher prevalence of HADS-d $\geq$8 and higher scores among endometriosis. Depression associated with worse sexual functioning and quality of life independently of pain/endometriosis
Chen et al. 2016 (Taiwan)[48]	Registered diagnosis of endometriosis and age-matched controls	10,439	10,439	Registered diagnosis	No diagnosis	Registered diagnosis	Higher risk of any depressive disorder and major depression among women with endometriosis

BDI, Beck Depression Inventory; *BSI,* Brief Symptom Inventory; *CES-D,* Center for Epidemiologic Studies Depression Scale; *cpp,* chronic pelvic pain; *HADS-d,* Hospital Anxiety and Depression Scale–depression subscale; *IBS,* irritable bowel syndrome; *MR,* magnetic resonance; *SCL,* Symptom Checklist; *SDS,* Zung Self-Rating Depression Scale; *US,* ultrasound.

[a] Of the controls without migraine, 9.6% had endometriosis.

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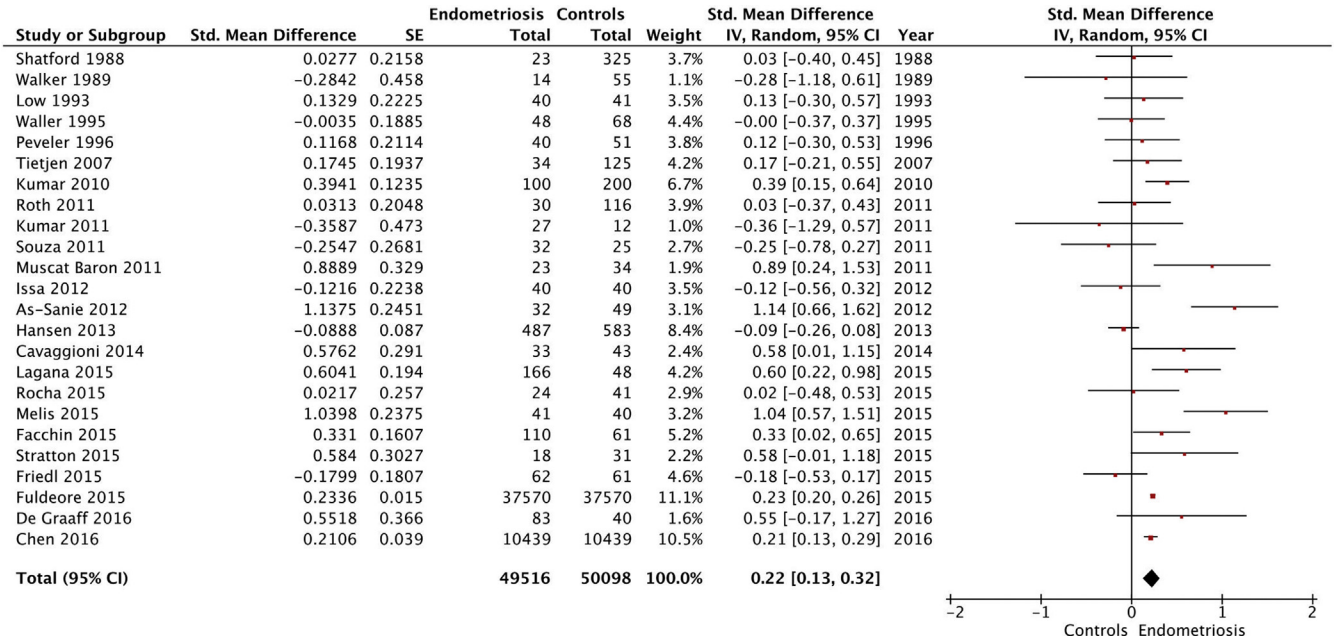
FIGURE 2
Difference in depressive symptoms between women with and without endometriosis



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by means of negative surgical findings.[23−26,30,32−34,36,37,43] In those studies, laparoscopy had been performed because of chronic pelvic pain, subfertility, or sterilization. In 20 studies, depressive symptoms were evaluated by means of questionnaires and psychometric scales.[22,24−27,29-31,34−37,39−41,43−47] The remaining studies considered clinical interviews,[23,33] previously registered diagnoses,[42,48] or self-reports.[28,32,38]

Study evaluation through the quality assessment form gave scores ranging from 1 to 6 out of a maximum possible score of 8 (median score, 4). The most common quality issues were related to the representativeness of the sample (no serious apparent threats in 2 of 27 articles) and the timing of psychological evaluation (previous to endometriosis diagnosis in 6 of 27 articles) (Appendix C).

A total of 22 studies[22−28,31−33,35,36,38−43,45−48] reported data that could be used in at least 1 of the meta-analyses, whereas in 3 cases[34,37,44] additional data were obtained from the corresponding authors. A total of 25 studies were therefore included in 1 or more meta-analyses.

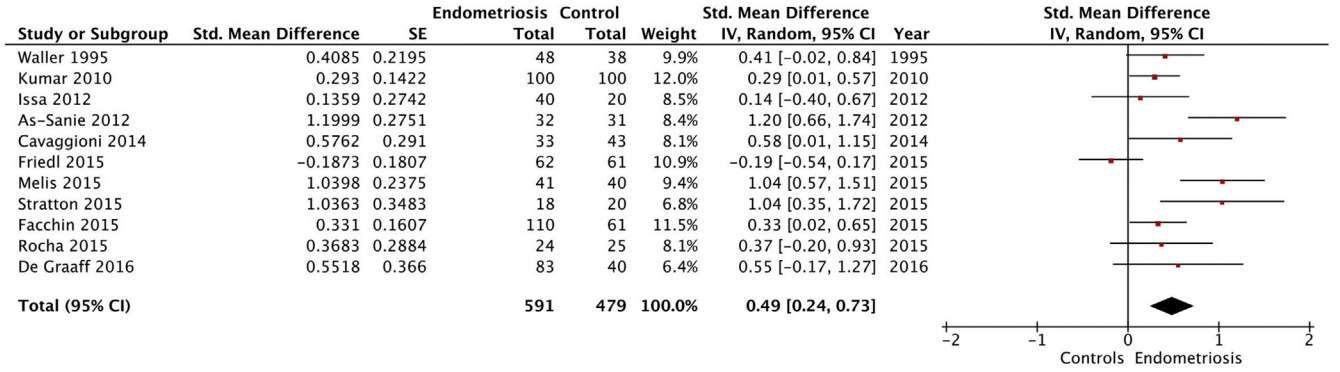
Quantitative synthesis

Women with endometriosis have higher depressive symptoms compared to women without endometriosis. In 24 identified studies (comprising a total of 99,614 women),[22−26,28,31−48] the levels of depression were significantly higher among women with endometriosis compared to those without, albeit with a small effect size (SMD, 0.22; 95% CI, 0.13−0.32, $P < .00001$) (Figure 2). There was some variability among the studies ($I^2 = 68\%$). The heterogeneity could not be explained by any of the moderating variables (region of the sample, method of ascertainment of endometriosis, or method of measurement of depression), but all subanalyses showed significantly increased levels of depression among women with endometriosis. The effects in the subanalyses ranged between SMD 0.16 and 0.28, with no significant differences within subgroups. Neither date of publication nor quality scores predicted effects of endometriosis on depressive symptoms in a meta-regression.

When only data from 11 studies (1070 women)[25,31,36,37,39−41,44−47] comparing women with endometriosis to healthy controls were considered, a larger endometriosis−depression effect was found (SMD, 0.49; 95% CI, 0.24−0.73; $P = .0004$) (Figure 3), but the sample remained equally heterogeneous ($I^2 = 69\%$). No significant differences in depression were observed in a subanalysis comparing women with endometriosis but without pain to healthy women (191 women, 3 studies;[25,36,40] SMD, 0.13; 95% CI, −0.40 to 0.65, $P = .64$; $I^2 = 65\%$) (Appendix D).

Women with endometriosis and pelvic pain have higher depressive symptoms compared to women with endometriosis but without pain. There were 4 studies (comprising 290 women)[25,27,36,40] with relevant information to investigate this hypothesis. Endometriosis patients reporting pelvic pain had significantly higher levels of depressive symptoms compared to those without pain. The effect was large and there was low variability among studies (SMD, 1.01; 95% CI, 0.71−1.31; $P < 0.00001$; $I^2 = 0\%$) (Figure 4).

FIGURE 3
Depressive symptoms in women with endometriosis compared to healthy controls



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Women with endometriosis and pelvic pain do not have higher depressive symptoms compared to women with pelvic pain but without endometriosis. A total of 11 studies (comprising 813 participants) [24–26,31,33–37,45,46] reported data relevant to this hypothesis. Interestingly, there was no significant difference in levels of depressive symptoms between women experiencing pelvic pain with and without endometriosis (SMD, −0.11; 95% CI, −0.25 to 0.04, $P = .15$) (Figure 5), and the sample was homogeneous ($\tau = .00$; $\chi^2 = 8.38$; df = 10; $P = .59$; $I^2 = 0\%$).

Comment

Main findings

This is, to the best of our knowledge, the first systematic review evaluating the association between endometriosis and depressive symptoms through meta-analysis. Quantitative data pooled from 24 studies (99,614 women) show that women with endometriosis have significantly higher depressive symptoms than women without, although the effect size of the association is relatively small (SMD, 0.22), whereas it increases to moderate (SMD, 0.49) when the comparator group includes only healthy controls (11 studies, 1070 women). However, the results of 3 additional analyses suggest that pain is a major determinant of depressive symptoms among endometriosis patients. First, women with endometriosis and associated pain have significantly higher depressive symptoms than women with endometriosis but without pain (SMD, 1.01 in 4 studies, 290 women). Second, the depressive symptoms among women with endometriosis but without pain are not significantly higher than among healthy women (3 studies, 191 women). Finally, no significant difference was found between women with endometriosis-related pain and women with non–endometriosis-related chronic pelvic pain (11 studies, 813 women).

Strengths and limitations

This study was based on structured searches and defined eligibility criteria, leading to the selection of 27 original peer-reviewed articles proceeding from 12 different countries. The papers underwent quality assessment, and several moderator analyses ruled out potential confounders (such as region, methods for diagnosing depression and endometriosis, date of publication, and study quality). The inclusion of a vast majority of studies evaluating symptoms through psychometric scales acknowledged the dimensional nature of depression and the relevance of subthreshold symptoms, which directly affect well-being and may become worse and chronic if overlooked.[16,17] A widely used standardized effect size addressed variations of depression measurements, and the

FIGURE 4
Depressive symptoms among women with endometriosis: women with pelvic pain compared to those without

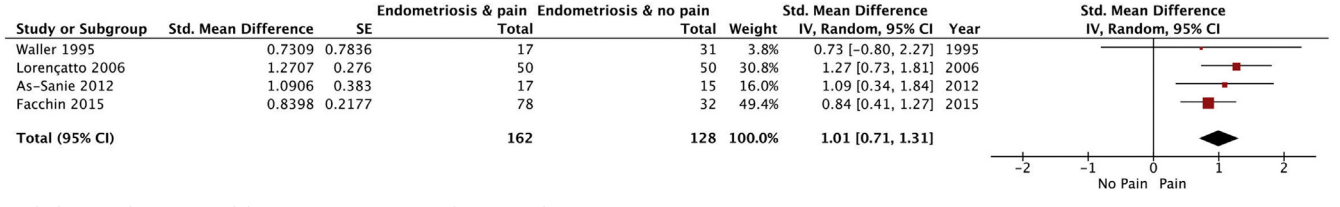

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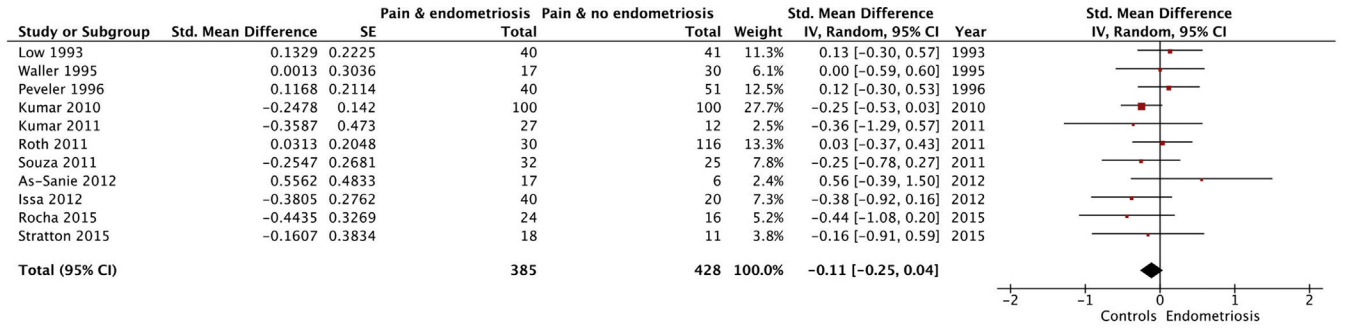
FIGURE 5
Depressive symptoms in women with pelvic pain: women with endometriosis compared to those without



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findings proved consistent regardless of the inclusion of studies with dichotomous outcomes. Multiple meta-analyses comprehensively addressed the important role of chronic pain, the most common and disabling symptom of endometriosis.[2]

The main limitation of the study is the reliance on cross-sectional data, which do not allow for inferences about directionality or causality between endometriosis and depressive symptoms. A longitudinal association is reported in 1 longitudinal registry study in which endometriosis patients who were followed up for 2−14 years were more likely to be diagnosed with a depressive disorder than women without endometriosis.[48] However, retrospective findings are based on coded diagnoses, and may misestimate exposure and outcomes. Another limitation is the unresolved heterogeneity in the meta-analysis comparing women with and without endometriosis. Although we suspected that varying operational definitions and practices in detecting endometriosis and depression among the samples, and/or regional differences among participants, would explain this heterogeneity, the moderator analyses based on the variables measuring these features could not. In view of the suboptimal sample representativeness in the studies, a possible interpretation of the heterogeneity concerns variations in depressive symptoms across socio-cultural groups.[8] It should also be acknowledged that the potential mediating effect of treatments, other symptoms (eg, dyspareunia or subfertility), or more nuanced patient characteristics (eg, endometriosis subtype, comorbidities, or life events) was not addressed because of inconsistent reporting.

Interpretation

The observed association between endometriosis and depressive symptoms is arguably more complex than a direct cause−effect relationship. As a matter of fact, the findings of individual articles included in this meta-analysis conflictingly range from none to large statistically significant differences in depressive symptoms between women with endometriosis and controls. The small pooled effect size observed when comparing women with and without endometriosis can be explained by a biased selection of controls on the basis of conditions that may still be related to depressive symptoms. In support of that explanation, the effect size of the association increased when women with endometriosis were compared to healthy controls. If the true association is stronger, however, our estimate may be explained by the relatively high prevalence of depression in the general population.[7] In addition, the findings of our multiple meta-analyses provide converging evidence that chronic pain, rather than endometriosis itself, is the main determinant of depressive symptoms. Such interpretation is consistent with literature data regarding depressive symptoms among people with other chronic pain conditions.[11] Nevertheless, because of the mentioned limitations regarding directionality, the possibility of a reverse or bidirectional relationship should not be excluded, especially because depression has been shown to precede a number of chronic physical diseases.[8] Although the putative mechanism of the association in many of these conditions, such as cardiovascular diseases, is related to poor health behaviors, this is less likely to be the case in endometriosis. Regardless of endometriosis, there is evidence that depression and chronic pain share similar precipitating stressors as well as genetic and neurologic characteristics.[49] The relationship between endometriosis and depression could similarly be grounded on a shared biological background, with common correlates such as stress, inflammation, altered immunity and abnormal sensitization.[30,34,45,50−52] Confirming any hypothesis on directionality is difficult, however, because patients are often managed empirically. Besides, depressive symptoms may enhance the likelihood of a diagnosis by influencing pain perception and quality of life, thus triggering targeted diagnostic pathways earlier rather than later. Finally, the timing of the diagnoses of depression and endometriosis is probably not representative of the true onset of symptoms.

Another important domain of interpretation is related to individual and context vulnerabilities, which could explain variations in the complex

relationship between endometriosis and depressive symptoms. Each patient's experience with the disease and the associated chronic pain is likely to be influenced by individual psychosocial factors. Self-esteem and self-efficacy are associated with psychological well-being of endometriosis patients, independently of pelvic pain.[53] Women with symptomatic endometriosis are characterized by catastrophizing and negative cognition related to pain, which independently influences their quality of life.[54,55] Depressive symptoms are correlated positively with emotional and avoidant coping, although negatively with rational and detached coping.[29] In addition, the chronic course of endometriosis, an early but often overlooked onset, and manifestations such as dyspareunia or subfertility all have clear potential for long-term repercussions in social and personal relationships.[2,5]

The heterogeneous level and quality of health care received by women with endometriosis may also influence the patients' individual and social experience with the disease. Treatment alternatives for endometriosis-related pain (eg, ovarian suppression or advanced surgery) and subfertility (eg, assisted reproduction) often have suboptimal results and are inevitably associated with psychological distress. Lack of noninvasive diagnostics and low awareness among nonspecialized practitioners contribute to a consistent delay in endometriosis detection and adequate management.[1] Poor health care access and interaction with caregivers are, not surprisingly, associated with worse psychological health among women with endometriosis,[56] and are therefore potential modulators of depressive symptoms. Finally, there is a gap between the particularly high levels of stigma perceived by individuals with chronic pain conditions and comorbid depression, and the underestimation of the same stigma by the healthy individuals surrounding them,[57] thus paving the way to self-perpetuating social vulnerability.

Implications

Clinicians who assist women with chronic pain and known or suspected endometriosis need awareness of the association with depressive symptomatology and its complex background in order to provide tailored and patient-centered management. Patients with chronic disease and comorbid depression report worse symptoms independently of the objective severity of their condition.[58,59] The association between chronic pain and depression potentially reduces the effect of treatments and enhances individual and social vulnerabilities.[40,57] Nevertheless, timely detection and treatment of depressive symptoms improves quality of life and physical symptoms, regardless of objective physiologic changes.[58,59] Screening for psychiatric symptoms among women with endometriosis has therefore been advocated,[15] and our findings would suggest particularly directing it to those with chronic pain. A multidisciplinary approach is often cited by authoritative guidelines, although the latter largely focus on the diagnosis and management of physical manifestations and symptoms.[60–63] Although no robust evidence yet exists to recommend a specific management of endometriosis patients with depressive symptoms, efforts to promote pragmatic guidelines are highly desirable because screening programs for depression are unlikely to be effective without structured care.[64] However, the first steps that clinicians may take towards the identification of depression among women with endometriosis could be as simple and affordable as asking 2 questions, as recommended by the United Kingdom's National Institute for Health and Clinical Excellence for adults with a chronic physical condition: "During the last month, have you often been bothered by feeling down, depressed or hopeless? During the last month, have you often been bothered by having little interest or pleasure in doing things?"[65]

Endometriosis research most commonly focuses on medical/surgical interventions and physical health outcomes, and its findings and relevance are being scrutinized.[3,66] A relevant and timely question concerns which core outcome measures should be studied and reported by endometriosis trials,[67] and it may be argued that mental health should be 1 of those. More specifically, mental health manifestations such as depression should be studied not just as a treatment target but also as potential harms associated with treatment interventions. In women with pain as their main complaint, it would also be relevant to understand whether and how screening and detection of depressive symptoms may modify the course of disease, and the effectiveness of established treatments. The cost-effectiveness of screening and care could be an interesting research topic, as both endometriosis and depression are associated with high health care utilization and costs, particularly when associated with pain symptoms.[14,42,68] It would be interesting to study whether increased physician awareness and/or a multimodal management approach may reduce the societal burden related to productivity loss, which accounts for two-thirds of the costs attributed to endometriosis.[7] Further research should also target subfertility, a known epidemiological correlate of depression and endometriosis, because existing evidence is scarce and inconclusive. Some authors reported no significant differences in depressive symptoms between subfertile women with and without endometriosis,[22] as well as between women with endometriosis with and without subfertility.[69] More knowledge about the association between endometriosis-related subfertility and depression would be useful, in view of the psychological burden of fertility treatments,[70] some evidence that depressed women have lower success rates,[71] and the strong association between preexisting depression and maternal perinatal depressive symptoms.[72]

Conclusion

This systematic synthesis of scientific literature data published during the last 30 years shows that endometriosis is associated with depressive symptoms and that pelvic pain is a major determinant of the association. Broader efforts could be directed toward improving the mental health of all women with chronic pelvic pain and comorbid depression, as

they may not fit into discrete categories depending on a diagnosis of endometriosis. Therefore, the modern paradigm shift from a clinical focus on endometriosis lesions and their removal, to the symptoms and their pragmatic treatment, appears justified. In addition, small to medium pooled effect sizes and a notable variability among the studies comparing women with and without endometriosis suggest that other factors, including individual and context vulnerabilities, modulate mental health outcomes. Awareness of the complex relationship between endometriosis and depressive symptoms is essential to inform tailored care and to define patient-centered research outcomes. Future studies into possible modulators of the association will hopefully provide further insights about how to improve the quality of life of women with endometriosis and/or pelvic pain. ■

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AUTHOR CONTRIBUTIONS

PG conceived and designed the study, selected and appraised the studies, analyzed and interpreted the findings, drafted the article, and is the lead and corresponding author. VC contributed to design, analysis and interpretation of the findings, and critically revised the paper for intellectual content. GH contributed to design, selected and appraised the studies, analyzed the findings and contributed to their interpretation, contributed to the article drafting, and critically revised the paper for intellectual content. All authors have read and approved the final version of the article.

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