Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Faustino R. Pérez-López , Lía Ornat , Gonzalo R. Pérez-Roncero , María T. López-Baena , Manuel Sánchez-Prieto & Peter Chedraui (2020): The effect of endometriosis on sexual function as assessed with the Female Sexual Function Index: systematic review and meta-analysis, Gynecological Endocrinology, DOI: 10.1080/09513590.2020.1812570

To link to this article: https://doi.org/10.1080/09513590.2020.1812570

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GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2020.1812570

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ARTICLE

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The effect of endometriosis on sexual function as assessed with the Female Sexual Function Index: systematic review and meta-analysis

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ABSTRACT

Aim: To systematically compare sexual function between non-treated women with and without endometriosis.

Methods: A systematic review was performed on PubMed/Medline, Scopus, EMBASE, Web of Science and Cochrane Library databases searching studies that analyzed sexual function (assessed with the 19-item Female Sexual Function Index [FSFI]), and dyspareunia, chronic pelvic pain and dysmenorrhea (assessed with a visual analogue scale [VAS]) in women with and with endometriosis.

Results: In 4 studies, non-treated women with endometriosis presented a higher risk of female sexual dysfunction (mean total FSFI score $\leq$ 26.55; OR = 2.38; 95% confidence interval [CI] = 1.12, 5.04). Although mean total FSFI scores were not significantly different between women with and without endometriosis (mean difference [MD] = −2.15; 95% CI −4.96, 0.67); all FSFI domain scores were significantly lower in women with endometriosis (n = 4 studies): desire (MD = −0.43; 95% CI −0.57, −0.19); arousal (MD = −0.66; 95% CI −1.15, −0.17); lubrication (MD = −0.41; 95% CI −0.79, −0.02); orgasm (MD = −0.40; 95% CI −0.73, −0.06); satisfaction (MD = −0.45; 95% CI −0.72, −0.18); and pain (MD = −1.03; 95% CI −1.34, −0.72). Women with endometriosis displayed differences (more severity) in terms of VAS scores (2 studies) for dyspareunia (MD = 1.88; 95% CI 0.38, 3.37) and chronic pelvic pain (MD = 2.92; 95% CI 1.26, 4.58); but not for dysmenorrhea.

Conclusion: Non-treated women with endometriosis displayed altered sexual function as evidenced by lower scores in all FSFI domains, and severity of dyspareunia and chronic pelvic pain.

ARTICLE HISTORY
Received 23 June 2020
Revised 17 August 2020
Accepted 17 August 2020
Published online 3 September 2020

KEYWORDS
Chronic Pelvic Pain; Dyspareunia; Endometriosis; Female Sexual Dysfunction; Female Sexual Function Index; Visual Analogue Scale

Introduction

Female sexual dysfunction, particularly painful sex, is a common complaint in adult women of all ages. During reproductive years, endometriosis is a highly prevalent gynecological disease. Persistent sexual pain related to endometriosis has been associated to biological, psychological, sexual and interpersonal factors [1]. Clinical symptoms of endometriosis include dysmenorrhea, chronic pelvic pain, dyspareunia, lumbar pain, dyschezia, dysuria and infertility. The prevalence of sexual dysfunction in women with endometriosis is almost double as compared to those with other gynecological disorders [2]. Dyspareunia and chronic pelvic pain negatively impact several domains of sexual function, especially in women with deep infiltrating endometriosis (DIE) and rectovaginal or bowel endometriosis as compared to other forms of endometriosis or healthy women [3–5]. There are also psychological consequences, including mood swings, depressive and anxious symptoms that, at the same time, may increase pelvic discomfort [6–8]. The objective of this systematic review and meta-analysis is to compare sexual function between non-treated women with and without endometriosis.

Methods

Protocol, search strategy, eligibility criteria and study selection

The systematic review and meta-analysis was carried out following the principles of the PRISMA guidelines [9]. Formal institutional review board approval was not required, as this analysis consisted of the pooling of published studies.

A systematic literature search was conducted in PubMed-Medline, Scopus, EMBASE, and Web of Science databases from inception through March 9 2020, and without language restrictions. We searched for free terms 'endometriosis' OR 'endometrioma' OR 'rectovaginal endometriosis' AND 'sexual functioning' OR 'sexual dysfunction' OR 'sexuality' OR 'dyspareunia' OR 'sexual life'. The Pubmed search strategy is available in Appendix A (Supplementary Table A1). An iterative process was used to ensure that all relevant articles were obtained. A further manual search of bibliographic references was also carried out in selected studies and in existing reviews to identify potential studies that were not captured by the electronic database searches.

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Supplemental data for this article is available online at https://doi.org/10.1080/09513590.2020.1812570.

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Eligible for inclusion were relevant cohort and case-control studies that: (i) assessed women of reproductive age with clinical endometriosis and those without endometriosis who were not receiving any hormonal treatment; (ii) evaluated sexual function/dysfunction as assessed with a validated sexual function/dysfunction questionnaire; (iii) were in any language irrespective of age, race, and date of publication; and (iv) were addressing the same population if they reported complementary information to the main paper. Articles were excluded if they were narrative reviews, abstracts and conference proceedings, or non-human studies. All disagreements regarding inclusion/exclusion were discussed and solved by consensus with all authors. Meta-analyses were predefined/planned for each validated sexuality questionnaire if reported in at least two different populations.

Data extraction and risk of bias assessment

A Microsoft Excel sheet was designed for data input. Two researchers extracted publication details, eligibility and exclusion criteria, as well as information about the study population and design, period of study, sample size and clinical characteristics of the studied population. Discrepancies and controversies of extracted data were discussed in order to reach a consensus. Due to the fact that some results were reported as medians and their 25% and 75% confidence intervals, appropriate calculations were performed to obtain mean and standard deviations that served for the meta-analysis [10].

The methodological quality of the selected studies was independently assessed by two authors using the Newcastle–Otawa Scale for case-controls studies [11]. This scale consists of three broad perspectives including the selection of the study group, the comparability of the groups, and the ascertainment of the primary outcome. The maximum score can be 9 stars. Studies with seven star-items or more are categorized as high quality and those with six star-items or less as low quality.

Data synthesis and analysis

Forest plots were planned for outcomes reported in at least two studies using any validated test to assess female sexual function, using DerSimonian and Laird random-effects models and the inverse variance method [12]. Associations among dichotomous outcomes are reported as odds ratio (OR); and for continuous outcomes mean differences (MDs), both with their corresponding 95% confidence interval (CI). We evaluated statistical heterogeneity using the Cochrane chi square (X^2), the I^2 statistic, and the between-study variance using the tau square (τ^2) [13,14]. I^2 values of 30–75% indicate a moderate level of heterogeneity. A $p < .1$ for the chi-square defined the presence of heterogeneity; and a $\tau^2 > 1$ defines the presence of substantial statistical heterogeneity. We planned to estimate the publication bias if there are at least 10 studies reporting the same outcome [15].

The Review Manager program (RevMan, version 5.3, Oxford, UK; The Cochrane Collaboration) was used for statistical analyses.

Results

Selection and characteristics of the studies

A total of 366 records were identified through systematic database searches and 3 through other sources (Figure 1). After the removal of duplicates, 314 items were screened by title, leaving 74 for review of abstract content. Eligibility was assessed in 23 full text articles, leaving a total of eleven. Seven of these papers were excluded, four that did not have a control group and three that reported in each one data of sexual function assessed by a different tool. There was one study using the Female Health Outcomes in Women questionnaires [2], one study with the McCoy Female Sexuality Questionnaire [16], one study with the Female Sexual Quotient [5], and four studies using the Female Sexual Function Index (FSFI) [17]. Therefore, a total of 4 studies reporting results with the FSFI were included in this meta-analysis (Figure 1) [18–21]. The general characteristics and main relevant clinical and socio-demographic findings of patients included in the 4 studies are presented in Table 1.

The FSFI is a 19-item self-reported instrument used to measure overall sexual function in the past 4 weeks in women who are sexually active and have a partner. The tool is composed of six domains of sexual function each providing a score. The sum of all domain scores yields a total FSFI score. These domains are: desire (2 items, questions 1&2), arousal (4 items, questions 3&4 and 5&6), lubrication (4 items, questions 7&8 and 9&10), orgasm (3 items, questions 11&12&13), satisfaction (3 items, questions 14&15&16), and pain (3 items, questions 17&18&19) [17]. A total FSFI score of $\leq$ 26.55 was used to define women at higher risk of sexual dysfunction [22].

Meta-analysis of sexual function and dyspareunia

There were no significant mean differences (MD) in terms of age (MD = 1.69 years, 95% CI −0.14, 3.53; Figure 2(A)) and total 19-item FSFI scores (MD = −2.15, 95% CI −4.96, 0.67; Figure 2(B)) when comparing women with and without endometriosis [18–21]. Despite finding no differences in mean total FSFI scores, women with endometriosis displayed a higher risk of sexual dysfunction (defined as a total FSFI score $\leq$ 26.55) [22] (OR = 2.38; 95% CI 1.12, 5.04, $n = 3$ studies; Figure 2(C)) [18,19,21]. Women with endometriosis displayed lower scores in each of the FSFI domains: desire (MD = −0.43; 95% CI −0.67, −0.19, Figure 3(A)); arousal (MD = −0.66; 95% CI −1.15, −0.17; Figure 3(B)); lubrication (MD = −0.41; 95% CI −0.79, −0.02; Figure 3(C)); orgasm (MD = −0.40; 95% CI −0.73, −0.06; Figure 3(D)); satisfaction (MD = −0.45; 95% CI −0.72, −0.18; Figure 3(E)), and pain (MD = −1.03; 95% CI −1.34, −0.72; Figure 3(F)) [18–21].

In two studies, visual analogue scale (VAS) pain scores for dyspareunia were significantly higher in women with endometriosis (MD = 1.88; 95% CI 0.38, 3.37; Figure 4(A)) [18,19]. Dyspareunia would had been worse if one takes into account that 7 additional women with endometriosis and one without endometriosis in the De Graaf et al. study were unable to maintain/have sexual intercourse [18]. Chronic pelvic pain was also assessed with a VAS, also showing significantly more pain severity in women with endometriosis as compared to controls (MD = 2.92; 95% CI 1.26, 4.58; Figure 4(B)) [18,19]. Finally, there were no significant differences in terms of dysmenorrhea intensity between women with and without endometriosis as assessed with the VAS (MD = 1.80: 95% CI −2.63, 6.23; Figure 4(C)) [18,19].

Risk of bias

Appendix A, Supplementary Table A2 displays the assessment of risk of bias by means of the Newcastle–Otawa Scale [11], showing a low risk of bias (score $\geq$ 7).

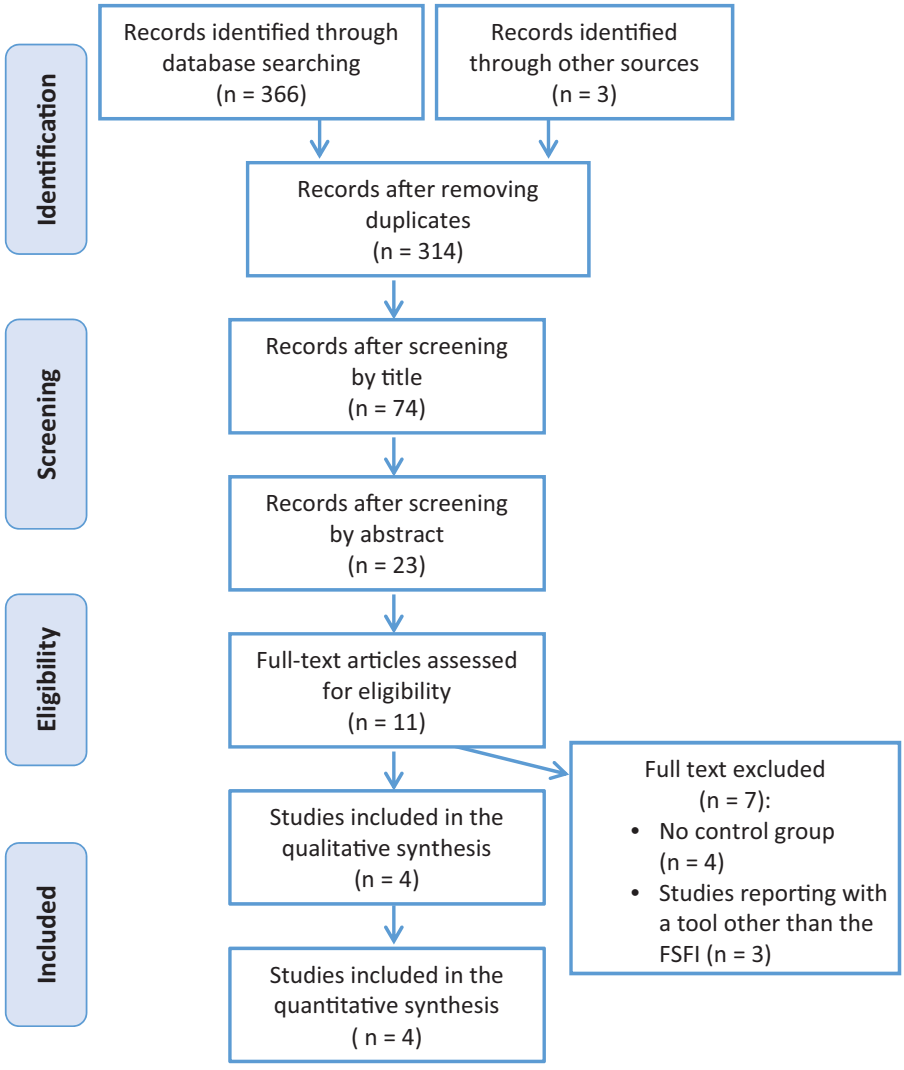

Figure 1. Flowchart of study selection.

Publication bias

Since there were only 4 studies, we were unable to calculate publication bias with the funnel plot and the Egger's test [15].

Discussion

The present meta-analysis found that un-treated women with endometriosis in their early fourth decade of life have an increased risk of sexual dysfunction, dyspareunia and chronic pelvic pain in comparison to those without endometriosis. Despite this, no significant differences were found in relation to the severity of dysmenorrhea. Endometriosis is a chronic gynecological disease that causes a negative impact on physical, psychological and sexual aspects of life. Regarding sexuality, the impact of the disease has been studied in different clinical conditions, treatment scenarios, associated to infertility, and general health and quality of life. Sexual function is severely compromised in women who smoke, have dyspareunia, severe chronic pelvic pain, bladder syndrome, and an increased body mass index or a family history of chronic pain [23,24].

Systematic reviews have analyzed sexual function or dysfunction among women with endometriosis who had been receiving various treatments, indicating that more than half of these women suffer some type of sexual dysfunction [25,26]. Although surgical and pharmacological treatments may improve sexual function among women with endometriosis, in some cases discomfort during intercourse and sexual dysfunction may persist [27]. Despite this, to date we are not aware of any meta-analysis that compares female sexual function and different forms of genital pain between untreated women with and without endometriosis.

Among the few available studies, we found 4 reporting the assessment of sexual function with the 19-item FSFI. This questionnaire is a useful tool for the evaluation of female sexual function, and its total score allows us to objectively screen women who are at a higher risk of sexual dysfunction [20, 28]. In our study, although mean total FSFI scores did not differ among cases and controls; significant lower scores for each of the domains of the FSFI were found in women with endometriosis, suggesting that endometriosis has impaired their sexuality. Alterations of sexual function in women with endometriosis are not only related to the disease *per se* and its stage, yet also to other factors such as anxiety, depression, sleep problems, excessive body weight and less physical activity [29].

Women with endometriosis may have severe chronic pelvic pain, dysmenorrhea, dischezia, and urinary symptoms. We found significant higher mean dyspareunia VAS scores in women with

Table 1. Characteristics of the included studies assessing sexual function with the Female Sexual Function Index in women with and without endometriosis.

Author; Date	Study location; Period. Aim of the study	Exclusion criteria	Study design and participants	Main findings
De Graaf 2016 [18]	Maastricht, The Netherlands; June 2011 to December 2012. Aim: to compare pain symptoms; medical history; aspects of mental functioning; sexual functioning and quality of life between women with endometriosis and a control group aged 18 to 42 years who had sexual relationship for at least three months duration.	Exclusion criteria: hysterectomy, being pregnant, breastfeeding or to have given birth in the past three months, have severe comorbidity such as Crohn's disease, type 1 diabetes or malignancies, and were on medication not related to endometriosis that could influence on sexual functioning such as anxiolytic and antipsychotic medication. Women who underwent surgery in the inclusion period were enrolled at least three months after surgery.	Cross-sectional study. Study population: 83 women with endometriosis established by means of laparoscopy or open surgery using the known visual aspects of the disease. Women had a median age of 25.4 [19.3-30.9]. Patients with a strong suspicion of the diagnosis of endometriosis based on symptoms in combination with a positive pelvic clinical examination, ultrasound or MRI were also included. Control group: 40 women attending the outpatient clinic due to issues related with contraception.	Dyspareunia and depressive symptoms were associated to impaired sexual functioning in women with endometriosis, whereas sexual functioning in their male partners was not affected. The majority of the participants were enrolled in a tertiary care center. This has led to an over-presentation of women needing tertiary care, and this could have also led to an over-presentation of their symptoms.
Evangelista 2014 [19]	Rio de Janeiro, Brazil; July to December 2011. Aim: to assess sexual function in women with deep infiltrative endometriosis as compared to women recruited in a family planning clinic.	Patients whose cognitive abilities were insufficient to comprehend and interpret the questionnaire were excluded; as well as those with debilitating chronic illnesses (diabetes mellitus, hypertension, lupus, thyroid disease, etc.) and those who had not engaged in penetrative vaginal intercourse during the month preceding the study enrollment.	Cross-sectional, prospective study. Study population: 57 women with DIE and chronic pelvic pain (aged 18 to 45), current sexual activity (onset of sexual activity at least 1 year prior to study enrollment). DIE diagnosis was based on pelvic pain and/or infertility associated with at least two of the following: detection of a hardened nodule in the vesico-uterine or rectouterine pouch on vaginal and/or rectal examination; transvaginal ultrasound or MRI findings consistent with infiltrating endometriosis in the pelvis; and surgical visualization or histopathological confirmation of endometriosis. Control group: 38 women (aged 18 and 45), sexually active, with onset of vaginal intercourse at least 1 year prior to study enrollment, no severe dysmenorrhea (visual analog scale score <8), no clinical evidence of endometriosis, and with a normal gynecological examination.	There was no significant difference in total FSFI scores, and also the desire, arousal and orgasm domains of the tool. However, there was a significant difference between the two groups in the pain domain. Both conclusions did not change after controlling for potential confounders.
Ghajarzadeh 2014 [20]	Tehran, Iran; January 2013 to August 2013. Aim: to evaluate sexual function in Iranian women with endometriosis in comparison with healthy controls.	Not stated.	Cross-sectional study. Study population: 44 women with laparoscopically diagnosed endometriosis (mean age 33.1 ± 6.8 years); BMI = kg/m2 25.9 ± 5.4. The most common clinical symptoms were dysmenorrhea (77.2 %), dyspareunia (47.7 %), pelvic pain (27.2 %) and pain during defecation (25 %). Control group: 80 healthy women from patient's families and hospital staff, aged 33.5 ± 7.1 years; BMI = 25.9 ± 5.4 kg/m^2.	FSFI total and three domain scores (arousal, orgasm and pain) were significantly different between patients and controls. Education level and BMI were significantly different in patients with and without sexual dysfunction. BMI was the independent predictor for total FSFI score in both case and control groups.
Melis 2015 [21]	Cagliari, Italy; January 2010 to June 2011. Aim: to assess sexual function, quality of life, and perceived body image among women with deep endometriosis as compared to healthy women.	Patients affected by vaginismus or vulvodynia without deep nodule tenderness. Women with any hormonal or antidepressant treatment during the study or during the month before the study. Most participants were patients who were sent after surgical diagnosis by other hospitals without any hormonal treatment. Patients with any chronic disease were excluded. Volunteers were healthy women consecutively recruited among those coming for a regional screening.	Cross sectional study. Endometriosis population: 41 women with deep endometriosis after clinical, biochemical, ultrasonography, MRI evaluation who were not taking any hormonal or antidepressant treatment during the study or the prior month. Mean age was 31.5 ± 6.4 years. A washout period of 2 months was prescribed for 2 patients under estroprogestin/progestin treatment. Control group: 40 women without endometriosis (mean age 30.4 ± 5.1 years).	Deep endometriosis has a significant impact on sexuality and body image. Women with endometriosis showed a greater intensity of pain during and after penetration. Moreover, significant differences were detected in sexual function between the women with and without endometriosis regarding the FSFI 'desire' domain. The differences in the domains of arousal, lubrication, orgasm, and satisfaction were not statistically significant.

BMI: body mass index; DIE: deep infiltrative endometriosis; FSFI: Female Sexual Function Index; MRI: magnetic resonance imaging.

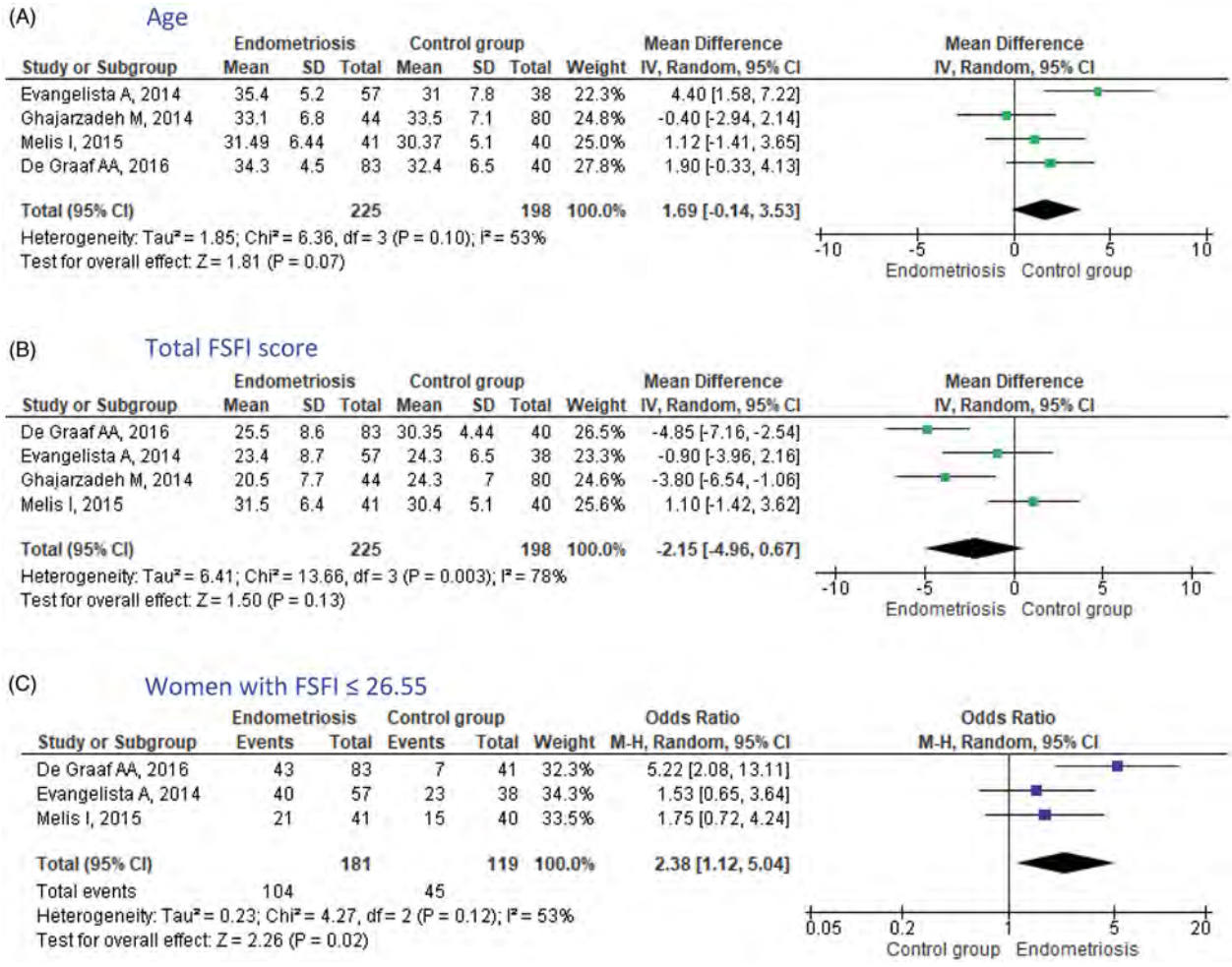

Figure 2. Forest plots comparing women with and without endometriosis according to mean difference of age expressed as years (A), mean difference in total Female Sexual Function Index score (B), and risk of female sexual dysfunction (odds ratio) according to the FSFI cutoff of ≤ 26.55 (C).

endometriosis in comparison to the controls. It is important to mention that 7 women with endometriosis and one without in the De Graaf et at.[18] study were unable to maintain sexual intercourse due to their history of extreme dyspareunia; hence it can be presumed that this outcome would be even worse (higher VAS score) if more studies and/or cases were available. Previous publications have reported that women with endometriosis who receive endocrine treatments achieve significant relief of their dyspareunia while increasing their total FSFI scores (better sexual function); although in some cases sexual function is not completely restored [30,31].

Chronic pelvic pain is a complex problem observed in women during their reproductive years. In this sense, endometriosis is a common cause, but symptoms are not constant and may vary among populations and throughout time, in fact decreasing or disappearing after menopause. In the present meta-analysis, we also found information regarding chronic pelvic pain, assessed with the VAS, in 2 of the 4 selected FSFI studies. Analysis found significant differences in terms of more intense chronic pelvic pain in women with endometriosis as compared to those without the disease. It seems that endometriosis alters peritoneal homeostasis and induces the production of pro-inflammatory and angiogenic cytokines [32]. Pelvic pain due to DIE may also be related to compression or infiltration of endometriotic implants in the sub-peritoneal space [33]. Endometriotic lesions are present in some 30 to 40% of women subject to laparoscopy due to chronic pelvic pain [34]. However, a 25% of cases can be asymptomatic which may be related to different factors with no clear or consistent patterns found [35]. Chronic pelvic pain may also be related to psychological dysfunction, anxiety and depression, decreased levels of self-compassion and emotional regulation, a history of sexual abuse, previous surgery, and urinary or digestive alterations [36–38].

The present meta-analysis found no significant differences in terms of VAS scores for dysmenorrhea. Dysmenorrhea may be associated to chronic pelvic and also non-pelvic causes. A recent meta-analysis pointed out that women with dysmenorrhea have a higher risk of chronic pelvic pain as compared to those without dysmenorrhea [39]. On the other hand, dyspareunia and dysmenorrhea are less intense in women who only have ovarian endometriosis in comparison to other locations [40]. In fact, as assessed with different tools, the extension and pain due to endometriosis are not consistently related.

Limitations

The principal limitation of our meta-analysis is the availability of few studies with only four publications directly comparing sexual function assessed with the FSFI among un-treated women with and without endometriosis. Unfortunately, three studies had to be excluded due to the fact that each one used a different tool

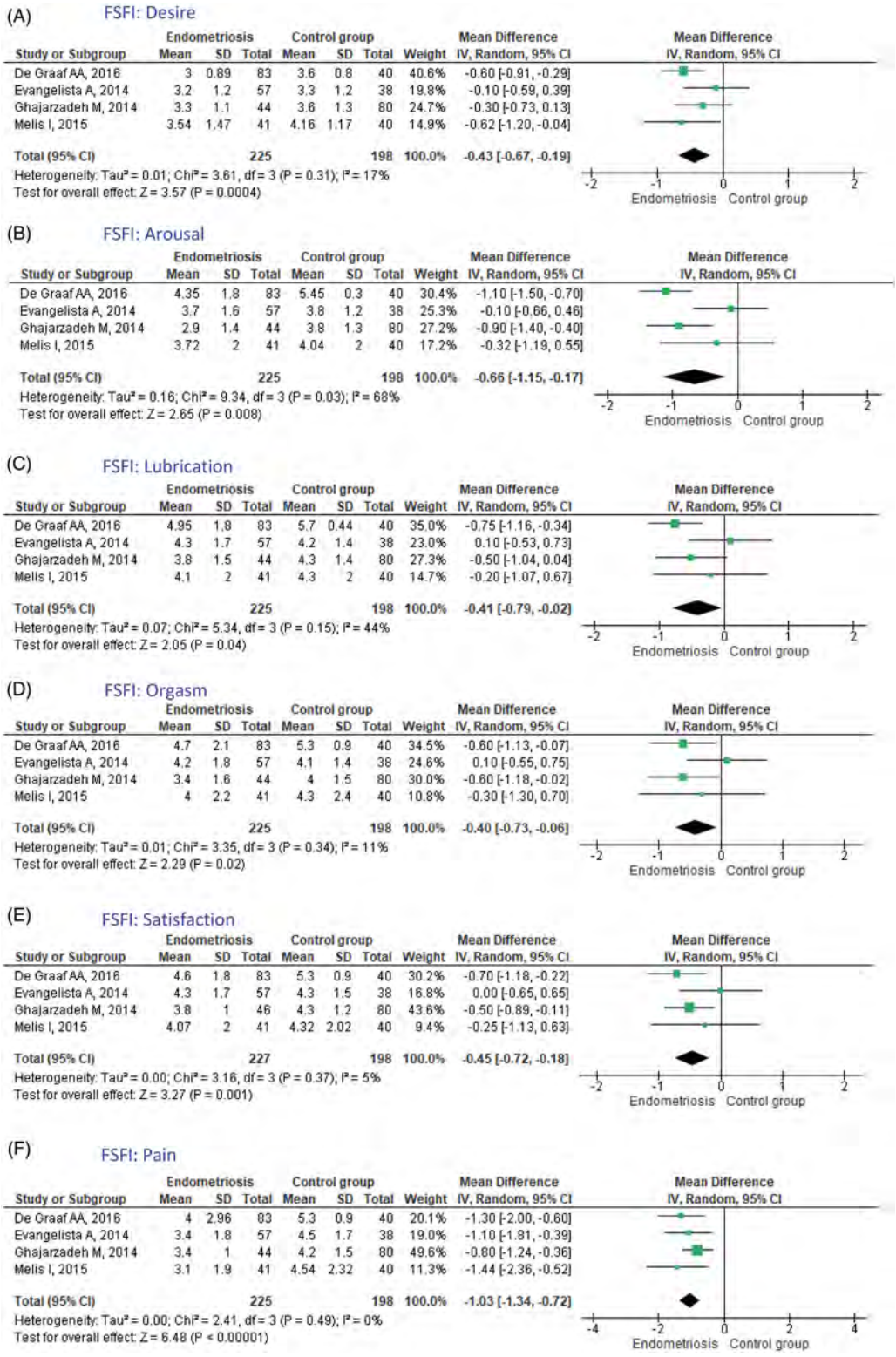

Figure 3. Forest plots comparing (mean difference) women with and without endometriosis according to scores obtained for each FSFI domain: desire (A), arousal (B), lubrication (C), orgasm (D), satisfaction (E), and pain (F).

[2, 5, 16]. These other tools may provide complementary information not found with the FSFI. Sexual life and expectations may change with age and the presence of endometriosis [41]. Women of our meta-analysis (with and without endometriosis) were in their early thirties; hence one should bear in mind that other age groups may have different sexual function characteristics. Another limitation of our meta-analysis is that controls were women without endometriosis who attended gynecological consultations for routine checkup, and although having a similar age and being free of symptoms, they were not subjected to any diagnostic laparoscopic procedure specific for women with endometriosis. However this approach would have been unethical.

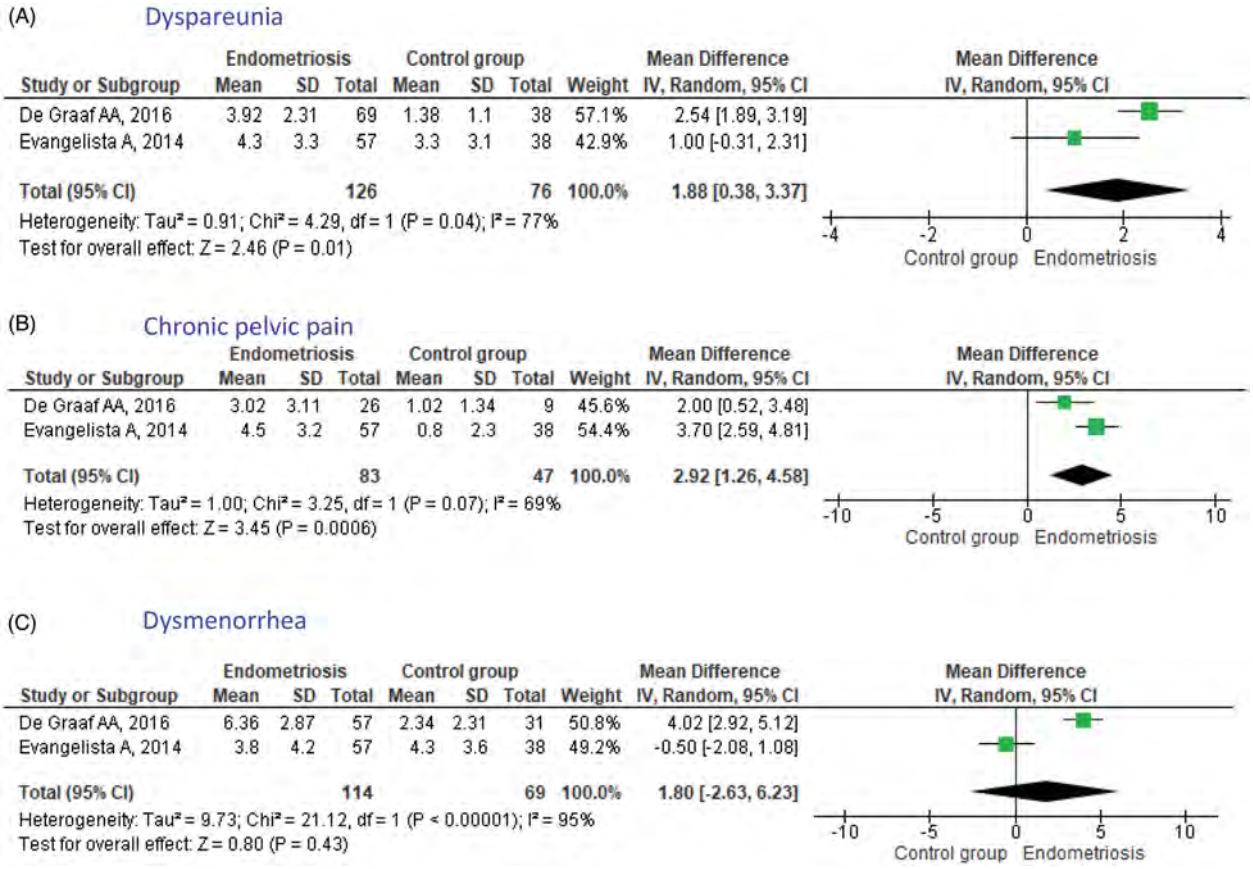

Figure 4. Forest plots comparing (mean difference) women with and without endometriosis according to VAS scores obtained for: dyspareunia (A), chronic pelvic pain (B), and dysmenorrhea (C).

Our meta-analysis of dyspareunia showed a significant trend for higher severity scores in women with endometriosis as compared to controls. Studies with larger samples have reported a higher prevalence of dyspareunia in women with endometriosis, although this symptom may also be unrelated to the disease [42,43]. Several studies have reported that dyspareunia is highly frequent in women with DIE who also present voiding alterations and psychological distress [25, 44,45]. Despite this, other causes of painful sex in women with endometriosis include depression or psychological stress [46]. Future studies should combine the assessment of dyspareunia along with the use of tools that evaluate depressive/anxiety symptoms, and emotional and sexual function.

Strengths

The first strength of our study is that it meta-analyzed data using the FSFI. This tool has been widely used to assess female sexual function, and its components, in quite different circumstances, diseases and populations throughout nearly two decades [47,48]. Secondly, we analyzed cases and controls that had a similar age, allowing equal comparisons in terms of social and sexual behavior. Despite these strengths, there is a need for studies performed in younger women in order to: i) assess the negative impact that the disease has over sexuality; and ii) once identified those with potential sexual dysfunction, evaluate overtime the impact of the disease or interventions.

Conclusion

Endometriosis is not a homogeneous disease in its anatomical characteristics and clinical symptoms. The meta-analyzed information could not identify these involved factors and also could not speculate about the types and extension of endometriosis due to the small number of included studies. In this sense, one should mention that higher rates of dyspareunia and chronic pain in women with endometriosis do not predict their sexual distress; with metacognitive beliefs having more influence on sexual distress than pain *per se* [49]. Despite the existence of previous systematic reviews, this is the first meta-analysis that objectively assesses female sexual dysfunction (and different forms of pelvic pain) in un-treated women with endometriosis using the FSFI that evaluates standardized components of sexuality.

Acknowledgements

The authors thank Prof. Stefano Angione, from the University of Cagliari (Italy), for providing complementary information about the paper by Melis et al. [21], included in the meta-analysis. The authors also thank Ms. M. Salas Valero for her assistance with the study.

Disclosure statement

The authors report no conflicts of interest and are alone responsible for the content and the writing of the article.

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