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ORIGINAL ARTICLE ***Psychology and counselling***

Physical pain and emotion regulation as the main predictive factors of health-related quality of life in women living with endometriosis

Gabriella Márki[1,2,*], Attila Bokor[3], János Rigó[3], and Adrien Rigó[2]

[1]Doctoral School of Psychology, Eötvös Loránd University, Budapest 1064, Hungary [2]Institute of Psychology, Eötvös Loránd University, Budapest 1064, Hungary [3]I. Department of Obstetrics and Gynecology, Semmelweis University, Budapest 1085, Hungary

*Correspondence address. E-mail: marki.gabriella@ppk.elte.hu

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STUDY QUESTION: To what extent are pain symptoms, psychological variables (anxiety, depression and distress) and emotion regulation associated with women's health in endometriosis?

SUMMARY ANSWER: Physical pain symptoms and emotion regulation difficulties via psychological stress negatively affect the health-related quality of life (HRQoL) of women living with endometriosis.

WHAT IS KNOWN ALREADY: There are some missing links in the definitive treatment and recovery from endometriosis. Women with chronic pain report a decrease in HRQoL and an increase in the frequency of psychological problems, but little is known about the complex relationship between these variables in the context of endometriosis.

STUDY DESIGN, SIZE, DURATION: This cross-sectional study was conducted between October 2014 and October 2015 on 193 women living with endometriosis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The sample consisted of women with a medically confirmed diagnosis of endometriosis who received treatment at the participating clinic. All participants completed the Short Form Health Survey (SF-36), the Hospital Anxiety and Depression Scale, the Perceived Stress Scale and the Difficulties in Emotion Regulation Scale. Spearman's rank correlation was used to explore the associations between the measured variables, and structural equation modeling was used to test the proposed mediation models.

MAIN RESULTS AND THE ROLE OF CHANCE: The response rate was 46%. In this study, 54.79% of the participants presented with anxiety and 20.3% with depressive symptoms. Pain symptoms, psychological variables and difficulties in emotion regulation were negatively associated with HRQoL. Mediation models revealed that physical pain, psychological stress and difficulties in emotion regulation explained 55% of the variance in the overall HRQoL, 41% of the variation in physical and 55% of the variation in mental HRQoL. Accordingly, severe physical pain ($\beta = -0.39$, $P < 0.001$) was directly, and difficulties in emotion regulation ($\beta = -0.38$, $P < 0.001$) was indirectly related to deterioration in overall HRQoL. Physical pain had a higher direct standardized effect ($\beta = -0.51$, $P < 0.001$) on physical HRQoL, and had no significant direct effect on mental HRQoL. Furthermore, both physical pain ($\beta = -0.07$, $P < 0.001$) and difficulties in emotion regulation ($\beta = -0.46$, $P < 0.001$) had a significant indirect effect on mental HRQoL.

LIMITATIONS, REASONS FOR CAUTION: The data were heterogeneous with regard to the severity of endometriosis. The validity of this cross-sectional study is limited to correlations; therefore, further longitudinal studies using a more representative sample are needed to explore valid causal relationships.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this study indicate that HRQoL can be improved through pain management and emotion regulation strategies. The authors believe that HRQoL would increase with concomitant application of physical treatment and psychological care.

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Key words: endometriosis / health-related quality of life / pain / psychological stress / emotion regulation

Introduction

Endometriosis is a common chronic gynecological disease that is characterized by the presence of endometrium-like tissue outside the uterus and is associated with severe pelvic pain and infertility (Giudice, 2010). This disease is prevalent in 10–15% of all women of reproductive age and in 20–50% of all women with infertility problems (Parazzini, 1999). Endometriosis is usually diagnosed 3.9–10.4 years after its onset (Hadfield *et al.*, 1996; Hudelist *et al.*, 2012; Bokor *et al.*, 2013), and this diagnostic delay has a negative impact on the health-related quality of life (HRQoL) (Seear, 2009).

Studies have emphasized the central role of pain associated with endometriosis (Giudice and Kao, 2004), which correlates negatively with HRQoL (Souza *et al.*, 2011), sexual functioning, the quality of relationships with partners (Ferrero *et al.*, 2005), mood (Sepulcri Rde and do Amaral, 2009) and work and social functioning (Fourquet *et al.*, 2010). Chronic pain can lead to social isolation (Mellado *et al.*, 2016) and can negatively affect emotional well-being as well (Sepulcri Rde and do Amaral, 2009). Endometriosis is associated with psychological problems, anxiety, depression, distress and poor coping ability (Petrelluzzi *et al.*, 2008; Sepulcri Rde and do Amaral, 2009; Carey *et al.*, 2014). It is notable, that there is a positive relationship between the level of anxiety symptoms and the intensity of pain (Sepulcri Rde and do Amaral, 2009), and a decrease in the level of depression symptoms is observed after pain management (Van den Broeck *et al.*, 2013; Vercellini *et al.*, 2013). Moreover, it should be mentioned, that women with asymptomatic endometriosis may not report impaired HRQoL and mental health (Facchin *et al.*, 2015).

Distress is also correlated with HRQoL and pain symptoms. Women with endometriosis report higher levels of health-related perceived distress as a result of their pain than women with chronic pelvic pain only or healthy controls (Mathias *et al.*, 1996; Petrelluzzi *et al.*, 2008). Distress and pain symptoms have a negative impact on each other, as the inflammatory nature of endometriosis may lead to the so called 'sickness response', associated with a vicious cycle caused by the underlying neuroendocrine–immune disequilibrium (Tariverdian *et al.*, 2007; Siedentopf *et al.*, 2008; Nasyrova *et al.*, 2011). A higher level of distress can lead to behavioral changes, exacerbate the health status and hinder improvement.

The mental conditions associated with endometriosis can be modulated by emotion regulation, which can be defined as goal-directed processes functioning to influence how we experience and express the intensity, type and duration of emotion (Gross and Barrett, 2011; Gyurak *et al.*, 2011). Lower capability for emotion regulation can increase the prevalence of negative emotions, and persistent pain and non-regulated negative emotions can reinforce each other (Gatchel, 2004; John and Gross, 2004). Although several studies on chronic pain focus on the role of emotion regulation, there has been little research on emotion regulation in women living with endometriosis.

Our research team hypothesized that besides pain symptoms, emotion regulation and psychological stress (anxiety, depression and distress) can have a notable effect on HRQoL. Thus, the aims of the present study are (i) to identify the main predictive factors of HRQoL and (ii) to examine the effect of pain symptoms, emotion regulation and negative emotions on HRQoL in women with endometriosis. To the best of our knowledge, this is the first study to define the explanatory variables related to the HRQoL of endometriosis patients based on the major factors that may contribute to HRQoL reported in previous research.

Materials and Methods

Study design, procedure and data collection

This cross-sectional survey was conducted at the I. Department of Obstetrics and Gynecology, Semmelweis University of Medicine, Budapest, Hungary, between October 2014 and October 2015. Every 18- to 50-year-old woman with a confirmed medical diagnosis of endometriosis was invited to the study. The participation was voluntary, and all participants provided their written consent before taking part in the survey. The questionnaire could be filled in on paper at the clinic or through a password-protected website at their home. All participants were informed about the basic goals of the study, and they were briefed about the confidentiality and anonymity terms. A total of 210 women living with endometriosis completed the questionnaire. Participants with self-reported comorbid psychiatric disorders ($N = 17$) were excluded from the sample, which made the number of study participants 193.

Measures

Demographic data, including age, marital status and occupation, were collected. The present pain symptoms caused by endometriosis were measured on a Likert scale (1: not painful, 10: very painful). Principal component analysis (PCA) was used to identify the linear components of pain. PCA of the pain symptoms was performed using six pain scores (described in Table I). The results revealed one factor with a variance of 45.98%, and the score for pain level that was loaded during the first day of menstruation was 0.75; additional bleeding days of menstruation, 0.78; bleeding-free days, 0.74; sexual intercourse, 0.65; urination, 0.44; and bowel movement, 0.66. The newly produced variable, named physical pain, was used for further mediation modeling.

The Short Form Health Survey (SF-36) is a 36-item, patient-reported survey of HRQoL (Ware and Sherbourne, 1992) that is used to measure both physical (physical HRQoL) and mental component of HRQoL (mental HRQoL). The questionnaire consists of eight subscales: physical and physical role functioning, bodily pain, general health perceptions, vitality, social and emotional role functioning and mental health. Higher scores indicate better health-related conditions. The questionnaire was found to have a high reliability index (Cronbach's $\alpha = 0.93$) in the current study.

Table I Demographic and endometriosis-related characteristics of the participants ($N = 193$).

Characteristic	Mean (SD)
Age (y)	33.87 (5.37)
Current marital status (%)	
Single	14.06
In a relationship	25.00
Married or living with a partner	57.29
Divorced	3.65
Occupation (%)	
Student	4.21
Active, full-time workers	83.16
Homemaker	9.47
Unemployed	3.16
Endometriosis-related characteristics (mean [SD])	
Pain during… (min: 1, max: 10)	
first day of menstruation	5.34 (3.39)
additional bleeding days of the menstrual cycle	3.73 (3.26)
bleeding-free days	2.07 (2.10)
sexual intercourse (dyspareunia)	2.60 (2.40)
urination (dysuria)	1.65 (1.75)
bowel movement (dyschesia)	2.36 (2.35)
Clinical characteristics	
Number of surgeries	1.85 (1.16)
Diagnostic delay (y)	3.74 (5.65)
Patient delay (y)	1.32 (2.81)
Period of time between the first time they sought medical aid and diagnosis (y)	2.50 (4.59)
Medical treatment (%)	51.80
Fertility problems (%)	21.80
Comorbid diseases (%)	33.70

The Hospital Anxiety and Depression Scale (HADS) is a 14-item, self-reported survey of mood. Seven items measure the level of depression and seven other the level of anxiety symptoms. The evaluations of the anxiety and depression subscales are aggregated separately (Zigmond and Snaith, 1983). Higher scores indicate a higher level of symptoms. In the current sample reliability for the HADS was found to be high (Cronbach's $\alpha_{depression} = 0.84$; Cronbach's $\alpha_{anxiety} = 0.84$).

The distress level was determined by the Perceived Stress Scale (PSS), which is a 14-item, self-reported survey used to measure the characteristics of thoughts and feelings related to a person's perception of stress (Cohen *et al.*, 1983). Higher scores indicate a higher frequency of stressful situations and unsuccessful coping with distress. In the present study, Cronbach's α for PSS was 0.89.

Psychological stress as a principal component of the anxiety, depression and distress scales was evaluated as a new principal component (Kaiser-Mayer-Olkin (KMO) test = 0.69; Bartlett's test of sphericity = 237.53; $P < 0.001$), and accounted for 76.75% of the explained variance. The component loadings were as follows: depression = 0.84, anxiety = 0.87, distress = 0.92.

The Difficulties in Emotion Regulation Scale (DERS) is a self-administered questionnaire that consists of 36 items arranged on six subscales: non-acceptance of emotional responses, difficulties engaging in goal-directed behavior, impulse control difficulties, lack of emotional awareness, limited access to emotion regulation strategies, lack of emotional clarity (Gratz and Roemer, 2004). A higher score indicates a higher level of emotion regulation problems. Our team followed the recommendation of Kökönyei *et al.* (2014), who suggested that the total DERS score be calculated independently of the awareness subscale. The reliability index in the current study was 0.96.

Statistical analysis

Spearman's rank correlation analysis was used to determine the relationship between perceived pain symptoms, psychological status and HRQoL, including physical and mental HRQoL, because the scales were not normally distributed. Structural equation modeling (SEM) was used to test three proposed mediation models, and to understand the complex relationship between the measured variables. Maximum likelihood estimation robust to non-normality (MLP) was used in SEM analyses, because the scales were not normally distributed. All the models were fully saturated; therefore, the usual fit indices (χ^2, confirmatory fit index, and root mean square error of approximation) of the overall model fit were not applicable because the degree of freedom was zero. Descriptive statistics and PCA were performed with IBM SPSS for Windows, version 22.0 (IBM SPSS Inc., Chicago, IL), and SEM analyses were performed using the MPlus 5.2 statistical modeling program (Muthén and Muthén, 1998).

Ethical approval

This study was approved by the Regional, Institutional Research and Ethics Committee of Semmelweis University, Budapest, Hungary (registration number TUKEB 60/2014), and the work was conducted in accordance with the tenets of the Declaration of Helsinki.

Results

Demographic, endometriosis-related and clinical characteristics

The study sample consisted of 193 endometriosis patients with a mean age of 33.87 years (SD = 5.37). Most women were married or were in relationships, and had an active, full-time job (Table I). The highest level of pain symptoms was reported for the first day of menstruation. Diagnostic delay was 3.7 years (SD = 5.65). Clinical characteristics (type of treatment, infertility problems) had no significant effect on the statistical analysis. Depressive symptoms affected 20.32% of the study sample (13.37%, mild; 4.81%, moderate; 2.14%, severe depressive symptoms), while 54.79% of the participants had anxiety symptoms (22.34%, mild; 22.87%, moderate; and 9.57%, severe).

Correlates of HRQoL

Table II displays Spearman's rank correlation coefficients. HRQoL was negatively associated with pain symptoms, psychological variables (depression, anxiety and distress) and difficulties in emotion regulation. The main pain symptoms showed a higher correlation with physical component of HRQoL than with mental component of HRQoL, which was highly associated with the psychological variables and difficulties in emotion regulation. These findings imply that there is a difference between the main predictive factors of physical and mental HRQoL.

Quality of life model

The overall model (model 1)

Physical pain, emotion regulation difficulties and psychological distress explained 55% of the variance in HRQoL (Fig. 1). Although a higher level of pain symptoms was associated with lower HRQoL, this effect was largely mediated by psychological distress. On the other hand, emotion regulation difficulties had no direct effect on the HRQoL. The effect of emotion regulation difficulties was fully mediated via psychological distress ($DERS_{indirect} = -0.38$; $P < 0.001$).

The models of the physical HRQoL (model 2) and mental HRQoL (model 3)

The results of physical and mental HRQoL were similar to those in Model 1 and to each other (Fig. 2).

Physical pain, emotion regulation difficulties and psychological distress explained 41% of the variance in physical HRQoL and 55% in mental HRQoL. Physical component of HRQoL was explained by a high negative effect of pain symptoms and moderate negative effect of psychological variables. Pain was significantly and substantially associated with mental component of HRQoL but only indirectly, via psychological stress. The significant positive effect of emotion regulation difficulties on physical HRQoL was explained by the statistical suppressor effect. This means that a connection between measured variables could be a statistically modified effect of an external, unidentified variable. However, both paths are partially mediated via psychological distress.

Discussion

Our results suggest that symptoms of physical pain and difficulties in emotion regulation are negatively associated with HRQoL via

Table II Correlations of HRQoL, pain symptoms and psychological variables.

	HRQoL	Physical HRQoL	Mental HRQoL
Health measure, pain during…			
first day of menstruation	−0.31***	−0.34***	−0.20*
additional bleeding days of the menstrual cycle	−0.41***	−0.57***	−0.19*
bleeding-free days	−0.35***	−0.43***	−0.23**
sexual intercourse (dyspareunia)	−0.36***	−0.41***	−0.28***
urination (dysuria)	ns	−0.18*	ns
bowel movement (dyschesia)	−0.40***	−0.35***	−0.31***
Psychological measure			
HADS–depression	−0.54***	−0.33***	−0.62***
HADS–anxiety	−0.60***	−0.42***	−0.70***
PSS	−0.55***	−0.34***	−0.64***
DERS	−0.38***	−0.17*	−0.52***

Note: HADS = Hospital Anxiety and Depression Scale; PSS = Perceived Stress Scale; DERS = Difficulties in Emotion Regulation Scale; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ns = not significant

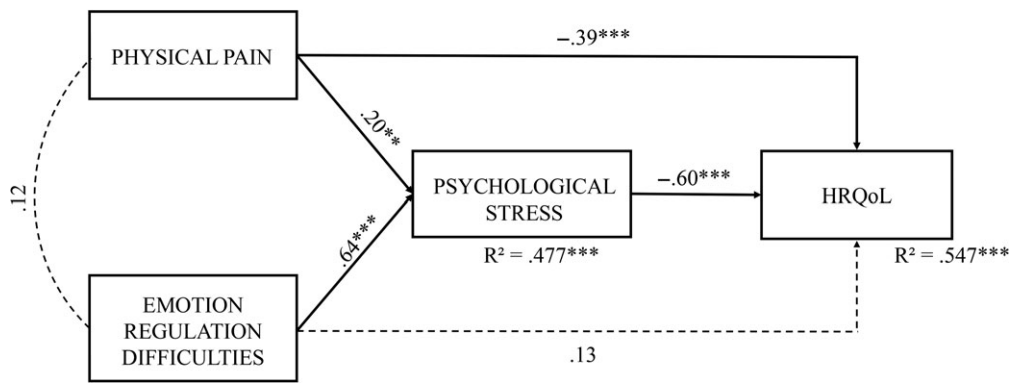

Figure 1 Mediation model for HRQoL with standardized path coefficients and explained variance of the variables (R-squared). All variables shown are the observed variables. Note: HRQoL = health-related quality of life; **$P < 0.01$; ***$P < 0.001$; solid line = significant path; dashed line = non-significant path.

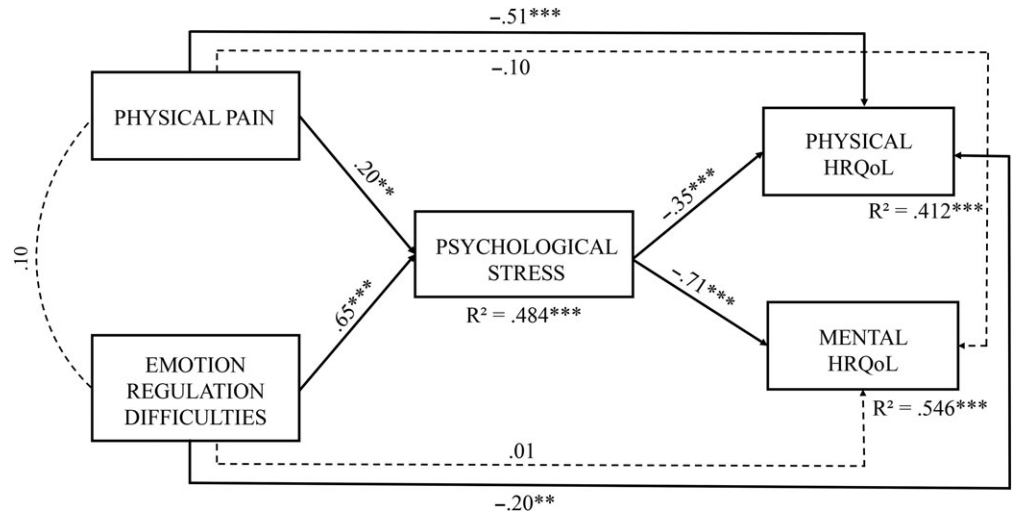

Figure 2 The comparison mediation model for physical and mental HRQoL with standardized path coefficients and explained variance of the variables (R-squared). All variables shown are the observed variables. HRQoL = health-related quality of life. Note: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; solid line = significant path; dashed line = non-significant path.

psychological stress (anxiety, depression and distress) in women living with endometriosis. Psychological stress is a major predictive factor of HRQoL, although there are differences in the mediation paths between the models of physical and mental HRQoL. To the authors' knowledge, this is the first study to explore the complex association between endometriosis-related pain symptoms, psychological variables and HRQoL in patients living with endometriosis.

The results supported the notion that women with a higher level of pain have a lower quality of life (Souza *et al.*, 2011), although physical quality of life is only related to physical pain (Garry *et al.*, 2000; Sepulcri Rde and do Amaral, 2009). According to the mediation models, increased physical pain and difficulties in emotion regulation both lead to increased psychological stress, which is associated with deterioration of the quality of life. The main goal of treatment should be to reduce pain symptoms in order to improve HRQoL, decrease societal burden and health care costs of endometriosis (Simoens *et al.*, 2012). This notion is supported by other studies as well (Vercellini *et al.*, 2009; Jia *et al.*, 2012).

Based on the present models, it seems that psychological stress acts as a mediator between physical pain and HRQoL, which supports the notion that perceived pain is associated with negative emotions (Petrelluzzi *et al.*, 2008; Carey *et al.*, 2014). Negative mood may alter pain experience by greater neurocircuitry (in the inferior frontal gyrus and amygdala) activation, which is linked to pain-induced changes in the emotion regulation mechanism (Berna *et al.*, 2010). Agar-Wilson and Jackson (2012) found that efficient emotion regulation is associated with better quality of life and the ability to cope with chronic pain. Besides medical pain management, the improvement of emotion regulation skills should be a treatment goal as well.

To date, only a few published studies have used health-psychological intervention programs for endometriosis patients. Zhao *et al.* (2012) confirmed the efficiency of a therapy that comprised hormonal therapy and progressive muscle relaxation in HRQoL and mood symptoms. Kold *et al.* (2012) managed to improve pain symptoms, as well, by mindfulness training. Mindfulness intervention (Kabat-Zinn *et al.*, 1985) helps women to the systematic cultivation of a flexible attentional capacity for detached observation of pain and as a self-help tool has lasting positive effects on HRQoL, and can enhance physical and mental HRQoL (Hansen *et al.*, 2017). Mindfulness training can have a successful impact on emotion regulation as well, which is reflected in improvements in amygdala-prefrontal functional connectivity (Hölzel *et al.*, 2013).

The results of Jones *et al.* (2004) and previous intervention studies suggest that psychological interventions for women living with endometriosis should focus on pain management, emotion regulation strategies, negative emotion reduction, improvement in work and sexual life, change in the attitude of members of the medical profession and (in)fertility and social support. To the authors' knowledge, there is no published thematic health promotion program for women living with endometriosis, despite biopsychosocial results have indicated the strong need for such a program. Women and their families, as well as the health care system, would highly benefit from an efficient complex medical and psychological treatment regime.

The authors acknowledge that there are certain limitations to the current study. First, the cross-sectional study design, self-selected and self-reported nature and the Hungarian-only data limit the generalizability of the findings. Consequently, a longitudinal design would provide us with a more accurate picture of the exact and causal relationships. Second, the validity of the models would increase by increasing the number of participating gynecological clinics, and by controlling the severity and type of endometriosis, and by excluding patients having comorbid diseases. Although we did not find any significant differences in measured variables neither while comparing fertile with infertile women nor while comparing patients with and without hormonal therapy. The stage and type of endometriosis, presence of comorbid physical diseases, personality, coping mechanism and (undiagnosed) psychiatric comorbidities may have a significant impact on pain perception and psychological

health of women living with endometriosis (Giudice, 2010; Kvaskoff et al., 2015; Pope et al., 2015; Facchin et al., 2016). These dimensions need to be observed for more comprehensive models in future studies. Third, the prevalence of negative emotional problems and the diagnostic delay was lower than those published in previous studies (Hadfield et al., 1996; Sepulcri Rde and do Amaral, 2009; Hudelist et al., 2012). Therefore, if more serious cases, such as cases of deep infiltrating endometriosis (Montanari et al., 2013) and comorbid psychological symptoms (Pope et al., 2015) had been included in the study, the associations would have been even more pronounced with regard to the impairment of HRQoL. In addition, the fact that women with a higher level of anxiety, depression and sleep disturbance tend to refuse to participate in research or drop out from studies (Bergqvist and Theorell, 2001) suggests that the severity of the problem in the current sample is underestimated.

Conclusion

HRQoL can be improved in different ways, for example, through the management of pain and emotion regulation. The present findings indicate the strong need for complex, combined treatments to increase the HRQoL in endometriosis patients, and also point to the need for screening for emotion regulation difficulties and physical symptoms in women with endometriosis. Intervention programs based on these findings should be developed in the near future and should become available for patients to successfully cope with pain and negative emotional problems, which are negatively correlated with adherence and compliance (Karkashian and Schlundt, 2003; Coifman et al., 2014).

Women with endometriosis would benefit from a complex treatment regimen, because physical markers and psychological status are inseparable, and both can negatively affect HRQoL at the individual level and increase the cost to the health care system at the societal level (Simoens et al., 2012). These health promotion programs may also help tackle issues related to fertility and IVF, which are common as well (Practice Committee of the American Society for Reproductive Medicine, 2006). Further research is needed to clarify the relationship between pain and emotion regulation, and to investigate the role of psychological stress and emotion regulation difficulties in the (re)emergence of endometriosis.

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Authors' roles

All authors were involved in designing this study. G.M., A.B. and J.R. assisted with the recruitment of participants. G.M. and A.R. were involved in the analysis and interpretation of data. This manuscript was drafted by G.M., and A.R. and A.B. edited the article. All the authors have approved of the final draft.

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Conflict of interest

None declared.

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