



RESEARCH

Stressful experiences impact clinical symptoms in people with endometriosis

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Abstract

Endometriosis is a chronic condition that affects ~10% of women globally. Its symptoms include chronic pelvic pain, heavy periods and tiredness/fatigue, which have been associated with poorer quality of life and mental health. We aim to explore the impact of the COVID-19 pandemic on pain and fatigue symptoms and their interactions with the impact on mental health in people with endometriosis. This global cross-sectional online survey study collected data from 4717 adults with self-reported surgical/radiological diagnosis of endometriosis between May and June 2020. The survey included questions on the current status and changes of endometriosis symptoms (pelvic pain, tiredness/fatigue, and bleeding patterns), mental health, pain catastrophising, and the impact of the COVID-19 pandemic on the respondents' lives. Compared to 6 months earlier, Respondents reported a marked worsening of their endometriosis symptoms (endometriosis-associated pain (39.3%; 95% CI: 37.7, 40.5), tiredness/fatigue (49.9%; 95% CI: 48.4, 51.2) and bleeding patterns (39.6%; 95% CI: 38.2, 41)) and mental health (38.6%; 95% CI: 37.2, 39.9). Those with a pre-existing mental health diagnosis (38.8%) were more likely to report their symptoms worsening. Worsening of pain and tiredness/fatigue was significantly correlated with worsening of mental health ($P < 0.001$). The relationship between changes in mental health and (a) change in pain and (b) change in fatigue was found to be weakly mediated by pain catastrophising scores (pain: $B = 0.071$, lower limit of confidence interval (LLCI) = 0.060, upper limit of confidence interval (ULCI) = 0.082, tiredness/fatigue: $B = 0.050$, LLCI = 0.040, ULCI = 0.060). This study demonstrates that stressful experiences impact the physical and mental health of people with endometriosis. The findings highlight the need to consider psychological approaches in the holistic management of people with endometriosis.

Lay summary

Endometriosis is a chronic condition in which tissue similar to that of the lining of the womb grows outside it. It affects around 10% of women globally, and the symptoms often include persistent pelvic pain, heavy periods and tiredness/fatigue. These symptoms are associated with impaired mental health and life quality. This study used an online questionnaire to assess the experiences of people with endometriosis during the first months of the pandemic. Results from 4717 adults revealed that pelvic pain, tiredness/fatigue and bleeding worsened in more than 39% of the participants. Poor mental health was also exacerbated and associated with worsening in tiredness/fatigue. Further analysis revealed

that this relationship could be partially explained by 'pain catastrophising', which measures how participants think about their pain. Our results suggest that stressful experiences like the pandemic negatively impact the already burdened mental health of people with endometriosis, who could benefit from psychological interventions.

Keywords: ► endometriosis ► COVID-19 ► survey ► women ► pandemic

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Introduction

Endometriosis is a chronic condition that affects ~10% of women globally. It is classically associated with a variety of pelvic pain syndromes and subfertility; however, many sufferers also describe heavy periods and tiredness/fatigue (TF). The nature and longevity of these symptoms, along with the currently long diagnostic delay of the disease, have been associated with impairments in the quality of life, including mental health and work productivity (Nnoaham *et al.* 2011, Facchin *et al.* 2017, Zondervan *et al.* 2018). The symptoms of infertility and dyspareunia add to the psychological burden of people suffering with endometriosis and increase the levels of perceived stress while also negatively affecting the patients' self-esteem and relationship with their partners (Denny & Mann 2007, Vitale *et al.* 2017). Fatigue has also been identified as one of the most intense and frequent symptoms of endometriosis (Hansen *et al.* 2013) and associated with pain, insomnia and depression (Ramin-Wright *et al.* 2018) but is often overlooked in clinics.

The coronavirus disease 2019 (COVID-19) that was declared as a pandemic by the World Health Organization (WHO) on 11 March 2020 (World Health Organization 2020) has been a disruptor to normal life and a source of significant stress (Kujawa *et al.* 2020). Studies have shown that during the early weeks of government lockdowns, there was a significant negative effect on mental health in the general population (Brooks *et al.* 2020) and particularly in women in Italy (Di Giuseppe *et al.* 2020). In addition, access to healthcare was severely affected at a global level. For people with endometriosis, this meant cancelled appointments with gynaecologists and other specialists, delayed or cancelled surgical procedures and fertility treatments and difficulties accessing medication (Yalçın Bahat *et al.* 2020, Demetriou *et al.* 2021).

Understanding the impact of the COVID-19 pandemic on those with endometriosis could help us to better understand how other large-scale stressful events that can disrupt access to normal healthcare and routines may impact this population, potentially identifying those

at risk of worsening symptoms during times of stress and informing the design of future multi-disciplinary treatment protocols. The objective of the present study is therefore to explore the impact of the early stages of the COVID-19 pandemic on mental health and endometriosis-associated symptomatology using data from a global survey. It is plausible that people with endometriosis are more adversely affected by an external stressor than an otherwise healthy population (Petrelluzzi *et al.* 2008, Sepulcri & do Amaral 2009, Quiñones *et al.* 2015, Facchin *et al.* 2017, Coxon *et al.* 2018) due to alterations in physiological and psychological mechanisms underlying resilience and homeostasis (Carbone *et al.* 2021, Lubián-López *et al.* 2021).

In line with other population-based studies (Brooks *et al.* 2020, Di Giuseppe *et al.* 2020, Kujawa *et al.* 2020, Yalçın Bahat *et al.* 2020), we expect to see a deterioration in mental health in our cohort. We hypothesise that in those whose mental health worsens, pain and fatigue symptoms will also increase. However, given the complex mechanisms involved in endometriosis-associated pain (Morotti *et al.* 2017) and in fatigue more generally (Norheim *et al.* 2011), we do not expect to see a direct relationship between measures of pain intensity and psychological well-being. We will also explore the impact of the early stages of the pandemic on bleeding patterns. Finally, any relationship between alterations in mental health and pain or fatigue could be mediated by either intrinsic psychological factors or extrinsic factors. Therefore, we will explore whether pain catastrophising (intrinsic) as a measure of how people perceive and worry about their pain, perceived stress or emotional support (both extrinsic) mediates any observed relationships.

Methods

This was an online cross-sectional study conducted between 11 May 2020 and 8 June 2020, and the data were collected

via a global online survey study (Jisc: <https://www.jisc.ac.uk/online-surveys>). The research was internally funded by the University of Oxford. The study obtained approval by The Central University Research Ethics Committee, University of Oxford (reference number: R69636/RE001) and was advertised widely on social media by endometriosis support groups around the world and by endometriosis and women's health researchers and clinicians.

The survey was designed in collaboration with the support group Endometriosis UK and consisted of both validated outcome measures (see section titled 'Domains assessed') and relevant multiple-choice questions, some of which had an extra option for a free text response if the answer was not already provided. It assessed a variety of areas relevant to endometriosis symptoms, mental health, and the impact of COVID-19 on the respondent's lives (available as Supplementary material online, see section on [supplementary materials](#) given at the end of this article). Whilst specific core outcome sets were not used, we aimed to assess all domains recommended for studies of chronic pain and endometriosis (Dworkin *et al.* 2005, Rogers *et al.* 2009). Many of the questions were taken directly from the EPHEct Clinical Covariates Questionnaire (Vitonis *et al.* 2014). The survey was prepared in English and then translated by native speakers into French, German, Spanish, and Portuguese. All free text responses were translated into English by these native speakers and categorised by two researchers (LD and KV). None of the questions was mandatory; therefore, the total number of respondents for each varies.

Participants

A total of 7246 respondents completed the survey, with 6729 of them meeting the inclusion criteria of age (≤ 18 years old) and confirmed endometriosis diagnosis by surgery or imaging. In addition, as per the inclusion/exclusion criteria, the participants needed to be able to read, write and understand one of the languages that the questionnaire was available in (thereby excluding participants with severe cognitive impairments) and have access to a computer, tablet or smartphone with internet connection. Additionally, for the purposes of the present analysis, exclusions were made if the respondents reported a change in their hormone treatments or if they had a change in their pregnancy or breastfeeding status compared to 6 months ago as changes in hormonal status such as these would be expected to influence endometriosis symptoms. The final dataset used for the analysis included 4717 respondents (mean age = 33.2).

Domains assessed

Endometriosis symptoms

The survey assessed a variety of pelvic pain symptoms, bleeding and TF. Pain was assessed with numerical rating scales (NRSs) for pain intensity anchored with 0 = no pain and 10 = worst pain imaginable. NRSs have been widely used in the pain literature and proven to have high sensitivity and reliability for assessing pain (Williamson & Hoggart 2005, Karcioglu *et al.* 2018). The self-reported change in pain and TF compared to 6 months ago was assessed with ordinal scales with the following response options available: very marked worsening, marked worsening, minimal worsening, no change, minimal improvement, marked improvement, I did not experience any pain/TF due to endometriosis and this has not changed. An extensive set of responses was provided for changes in the regularity and frequency of bleeding pattern to allow all possible options to be assessed (Supplementary Appendix 1. Question B.6).

Mental health measures

Self-reported change in mental health compared to 6 months ago was assessed with an ordinal scale with the same response options as for pain and TF.

The respondents' current-state mental health was assessed using Patient-Reported Outcomes Measurement Information System (PROMIS) and NIH Toolbox validated scales (Cella *et al.* 2007, Gershon *et al.* 2013, Hanmer *et al.* 2020). The scales assessed depression, anxiety and pain interference during the last 7 days and perceived stress and emotional support since the pandemic was announced. Validated translations of some of these measures were not available and thus could not be included in the survey in that language. This applied to the perceived stress measure in German and the emotional support scale in French and Portuguese.

Pain catastrophising as a measure of how participants worry and distress about their physical pain (Crombez *et al.* 2020, Petrini & Arendt-Nielsen 2020) was assessed using the Pain Catastrophising Scale (PCS) (Cronbach's $\alpha = 0.87$) (Sullivan *et al.* 1995, Osman *et al.* 2000). This is a 13-item questionnaire that used a 5-point scale ranging from 0 (not at all) to 4 (all the time); the total PCS score was computed by summing the responses to all 13 items (Sullivan *et al.* 1995).

Previous diagnoses of anxiety and depression requiring therapy or medication were extracted from a question assessing comorbidities. The participants were asked to tick a 'Yes' box if they had received a

diagnosis for any of those comorbidities (Supplementary Appendix 1. A.7).

COVID-19 pandemic impact

A set of questions assessed the impact of the COVID-19 pandemic on personal and work life (Supplementary Appendix 1. C.10) and access to medication or planned appointments/treatments for both endometriosis and other reported comorbidities (Supplementary Appendix 1. B.1–3) (Demetriou *et al.* 2021).

Statistical analysis

Data were extracted and processed using the IBM SPSS Statistics software, Version 27. A mean score for all respondents was calculated for each NRS pain scale. The scoring for the PROMIS and NIH Toolbox scales was done using the HealthMeasures tool which produces a t-score value per respondent per scale. A mean of t-scores was then calculated for each scale. Descriptive statistics were calculated for all the variables, including mean, s.d. and s.e. and median, where appropriate. Frequencies and percentages were calculated for the effect of the pandemic on endometriosis symptoms and mental health.

Non-parametric tests (chi-square and Spearman's bivariate correlations) were used for analyses that included ordinal data (change in endometriosis pain, TF and mental health), while parametric statistical testing (ANOVAs and Pearson's bivariate correlations) was used for the continuous variables (PROMIS scales and PCS).

A mediation analysis was employed to explore whether the relationship between the reported change in mental health as a predictor and changes in pain or TF as outcomes was facilitated by the following hypothesised mediators: pain catastrophising, perceived stress or emotional support. As a sensitivity analysis, the mediation analyses were repeated on the population of respondents who reported no alteration of their endometriosis medication treatment due to the pandemic. The mediation analysis was run using PROCESS on IBM SPSS Statistics software, Version 27 (Hayes 2013).

Results

Pelvic pain was reported as the most bothersome endometriosis symptom before the pandemic by more than half of our respondents (55.3%). For further demographic information and characteristics for our respondents, please refer to Table 1.

Table 1 Summary of participants' characteristics presented as mean \pm s.d. or frequencies and percentages (%), where appropriate.

Characteristics	Values
Age	33.2 \pm 7.9
Work status before the pandemic	
Working in a paid job, as a full-time employee or worker	2632 (56.3)
Working in a paid job, as a part-time employee or worker	801 (17.1)
Self-employed	483 (10.3)
Not in paid work force	758 (16.2)
Highest level of education	
Primary/grade school	23 (0.5)
Lower secondary/middle school or upper secondary/high school	109 (13.2)
Post-secondary, not university/some college or vocational school	1184 (25.2)
University	1866 (39.8)
Postgraduate	998 (21.3)
Living situation	
Alone	546 (11.6)
Flatmates/roommates/friends	189 (4)
Parents/family partner, no children	770 (16.4)
Partner, no children	1904 (40.5)
Partner and children	1050 (22.3)
Children, no other adults	129 (2.7)
Other – please describe	118 (2.5)
Geographical region of residence	
Europe	3201 (67.9)
North America	701 (14.9)
Latin America and the Caribbean	430 (9.1)
Asia	21 (0.4)
Oceania	249 (5.3)
Africa	19 (0.4)

Overall, as a result of the COVID-19 pandemic, approximately half of the respondents (50.8%) reported no major life changes more than most people (of the general population), while 17.5% reported a significant decrease in their earnings and 14% reported that they had to work for much longer hours (Table 2). About 31.3% described alteration of their medications related to endometriosis (hormones or analgesics). Although perceived stress of the cohort (mean t-score = 50.2, s.d. = 8.0) was in line with the score of the reference population, 12% of our respondents had scores ≥ 60 , which suggest higher than average stress potentially needing surveillance by a mental health professional (Scoring 2018).

Impact of pandemic on mental health

About 38.6% of the respondents reported a marked worsening in their mental health, while 55.4% reported minimal or no change and 3.7% marked improvement.

A sensitivity analysis was undertaken to explore whether a pre-existing diagnosis of anxiety or depression disorder was associated with the reported change in mental health. A greater percentage of participants with a diagnosis reported a marked worsening of mental health, while a greater percentage of respondents without a diagnosis reported minimal worsening, with no change or improvement in their mental health (significant chi-square test: $\chi^2(6) = 342.83$, $P < 0.001$, Cramer's $V = 0.279$, N of diagnosis = 1831). However, in both groups, more than 30% of the respondents reported a marked worsening of their mental health (Fig. 1A).

Additionally, we explored whether other factors associated with an individual's experience of the pandemic may have impacted on their mental health. There was no significant correlation between pandemic-associated major life changes and reported change in mental health ($r = 0.005$, $P = 0.073$) nor for perceived stress ($r = 0.019$, $P = 0.408$). Participants who worried that endometriosis made them vulnerable to COVID-19 and those who

reported being at high risk for COVID did experience greater worsening of mental health, but these relationships were weak ($r = 0.149$, $P < 0.001$ and $r = 0.087$, $P < 0.001$, respectively).

Impact of pandemic on endometriosis-associated symptomatology

About 39.3% of the respondents reported a marked worsening of their endometriosis-associated pain, while 54.1% reported minimal or no change and only 3.8% marked improvement (Fig. 1B). Similarly, 49.9% of the respondents reported marked worsening of their TF, while 43.3% had minimal or no worsening and 4.3% had minimal improvement (Fig. 1C). Findings followed a similar pattern when analysed by geographical region, ranging from 27.3% to 51.2% for reported marked worsening in pain and from 33.3% to 57% for reported marked worsening in TF (Supplementary Table 1). When asked about changes in their bleeding pattern, 59.2% of the respondents reported

Table 2 Summary of altered medications, altered planned treatments, mental health diagnosis and COVID-19 impact, presented as frequencies and percentages (%).

	Frequency	Percent (%)
Altered medication and planned treatments	3663	78.4
Altered medication treatment	1476	31.3
Altered planned treatment	3151	66.8
Mental health diagnosis	1831	38.8
COVID-19 impact		
Had symptoms of COVID-19	753	16
Had a positive test for COVID-19	79	1.7
Been admitted to hospital because of COVID-19	18	0.4
Has anyone you live with had symptoms of COVID-19	591	12.6
Has anyone you live with had a positive test for COVID-19	67	1.4
Has someone close to you (family or friend) died because of COVID-19	381	8.1
Are you considered 'vulnerable'/at high risk from COVID-19	990	21.1
Live with someone considered 'vulnerable'/at high risk from COVID-19	1162	24.7
Worry that endometriosis makes you more vulnerable to COVID-19	2534	53.9
COVID-19 pandemic impact on major life changes		
No, nothing more than for most people	2397	50.8
I have lost my job	352	7.5
I have had to work much longer hours	662	14
I have had a significant decrease in my earnings	824	17.5
I cannot run my business	239	5.1
I have had to move out of my home	132	2.8
My relationship with my partner has fallen apart	241	5.1
I have had to postpone/cancel my wedding	115	2.4
Most important/bothersome before the pandemic		
Pelvic pain	2602	55.3
Heavy and/or irregular bleeding	395	8.4
Fatigue	293	6.2
Bowel problems	403	8.6
Urinary/bladder problems	109	2.3
Pain during or after sex	263	5.6
Infertility/difficulty getting pregnant	410	8.7

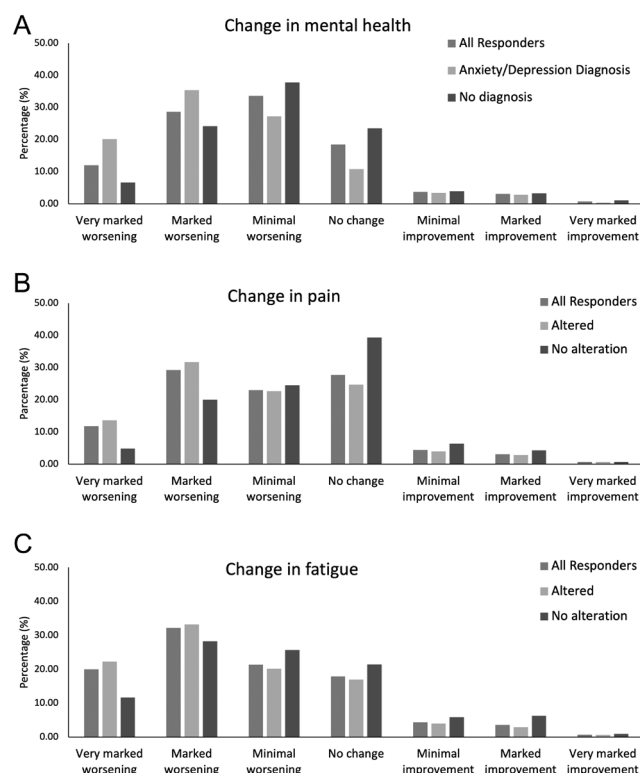


Figure 1 (A) Change in mental health for all responders (medium grey), responders with pre-existing anxiety and or depression diagnosis (light grey) and responders without pre-existing diagnosis (dark grey) presented as percentages (%) ($N = 4381$). (B and C) Change in (B) pain and (C) fatigue for all responders (medium grey), responders with alterations to their endometriosis medication (light grey) and responders without alterations to their endometriosis medication (dark grey) presented as percentages (%) ($N = 4343$).

no change, while 17.4% reported increased or more frequent bleeding and 15.2% reported decreased or less bleeding during the pandemic.

Further analysis on the effect of treatment alterations on the changes in symptoms revealed a significant effect between respondents that reported an alteration of their current treatments and those who did not both for pain ($\chi^2(6) = 244.6$, $P = 0.000$) and TF ($\chi^2(6) = 164.7$, $P = 0.000$). Both these effects were moderate, as evidenced by the Cramer's V values (pain: Cramer's $V = 0.235$ and TF: Cramer's $V = 0.192$). A greater percentage of respondents with alterations in their treatments or medications reported a marked worsening of pain and TF, while a greater percentage of the respondents that had no alteration to their current treatment or medication reported minimal worsening, no change or improvement of their pain and TF. However, of those who did not have a medication alteration, we still found that 24.8% had a marked

worsening of their pain and 39.9% had marked worsening of their TF. Of the responders who reported alterations to their current treatment or medication, 47.2% also reported alterations to their bleeding pattern.

Relationship between reported changes in mental health and endometriosis symptoms

Spearman's correlation analyses revealed a significant positive relationship between changes in mental health and changes in pain ($r = 0.33$, $P < 0.001$) and TF ($r = 0.48$, $P < 0.001$).

Relationship between reported changes in endometriosis symptoms and other factors related to the pandemic

No significant effects were found in the correlations between perceived stress and changes in pain or TF (Spearman's correlation $P > 0.05$). Similarly, there was no relationship between major life changes associated to the COVID-19 pandemic and reported changes in pain or TF ($r = 0.008$, $P = 0.624$ and $r = -0.018$, $P = 0.263$ respectively). Those participants who worried about endometriosis making them vulnerable to COVID-19 or who were at high risk for another reason did report an increased pain and TF; however, the effect sizes were small for all these relationships ($r = 0.046$ – 0.126).

Relationship between psychological measures and current pain intensity

There were no significant correlations between absolute levels of anxiety, depression, perceived stress and the intensity of any of the pain symptoms (Spearman's correlations $P > 0.05$).

Interaction between changes in mental health and endometriosis symptoms via pain catastrophising, emotional support and perceived stress

A mediation analysis on the relationship between change in mental health and change in pain explained by PCS revealed a weak significant effect ($B = 0.071$, lower limit of confidence interval (LLCI) = 0.060, upper limit of confidence interval (ULCI) = 0.082) of PCS as a mediator (Fig. 2A). A similarly significant but weak effect ($B = 0.050$, LLCI = 0.040, ULCI = 0.060) was also found for the relationship between change in mental health and change in TF mediated by PCS (Fig. 2B).

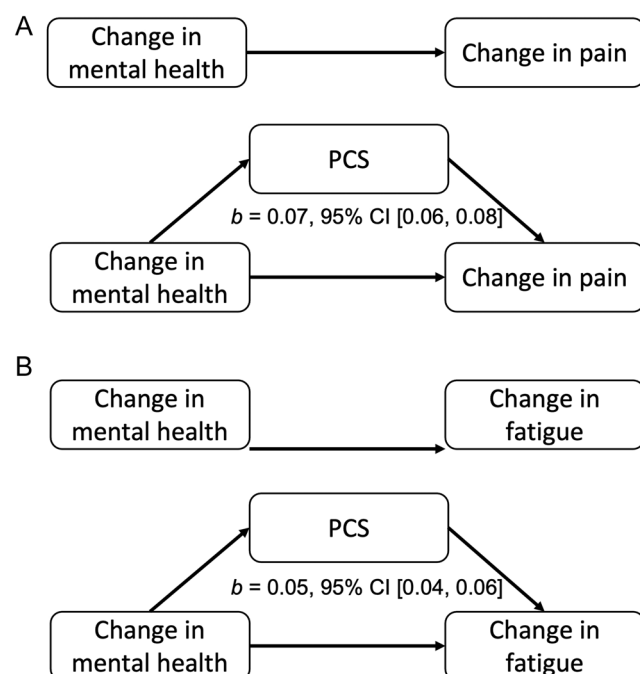


Figure 2 Model for mediation analyses for the relationship between changes in mental health and (A) pain and (B) fatigue mediated by PCS.

As a sensitivity analysis, the above mediation analyses were repeated on the sample of respondents who had no alterations in their medication. The results showed that the first mediation between the change in mental health and change in pain had a weak but significant effect ($B = 0.058$, $LLCI = 0.046$, $ULCI = 0.070$) of PCS. Results of the second mediation revealed a similar result of a weak significant effect ($B = 0.050$, $LLCI = 0.038$, $ULCI = 0.062$) of PCS on the relationship between the change in mental health and the change in TF.

Further mediation analyses exploring the relationship between change in mental health and change in endometriosis symptoms explained by perceived stress and emotional support as mediators revealed no significant effects of either mediator (perceived stress: pain: $B = 0.00$, $LLCI = -0.011$, $ULCI = 0.011$ and TF: $B = 0.00$, $LLCI = -0.015$, $ULCI = 0.014$; emotional support: pain: $B = 0.00$, $LLCI = -0.001$, $ULCI = 0.002$ and TF: $B = 0.00$, $LLCI = -0.001$, $ULCI = 0.011$).

When the mediation analyses were repeated on the respondents who reported no alterations to their medications due to the pandemic, the results remained not significant (perceived stress: pain: $B = 0.00$, $LLCI = -0.002$, $ULCI = 0.003$ and TF: $B = -0.0004$, $LLCI = -0.003$, $ULCI = 0.002$; emotional support: pain: $B = -0.003$, $LLCI = -0.003$, $ULCI = 0.002$ and TF: $B = 0.00$, $LLCI = -0.001$, $ULCI = 0.003$).

Discussion

Main findings

In this study, we found that the early stages the COVID-19 pandemic were perceived by people with endometriosis as having a negative impact on mental health and endometriosis symptoms, with almost 40% reporting a marked worsening of their mental health and endometriosis-associated pain and approximately half reporting a marked worsening of their TF. Additionally, approximately a third of respondents described a change in their bleeding pattern. Reports of worsening of symptoms were not limited to those who reported changing their medication due to the pandemic measures nor those with a pre-existing mental health diagnosis; this was seen in responses from all regions of the world.

Reported changes in mental health were significantly correlated with reported changes in pain and TF. Interestingly, reported changes in endometriosis symptoms had no significant association with perceived stress. Increased pain catastrophising appears to play a role in mediating the relationships between mental health and pain and TF; however, this was not the case for either perceived stress or perceived emotional support.

Strengths and limitations

The major strength of this study is the large sample size, collected over a relatively short time-period. This was crucial to capture the responses of the participants during the first wave of the pandemic when similar measures were taken across countries, and the COVID-19 pandemic was still a novel stressful event for most people without the lockdown/pandemic fatigue that it is currently associated with. Respondents resided in 70 different countries, including regions usually overlooked or under-represented in similar studies (Rogers *et al.* 2009). Moreover, we captured a wide age range and varied socio-economic backgrounds, although our study did require people to have access to the internet and be able to complete an online study.

However, the study design meant we had no access to healthcare records to confirm the endometriosis diagnosis. We aimed to mitigate against this, by questioning how the endometriosis diagnosis had been made and including only respondents who reported a surgical or imaging diagnosis. Furthermore, effect sizes were small and therefore results should be interpreted with caution; however, they can be indicative of the associations between changes in clinical symptoms and the COVID-19 pandemic as a stressful event.

Additionally, our sample may not fully reflect the background population of people with endometriosis, focusing instead on those who follow support groups or researchers online or those who actively visited these sites during the pandemic perhaps because they felt the need for additional support. Importantly, there was no possibility of performing a face-to-face study or recruiting directly from clinic cohorts at this time as most benign gynaecology services were paused. Finally, as this is a cross-sectional online study, our data were derived from patients' reports of changes in their endometriosis symptoms and quality of life which could have biased our results. However, fatigue is a subjective experience; therefore, the reported changes by the respondents still provide valuable information.

Interpretation

Relatively early in the pandemic, concerns were being expressed about the potential for a pandemic-related increase in chronic pain (Clauw *et al.* 2020). Of the three potential mechanisms discussed, two may be particularly relevant to our study: (i) worsening of chronic pain secondary to an exacerbation of pre-existing pain-associated physical or psychological factors and (ii) new-onset chronic pain triggered by exacerbation of other risk factors. Thus, it is plausible that some of the reported worsening of pain we saw in our cohort is correlated with increased disease activity either due to an inability to obtain hormonal therapies that normally keep the disease suppressed or due to altered endogenous hormone activity. However, we do not believe that altered hormone therapies is the sole factor as we excluded people who described a complete change in hormone therapy when compared to that 6 months ago and less than a third of our cohort reported having to change/stop medications including hormonal therapies. Moreover, even from those who reported no change in any medication, approximately a quarter reported worsening pain. Many people with endometriosis will describe a flare in their symptoms with either regular or unscheduled bleeding and over 40% of our cohort reported a change in the bleeding pattern. Both physiological and psychological stress can disrupt the activity of the hypothalamic–pituitary–ovarian axis, and studies have shown that during the pandemic both elite athletes (McNamara & Harris Rachel 2020) and women with a confirmed diagnosis of COVID-19 (Li *et al.* 2021) have experienced changes in their cycle. Other factors such as deteriorating mental health, poor sleep, reduced ability/desire to undertake physical activity or stress are

also likely to be playing a role. It is interesting to consider whether these factors may also have contributed to the development of pain in those in whom this was not the predominant symptom previously (~40% of our cohort). We are certainly increasingly aware that there is little relationship between pain symptoms and extent/location of endometriosis as visualised at laparoscopy (Vercellini *et al.* 1996) and that the factors contributing to pain in association with endometriosis are complex (Stratton & Berkley 2011, Coxon *et al.* 2018).

The interdependency of physical and mental health is increasingly being considered in health research and policy (HM Government Department of Health 2011, Naylor *et al.* 2012). In keeping with this, there has been a greater focus on mental health in people with endometriosis over the recent years. Endometriosis appears to increase the risk for mental health disorders, although the mechanisms remain unclear and could include aspects of endometriosis itself (e.g. inflammation) as well as wider factors (e.g. chronic pain and infertility) (Pope *et al.* 2015, Laganà *et al.* 2017). Our findings are in line with the literature suggesting high comorbidity between endometriosis and common mental health disorders (Sepulcri & do Amaral 2009, Facchin *et al.* 2017): 38.8% of the participants had a pre-existing diagnosis of anxiety and/or depression requiring therapy or medication. As in the general population, it is likely that many more individuals experienced clinically significant symptoms but were undiagnosed (Williams *et al.* 2017). Those with a pre-existing diagnosis were more likely to describe a marked worsening of their mental health in the early stages of the pandemic.

As we expected, there was a close relationship between changes in mental health and in pain and TF. Generally, these relationships are considered bidirectional with, for example, a worsening of pain impacting negatively on mood and a deteriorating mood amplifying the experience of pain (Hooten 2016). Our data, being cross-sectional, can tell us nothing about directionality. However, given that in the population as a whole mental health was seen to deteriorate from early on in the pandemic (Brooks *et al.* 2020, Di Giuseppe *et al.* 2020, Kujawa *et al.* 2020) and disease activity is likely to have stayed stable for many, we hypothesise that a change in mental health status is likely to be a driver for pain and fatigue for a proportion of our cohort. It is interesting that pain catastrophising but not perceived stress or emotional support appears to play a role in mediating the relationships between worsening mental health and increased pain and TF. Pain catastrophising is increasingly being identified as a predictor of poor response

to treatment and exacerbation of symptoms across a range of chronic pain conditions (Severeijns *et al.* 2001, Martin *et al.* 2011) and thus should be a focus of future research in endometriosis. It is plausible that sleep disturbance could be a factor relating to the change in all the measures assessed, and recent evidence has shown a negative impact of the pandemic on sleep and a subsequent worsening of mental health (Villadsen *et al.* 2021). Unfortunately, a measure of sleep was not obtained at the present study, in order to keep the questionnaire shorter and reduce the participant's burden.

Conclusion

Our study demonstrates the impact the COVID-19 pandemic has had on the physical and mental health of people with endometriosis. Whilst our data specifically apply to the impact of the early stages of the pandemic, we believe these findings have applicability beyond this period. We are increasingly aware of the need to manage endometriosis as a chronic condition with a relapsing remitting course and symptoms that are variable, unpredictable and difficult to manage (Zondervan *et al.* 2018). Stressful events (either repeated/prolonged minor stressors or single major life events) are common, and the data presented here would support the idea that stressful events can exacerbate mental ill health, fatigue and endometriosis-associated pain. Our findings highlight the potentially important role for psychological approaches in the management of physical symptoms: approaches such as cognitive behavioural therapy which can reduce pain catastrophising and increase coping skills may well positively impact on pain and fatigue in addition to improving mental health symptoms (Schütze *et al.* 2018). Identifying those most vulnerable to the adverse effects of stress, including individuals with undiagnosed mental health conditions, would allow interventions to be selected most effectively.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/RAF-22-0028>.

Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Completed ICMJE disclosure of interest forms for each author are available.

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Author contribution statement

K V conceived the study. E C, C L, C B, A I, B M, M K, K G, E E, E F, K Z and K V designed the study including translations. L D, R S, C B, A I, B M and M K analysed the data. L D and K V drafted the manuscript. All authors contributed to revising the manuscript.

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