BMC Women's Health

SYSTEMATIC REVIEW Open Access

Long COVID and endometriosis: a systematic review and meta-analysis

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Abstract

Long COVID conditions entail the persistence of COVID-19-related symptoms for at least eight weeks following SARS-CoV-2 infection. The prevalence of long COVID is estimated to range from 10 to 30% among individuals infected with SARS-CoV-2. Despite its growing impact on healthcare systems, long COVID remains poorly understood. In parallel, endometriosis, a chronic inflammatory condition affecting around 10% of reproductive-age women, is marked by symptoms such as pelvic pain and infertility. The aim of this study was to assess the association between endometriosis and long COVID. We performed a systematic review of long COVID among endometriosis patients in Pubmed/Medline, Cochran Library and Science Direct databases from inception to August 2023. We independently selected studies, extracted data, assessed risk of bias, and compared endometriosis versus non endometriosis patients for long. Pooled analyses were based on random-effect models, and the I^2 statistic was used to quantify heterogeneity across studies. A total of 2 cross-sectional studies ($N = 216{,}095$ participants) were included. The pooled analysis comparing endometriosis to non-endometriosis patients significantly showed association for long COVID (pooled RR = 1.41 [1.31–1.52], $I^2 = 29\%$, $p < 0.001$). Women, who are disproportionately affected by long COVID, particularly those with endometriosis, may face compounded health challenges. While our findings suggest a possible association between endometriosis and long COVID, the evidence is currently limited to two observational studies. Further research involving diverse populations and robust study designs is needed to confirm this relationship and clarify underlying mechanisms.

Keywords long-COVID, Endometriosis, Inflammation, ACE2, SARS-CoV-2, COVID-19

Capsule: Comprehensive research is required into the underlying mechanisms and the potential benefits of managing endometriosis in mitigating the risk of long COVID and related post-infection syndromes.

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Introduction

Post COVID-19 conditions, commonly referred to as "long COVID", are characterized by the persistence or emergence of COVID-19-related symptoms lasting for at least eight weeks following SARS-CoV-2 infection [1, 2]. Long COVID can manifest in various bodily systems, with typical symptoms including fatigue, heart palpitations, depression, muscle pain, and memory difficulties, either individually or in combination, often leading to impaired daily functioning [3, 4]. The prevalence of long COVID is estimated to range from 10 to 30% among individuals infected with SARS-CoV-2 [5–7]. With ongoing waves of SARS-CoV-2 infections, the rising number of long COVID cases have posed a significant burden on healthcare systems in Europe and United-States for example. Nevertheless, long COVID remains poorly understood.

Endometriosis, on the other hand, is a common and often chronic inflammatory condition that affects approximately 10% of women in their reproductive years [8, 9]. Associated symptoms include chronic pelvic pain, dysmenorrhea, and infertility [8, 9]. Female sex is a well-established risk factor for long COVID, but there is a dearth of research exploring female-specific risk factors [3, 10–13]. Interestingly, the mechanisms proposed for the development of long COVID, such as chronic inflammation, blood clotting disorders, and autoimmunity, are also implicated in the pathophysiology of endometriosis [14]. To date, very few studies have highlight the possible interaction between endometriosis and long COVID [15]. Thus, the objective of this review was to evaluate the relationship between endometriosis and long COVID among randomized and nonrandomized controlled studies.

Methods

Search strategy

The following search strategy was used: "Long COVID" OR "Post-COVID" AND "Endometriosis" in Pubmed/Medline, Cochran Library and Science Direct databases among studies published from inception to December 30, 2024.

Reporting standards

We conducted and reported our study according to PRISMA guidelines [16] and Cochrane systematic review guidelines [17].

Eligibility criteria

Inclusion criteria for studies were based on the PICOS (population, intervention, comparison, outcome, and study design) framework.

Studies were included if they were conducted among women patients with long COVID patients and having endometriosis, involving a comparison of quantitative outcomes, and were randomized controlled trials or nonrandomized studies. Abstract-only publications were excluded. Only studies published in English were included. Given the limited number of studies on the association between endometriosis and long COVID, both randomized and non-randomized studies were eligible for inclusion to ensure comprehensive coverage. As anticipated, the final selection included only observational cohort studies, which are appropriate for assessing long-term outcomes in large populations where randomization is not feasible. Long COVID was defined as more than eight weeks of symptoms according to the WHO definition.

Study selection

Using the eligibility criteria, AV and JMA independently screened all articles and abstracts and reviewed the full text of potentially eligible abstracts. Supplemental file showed the articles included and excluded from the analyses.

Data extraction

AV and JMA independently extracted relevant characteristics related to participants, intervention, comparators, outcome measures, and results from the studies that were found to be eligible using a standard data collection form. Any disagreements were resolved through discussion with a third research team member (MA) until agreement was reached.

Risk of bias assessment

During the data extraction process, researchers independently assessed the risk of bias for each study using the Cochrane Collaboration's risk of bias tool [18]. Evaluation criteria included the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, or other which included publication bias. Funnel plots were used to evaluate publication bias. Risk of bias for each criterion was rate as low, high, or unclear according to the Cochrane risk of bias instructions.

Data synthesis

Pooled estimates and 95% confidence intervals (CI) were calculated for the prevalence of long COVID in endometriosis patients, along with the health impacts of the long COVID in endometriosis patients, using the generic inverse-variance method. We used the random effects method. The total prevalence was reported as a percentage among the included studies.

The I^2 statistic was used to quantify heterogeneity across studies [19]. When the estimated I^2 was equal to or greater than 50%, this indicated a large amount of

heterogeneity. As the studies were functionally different and involved different study designs, participants, interventions, and settings; a random-effects model that allowed more heterogeneity was used. Forest plots were created to display the meta-analysis findings. To explore publication bias, funnel plots were created, and Begg tests were performed (statistically significant if $P < 0.05$) [20]. Analyses were performed using SAS software (version 9.4; SAS Institute).

Results

The search strategy identified 624 articles. After scanning the titles and abstracts, 4 articles were found to be potentially eligible, and their full texts were read for further assessment. Of these, 2 articles were included [12, 21] (Fig. 1). All articles that were included had been published in peer-reviewed journal.

Wang et al. [21] reported on 3,551 US-Nurses that women with endometriosis have higher risk of long COVID, defined as symptoms over 8 weeks, at adjusted RR = 1.28 [1.09–1.50], with adjustment for age, race, partner's education, smoking, body mass index, asthma, hypertension history, high cholesterol history, cancer history and infertility history). When considering Long COVID as defined > 4 weeks of symptoms, the adjusted RR = 1.22 [1.05–1.42]. Subramanian et al. [12] reported on 212,544 non-hospitalized US women an adjusted HR = 1.19 [1.11–1.28], with adjustment for age, sex, ethnic group, socioeconomic status, index year, vaccination status, symptoms recorded before COVID-19 and comorbidities (Table 1).

A total of two studies [12, 21] comprising 216,095 participants were included in the meta-analysis. Figure 2 illustrates the forest plot of the prevalence of long-COVID in endometriosis participants, and the risk of long-COVID in endometriosis participants. The pooled prevalence of long COVID was 16.2% among endometriosis patients while only 10% of non-endometriosis patients had long COVID. The pooled risk ratio for these two studies was RR = 1.41 [1.31–1.52], $I^2 = 29\%$, $p < 0.001$, as shown in the forest plot in Fig. 2.

The risk of bias and applicability assessment for the two studies is shown in Fig. 3. Visual inspection of the funnel plot was inconclusive for risk of publication bias. Given that only two studies were included in the meta-analysis, funnel plot asymmetry and statistical tests for publication bias (Begg's test) were not considered informative and should be interpreted with caution (Fig. 4).

Sensitivity analysis

When using the definition of long COVID (symptoms ≥ 4 weeks), the pooled risk ratio remained elevated (RR = 1.22 [1.05–1.42]). When applying the more stringent ≥ 8-week threshold for symptom persistence, the association persisted (RR = 1.28 [1.09–1.50]) [21]. The inclusion of all self-reported endometriosis cases, regardless of laparoscopic confirmation, did not significantly alter the risk estimate. Age-stratified analysis indicated a stronger effect in women under 50 years of age (RR = 1.37 [1.00–1.88]) compared to those aged 50 and over (RR = 1.19 [1.01–1.41]), although interaction testing did not reach statistical significance ($p = 0.39$) [21].

Discussion

The COVID-19 pandemic has affected millions of people around the world. Our meta-analysis shows that 16% of endometriosis patients were infected with long COVID while only 10% of non-endometriosis patients had long-COVID.

Long COVID in women populations

While men are known to have a doubled risk of experiencing severe COVID-19 outcomes and mortality [22], recent data suggests that women infected with SARS-CoV-2 may face a 50% higher risk of developing long COVID compared to men [10, 12, 13]. Despite calls for research into how gynecologic disorders have been affected during the pandemic and their potential link to long COVID, limited studies have specifically examined women with pre-existing gynecologic conditions as a high-risk group [23, 24]. Wang et al. study revealed that those with a history of endometriosis had a 22% increased risk of experiencing long COVID [21], aligning with findings from a prior retrospective cohort study analyzing medical records. In Subramanian et al. study of encompassing 212,544 women in the United Kingdom who had a documented SARS-CoV-2 infection, it was observed that endometriosis was associated with a higher risk of persistent or post-COVID-19 symptoms lasting for at least 12 weeks (with an adjusted risk ratio of 1.19; 95% CI, 1.11–1.28) [12]. Notably, this association between endometriosis and long COVID-19 was comparable in magnitude to other established risk factors for long COVID – 19, including asthma, type 2 diabetes mellitus, and hypertension (RR range, 1.1–1.2) [12, 25].

Long COVID is a debilitating condition that can develop in individuals following a SARS-CoV-2 infection, irrespective of the severity of their initial COVID-19 illness. Long COVID is characterized by the presence of symptoms emerging within three months of the initial infection and persisting for at least two months [26]. These symptoms encompass fatigue, cognitive impairment, post-exertional malaise (PEM), headaches, sleep disturbances, and muscle pains [2, 27, 28]. The underlying pathophysiology of long COVID involves immune dysregulation, autoimmunity, pathogen persistence/reactivation, neurological anomalies, neuroinflammation, tissue and organ damage, hypoperfusion, autonomic

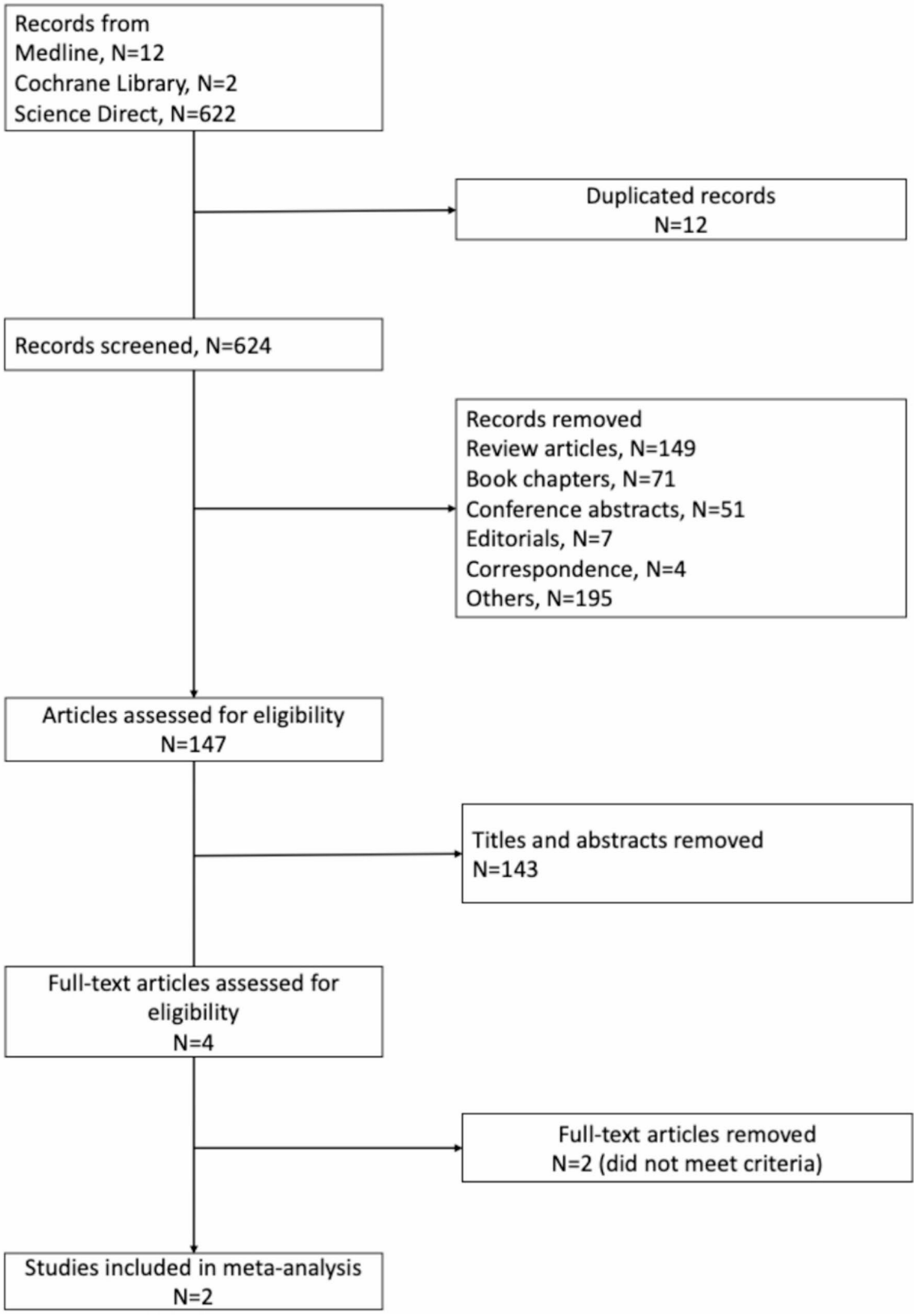

Fig. 1 Flow diagram of the included studies

Table 1 Descriptive characteristics of the studies included

Study	Study site	Period	Follow-up time	Population	Study design	Sample size	RR/HR, 95% CI	Reference
Wang, 2023	US	April to May 2020	August 202 to November 2021 and for NHS3 participants: July 2021 to August 2022 with addendum about COVID-19	Nurses	Cross-sectional	3,551	Long COVID > 4 weeks, adjusted RR = 1.22 (1.05–1.42) Long COVID > 8 weeks, adjusted RR = 1.28 (1.09–1.50), Ongoing symptoms, adjusted RR = 1.32 (1.1–1.58)	[18]
Subramanian, 2022	UK	February to April 2021	Total follow-up was 0.29 years (IQR: 0.24–0.42) for the cohort of COVID-19 patients and 0.29 (IQR 0.24–0.41) for patients without COVID-19 infection.	Non-hospitalized individuals	Cross-sectional	212,544	unadjusted HR = 1.86 (1.81–1.90) adjusted HR = 1.52 (1.48–1.56)	[9]

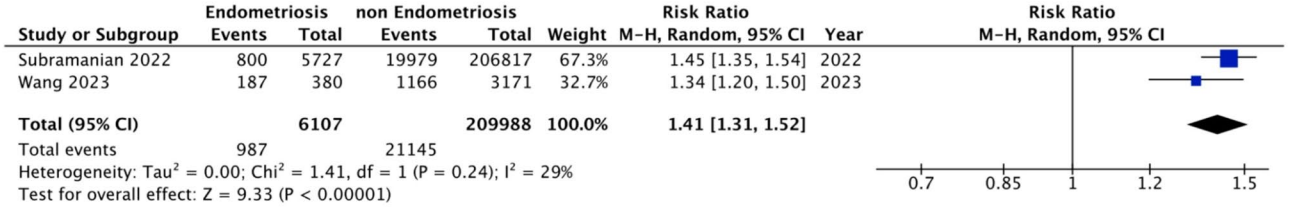

Fig. 2 Prevalence and risk of long COVID in endometriosis patients

dysfunction, fibrin amyloid microclots, and dysregulation of the microbiome [28]. As said previously, many studies indicate that long COVID affects approximately twice as many women as men [10, 12, 13, 29]. Premenopausal women are at an elevated risk for long COVID [29], hinting at the possible involvement of sex hormones in long COVID development [30]. Reproductive health conditions are common within the spectrum of Long COVID, yet they remain significantly underexplored. Only two studies have shown an increased risk of Long COVID among endometriosis [12, 21]. However, further research is necessary to comprehend the contributing factors [15]. Endometriosis, a chronic systemic ailment characterized by the presence of tissue similar to the uterine lining growing outside the uterus [31], affects approximately 10% of girls and women of reproductive age [8]. Endometriosis is associated with a range of severe and incapacitating symptoms, including but not limited to menstrual pain, pain during intercourse, bowel movements, and urination, chronic pain, infertility, fatigue, and complications such as preeclampsia and adverse pregnancy outcomes [32]. Due to lack of awareness among healthcare practitioners [8], there are substantial diagnostic delays, often averaging up to 11 years [33]. These delays may hinder a comprehensive understanding of the prevalence of endometriosis in individuals with long COVID.

Emerging evidence suggests that microRNAs (miRNAs) play a pivotal role in the molecular pathogenesis of endometriosis [34]. Several dysregulated miRNAs in endometriosis patients could be implicated in key molecular pathways, such as cell proliferation, apoptosis, angiogenesis, inflammation, and cytoskeletal remodeling. Notably, altered expression of miR-21-5p, miR-145, and miR-200c may promote the invasive and neoplastic-like behavior of endometrial stromal cells through modulation of epithelial-mesenchymal transition and reduced E-cadherin expression. These epigenetic alterations may contribute to disease persistence, recurrence, and potentially the exacerbation of systemic symptoms, especially in the context of immune dysregulation, as seen in long COVID [35].

Long COVID, chronic inflammation, autoimmune dysregulation, and ACE2 hypothesis

The genetic material of the SARS-CoV-2 virus consists of a simple RNA strain and is comprised of three protein structures: the spike, envelope, and membrane proteins. The spike protein attaches to the Angiotensin-Converting Enzyme 2 receptor (ACE2), while both the envelope and membrane proteins are involved in genetic material replication [36].

SARS-CoV-2 enters host cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor, aided by the serine protease TMPRSS2 which primes the viral spike protein [36]. ACE2 is expressed not only in the lungs and gastrointestinal tract but also in female reproductive tissues, including the eutopic and ectopic endometrium [37, 38]. This widespread expression suggests that tissues affected by endometriosis could be directly vulnerable to SARS-CoV-2 infection.

The interaction between SARS-CoV-2 and ACE2 leads to a decrease in ACE2 enzymatic activity [39, 40]. This

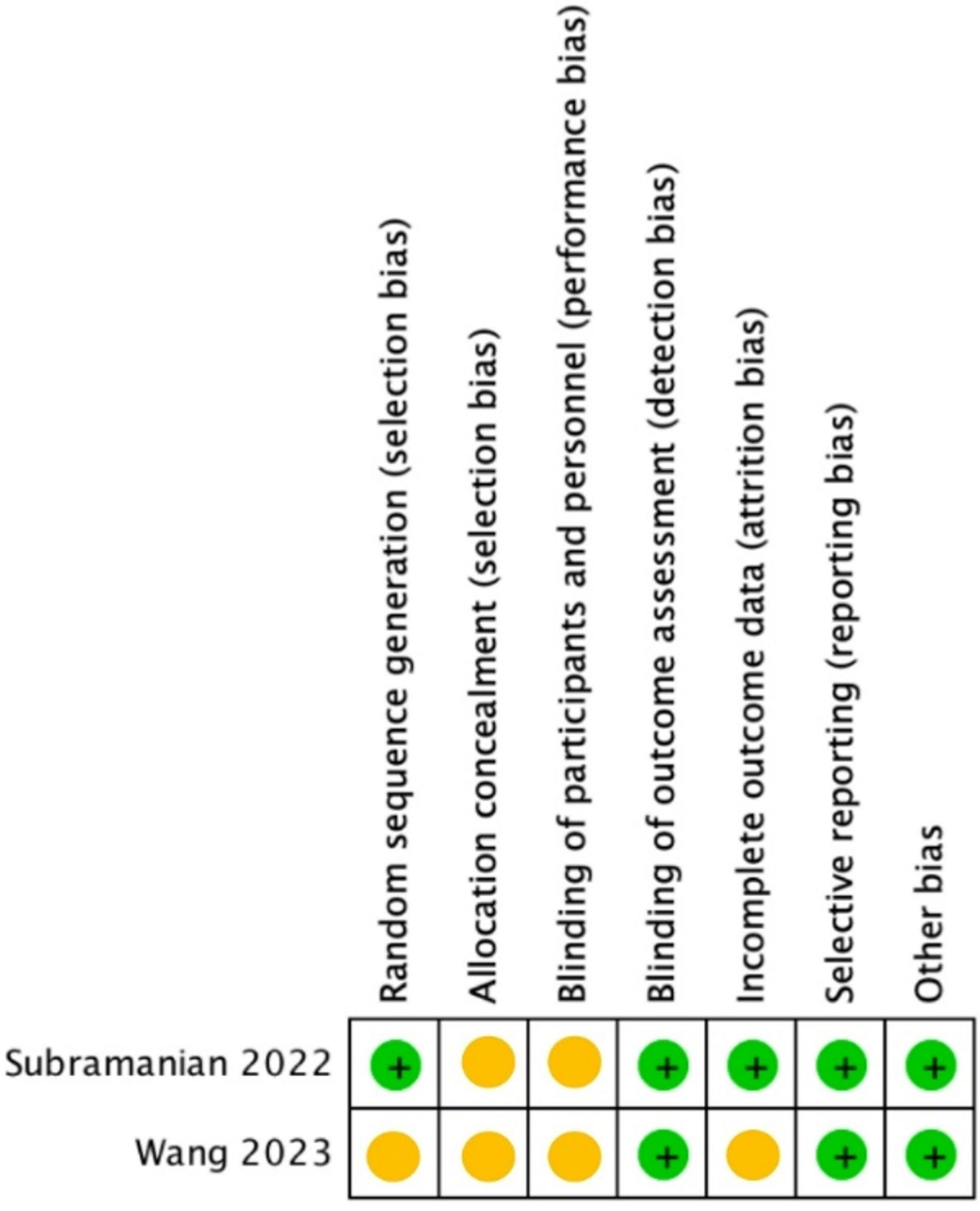

Fig. 3 Risk of bias and quality assessment of studies

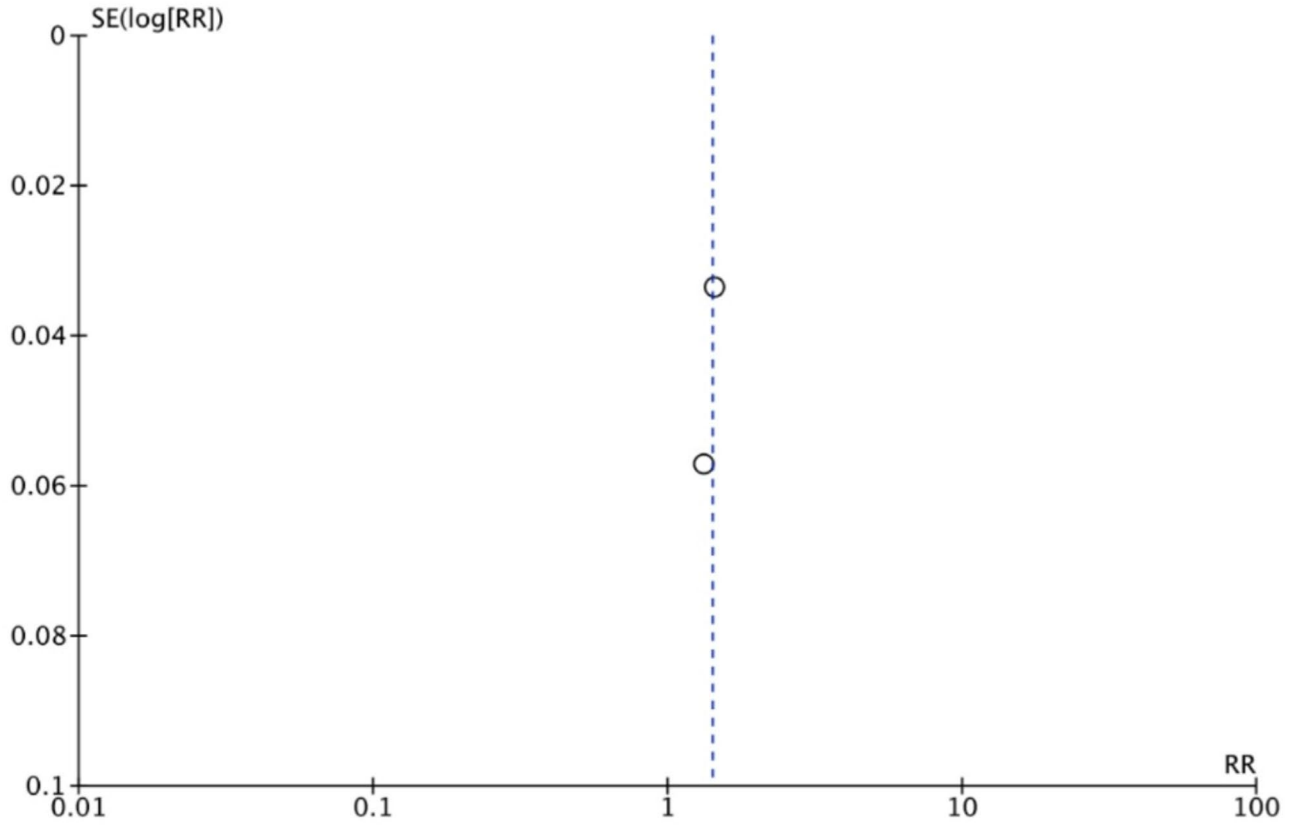

Fig. 4 Funnel plot of studies

downregulation disrupts the renin–angiotensin system (RAS), shifting the balance toward increased angiotensin II (Ang II) signaling through AT1 receptors. This promotes inflammation, fibrosis, oxidative stress, and thrombosis [41–43]. Under normal conditions, ACE2 counteracts these effects by converting Ang II into angiotensin-(1–7), which has anti-inflammatory and vasodilatory effects via the Mas receptor [44].

Recent studies have proposed that patients with long COVID may develop antibodies against ACE2 itself, further impairing its regulatory function and enhancing proinflammatory Ang II effects [45, 46]. Anti-ACE2 antibodies could disrupt both membrane-bound and soluble ACE2, contributing to immune overactivation and vascular damage. Moreover, soluble ACE2 has been proposed as a biomarker of vascular and blood-brain barrier integrity, especially in pericytes, which also express TMPRSS2 and may be targeted in long COVID-related neuroinflammation [2, 47, 48].

Endometriosis shares many of these immune-inflammatory features. It is characterized by chronic, estrogen-driven inflammation, with elevated levels of IL-1β, IL-6, TNF-α, and reactive oxygen species (ROS) in both peritoneal fluid and endometrial tissues [8]. Impaired cytotoxicity of natural killer (NK) cells, macrophage polarization, and T-cell imbalances are well-documented [49, 50]. Similar immune dysfunctions are implicated in post-viral syndromes, including long COVID and with myalgia, encephalomyelitis/chronic fatigue syndrome (ME/CFS), with which endometriosis often overlaps. For instance, 36% of women with (ME/CFS) and 20% with postural orthostatic tachycardia syndrome (POTS) report a history of endometriosis [15]. These commonalities underscore the significance of dysfunctional immune and endocrine systems in both conditions. Some of these mechanisms may also play a role in long COVID [51, 52].

Both long COVID and endometriosis involve persistent immune activation, with production of autoantibodies, including antinuclear and antiphospholipid antibodies [11, 14]. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and reduced cortisol levels have been found in both conditions [53]. These features may contribute to the chronic fatigue, brain fog, and autonomic symptoms frequently observed in long COVID.

Additionally, the "bacterial contamination hypothesis" in endometriosis posits that pathogen-associated molecular patterns (PAMPs) may activate toll-like receptors (TLRs) such as TLR4, triggering sterile inflammation [54, 55]. This parallels evidence in long COVID showing intestinal dysbiosis, antigen persistence, and immune

stimulation by viral reservoirs or pathobionts [56–58]. Finally, coagulation abnormalities, a hallmark of long COVID, are also observed in endometriosis. Both conditions are associated with hypercoagulability, endothelial dysfunction, and increased risk of thromboembolic events [59–61].

The connection between endometriosis and autoimmune diseases underscores a critical interplay of immune dysregulation mechanisms that extend beyond localized pathology. For instance, women with endometriosis have a higher prevalence of infertility due to impaired embryo implantation, likely mediated by inflammatory disruption in the endometrial milieu [62]. Moreover, they are at increased risk for adverse pregnancy outcomes, including preterm birth and preeclampsia, due to systemic vascular inflammation and endothelial dysfunction. Beyond reproductive complications, women with endometriosis frequently experience systemic manifestations such as chronic fatigue, autoimmune thyroid disease, and heightened susceptibility to connective tissue disorders, reflecting its systemic nature [63].

Recent findings suggest that women with endometriosis exhibit higher circulating autoantibody levels, including antinuclear and antiphospholipid antibodies, which are also implicated in long COVID pathophysiology [21, 28, 64]. The overlap in mechanisms, chronic inflammation, oxidative stress, and dysregulated immune cell function, could provide a biologic basis for their shared susceptibility.

Impact of COVID on symptoms related to endometriosis

Endometriosis patients may experience an exacerbation of symptoms such as dysmenorrhea and dyspareunia following SARS-CoV-2 infection [65, 66]. The shared pathophysiological mechanisms between endometriosis and long COVID, including chronic systemic inflammation, immune dysregulation, and hormonal imbalances, likely contribute to this worsening symptomatology [67]. The persistence of inflammatory cytokines such as IL-6 and TNF-α, which are elevated in both conditions, may amplify pelvic pain and menstrual discomfort, leading to heightened dysmenorrhea [68]. Long COVID is also associated with neuromuscular and autonomic dysfunction, which may contribute to increased dyspareunia through mechanisms such as hyperalgesia, pelvic floor dysfunction, and central sensitization [2]. Moreover, clotting abnormalities observed in both endometriosis and long COVID could lead to increased ischemic pain and vascular inflammation within endometrial lesions, further intensifying symptom severity. These findings underscore the need for multidisciplinary management strategies that address both the inflammatory and neurological components of pain in endometriosis patients who develop long COVID. Future research should focus on longitudinal studies to further elucidate the relationship between these conditions and explore targeted therapeutic interventions aimed at mitigating the compounded symptom burden in affected individuals.

Impact of the COVID-19 pandemic on symptom exacerbation in endometriosis

Beyond biological mechanisms, the COVID-19 pandemic introduced significant healthcare system disruptions that have adversely impacted the clinical course of endometriosis, even in women not infected with SARS-CoV-2 [24, 69]. Studies have reported worsening of endometriosis-related symptoms—including pelvic pain, dysmenorrhea, dyspareunia, and psychological distress—during lockdown periods and in the aftermath of healthcare service disruptions [70]. These exacerbations were attributed to reduced access to gynecologic consultations, delays or cancellations of elective surgeries such as laparoscopies, limited access to pharmacologic pain management, and decreased availability of physical therapy and psychological support services [71]. Moreover, heightened levels of stress and anxiety induced by the pandemic may have further amplified pain perception and inflammatory responses in individuals with endometriosis. This multidimensional burden highlights that symptom aggravation may stem not only from potential biological susceptibility to SARS-CoV-2 and long COVID, but also from system-level barriers and psychosocial stressors. Thus, any investigation of long COVID in women with endometriosis must consider both biological and structural determinants of health to fully contextualize the complexity of disease exacerbation during the pandemic.

Endometriosis, age and long COVID

A potential correlation between age and long COVID in endometriosis patients warrants further investigation, as both conditions exhibit distinct but potentially overlapping epidemiological patterns. Endometriosis predominantly affects young women of reproductive age, with an early onset often during adolescence [8, 9]. The prevalence ranges of endometriosis from 10 to 35% in women with chronic pelvic pain, underscoring its significant impact on younger populations [72, 73]. In contrast, long COVID has been reported across all age groups, but evidence suggests that younger, premenopausal women may be disproportionately affected compared to men and older individuals [15]. Studies indicate that women under 50 have a higher likelihood of developing long COVID, possibly due to sex-based immune response differences, hormonal influences, and pre-existing inflammatory conditions such as endometriosis [74, 75]. Given that both endometriosis and long COVID are associated with chronic inflammation and immune dysregulation, younger women with endometriosis may face a

compounded risk for prolonged post-COVID sequelae. The heightened inflammatory state characteristic of endometriosis could predispose younger women to more severe and persistent symptoms of long COVID, including exacerbated pelvic pain (dysmenorrhea, dyspareunia), fatigue, and autonomic dysfunction [21].

Endometriosis stage (rASRM) and severity and duration of long COVID

The rASRM system categorizes endometriosis into four stages (I–IV) based on lesion location, extent of adhesions, and degree of organ involvement. More advanced stages (III–IV) are often associated with widespread inflammation, extensive fibrosis, and higher systemic cytokine levels [76], which may contribute to an increased vulnerability to long COVID. Given that chronic systemic inflammation and immune dysregulation are key mechanisms in both endometriosis and long COVID, it is plausible that women with more advanced endometriosis (stages III–IV) may experience a prolonged or more severe course of long COVID due to a pre-existing hyperinflammatory state. Higher levels of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) observed in advanced-stage endometriosis [77] may exacerbate the immune dysregulation, vascular dysfunction, and autonomic disturbances seen in long COVID, potentially leading to prolonged symptoms such as severe fatigue, cognitive impairment, and exacerbated pelvic pain (dysmenorrhea, dyspareunia). Furthermore, advanced-stage endometriosis is frequently associated with deep infiltrating endometriosis (DIE) [78], which has been linked to neuropathic pain and central sensitization [79], mechanisms that are also implicated in long COVID. Conversely, earlier-stage endometriosis (I–II) is typically associated with less extensive peritoneal involvement but can still present with significant pain and inflammatory activity [79]. While these patients may also be susceptible to long COVID, the severity and duration of symptoms may differ from those with deeply infiltrating or more extensive disease.

Role of adenomyosis in long COVID

Adenomyosis, often coexisting with endometriosis [80], is characterized by chronic inflammation, estrogen dependence, and immune dysregulation, all of which may contribute to increased susceptibility to long COVID. Elevated pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) in adenomyosis parallel immune activation in long COVID, potentially exacerbating dysmenorrhea, pelvic pain, and systemic inflammatory symptoms. Additionally, hormonal imbalances and vascular dysfunction in adenomyosis [81] may worsen microvascular complications and autonomic dysregulation observed in long COVID.

Limitations

A major strength of this study lies in its originality, being the first systematic review and meta-analysis to investigate the potential association between endometriosis and long COVID. By focusing on a large cumulative sample of over 216,000 participants across two high-quality studies, this analysis offers valuable insights into an underexplored intersection between a prevalent gynecological condition and a widespread post-viral syndrome. Furthermore, the study emphasizes a critical gap in the current literature, highlighting the need for integrative approaches in women's health research that consider immune, hormonal, and systemic inflammatory factors shared between chronic conditions such as endometriosis and long COVID.

Regarding the main finding of this meta-analysis, the observed pooled relative risk for long COVID among women with a history of endometriosis was modest, falling below the commonly cited threshold of 1.5 (i.e., RR = 1.41 [1.31–1.52]). Although statistically significant, such a magnitude of association must be interpreted with caution. In large samples and for highly prevalent conditions like endometriosis, even low relative risks can achieve statistical significance without necessarily reflecting a strong clinical effect at the individual level. However, due to the high prevalence of both endometriosis and long COVID in the general population, a modest increase in risk may still have meaningful public health implications.

Some limitations must be considered. The systematic literature search encompassed three databases with few exclusion criteria. The quality of the analyses was dependent on the quality of data from the included studies. Only two cross-sectional studies have been found at this date for this topic. No information was provided concerning the possible different endometriosis status in the two studies. Since variability of study interventions, assessment instruments, circumstances were not assessed and could be potential sources of heterogeneity, this should also be cause for cautious interpretation of results. Finally, publication bias was also found.

A key limitation of this meta-analysis is the variability in how endometriosis was diagnosed across the included studies. While one study relied on laparoscopically confirmed diagnoses, which is the clinical gold standard, large-scale population-based or registry-based studies often depend on self-reported or clinically inferred diagnoses. This reliance on heterogeneous diagnostic criteria may introduce misclassification bias, leading to under- or overestimation of the association between endometriosis and long COVID. Such inclusion bias is particularly relevant given that self-reported endometriosis is subject to recall inaccuracies and diagnostic delay, which could

affect both the exposure classification and subsequent interpretation of findings.

Conclusion

The recent literacy could suggest that women with endometriosis presented higher risk of long COVID compared to healthy women. This condition can further deteriorate the health and quality of life of women with endometriosis. The analysis was based on two studies with a total of 216,095 participants, which, while large in absolute terms, is insufficient given the variability of patient populations and the multifaceted nature of both long COVID and endometriosis. The studies included varied in design, population, and methodologies, leading to potential inconsistencies that could not be fully explored due to the limited number of studies. Since the studies do not comprehensively represent the global population or consider diverse demographic and clinical variables, the findings could be not broadly applicable. Although our meta-analysis indicates a potential association between endometriosis and an increased risk of long COVID, this finding should be interpreted with caution. The analysis is based on a limited number of studies, both observational in nature, and therefore cannot establish causality. Larger, prospective studies are warranted to confirm these preliminary findings and to better understand the biological and clinical interplay between these two conditions. The limited number of available studies, along with inherent limitations of cross-sectional and cohort designs, precludes any definitive conclusions regarding causality. These early signals underscore the urgent need for large-scale, longitudinal research to better understand the temporal relationship, underlying biological mechanisms, and clinical implications of long COVID among women with endometriosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03761-9.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Conceptualization: AV; selection articles: AV, JMA and MA; formal analysis: AV; writing– original draft preparation: A.V.; Writing– Review & Editing: J.M.A., P.F.C., M.A., A.F.; validation: A.V., J.M.A., A.F. The authors have read and agreed to the published version of the manuscript.

Funding
None.

Data availability
The dataset used and analyzed during the current study is available from the corresponding author on reasonable request. Data regarding any of the subjects in the study has not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request.

Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare no conflict of interest with this work.

Received: 15 December 2023 / Accepted: 29 April 2025
Published online: 15 May 2025

References

1. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med. 2021;9:129.
2. Barizien N, Le Guen M, Russel S, Touche P, Huang F, Vallée A. Clinical characterization of Dysautonomia in long COVID-19 patients. Sci Rep. 2021;11:14042.
3. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021;374:n1648.
4. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021;372:n136.
5. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global Prevalence of Long COVID, its Subtypes and Risk factors: An Updated Systematic Review and Meta-Analysis. medRxiv [Preprint]. 2025 Jan 6:2025.01.01.24319384. doi: 10.1101/2025.01.01.24319384.
6. Qasmieh SA, Robertson MM, Teasdale CA, Kulkarni SG, Jones HE, McNairy M, et al. The prevalence of SARS-CoV-2 infection and long COVID in U.S. Adults during the BA.4/BA.5 surge, June–July 2022. Prev Med. 2023;169:107461.
7. Hastie CE, Lowe DJ, McAuley A, Mills NL, Winter AJ, Black C, et al. True prevalence of long-COVID in a nationwide, population cohort study. Nat Commun. 2023;14:7892.
8. Zondervan KT, Becker CM, Missmer SA, Endometriosis. N Engl J Med. 2020;382:1244–56.
9. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. BMJ. 2022;379:e070750.
10. Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. Nat Commun. 2022;13:3528.
11. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022;185:881–e89520.
12. Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. Nat Med. 2022;28:1706–14.
13. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021;27:626–31.
14. Son K, Jamil R, Chowdhury A, Mukherjee M, Venegas C, Miyasaki K, et al. Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long COVID symptoms. Eur Respir J. 2023;61:2200970.
15. Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK, et al. Female reproductive health impacts of long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. Front Rehabil Sci. 2023;4:1122673.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1–34.
17. Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester, UK: John Wiley & Sons, Ltd; 2008.
18. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

21. Wang S, Farland LV, Gaskins AJ, Mortazavi J, Wang Y-X, Tamimi RM, et al. Association of laparoscopically-confirmed endometriosis with long COVID-19: a prospective cohort study. Am J Obstet Gynecol. 2023;228:e7141–71413.
22. Jin J-M, Bai P, He W, Wu F, Liu X-F, Han D-M, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health. 2020;8:152.
23. Aolymat IA, Cross-Sectional. Study of the impact of COVID-19 on domestic violence, menstruation, genital tract health, and contraception use among women in Jordan. Am J Trop Med Hyg. 2020;104:519–25.
24. Leonardi M, Horne AW, Armour M, Missmer SA, Roman H, Rombauts L, et al. Endometriosis and the coronavirus (COVID-19) pandemic: clinical advice and future considerations. Front Reprod Health. 2020;2:5.
25. Wang S, Quan L, Chavarro JE, Slopen N, Kubzansky LD, Koenen KC, et al. Associations of depression, anxiety, worry, perceived stress, and loneliness prior to infection with risk of Post-COVID-19 conditions. JAMA Psychiatry. 2022;79:1081–91.
26. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22:e102–7.
27. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38:101019.
28. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21:133–46.
29. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO clinical characterisation protocol. Lancet Reg Health Eur. 2021;8:100186.
30. Stewart S, Newson L, Briggs TA, Grammatopoulos D, Young L, Gill P. Long COVID risk - a signal to address sex hormones and women's health. Lancet Reg Health Eur. 2021;11:100242.
31. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. Lancet Lond Engl. 2021;397:839–52.
32. Farland LV, Prescott J, Sasamoto N, Tobias DK, Gaskins AJ, Stuart JJ, et al. Endometriosis and risk of adverse pregnancy outcomes. Obstet Gynecol. 2019;134:527–36.
33. Pino I, Belloni GM, Barbera V, Solima E, Radice D, Angioni S, et al. Better late than never but never late is better, especially in young women. A multicenter Italian study on diagnostic delay for symptomatic endometriosis. Eur J Contracept Reprod Health Care Off J Eur Soc Contracept. 2023;28:10–6.
34. Bjorkman S, Taylor HS. MicroRNAs in endometriosis: biological function and emerging biomarker candidates. Biol Reprod. 2019;100:1135–46.
35. Ronsini C, Fumiento P, Iavarone I, Greco PF, Cobellis L, De Franciscis P. Liquid biopsy in endometriosis: A systematic review. Int J Mol Sci. 2023;24:6116.
36. Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, et al. The cellular basis of loss of smell in 2019-nCoV-infected individuals. Brief Bioinform. 2021;22:873–81.
37. Chadchan SB, Popli P, Maurya VK, Kommagani R. The SARS-CoV-2 receptor, angiotensin-converting enzyme 2, is required for human endometrial stromal cell decidualization†. Biol Reprod. 2021;104:336–43.
38. Moazzami B, Chaichian S, Samie S, Zolbin MM, Jesmi F, Akhlaghdoust M, et al. Does endometriosis increase susceptibility to COVID-19 infections? A case-control study in women of reproductive age. BMC Womens Health. 2021;21:119.
39. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11:875–9.
40. Verma S, Abbas M, Verma S, Khan FH, Raza ST, Siddiqi Z, et al. Impact of I/D polymorphism of angiotensin-converting enzyme 1 (ACE1) gene on the severity of COVID-19 patients. Infect Genet Evol J Mol Epidemiol Evol Genet Infect Dis. 2021;91:104801.
41. Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1–7) and Mas receptor axis in inflammation and fibrosis. Br J Pharmacol. 2013;169:477–92.
42. Vallée A. Dysautonomia and implications for anosmia in long COVID-19 disease. J Clin Med. 2021;10:5514.
43. Vallée A, Lecarpentier Y, Vallée J-N. Interplay of opposing effects of the WNT/β-Catenin pathway and PPARγ and implications for SARS-CoV2 treatment. Front Immunol. 2021 Apr 13;12:666693. doi: 10.3389/fimmu.2021.666693. Vallée A, Lecarpentier Y, Vallée J-N. Interplay of opposing effects of the WNT/β-Catenin pathway and PPARγ and implications for SARS-CoV2 treatment. Front Immunol. 2021;12.
44. Nataraj C, Oliverio MI, Mannon RB, Mannon PJ, Audoly LP, Amuchastegui CS, et al. Angiotensin II regulates cellular immune responses through a calcineurin-dependent pathway. J Clin Invest. 1999;104:1693–701.
45. Lecarpentier Y, Vallée A. The key role of the level of ACE2 gene expression in SARS-CoV-2 infection. Aging. 2021;13:14552–6.
46. Patel SK, Juno JA, Lee WS, Wragg KM, Hogarth PM, Kent SJ, et al. Plasma ACE2 activity is persistently elevated following SARS-CoV-2 infection: implications for COVID-19 pathogenesis and consequences. Eur Respir J. 2021;57:2003730.
47. Lindahl P, Johansson BR, Levéen P, Betsholtz C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. Science. 1997;277:242–5.
48. Edén A, Simrén J, Price RW, Zetterberg H, Gisslén M. Neurochemical biomarkers to study CNS effects of COVID-19: A narrative review and synthesis. J Neurochem. 2021;159:61–77.
49. Roerink ME, Roerink SHPP, Skoluda N, van der Schaaf ME, Hermus ARMM, van der Meer JWM, et al. Hair and salivary cortisol in a cohort of women with chronic fatigue syndrome. Horm Behav. 2018;103:1–6.
50. Gottschalk G, Peterson D, Knox K, Maynard M, Whelan RJ, Roy A. Elevated ATG13 in serum of patients with ME/CFS stimulates oxidative stress response in microglial cells via activation of receptor for advanced glycation end products (RAGE). Mol Cell Neurosci. 2022;120:103731.
51. Sasso EM, Muraki K, Eaton-Fitch N, Smith P, Lesslar OL, Deed G, et al. Transient receptor potential melastatin 3 dysfunction in post COVID-19 condition and myalgic encephalomyelitis/chronic fatigue syndrome patients. Mol Med Camb Mass. 2022;28:98.
52. Villaume WA. Marginal BH4 deficiencies, iNOS, and self-perpetuating oxidative stress in post-acute sequelae of Covid-19. Med Hypotheses. 2022;163:110842.
53. Eaton-Fitch N, du Preez S, Cabanas H, Staines D, Marshall-Gradisnik S. A systematic review of natural killer cells profile and cytotoxic function in myalgic encephalomyelitis/chronic fatigue syndrome. Syst Rev. 2019;8:279.
54. Chadchan SB, Naik SK, Popli P, Talwar C, Putluri S, Ambati CR, et al. Gut microbiota and microbiota-derived metabolites promotes endometriosis. Cell Death Discov. 2023;9:28.
55. Cousins FL, McKinnon BD, Mortlock S, Fitzgerald HC, Zhang C, Montgomery GW, et al. New concepts on the etiology of endometriosis. J Obstet Gynaecol Res. 2023;49:1090–105.
56. Haran JP, Bradley E, Zeamer AL, Cincotta L, Salive M-C, Dutta P, et al. Inflammation-type dysbiosis of the oral Microbiome associates with the duration of COVID-19 symptoms and long COVID. JCI Insight. 2021;6:e152346.
57. Natarajan A, Zlitni S, Brooks EF, Vance SE, Dahlen A, Hedlin H, et al. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged Gastrointestinal infection. Med N Y N. 2022;3:371–e3879.
58. Zollner A, Koch R, Jukic A, Pfister A, Meyer M, Rössler A, et al. Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology. 2022;163:495–e5068.
59. Sharma RP, Delly F, Marin H, Sturza S. Endometriosis causing lower extremity deep vein thrombosis - case report and review of the literature. Int J Angiol Off Publ Int Coll Angiol Inc. 2009;18:199–202.
60. Chiaramonte R, Castorina S, Castorina EG, Panarello A, Antoci SAM. Thrombosis of Iliac vessels, a rare complication of endometriosis: case report and review of literature. J Adv Res. 2017;8:1–5.
61. Prasannan N, Heightman M, Hillman T, Wall E, Bell R, Kessler A, et al. Impaired exercise capacity in post-COVID-19 syndrome: the role of VWF-ADAMTS13 axis. Blood Adv. 2022;6:4041–8.
62. Salmeri N, Gennarelli G, Vanni VS, Ferrari S, Ruffa A, Rovere-Querini P, et al. Concomitant autoimmunity in endometriosis impairs Endometrium-Embryo crosstalk at the implantation site: A multicenter Case-Control study. J Clin Med. 2023;12:3557.
63. Zhang T, De Carolis C, Man GCW, Wang CC. The link between immunity, autoimmunity and endometriosis: a literature update. Autoimmun Rev. 2018;17:945–55.
64. Barretta M, Savasta F, Pietropaolo G, Barbasetti A, Barbera V, Vignali M. COVID-19 susceptibility in endometriosis patients: A case control study. Am J Reprod Immunol. 2022;88:e13602.
65. Schwab R, Anić K, Stewen K, Schmidt MW, Kalb SR, Kottmann T, et al. Pain experience and social support of endometriosis patients during the COVID-19 pandemic in Germany - results of a web-based cross-sectional survey. PLoS ONE. 2021;16:e0256433.
66. Kabani Z, Ramos-Nino ME, Ramdass PVAK. Endometriosis and COVID-19: A systematic review and Meta-Analysis. Int J Mol Sci. 2022;23:12951.

67. Maham S, Yoon M-S. Clinical spectrum of long COVID: effects on female reproductive health. Viruses. 2024;16:1142.
68. Wei Y, Liang Y, Lin H, Dai Y, Yao S. Autonomic nervous system and inflammation interaction in endometriosis-associated pain. J Neuroinflammation. 2020;17:80.
69. Arena A, Orsini B, Degli Esposti E, Raimondo D, Lenzi J, Verrelli L, et al. Effects of the SARS-CoV-2 pandemic on women affected by endometriosis: a large cross-sectional online survey. Ann Med. 2021;53:1924–34.
70. Saponara S, Ciebiera M, Vitale SG, Agus M, Piselli A, D'Alterio MN et al. Impact of the COVID-19 pandemic on patients affected by endometriosis: A questionnaire-based cross-sectional online survey. J Endometr Pelvic Pain Disord. 2025;0(0):22840265251314992.
71. Ashkenazi MS, Huseby OL, Kroken G, Soto-Mota A, Pents M, Loschiavo A, et al. COVID-19 pandemic and the consequential effect on patients with endometriosis. Hum Reprod Open. 2022;2022:hoac013.
72. Guo S-W, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest. 2006;62:121–30.
73. Janssen EB, Rijkers ACM, Hoppenbrouwers K, Meuleman C, D'Hooghe TM. Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. Hum Reprod Update. 2013;19:570–82.
74. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2022;28:611.e9-611.e16.
75. Riemma G, Etrusco A, Laganà AS, Torella M, Vastarella MG, Della Corte L, et al. Susceptibility to infection and impact of COVID-19 vaccines on symptoms of women with endometriosis: A systematic review and Meta-Analysis of available evidence. Reprod Sci Thousand Oaks Calif. 2024;31:3247–56.
76. Smolarz B, Szyłło K, Romanowicz H, Endometriosis. Epidemiology, classification, pathogenesis, treatment and genetics (Review of Literature). Int J Mol Sci. 2021;22:10554.
77. Malutan AM, Drugan T, Costin N, Ciortea R, Bucuri C, Rada MP, et al. Pro-inflammatory cytokines for evaluation of inflammatory status in endometriosis. Cent-Eur J Immunol. 2015;40:96–102.
78. D'Alterio MN, D'Ancona G, Raslan M, Tinelli R, Daniilidis A, Angioni S. Management challenges of deep infiltrating endometriosis. Int J Fertil Steril. 2021;15:88–94.
79. Morotti M, Vincent K, Brawn J, Zondervan KT, Becker CM. Peripheral changes in endometriosis-associated pain. Hum Reprod Update. 2014;20:717–36.
80. Leyendecker G, Bilgicyildirim A, Inacker M, Stalf T, Huppert P, Mall G, et al. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Arch Gynecol Obstet. 2015;291:917–32.
81. Zhai J, Vannuccini S, Petraglia F, Giudice LC. Adenomyosis: mechanisms and pathogenesis. Semin Reprod Med. 2020;38:129–43.

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