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REVIEW ARTICLE

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Unveiling the connection: asthma and endometriosis - a comprehensive systematic review and meta-analysis

Masoud Hassanzadeh Makoui[a], Shiva Fekri[b], Reza Hassanzadeh Makoui[c], Negar Ansari[d], Shima Shokrzadeh[e], Seyyed Shamsadin Athari[a,f]*

[a]*Department of Immunology, School of medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[b]*Department of Gynecology and Obstetrics, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[c]*Department of Cardiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[d]*Department of Internal Medicine, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
[e]*Department of Animal Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran*
[f]*Cancer Gene therapy Research Center, Zanjan University of Medical Science, Zanjan, Iran*

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Abstract
Introduction and Objective: Asthma and endometriosis are two prevalent chronic conditions that affect a significant portion of the population. Both conditions have been linked to inflammatory processes and immune dysregulation, suggesting the possibility of a shared pathophysiological mechanism. Despite the growing interest in the connection between asthma and endometriosis, the current literature remains inconclusive. This systematic review and meta-analysis aim to consolidate the available evidence and provide a comprehensive understanding of the association between asthma and endometriosis.
Materials and Methods: We searched Embase, PubMed, Scopus, Web of Science, and Google Scholar to identify studies that met our criteria. The random effects model was used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) for individuals with endometriosis and non-endometriosis controls who have asthma. Additionally, we performed subgroup analyses based on geographic region to identify potential sources of heterogeneity. The research protocol was registered on PROSPERO (CRD42024567249).
Results: Six eligible case-control studies involving 66,997 cases and 3,253,658 controls were used to examine the association between asthma and endometriosis. Through a comprehensive search and analysis of relevant studies, a significant association between asthma and endometriosis was identified (OR: 1.786, 95% CI: 1.511-2.111, P < 0.001). The correlation showed significant heterogeneity in the study (I^2 = 75.709; P-value = 0.001), with geographic region identified as a significant factor contributing to this variation.
Conclusion: Our meta-analysis demonstrates a significant link between asthma and endometriosis, highlighting the need for comprehensive management that addresses both conditions.

***Corresponding author**: Seyyed Shamsadin Athari, Department of Immunology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. *Email address*: ss.athari@gmail.com, ss.athari@zums.ac.ir

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Introduction

Endometriosis is a gynecological condition in which endometrial-like tissue is found outside the uterus. It affects about 10-15% of women of reproductive age and often causes pelvic pain, infertility, and irregular periods.[1] The development of endometriosis involves a complex interaction of inflammatory, hormonal, and immune factors. The dysregulation of the immune response is particularly important in the progression of endometriosis.[2] Recent research has highlighted the role of T-helper 2 (Th2) immune responses in the development of endometriosis. Th2 cells release cytokines that contribute to tissue inflammation, blood vessel formation, and fibrosis, all of which support the establishment and persistence of endometriotic lesions.[3,4] The dysregulated immune response in endometriosis not only sustains chronic inflammation but also disrupts normal tissue balance, ultimately leading to the symptoms associated with this challenging condition.[5]

Asthma, on the other hand, is a chronic respiratory condition that affects approximately 262 million people globally, with a higher prevalence in women.[6,7] It is characterized by airway inflammation, bronchoconstriction, and hyperresponsiveness, leading to recurrent wheezing, coughing, chest tightness, and shortness of breath.[8] The pathophysiology of asthma involves a complex interaction of various immune and inflammatory processes. There are two distinct pathways in the pathogenesis of asthma: the Th2-dependent and Th2-independent pathways.[9] The Th2-dependent pathway involves the activation of Th2 cells, leading to the release of cytokines such as IL-4, IL-5, and IL-13, which promote eosinophilic inflammation, mucus production, and airway remodeling.[10] Conversely, the Th2-independent pathway is characterized by the activation of other immune cells, such as T-helper 1, T-helper 17, neutrophils, and macrophages, which release pro-inflammatory mediators.[9] Asthma is often associated with type 1 hypersensitivity reactions, in which exposure to allergens triggers the release of immunoglobulin E (IgE) antibodies, leading to the activation of mast cells and the release of histamine and other inflammatory mediators, further worsening airway inflammation and bronchoconstriction.[11]

The pathophysiology of asthma and endometriosis involves inflammatory processes and immune dysregulation. Certain immune mechanisms, such as Th2 cells and mast cells, along with the cytokines they produce, play a proven role in the development of both diseases and are shared between them.[12-14] Due to their shared inflammatory nature, these conditions may be linked through common underlying mechanisms, and the development of one may increase the incidence of the other.

Despite the growing interest in the potential association between asthma and endometriosis, the existing literature remains incomplete and inconclusive. While some studies have reported a higher prevalence of asthma in women with endometriosis and vice versa, others have found no significant association. The conflicting findings highlight the need for a systematic review and meta-analysis to synthesize the available evidence and provide a comprehensive understanding of the relationship between asthma and endometriosis. In this manuscript, by pooling data from relevant studies and applying rigorous statistical methods, we aim to elucidate the strength and direction of the link between asthma and endometriosis.

Materials and Methods

Design and search strategy

The methodology of this meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[15] The research protocol has been registered on the PROSPERO website under ID CRD42024567249. Our study question was: In women diagnosed with endometriosis (Population), how does the prevalence of asthma (Exposure) compare to women without endometriosis (Comparison), in terms of the association between the two conditions (Outcome)? We performed a comprehensive search of electronic databases, including Embase, PubMed, Scopus, and Web of Science, to identify relevant studies. Additionally, 30 pages of Google Scholar and the references of the identified articles were manually reviewed to find related studies. We also searched grey literature sources to identify any additional studies that met the inclusion criteria. The search covered the time period up to August 2024 and was not limited by language. The search strategy was developed using a combination of medical subject headings (MeSH) terms and keywords, specifically focusing on "asthma," "endometriosis," and their related synonyms.

Study selection criteria

This meta-analysis included all relevant studies that investigate the relationship between asthma and the risk of endometriosis. The selected studies provide precise and relevant data on the connection between the two conditions, follow a systematic approach in their planning and data collection, include well-defined diagnostic criteria for both asthma and endometriosis, and have been published in peer-reviewed journals with accessible full-text articles. Publications were excluded based on specific criteria if they lacked adequate data or clarity regarding the association between asthma and endometriosis. Additionally, animal studies, letters, editorials, abstracts, studies with a high risk of bias or methodological defects, and studies not published in peer-reviewed journals were not considered. Studies with incomplete or missing data, as well as those with unclear definitions or diagnostic criteria for asthma or endometriosis, were also excluded.

Data extraction process

Relevant data extracted from eligible studies included study design, sample size, outcomes, and effect estimates. Two reviewers independently performed data extraction to ensure accuracy, and any discrepancies were resolved through discussion with a third party. The extracted data included the first author, year of publication, study location, age range, and the number of endometriosis patients

with and without asthma, as well as the number of controls with and without asthma.

Quality assessment

The quality of the articles was evaluated by two reviewers, RHM and SS, using the Newcastle-Ottawa Quality Assessment Scale (NOS). In the case of any disagreements, a third reviewer, either MHM or SF, was consulted to resolve the differences. Articles scoring seven or higher on the NOS were considered high quality, while those scoring between five and seven were classified as moderate quality.

Statistical analysis

The data were analyzed using Comprehensive Meta-analysis software version 4.0 (Biostat, USA). Odds ratios and their corresponding 95% confidence intervals were determined by analyzing the sample sizes of the endometriosis and non-endometriosis groups, along with the number of asthma-positive cases in both groups. To assess the heterogeneity of the studies, Cochrane Q and I^2 statistics were used. When the Cochrane Q P-value was less than 0.1 and the I^2 value exceeded 50%, indicating statistical heterogeneity, the random-effects model was employed to estimate the outcome data. Otherwise, a fixed-effects model was used. Subgroup analysis was carried out to evaluate the impact of confounding variables on the outcomes of the meta-analysis. Additionally, a sensitivity analysis was performed by systematically excluding each study to assess the stability of the results.

Ethical considerations

This meta-analysis was conducted following ethical guidelines and did not involve human or animal subjects, ensuring the protection of participants' rights and confidentiality.

Search equations

Embase: (endometriosis:ti,ab,kw OR endometrioses:ti,ab,kw OR emdometrioma*:ti,ab,kw) AND asthma:ti,ab,kw
PubMed: (Endometriosis[Title/Abstract] OR ensometrioses [Title/Abstract] OR endometrioma*[Title/Abstract]) AND (asthma*[Title/Abstract] OR "Chronic Obstructive Pulmonary Disease"[Title/Abstract])
Scopus: (TITLE-ABS-KEY (endometriosis OR endometrioses OR endometrioma*) AND TITLE-ABS-KEY (asthma))
Web of Sciences: endometriosis or endometrioses or endometrioma* (Topic) and asthma (Topic)

Results

Study characteristics

To carry out the selected research methodology, six suitable case-control studies, including a total of 66,997 cases and 3,253,658 controls, were used to investigate the link between asthma and endometriosis. Among the chosen studies, two were conducted in Asia,[16,17] two in Europe,[18,19] and two in North America.[20,21] The process of reviewing the literature and its findings is presented in Figure 1. The key characteristics of the selected studies are outlined in Table 1. The NOS scoring scale was used to assess the quality of the studies. Five studies were rated as high quality, while one was rated as medium quality (see Table 1).

Quantitative synthesis

The data were analyzed using the random effects model due to its heterogeneity. The results of the meta-analysis demonstrate a significant association between the presence of asthma and susceptibility to endometriosis (OR: 1.786, CI 95%: 1.511-2.111, P<0.001). Figure 2 displays the corresponding forest plot.

Heterogeneity test

The correlation between asthma and endometriosis was found to exhibit heterogeneity among studies, as indicated by the I^2 test and Cochrane Q statistic (I^2 = 75.709; P-value = 0.001). To explore the source of this heterogeneity, subgroup analysis was performed based on geographic region. This analysis identified region as a significant factor contributing to the heterogeneity observed in the study (P=0.03).

Sensitivity analysis

A sensitivity analysis was conducted to test the reliability of the results and assess the impact of individual studies on the overall findings of the meta-analysis. This involved systematically excluding one study at a time and re-analyzing the data to observe each study's influence on the combined effect size. The sensitivity analysis results showed that the overall findings were not significantly affected by excluding any single study. This suggests that the results of the meta-analysis are consistent and reliable. This analysis increases confidence in the validity and applicability of the findings presented in this study.

Publication bias assessment

Publication bias was assessed using a funnel plot, Begg's rank correlation, and Egger's regression tests. The funnel plot presenting the publication bias is shown in Figure 3. The statistical tests indicated no significant publication bias among the studies (P-value for Begg's rank correlation test = 0.850; P-value for Egger's regression test = 0.132). However, the analysis of funnel plot asymmetry indicated a potential publication bias in the studies. The funnel plot diagrams were modified using the trim and fill test, but these modifications did not lead to significant changes in the results (data not presented).

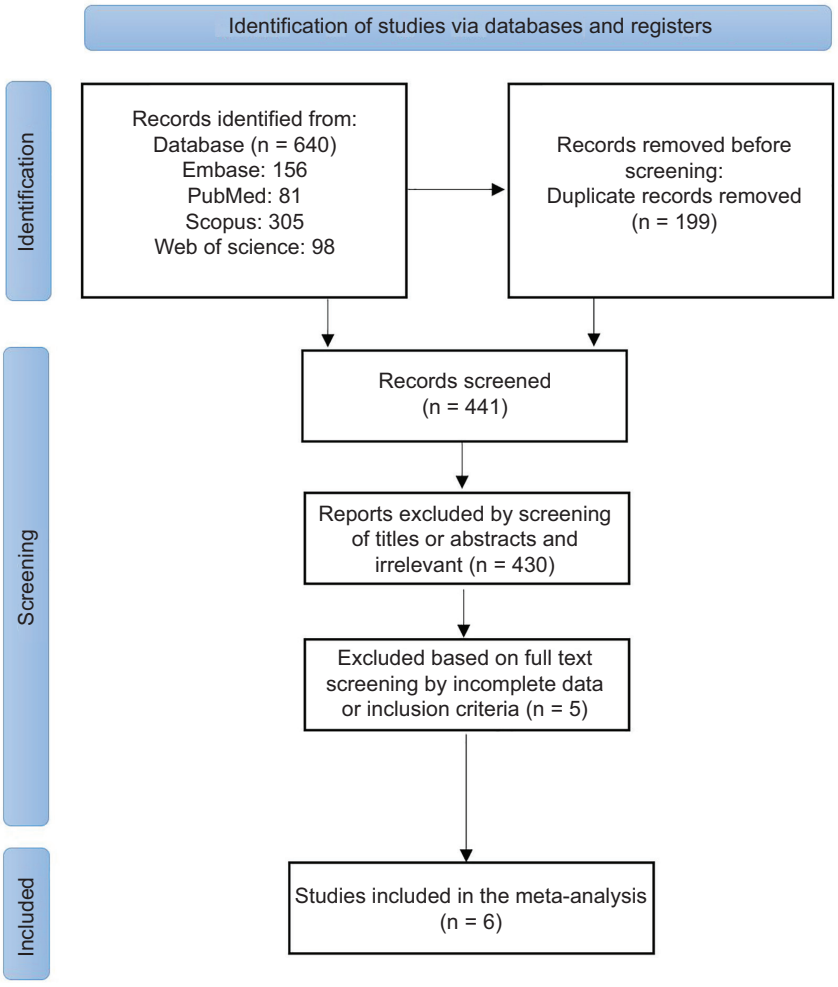

Figure 1 Literature search and study selection flowchart.

Table 1 Basic characteristics of the included studies.

First author	Year	Country	Region	Number of asthmatic cases	Total number of cases	Number of asthmatic controls	Total number of controls	Total mean age or age range	NOS score
Ferrero (18)	2005	England	European	23	467	22	412	34.39	7
Matalliotakis (20)	2012	USA	North American	45	501	8	188	34.49	7
Peng (16)	2017	Taiwan	Asia	371	1297	6966	35388	34.80	8
Alqaisi (21)	2018	USA	North American	15268	64150	423439	3207870	20-40	8
Gyawali (19)	2023	Northern Europe	European	30	202	425	4624	40-65	8
Pan (17)	2024	China	Asian	88	380	694	5176	37.19	6

NOS scale: Newcastle - Ottawa Quality Assessment scale for case control studies.

Discussion

Asthma and endometriosis are common health conditions that can significantly impact an individual's health. Some research has suggested a potential connection between these two conditions due to the involvement of chronic inflammation in their development and the activation of similar inflammatory mechanisms. The current study focuses on conducting a meta-analysis to provide a comprehensive overview of the background and significance of this connection between asthma and endometriosis. Our results found a significant link between asthma and

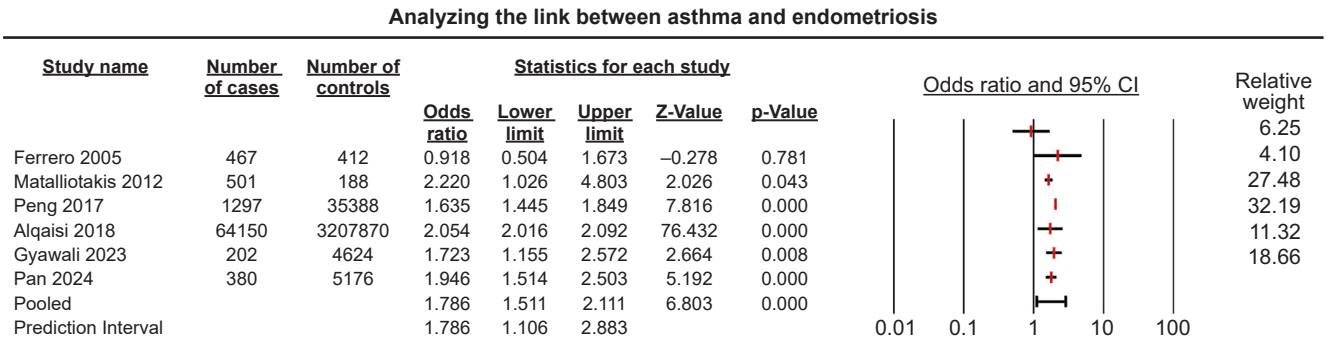

Figure 2 Forest plot investigating the link between asthma and the risk of endometriosis.

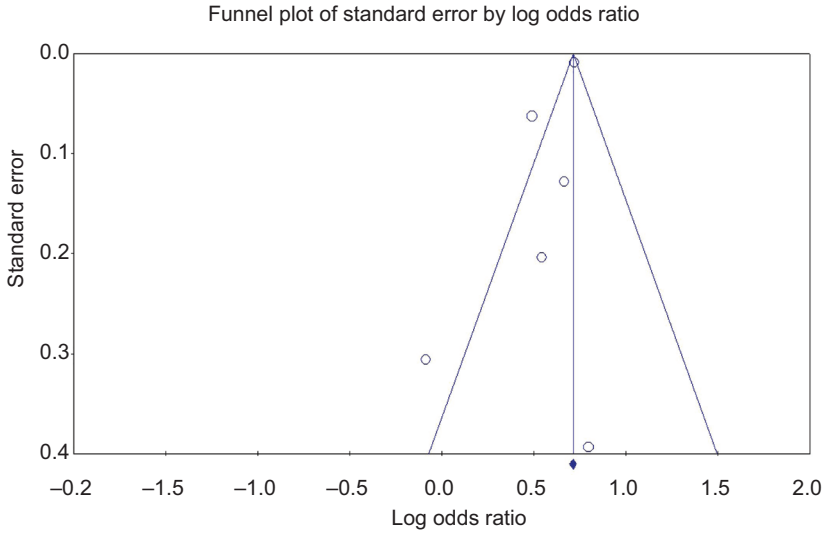

Figure 3 Begg's funnel plots displaying the studies that investigated the relationship between asthma and endometriosis to detect any potential publication bias.

endometriosis, emphasizing the need for further investigation into the possible correlation between these two disorders.

The potential mechanisms underlying this association are still unclear and complex. Asthma involves persistent airway inflammation, resulting in elevated levels of inflammatory factors such as TNF-α, IL-4, IL-6, TGF-β, and VEGF. These factors initiate an inflammatory reaction in the lungs, leading to structural changes in the airways.[22-26] Numerous studies have observed the role of inflammatory responses in the development of endometriosis.[27,28] These studies revealed that women diagnosed with endometriosis exhibited elevated levels of inflammatory cytokines in the serum compared to healthy individuals.[3,29,30] Considering the fact that both endometriosis and asthma are linked to inflammatory and immune system reactions, it is suggested that women with endometriosis may be at a higher risk of developing asthma. The primary mechanism that causes the development of asthma is type 2 inflammation and its key player, Th2.[31] Studies have shown a shift from Th1 to Th2 in endometriosis. This change, along with the cytokines produced by these cells, results in an increase in the conversion of antibody types to IgE in this disease.[3] Another vital cell that may link asthma and endometriosis is the mast cell. Mast cells actively contribute to type 1 hypersensitivity, which is associated with diseases like asthma.[32,33] Research has shown that mast cells are significantly present in endometriosis, and their degranulation leads to various complications such as pain, angiogenesis, fibrosis, cell proliferation, and infertility.[3,34-37] Another factor that may contribute to the development of asthma in endometriosis patients is hormonal influences, particularly estrogen. Estrogen levels tend to increase in endometriosis,[38] and studies have revealed a correlation between elevated estrogen levels and more severe asthma symptoms.[39] Genetics can also play a significant role in the association between asthma and endometriosis. The investigation by Adewuyi et al. revealed a significant relationship between single-nucleotide polymorphisms (SNPs) linked to endometriosis and asthma. Their analysis showed

a strong positive genetic correlation between the two disorders. Furthermore, the results indicated a genetic overlap at the gene level, suggesting that endometriosis and asthma may share a common genetic basis.[40]

Our analysis identified regional differences as a critical factor contributing to the observed heterogeneity. It is important to note that there may be other sources of heterogeneity that we could not thoroughly investigate due to insufficient data. These factors could include variations in study design, differences in patient demographics, the type and severity of asthma and endometriosis, comorbidities, genetic predispositions, environmental factors, and treatment regimens. While these factors may contribute to the observed heterogeneity, further research is needed to comprehensively explore their impact on the relationship between asthma and endometriosis. In this context, Pan et al. found that endometriosis is associated with higher odds of asthma in women aged 40 to 49 years who have a body mass index (BMI) of 25 to 29.9 kg/m^2 or a history of pregnancy. Additionally, they identified that the use of estrogen and progesterone hormones, smoking cigarettes, using birth control pills, having uterine fibroids, and undergoing ovary removal are among the potential confounding factors that could affect the association between asthma and endometriosis.[17] In another study, Peng et al. revealed that asthma can significantly increase comorbidities such as inflammatory diseases of the cervix, vagina, or vulva in patients with endometriosis. However, it is not significantly associated with infertility or uterine leiomyoma in these patients.[16] Simorgick et al. investigated the impact of asthma on comorbid pain syndromes in endometriotic patients and found no significant relationship.[41]

Our study has several strengths. To the best of our knowledge, this is the first meta-analysis to investigate the link between asthma and endometriosis. Our meta-analysis used a thorough and systematic search strategy to identify relevant studies, ensuring a comprehensive review of the literature. By pooling data from multiple studies, we achieved a larger sample size, increasing the statistical power and precision of the results. We also employed rigorous statistical methods to analyze the data from the included studies, enhancing the reliability and validity of our findings. However, there are some limitations that need to be addressed. The meta-analysis may be affected by publication bias, as studies with significant results are more likely to be published, potentially influencing the overall findings. Variability in study designs, populations, and methodologies among the included studies may introduce heterogeneity, limiting the generalizability of the results. Additionally, the meta-analysis may not account for all potential confounding factors that could influence the association between asthma and endometriosis, leading to biased results.

Conclusions

In conclusion, our meta-analysis has revealed a significant association between asthma and endometriosis. Our findings suggest a potential shared pathogenesis between these two conditions, emphasizing their interconnected nature. Given the complex pathogenesis of endometriosis and the limited understanding of effective treatment strategies, we propose that asthma treatments could be utilized to help manage endometriosis symptoms. Screening patients with asthma for the possible presence of endometriosis could lead to earlier detection and more effective control of the condition. Early identification of endometriosis is crucial for timely interventions to prevent disease progression and the formation of adhesions. By recognizing and addressing the relationship between asthma and endometriosis, we can potentially improve diagnostic accuracy, treatment outcomes, and the overall quality of care for individuals affected by these conditions.

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Authors Contributions

SSA, MHM and SF designed the study, analyzed the data, and wrote the article. MHM conducted the literature search. RHM, NA and SS reviewed the articles, assessed the study quality, and extracted the data. All authors have read and agreed to the final version of the article.

Conflict of Interest

The authors declare no conflict of interest.

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