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Systematic Review and Meta-Analysis

Economic Burden of Endometriosis: A Systematic Review and Meta-Analysis

Ripandi Yuspa*

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya/dr. Saiful Anwar Hospital, Malang, East Java, Indonesia

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CORRESPONDING AUTHOR*
Ripandi Yuspa
yupppdsobgynub@gmail.com
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya/dr. Saiful Anwar Hospital, Malang, East Java, Indonesia

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ABSTRACT

Introduction: Endometriosis, marked by uterine-like tissue growth outside the uterus, causes severe pelvic pain and infertility. Delayed diagnosis contributes to its significant global economic burden, especially in Europe and the USA. Despite treatment advances, managing endometriosis remains challenging. Comprehensive strategies are urgently needed to reduce its economic impact and improve patient outcomes.

Material and Methods: We searched for English-language full-text literature from PubMed, Cochrane, Wiley Library, and ScienceDirect databases from January 2013 to January 2024. Total of 951 studies were identified, and 14 studies were included, providing comprehensive data on the economic burden of endometriosis, including direct healthcare costs and productivity losses.

Results: The economic burden of endometriosis, based on 14 studies, is substantial, reflecting both direct healthcare costs and productivity losses. Average annual costs per woman ranged from EUR 8,768 in Sweden to Int $16,970-$20,898 in Australia. Non-surgical treatments in the USA were more cost-effective than surgery, costing $100,000 per QALY. In the UK, the LNG-IUS was the most expensive treatment at £650.94. Costs in China for various therapies ranged up to $10,728 with differing ICERs.

Conclusion: These findings underscore the significant economic impact and the need for cost-effective management strategies: costs and productivity losses. Effective management strategies are essential to mitigate these costs.

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INTRODUCTION

Endometriosis, a prevalent and often chronic inflammatory condition affecting women, manifests when tissue resembling the uterine lining proliferates outside the uterus. This aberrant tissue growth occurs predominantly within the pelvic region, encompassing areas such as the ovaries, ligaments, peritoneal surfaces, as well as the bowel and bladder. The disease exhibits a spectrum of presentations, ranging from superficial lesions to cysts within the ovaries (endometriomas) and deeper nodules, frequently accompanied by scarring and adhesions. Notably, endometriosis is closely linked with severe pelvic pain, occurring cyclically and often exacerbated during sexual intercourse, alongside infertility issues [1,2]. Delays in diagnosing endometriosis, as demonstrated by Nengsih et al. (2021), significantly contribute to prolonged infertility, further complicating treatment outcomes in the Indonesian context [3]. Additionally, Nurindah et al. (2024) reported that patients with endometriosis undergoing IVF in Indonesia exhibited lower pregnancy rates compared to those with tubal factor infertility, underscoring the unique challenges posed by endometriosis-associated infertility in the region [4].

Determining the epidemiological features of endometriosis poses challenges due to many women remaining asymptomatic and undiagnosed. The definitive diagnosis requires a laparoscopic examination, complicating prevalence estimation. Nonetheless, endometriosis is estimated to affect approximately 10% to 15% of women of reproductive

age, with prevalence rising to 70% in women with chronic pelvic pain [5].

In the United States, recent surveys indicate significant prevalence rates. According to the National Hospital Discharge Survey, 11.2% of women hospitalized for genitourinary causes aged 18 to 45 were diagnosed with endometriosis, while approximately 10.3% of women undergoing gynecologic surgeries were found to have the condition [1]. In Indonesia, while data on the incidence and prevalence of endometriosis remain unclear due to limited studies, a report from RSUD Dr. Soetomo in Surabaya indicates that 13.6–69% of women experiencing infertility are affected by endometriosis [6].

Endometriosis imposes a substantial burden globally, with particularly high costs in Europe and the United States. In Europe, the average annual cost per patient, encompassing healthcare expenses and productivity losses, amounts to approximately €10,000. In comparison, healthcare costs in the United States are 63% higher than the European average [7].

Endometriosis is a gynecological illness that is characterized by endometrial-like tissue outside of the uterus. This tissue is primarily seen in the pelvic peritoneum, ovaries, and rectovaginal septum. Endometriosis is inflammatory, fibrous, and estrogen-dependent. Rarely, endometrial-like tissue has also been reported to be present in the brain, pericardium, pleura, diaphragm, and diaphragm [8]. It affects 5–10% of women who are fertile, and it is linked to infertility and pelvic pain [9]. Typically, endometriosis is categorized using the standards established by the American Society of Reproductive Medicine (ASRM). levels I, II, III, and IV are the four levels that make up their criteria: minimal, moderate, moderate, and severe. From the minimal to the severe stage, these stages comprise the lesion's size, location, and amount of tissue growth [7, 8]. The probability of infertility is not correlated with the pain symptoms according to this staging approach, though [5].

On average, it takes between four and eleven years from the onset of symptoms for the condition to be diagnosed. This phenomena can be found in wealthy cultures with universal access to healthcare as well as in low- and middle-income nations [10]. The lack of a pathognomonic test or biomarker to identify the disease, the variety of symptoms that may be regarded as physiological reactions during menstruation (such as pain and discomfort), and the extensive overlap of reported symptoms with other gastrointestinal or gynecological causes are all blamed for this delay. Endometriosis is more easily diagnosed when there is a positive family history, pelvic pain, benign ovarian cysts, pelvic operations, and infertility problems [10]. The results of a physical examination vary based on the size and location of the endometriotic lesion. Endometriosis can be diagnosed by looking for symptoms such as vaginal tenderness, immobility of the uterus, adnexal masses, and palpable nodules in the posterior fornix [11].

Diagnosing endometriosis typically requires surgical visualization, commonly through laparoscopy, which remains the most reliable diagnostic technique. During laparoscopy, suspicious lesions are biopsied for histological confirmation, which is crucial for accurate diagnosis. Although imaging techniques like ultrasonography or MRI can aid in detecting specific types of lesions, no individual markers have been identified that are specific to the diagnosis of endometriosis, and there are no detectable laboratory abnormalities. An experienced physician may sometimes establish a presumptive diagnosis based on patient history or pelvic palpation; however, definitive diagnosis requires surgical assessment and histological evaluation [9,12].

Treatment strategies for endometriosis include the surgical removal of ectopic tissue and pharmacologic therapies aimed at alleviating pain and inflammation. Hormonal therapies, such as combined estrogen-progestin contraceptives, progestin-only preparations, GnRH agonists, and aromatase inhibitors, play a central role in reducing endometrial proliferation and managing symptoms. However, these approaches often come with side effects, including hypoestrogenic symptoms, contraceptive implications, and risks like bone loss or thromboembolism. NSAIDs are commonly used alongside hormonal treatments to address pain but are limited by potential gastrointestinal and renal side effects. Despite advancements in understanding and managing the condition, the multifaceted challenges of endometriosis, including balancing efficacy and side effects, make its treatment a complex endeavor [9,12].

Endometriosis imposes a considerable burden on both individuals and healthcare systems due to its debilitating symptoms, primarily centred around pain, which profoundly impacts the quality of life and productivity. This burden extends to significant financial implications, encompassing direct healthcare costs (such as inpatient, outpatient, surgical, and medication expenses) as well as indirect costs related to loss of productivity at work [13].

For instance, a recent review synthesized findings from 12 studies spanning 2000 to 2013 across multiple countries, including the USA, Austria, Belgium, Brazil, Canada, Finland, Germany, and Italy. Notably, some studies encompassed data from up to 10 countries, revealing a wide spectrum of cost estimates. Direct costs ranged from USD 1,109 to USD 12,118 per woman per year, showcasing substantial variations influenced by diverse healthcare systems, methodologies, and regional factors. Similarly, indirect costs demonstrated significant disparities, with the highest estimates

reaching USD 15,737 per woman per year in the United States and the lowest observed in Austria at USD 3,314 per woman per year [14]. These findings underscore the multifaceted impact of endometriosis, emphasizing the urgent need for comprehensive strategies to mitigate its economic burden and improve patient outcomes.

MATERIAL AND METHODS

This review was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Systematic Review

Eligibility Criteria

Reviewers independently evaluated each paper that was retrieved for consideration; differences were settled by consensus. The following inclusion criteria were set: (1) Female diagnosed with Endometriosis (2) Including Randomised Controlled Trials (RCTs) and prospective or retrospective observational research (3) Full-text versions are accessible. Research carried out using the English language only (5). Using a standardized data-collecting form, investigators carried out the data extraction process independently. Each study's author, publication year, study design, sample size, treatment stated, and economic burden or cost.

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were followed in our systematic review, guaranteeing a consistent framework for methodical conduct and clear reporting of our research [15]. We conducted a systematic search of English-language literature in PubMed, ProQuest, Cochrane, and SpringerLink databases, spanning from January 2014 to January 2024. We identified relevant articles by utilizing the following terms: ("endometriosis" OR "endometrioma") AND ("cost of illness" OR "health expenditures" OR "economic burden"). We added to this search by manually looking through a reference list of pertinent papers (**Fig.1**).

Data Extraction and Analysis

A total of 951 studies were identified, consisting of 81 studies from PubMed, 6 studies from Cochrane, 606 studies from ProQuest, and 258 studies from SpringerLink. After deduplication (156) and screening for inclusion criteria (231) and document type, 398 records proceeded to screening. Of these, 367 were excluded, leaving 31 for retrieval. Fourteen reports were not retrieved, resulting in 17 assessed reports, with 3 excluded for focusing solely on medication costs. Finally, 14 studies were included, providing comprehensive data on the economic burden of endometriosis, including direct healthcare costs and productivity losses. From these 14 studies, we included only 4 studies that have a control sample and can be evaluated for mean and standard deviation for meta-analysis cost evaluation (**Fig.2**).

Risk of Bias Assessment

The authors evaluated the possibility of bias in observational studies using the Risk of Bias In Non-randomized Studies of Exposure (ROBINS-E). The results are shown graphically in **Table 1**. Consensus was used to settle disagreements. The assessment of fourteen reviewed studies reveals that most studies have a low risk of bias in random sequence generation and blinding of outcome assessment.

Meta-Analysis

Statistical Analysis

We conducted a meta-analysis to combine the findings of the studies included and compute a consolidated measure of the effect size. The selection of a random-effects model for this meta-analysis was based on the expected heterogeneity in study populations and techniques. The standardized mean difference (SMD) was utilized to measure the magnitude of the effect for continuous outcomes. The statistical analyses were performed using RevMan 5.4, a software developed by The Cochrane Collaboration in Copenhagen. Studies lacking standard deviations were omitted from the meta-analysis. The study provided aggregated effect sizes along with 95% confidence intervals.

Heterogeneity Assessment

An assessment was conducted to evaluate the heterogeneity among the studies that were included. This was done to explain the differences in effect sizes and to assure the reliability of the combined results. The assessment of heterogeneity was conducted using the I^2 statistic and the Chi^2 test. A heterogeneity score ranging from 0% to 25% was classified as low, from 25% to 50% as moderate, from 50% to 75% as substantial, and above 75% as considerable. The I^2 score for the main analysis was 75%, indicating a significant level of heterogeneity ($p < 0.001$).

Publication Bias

Publication bias was assessed by employing a funnel plot to visually examine any asymmetry, which may suggest the selective publication of papers with favourable results. In addition, the Egger's test was conducted to statistically evaluate the existence of publication bias, where a p-value below 0.05 indicates a significant bias.

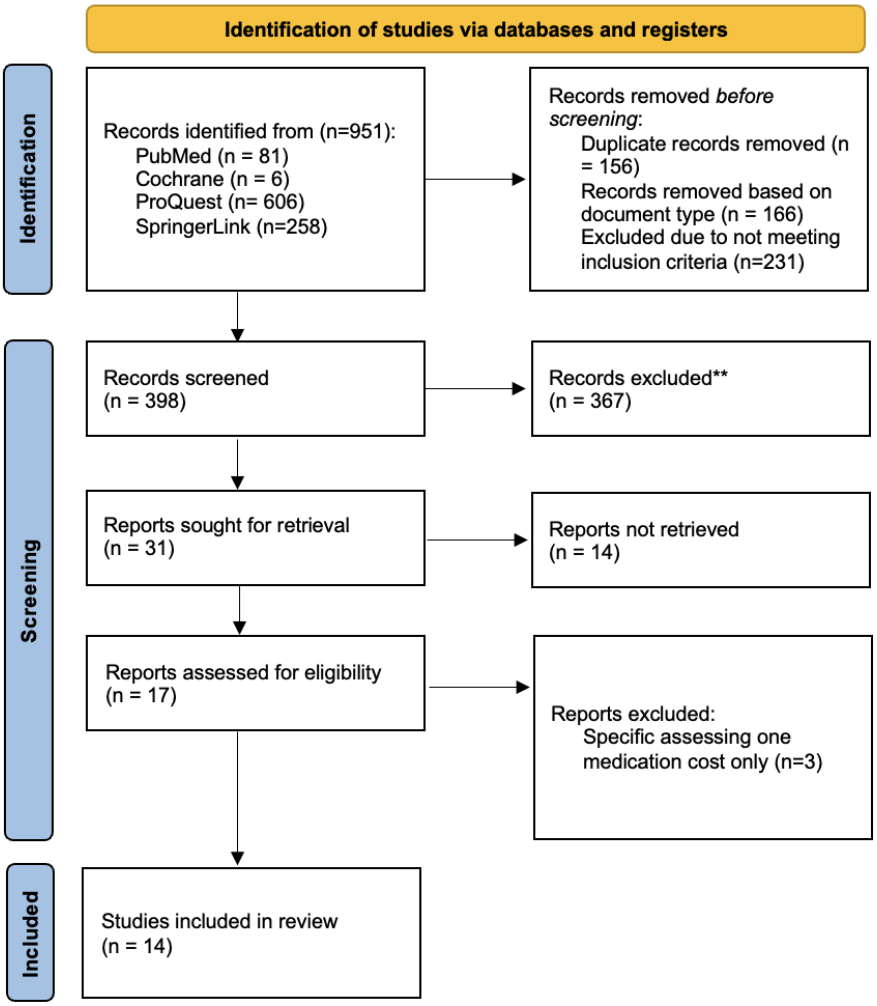


Fig. 1. PRISMA Flow Chart

RESULTS

Systematic Review

Study Characteristics

The systematic review comprises 14 studies, each with distinct characteristics. Grundström et al. (2020) from Sweden conducted a cross-sectional study with 423 women [16]. Cezar et al. (2018) from Germany performed a quasi-randomized study involving 47 women [17]. Armour et al. (2019) from Australia executed a cross-sectional study on 407 women [18]. Bohn et al. (2021) from the USA used a cohort design with a substantial sample size of 4,817,894 women. Sanghera et al. (2016) from the UK applied a Markov model to a sample of 1,000 women [19]. Arakawa et al. (2018) from Japan also utilized a Markov model, examining 210,000 women. Wu et al. (2017) from China used a Markov model with 1,000 women [20]. Surrey et al. (2020) from the USA conducted a cohort study with 11,793 women over a pre-diagnosis period [21].

Soliman et al. (2019) from the USA undertook a cohort study involving 15,615 women with Medicaid insurance [22]. Estes et al. (2019) from Italy conducted a cross-sectional study over multiple years with varying sample sizes, peaking at 101,733 in 2006-2007 [23]. Soliman et al. (2018) from the USA performed a cohort study on 113,506 endometriosis patients and 927,599 controls [24]. Fuldeore et al. (2015) from the USA conducted a cohort study involving 37,570 women over ten years [25]. Koltermann et al. (2016) from Germany undertook a cohort study on 825 women with deep infiltrating endometriosis [26]. Malik et al. (2022) from Australia performed a cohort study on 340 women with endometriosis and 69 with chronic pelvic pain [27].

Follow-up Duration and Treatment

The follow-up durations and treatments varied across studies. Grundström et al. (2020) did not specify follow-up duration or treatment [16]. Cezar et al. (2018) had follow-up periods of 4.17 and 9.07 months assessing

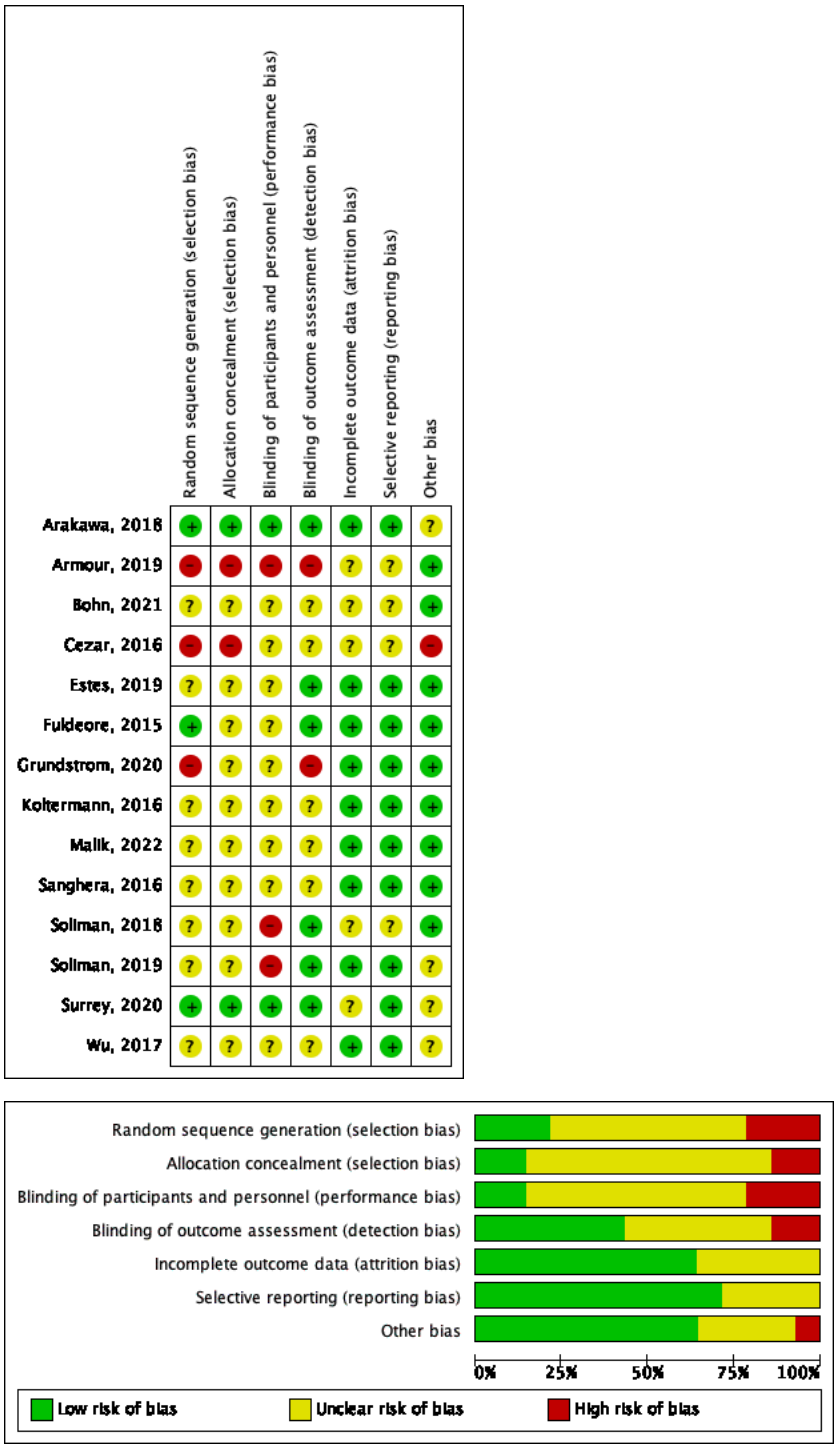


Fig. 2. Risk of Bias Assessment

lynestrenol and medrogeston. Armour et al. (2019) conducted a 6-month follow-up without specific treatments [18]. Bohn et al. (2021) followed up for 6 months, comparing multiple strategies involving NSAIDs, SARCs, LARCs, and GnRH modulators [28].

Sanghera et al. (2016) had a 36-month follow-up, comparing LNG-IUS, DMPA, COCP, and no treatment [19]. Arakawa et al. (2018) had a 12-month follow-up without specific treatments [29]. Wu et al. (2017) followed up for 6 months, comparing no medical therapy, oral contraceptive therapy, and GnRH-a therapies [20]. Surrey et al. (2020) analyzed a 60-month pre-diagnosis period without specifying treatments [21]. Soliman et al. (2019) had a 12-month follow-up,

examining various medications and surgeries [24]. Estes et al. (2019) covered a period from 2006 to 2015 without specifying treatments [23]. Soliman et al. (2018) had a 12-month follow-up, analyzing the use of opioids, NSAIDs, antidepressants, and estrogen/progestin oral contraceptives [24]. Fuldeore et al. (2015) conducted a 10-year follow-up without specifying treatments [25]. Koltermann et al. (2016) analyzed costs before and after an index year in a 12-month period without specific treatments [26]. Malik et al. (2022) had an 8-week follow-up without specifying treatments but noted the use of allied health and complementary therapies [27].

Economic Burden

The economic burden of endometriosis is extensive and varies across different studies, reflecting both direct healthcare costs and indirect costs related to productivity losses. Grundström et al. (2020) identified that the average annual cost for women with endometriosis in Sweden is EUR 8,768 per woman. This cost is divided into direct healthcare costs of EUR 4,282 and indirect costs of EUR 4,486. In Germany, Cezar et al. (2018) found that progestin medications, while well-tolerated, are relatively low-cost compared to other treatments [16,17].

In Australia, Armour et al (2019) reported a significant economic burden primarily due to productivity losses [18]. The estimated annual cost per woman ranged from Int $16,970 to $20,898, regardless of whether they had a diagnosis of endometriosis. In the USA, Bohn et al. (2021) conducted a cost-effectiveness analysis of various treatment strategies for endometriosis-related dysmenorrhea. They found that non-surgical interventions, such as NSAIDs and contraceptives, were more cost-effective compared to immediate surgery, with the most cost-effective strategy costing $100,000 per quality-adjusted life year (QALY) [18,28].

Sanghera et al. (2016) in the UK reported that the levonorgestrel-releasing intrauterine system (LNG-IUS) was the most expensive treatment at £650.94, followed by DMPA at £622.56, COCP at £599.93, and no treatment at £371.34. In Japan, Arakawa et al. (2018) calculated the incremental cost-effectiveness ratio (ICER) of recommended medical interventions for endometriosis treatment to be approximately 115,000 JPY ($958) per QALY gained, with an incremental cost of 300,000 JPY ($2,500) and incremental effectiveness of 2.6 QALYs. The societal monetary value (SMV) was estimated to be positive 3,130,000 JPY ($26,000) [19,29].

Wu et al. (2018) from China provided a detailed cost and ICER analysis for various therapies to prevent recurrent endometriosis after conservative surgery. For ovarian endometriosis, the cost of oral contraceptive therapy ranged from $5,257 to $6,872, with ICERs reaching up to $10,684. For peritoneal endometriosis, costs ranged from $5,467 to $7,069, with ICERs up to $10,630. For deep endometriosis, costs ranged from $4,853 to $6,452, with ICERs up to $10,589. Lastly, for other types of endometriosis, costs ranged from $5,341 to $6,954, with ICERs up to $10,728 [20].

Surrey et al. (2020) in the USA found that pre-diagnosis healthcare costs averaged $28,376. The study demonstrated that all-cause pharmacy costs were significantly lower for patients with short diagnostic delays ($4,351) compared to those with intermediate ($5,565) or long delays ($6,106). All-cause medical costs also rose with longer diagnostic delays, with short delay costs at $17,138, intermediate at $24,465, and long delay costs at $28,354 [21]. Soliman et al. (2019) noted that endometriosis patients with Medicaid in the USA had significantly higher healthcare utilization compared to controls without endometriosis. Mean total direct healthcare costs were $13,670 for endometriosis patients versus $5,779 for controls. Estes et al. (2019) in Italy observed a rise in inpatient admission costs over a decade, with mean total charges increasing from $22,642 in 2006-2007 to $39,662 in 2014-2015 [22,23].

A previous study by Soliman et al. (2018) reported mean annual total adjusted direct costs of $16,573 per endometriosis patient in the USA, with an incremental

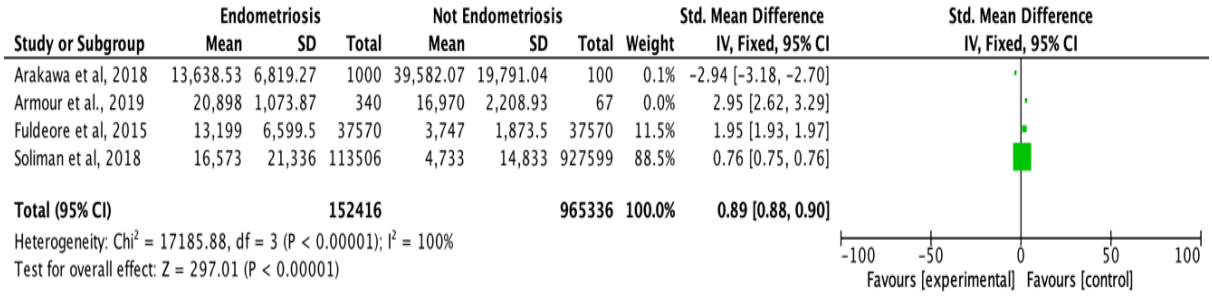


Fig. 3. The forest plot presents the individual and pooled standardized mean differences (SMD) for the studies included in the meta-analysis

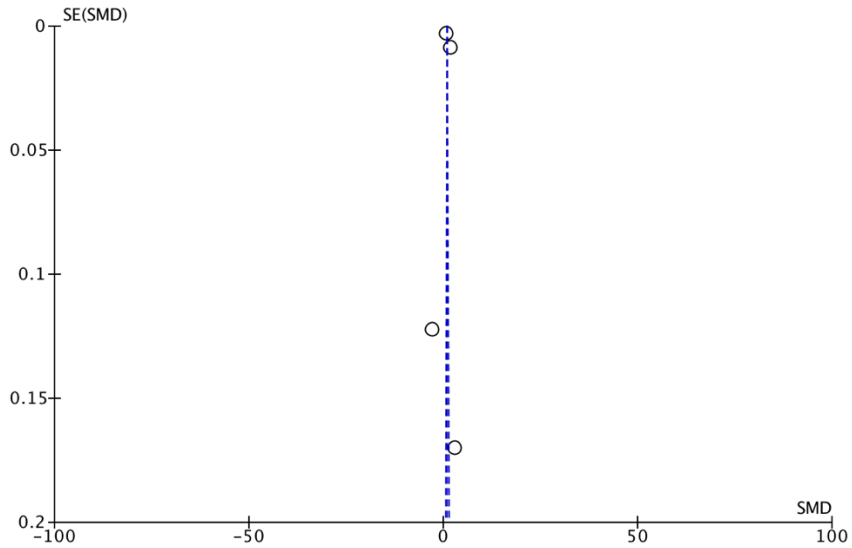


Fig. 4. Funnel Plots for The Publication Bias of The Meta-Analysis

cost of $10,002 compared to controls. Additionally, the study identified incremental indirect costs of $2,132 per endometriosis patient. In the USA, Fuldeore et al. (2015) found that over a ten-year period, endometriosis patients incurred significantly higher all-cause total costs, peaking in the first year post-diagnosis. The incremental healthcare costs were $7,028 during the five-year pre-diagnosis period and $19,277 in the five-year post-diagnosis period. Koltermann et al. (2016) in Germany reported that the mean annual costs for patients with deep infiltrating endometriosis ranged from 544 to 2,817 Euros in subsequent years, with younger patients incurring higher costs [23–26].

Finally, Malik et al. (2022) in Australia demonstrate spending on allied health and complementary therapies. The total expenditure by the endometriosis cohort was $53,315, averaging $460.04 per woman. Significant amounts were spent on physiotherapists ($10,525), mental health workers ($7,555), naturopaths ($7,320), and acupuncturists ($6,587). These findings collectively underscore the substantial and multifaceted economic burden of endometriosis, emphasizing the importance of cost-effective management strategies to alleviate both direct healthcare costs and productivity losses [27].

Meta-Analysis

Main Finding

The meta-analysis aimed to assess the economic burden associated with endometriosis compared to non-endometriosis conditions. Using a fixed-effect model to pool data from four studies, it was assumed that the included studies measured the same underlying effect. The SMD was calculated for continuous outcomes to quantify the effect size. The analysis revealed a significant pooled effect size of 0.89 (95% CI 0.88 to 0.90, $p < 0.0001$), indicating a substantial difference in the economic burden between individuals with endometriosis and those without. This consistent effect size across the studies underscores a significant economic burden attributable to endometriosis.

Individual study results varied, underscoring some variability in the reported effect sizes. Arakawa et al. (2018) reported an SMD of -2.94 (95% CI -3.18 to -2.70), indicating a significant economic disadvantage for endometriosis. Armour et al. (2019) found an SMD of 2.95 (95% CI 2.62 to 3.29), showing a high economic burden. Fuldeore et al. (2015) reported an SMD of 1.95 (95% CI 1.93 to 1.97), indicating a substantial economic impact, while Soliman et al. (2018) observed an SMD of 0.76 (95% CI 0.75 to 0.76), also supporting the economic burden of endometriosis. It is important to note that the calculations by Arakawa et al. (2018) and Fuldeore et al. (2015) were particularly focused on providing reasonable estimations needed for accurate economic assessment, ensuring robust and reliable results.

Heterogeneity

The heterogeneity assessment indicated a high degree of variability among studies ($Chi^2 = 17185.88$, $df = 3$, $p < 0.00001$, $I^2 = 100\%$), suggesting that while the overall trend is clear, individual study contexts and populations might have contributed to differing effect sizes. Overall, the meta-analysis confirms that endometriosis poses a significant economic burden compared to non- ndometriosis conditions. The pooled effect size of 0.89 underscores the substantial impact of endometriosis on economic outcomes, with individual studies consistently pointing towards higher costs

associated with the condition. These findings suggest that addressing endometriosis not only has health benefits but also economic advantages, warranting policy attention, and healthcare prioritization.

Publication Bias

The provided funnel plot in Fig. 4 displays SMD of studies against their standard errors (SE(SMD)), revealing a symmetrical distribution around the vertical line at SMD = 0. This symmetry indicates no significant publication bias, as studies with both large and small effects are evenly distributed around the combined effect size. Most studies cluster at the top of the plot, reflecting larger sample sizes and more precise estimates, while a few studies spread further down indicate smaller sample sizes and less precision. The absence of significant outliers further supports the lack of publication bias. Thus, the results of the meta-analysis appear robust and not significantly influenced by selective publication of studies with positive results.

DISCUSSION

Endometriosis imposes a significant burden on affected individuals, both before and after diagnosis. Chronic pelvic pain and infertility are hallmark symptoms, contributing to emotional distress, strained relationships, and employment challenges. The World Health Organization (WHO) underscores that endometriosis significantly reduces quality of life by limiting daily activities such as attending school or work, while also creating a heavy economic strain on individuals and healthcare systems globally [30].

Patients with endometriosis incur significantly higher healthcare costs than those without the condition, including direct medical costs and indirect costs such as productivity losses [31]. For instance, Grundström et al. (2020) reported a mean annual cost of EUR 8,768 per patient in Sweden, with nearly equal contributions from direct and indirect healthcare costs. This global pattern highlights that indirect costs, particularly workplace productivity losses, often surpass direct medical expenses [16].

This meta-analysis quantitatively illustrates the substantial economic burden of endometriosis, shedding light on the consistent trend of increased costs across diverse healthcare settings. The pooled standardized mean difference (SMD) of 0.89 (95% CI: 0.88–0.90, $p < 0.0001$) highlights consistently higher direct and indirect costs across diverse healthcare settings globally. This result confirms that endometriosis imposes significant additional costs compared to other conditions. Furthermore, individual study results included in the meta-analysis underscore variability in economic outcomes, with SMDs ranging from -2.94 to 2.95. For instance, Armour et al. (2019) and Fuldeore et al. (2015) reported high economic burdens with SMDs of 2.95 and 1.95, respectively, emphasizing the financial toll on patients with endometriosis [18,25]. In contrast, Soliman et al. (2018) observed a more moderate burden (SMD = 0.76), while Arakawa et al. (2018) documented an SMD of -2.94, demonstrating the variability in economic impact across populations and contexts [24,29].

Cost analyses reveal that endometriosis-related expenses vary significantly across regions, healthcare systems, and treatment strategies. For instance, Koltermann et al. (2016) reported that women with deep infiltrating endometriosis (DIE) in Germany faced mean annual healthcare costs of EUR 12,868 during the year of surgery, with hospital care (EUR 11,236) comprising the largest proportion. In contrast, Swift et al. (2023) highlighted significant productivity losses of Int$9,864 annually in the Eastern Mediterranean, exacerbated by diagnostic delays and limited pain management options [32]. These findings underscore the importance of effective surgical interventions and post-operative strategies to manage costs in later years [26].

The results from the meta-analysis further substantiate the economic burden associated with endometriosis. Despite heterogeneity among studies ($Chi^2=17185.88$, $df = 3$, $p<0.0001$, $I^2 = 100\%$), the consistent pattern of higher economic costs among endometriosis patients. The high heterogeneity ($I^2 = 100\%$) reflects the diversity of study designs, healthcare systems, and populations analysed, highlighting the need for context-specific research to better understand localized economic impacts. This variability underscores the importance of localized interventions and further research to understand regional differences in healthcare access and cost structures.

The cost-effectiveness of different therapeutic strategies is also a critical factor in determining the economic burden of endometriosis. Wu et al. (2017) explored the cost-effectiveness of hormonal therapy options in China, focusing on GnRH-a regimens and oral contraceptives (OC). They found that six months of GnRH-a therapy (GnRH-6) was more cost-effective than shorter regimens or OC, particularly for ovarian and peritoneal endometriosis, with incremental cost-effectiveness ratios (ICERs) ranging between $6,364 and $6,425. These findings align with Koltermann et al. (2016) emphasis on the financial burden of continued management, as longer and more effective treatments could reduce the likelihood of repeated interventions [26]. Kim et al. (2022) demonstrate the importance of patient-centered management in Asia recommending individualized hormonal treatments as first-line therapies to reduce economic and clinical burdens [33].

Hospitalization-related expenses further illustrate the financial toll of advanced endometriosis. Estes et al.

(2019) examined inpatient costs for endometriosis patients in Italy over a 10-year period. They reported a steady rise in mean hospitalization charges, from USD 22,642 in 2006–2007 to USD 39,662 in 2014–2015, reflecting the growing financial strain of managing advanced disease. These costs may reflect inflation and increasing reliance on complex surgical interventions. Estes et al.'s findings underscore the need for early diagnosis and treatment to mitigate hospitalization rates and associated costs, aligning with Wu et al. (2017) focus on the value of effective medical therapies to reduce severe complications [20,23].

Comparing treatment strategies highlights the importance of balancing initial treatment costs with long-term outcomes. Bohn et al. (2021) evaluated four strategies in the United States, finding that NSAIDs followed by surgery (Strategy 1) and stepwise approaches incorporating hormonal therapy (Strategies 2 and 3) were more cost-effective than proceeding directly to surgery (Strategy 4). While Strategies 2 and 3 involved higher initial costs due to the inclusion of hormonal therapy or LARCs, these approaches ultimately yielded better long-term outcomes and lower overall expenses compared to immediate surgery. These findings align with Wu et al. (2017) conclusion that effective hormonal therapies can offset higher upfront costs by preventing recurrent interventions, and with Koltermann et al. (2016) observation that long-term management costs can vary significantly depending on initial treatment decisions [20,26,28].

Diagnostic delays remain a critical contributor to the economic burden of endometriosis. A recent study reports a global average diagnostic delay of 6.6 years, with significant variability across regions, including delays as long as 8–10 years in some resource-limited settings [34]. These delays amplify costs by increasing reliance on advanced interventions, prolonging symptom management, and compounding productivity losses. In Indonesia, these barriers are further compounded by limited access to specialized care, the cultural stigma surrounding menstrual health, and financial constraints. Addressing these delays through comprehensive clinical, educational, and cultural interventions is crucial to alleviating the economic and emotional toll of endometriosis, particularly in resource-limited settings where late diagnoses drive higher healthcare costs. Feng et al. (2019) demonstrate that diagnostic inefficiencies and increasing incidence trends globally contribute significantly to the overall burden of the disease [35].

The socio-ecological framework proposed by Fryer et al. (2024) underscores the need for multi-level interventions to address diagnostic inefficiencies. Individual-level interventions could focus on improving awareness of endometriosis symptoms among women, while community-level programs might address stigma and promote health literacy. On a systemic level, subsidized diagnostic tools and telemedicine platforms could improve accessibility, particularly in rural or underserved areas. These strategies align with findings from Koltermann et al. (2016) and Estes et al. (2019), which underscore the escalating costs of delayed diagnoses and advanced interventions. By addressing diagnostic inefficiencies, healthcare systems can significantly reduce both the clinical and economic burdens of endometriosis, particularly in resource-constrained settings like Indonesia [23,26].

Armour et al. (2019) similarly found that in Australia, 75–84% of total costs stemmed from productivity losses [18]. Additionally, Young (2019) estimated the total economic cost of endometriosis in Australia to be approximately AUD 7.4 billion annually, driven by absenteeism, presenteeism, and direct healthcare costs. Women with endometriosis reportedly use up to 60% of their sick leave solely for managing chronic pain, underscoring the significant impact on workforce participation [36]. These findings are echoed in recent studies exploring the indirect costs of chronic illnesses in Southeast Asia, which underscore the substantial economic burden of productivity losses. Velarde et al. emphasized that indirect costs, including absenteeism and presenteeism, significantly contribute to the overall economic impact of chronic illnesses in this region, with women disproportionately affected due to dual work and household responsibilities [37]. These findings underscore the critical need for strategies to address this financial burden, including early diagnosis and timely management, which can mitigate both economic and clinical impacts.

In Indonesia, data on the economic burden remain scarce. However, endometriosis is prevalent among women with infertility, affecting 13.6–69% of cases [6]. Such a high prevalence underscores the emotional and financial toll on affected women. Muharam et al. (2022) reported that chronic pelvic pain significantly reduces the quality of life (QoL) in Indonesian women, with pain severity often assessed using the Visual Analog Scale (VAS) [38]. Diagnostic delays and comorbidities, such as chronic pelvic pain, further exacerbate the economic burden of endometriosis. Malik et al. (2022) conducted a study in Australia, while Fuldeore et al. (2015) explored the burden in North Chicago, USA [25,27]. These studies underscore how delays in diagnosis increase healthcare costs and negatively impact quality of life. Moreover, diagnostic delays in Indonesia are compounded by limited access to specialized care and cultural stigmas, exacerbating suffering and financial strain. Addressing diagnostic delays through comprehensive clinical, educational, and cultural interventions is crucial to alleviating the economic strain and improving the quality of life for endometriosis patients, particularly in resource-limited settings where

delayed diagnosis exacerbates healthcare costs and productivity losses.

Treatment strategies for endometriosis must balance clinical efficacy with economic feasibility. Various studies have demonstrated significant variability in costs and outcomes among therapies such as hormonal treatments, GnRH agonists, and surgery. For instance, Tuletova et al. (2014) demonstrated that hormonal therapy was the most cost-saving option in Kazakhstan, while combined therapy (surgery followed by hormonal treatment) was the most effective [39]. Similarly, Sanghera et al. (2016) found that LNG-IUS and COCP offered favorable cost-effectiveness for recurrence prevention [19]. Oral contraceptives were shown to be cost-saving while adding 0.43 QALYs [40]. These findings highlight the importance of improving access to hormonal therapies and tailoring healthcare policies to address region-specific disparities in treatment and outcomes. Al-Worafi also highlighted the growing availability of hormonal treatments in middle-income countries, though disparities persist in low-resource settings. Future comparative evaluations of hormonal therapies in Southeast Asia are necessary to inform region-specific treatment guidelines and policymaking [41].

Because of adverse effects and poor communication with medical professionals, women with endometriosis frequently express dissatisfaction with conventional treatments. Malik et al. (2022) noted that dissatisfaction often leads patients to seek care from allied health (AH) or complementary therapy (CM) providers, reflecting a desire to feel more empowered within the healthcare system [27]. Soliman et al. (2018) reported that CAM utilization, including therapies provided by physiotherapists and naturopaths, adds significantly to the financial burden. While CAM addresses some unmet needs, its cost-effectiveness and integration into conventional care remain areas requiring further research, particularly in low-resource settings where healthcare access is limited [24].

Finally, uncertainty persists regarding the cost-effectiveness of treatments aimed at preventing recurrence following conservative surgery. Sanghera et al. (2016) emphasized the variability in treatment outcomes, underscoring the need for robust evidence to guide clinical practice. Comprehensive trials evaluating emerging treatments are critical, particularly in low- and middle-income countries [19]. In Indonesia, tailored research into the healthcare system's specific needs could refine strategies for personalized care, addressing both clinical and economic challenges effectively.

In conclusion, the findings from this systematic review and meta-analysis reinforce the significant clinical and economic burden of endometriosis. To mitigate this profound burden, healthcare systems must prioritize region-specific interventions, innovative diagnostic tools, and personalized treatment approaches. Future research should focus on region-specific interventions, innovative diagnostic tools, and holistic treatment models to promote equitable, cost-effective outcomes for all endometriosis patients.

Strength and Limitation

The studies shed light on the economic impact of endometriosis, but they come with limitations and strengths. The meta-analysis demonstrates the significant economic impact of endometriosis, but it comes with limitations and strengths. The inclusion of only four studies restricts the generalizability of the findings, and the notable variability in reported SMDs indicates potential heterogeneity among studies. Additionally, the standard deviations in some studies, particularly Arakawa et al. (2018) and Fuldeore et al. (2015) were calculated based on reasonable estimations, introducing some uncertainty. However, the analysis's strengths lie in the use of standardized mean differences, allowing effective comparisons across different measurement scales.

The comprehensive cost analysis, detailing healthcare costs, productivity losses, and carer costs, provided a thorough view of the economic burden of endometriosis. Sophisticated statistical analyses and the ethical conduct of the studies further enhance credibility. Despite its limitations, this systematic review and meta-analysis offers valuable insights into the economic burden of endometriosis, aiding healthcare decision-making.

CONCLUSION

The studies provide a thorough understanding of endometriosis's economic impact, revealing significant burdens on healthcare systems and individuals. These insights underscore the need for ongoing research to inform healthcare decisions and enhance care for endometriosis patients.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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Table 1. Studies Characteristics

No	Author	Study (year)	Country	Study Design	Sample	Follow up duration	Treatment	Economic Burden
1.	Grundstrom et al. [16]	2020	Sweden	Cross-sectional study	423	>10 years from the total sample	N/A	- All women had an average annual expenditure of EUR 8,768/woman. - The indirect cost of treating the sickness was EUR 4,486 while the direct cost was EUR 4,282 in hospital.
2.	Cezar et al. [17]	2018	Germany	Quasi-randomized study	47	4.17 and 9.07 months	Lynestrenol and medrogeston were compared in a group of 47 patients	Progestins are well-tolerated and affordable.
3.	Armour et al. [18]	2019	Australia	Cross-sectional study	407	6 months	N/A	- Regardless of whether endometriosis was diagnosed, women with chronic pelvic discomfort had a considerable cost of sickness burden (Int $16,970 to $20,898 per woman per year). - Productivity loss accounted for 75-84% of the total costs.
4.	Bohn et al. [28]	2021	USA	Cohort	4,817,894	6 months	Strategy 1: NSAIDs followed by Surgery. Strategy 2: NSAIDs, then SARCs or LARCs, followed by Surgery. Strategy 3: NSAIDs, then SARCs or LARCs, then LARCs or GnRH Modulator, followed by Surgery. Strategy 4: Proceeding directly to Surgery.	- For a $100,000 per QALY willingness-to-pay threshold, Strategies 1, 2, and 3 are more cost-effective than Strategy 4 (urgent surgery). - Strategy 1 (NSAIDs): Second-highest cost due to high failure rates and surgery. - Strategy 2: Lowest overall cost and most cost-effective. - Strategy 3: Higher cost with fewer QALYs than Strategy 2 - Strategy 4 (Immediate Surgery): Highest cost.
5.	Sanghera et al. [19]	2016	UK	Markov	1000	36 months	(1) no treatment (2) LNG-IUS (3) DMPA (4) COCP	- The most expensive intervention is LNG-IUS, costing £650.94. Then come DMPA, £622.56, and COCP, £599.93. - The lowest-cost intervention is not a treatment (£371.34).
6.	Arakawa et al. [29]	2018	Japan	Markov	210,000	12 months	N/A	- ICER was at 115,000 JPY ($958) per QALY gained for healthcare payers. This was achieved by incremental cost gains of 300,000 JPY (US$ 2500) and effectiveness gains of 2.6 QALYs, retrospectively assessed. - The cost-benefit estimate for the SMV was close to $3,130,000 JPY (US$ 26,000.)
7.	Surrey et al. [21]	2020	USA	Cohort	11,793	Prediagnosis period of 60 months	N/A	- Healthcare costs averaged $28,376 for all reasons before diagnosis. - Patients with short delays had significantly reduced all-cause pharmacy expenses ($4,351) compared to intermediate ($5,565) or long delays ($6,106). - Costs on all-cause medical care rose significantly with longer diagnostic delays: - Short delays resulted in $17,138 in patient costs. - Individuals with moderate delays faced $24,465 in costs.

Table 1. Continued.

								- The most costly patients were those with prolonged delays, costing $28,354.
8.	Wu et al. [20]	2017	China	Markov	1000	6 months	1) No medication (Control approach) 2) oral contraception 3) GnRH-a treatment for three months 4) GnRH-a therapy for six months.	• Ovarian Endometriosis Costs: - OC: $5,257-$6,872 - GnRH-3: $5,467-$7,069 - GnRH-6: $4,853-$6,452 • ICERs: - OC: $10,684 - GnRH-3: $7,709 - GnRH-6: $6,364 • Peritoneal Endometriosis Costs: - OC: $5,467-$7,069 - GnRH-3: $5,467-$7,069 - GnRH-6: $5,341-$6,954 • ICERs: - OC: $10,630 - GnRH-3: $7,759 - GnRH-6: $6,425 • Deep Endometriosis Costs: - OC: $4,853-$6,452 - GnRH-3: $5,467-$7,069 - GnRH-6: $4,853-$6,452 • ICERs: - OC: $10,589 - GnRH-3: $7,523 - GnRH-6: $6,185 • Other Endometriosis Costs: - OC: $5,341-$6,954 - GnRH-3: $5,341-$6,954 - GnRH-6: $5,341-$6,954 • ICERs: - OC: $10,728 - GnRH-3: $7,759 - GnRH-6: $6,407
9.	Soliman et al. [22]	2019	North Chicago	Cohort	15,615	12-month	Endometriosis medication utilization: - Oral contraceptives (combined estrogen and progestin) - Progestins only - Gonadotropin-releasing hormone (GnRH) agonists - Danazol (synthetic derivative of testosterone) Patients with endometriosis-related surgery:	- Patients with endometriosis had considerably more prescription claims than those without endometriosis, with 45.9 (42.0) versus 25.1 (39.1). - The mean total direct health care costs for cases were $13,670 ($29,843), while the mean total costs for controls were $5,779 ($23,614).

Table 1. Continued.

							- Laparotomy - Laparoscopy - Hysterectomy - Hysterectomy with same day oophorectomy - Oophorectomy - Other excision/ablation	
10.	Estes et al. [23]	2019	Italy	Cross-sectional	2006-2007: 101,733 2010-2011: 60,080 2014–2015: 27,630	2006-2015	N/A	- Mean Total Charges per Stay (2015 USD): 2006-2007 : 22,642 2010-2011 : 30,977 2014–2015 : 39,662
11.	Soliman et al. [24]	2018	USA	Cohort	- 113,506 endometriosis patients - 927,599 controls	12 months	Opioids NSAIDS Antidepressants Estrogen/progestin oral contraceptives	- The mean annual total adjusted direct costs per endometriosis patient during the 12-month post-index period were $16,573 (SD = $21,336). - The mean annual total adjusted direct costs per non-endometriosis control during the same period were $4,733 (SD = $14,833). - Direct costs per endometriosis patient increased by $10,002 in comparison to controls. - The incremental indirect costs per endometriosis patient in comparison to controls are $2,132.M26.
12.	Fuldeore et al. [25]	2015	North Chicago	Cohort	37,570	10 years	N/A	- The all-cause total costs of endometriosis patients were substantially higher than those of controls over a 10-year period, with the highest costs occurring in the first year following diagnosis. - The mean total healthcare costs for endometriosis patients in the first year after diagnosis were $13,199, while controls spent an average of $3,747. This difference in costs amounted to $9,452. - The annual total healthcare costs for endometriosis patients remained substantially higher than those of controls over the course of the subsequent nine years. - The estimated incremental total healthcare costs for a woman with endometriosis were $7,028 during the 5-year pre-diagnosis period and $19,277 during the 5-year post-diagnosis period.
13.	Koltermann et al. [26]	2016	Germany	Cohort	825 women with DIE	Before and after the index year within a 12-month period	N/A	- Index Year: • The average annual total cost per patient is 12,868 Euros. • The cost of hospital care is 11,236 Euros. • The cost of ambulatory care is 789 Euros. • The cost of prescription drugs is 784 Euros. • The cost of remedies is 59 euros. • Subsequent Years (Without the Index Year): - The average annual total healthcare expenditures per patient range from 544 to 2,817 Euros.

Table 1. Continued.

								- Inpatient expenses range from 114 to 1,360 Euros per patient. - The cost of ambulatory care ranges from 338 to 748 Euros per patient. - The cost of prescription drugs ranges from 86 to 886 Euros per patient. - The cost of medicine ranges from 11 to 131 Euros per patient. - Age Groups: • Across all time periods, the mean costs of younger patients were 616 Euros higher than those of older patients.
14.	Malik et al. [27]	2022	Australia	Cohort	- Patient with endometriosis: 340 - Patient with CPP (control) : 69	8 weeks	A/N	- Total Spending: Cumulative spending by the endometriosis cohort: $53,315. Total sessions across all respondents: 530. - Average spending per woman in the endometriosis cohort: $460.04. - The most significant expenditures are as follows: • Physiotherapists: $10,525 • Mental health professionals: $7,555 • Naturopaths: $7,320 • Acupuncturists: $6,587 Cost per Session (Excluding Therapists with Only One Respondent): • Naturopaths: $187.65 • Dietitians and nutritionists: $131.07 • Mental health professionals: $127.27 • Acupuncturists: $87.83