Economic implications of endometriosis: A review

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Abstract

Endometriosis is a chronic inflammatory disease that can have serious physical and emotional consequences for patients in terms of pain, quality of life and infertility. Despite affecting about 10% of women, the pathophysiology and economic impact of the disease are not fully understood. This study aimed to review and summarize research articles quantifying the direct and indirect costs of endometriosis in the context of current national and international treatment guidelines. A search including the terms 'endometriosis' AND 'costs' OR 'cost of illness' OR 'cost analysis' OR 'economic burden' was performed, focusing on studies published between January 2000 and May 2022. Total costs, costs of primary and secondary care, productivity losses and indirect costs were reported. The medical costs of endometriosis were principally registered in secondary care settings, where surgery was the main cost driver. There was great variability of populations and study settings, with the overall direct medical cost of endometriosis ranging from 2022US$ 1459 to 2022US$ 20,239 per patient per year. An increasing trend has been reported in secondary care costs over time; however, not enough data was available at this time to evaluate inpatient and outpatient costs versus treatment strategies. Similarly, further research is required to evaluate the costs and potential savings associated to new therapies. Numerous studies have evaluated the indirect costs of endometriosis in the past years, finding costs between 2022US$ 4572 and 2022US$ 14,079. At this time, limited data is available on the economic burden of the disease at the patient level.

Key points for decision makers

- Surgery was one of the main factors contributing to endometriosis medical costs, which ranged from 2022US$ 1459 to 2022US$ 20,239 per patient per year.
- The medical costs of endometriosis in hospital settings increased over the past decade.
- The burden of endometriosis in terms of work loss, disability and reduced productivity was 2022US$ 4572-14,079 per patient per year.

1. Introduction

Endometriosis is a poorly understood chronic disease, with profound consequences for patients in terms of pain, quality of life and infertility [1]. Endometriosis appears to be multifactorial, and its pathogenesis is still not fully understood [1]. Despite the limited understanding of the disease, with scarce data published before the 2000s, endometriosis is estimated to affect about 10% of women [2,3]. Over the past two decades, efforts have been made to improve the diagnosis of the disease, aiming to find reliable tests or biomarkers to diagnose endometriosis; however, the diagnosis and management of the disease still presents several limitations. Diagnosis delays are frequent, and they have been associated with a reduced life quality and a greater number of pelvic symptoms [3]. Moreover, the systemic nature of the disease still poses a significant difficulty in terms of finding an adequate treatment [3].

Numerous diagnosis and treatment guidelines have been issued by national and international organizations over the past decades, aiming to provide standardized tools for the management of patients with suspected and confirmed endometriosis; current guidelines are summarized in Table 1 [4-9]. International consensus was reached to recommend incorporating the diagnosis and management of endometriosis into primary care settings, as included in the guidelines issued by the World Endometriosis Society (WES) [8]. In general terms, diagnosis should be based on the patient's history, symptoms and non-invasive imaging techniques. Similarly, the treatment choice should be guided by the specific needs and preferences of the patient, considering contraindications and potential adverse effects. NSAIDs are recommended as first-line therapy for endometriosis pain in all current guidelines, often in combination with oral progestines or combined oral contraceptives [1]; however, long-term NSAIDs therapy is

not recommended due to its gastric and renal side effects [4,8]. The European Society of Human Reproduction and Embryology (ESHRE) recommends the use of gonadotropin-releasing hormone (GnRH) agonists as a second-line treatment for endometriosis-related pain [5]. Similarly, GnRH antagonists can be offered as second-line treatment although the evidence in terms of dosage or duration of treatment is still limited [5,10]. In addition to pharmacological treatment many patients require surgical removal of endometriotic tissue, in order to reduce pain and other symptoms [3]. Surgical treatment can be offered as an option to reduce pain and improve quality of life. The most common interventions include laparoscopy, laparotomy and hysterectomy, with specific recommendations issued depending on the tissue affected, aiming to reduce post-surgical recurrence rates [5,6]. European guidelines recommend complete surgical removal of lesions in patients with deep infiltrating endometriosis involving vagina, bowel, bladder and ureters, after considering the possible risks and benefits [5,6].

The long-term healthcare requirements of patients with endometriosis and the shortcomings in the diagnosis and treatment of the disease are associated with a significant economic burden, both in terms of direct and indirect costs [11]. Four publications have reviewed various aspects around the burden of endometriosis, published in 2006, 2007, 2016 and 2017, respectively [11,12-14]. Despite being associated to significant economic costs, the total burden of endometriosis remains poorly understood, considering the number of undiagnosed and untreated patients. In addition, previous reviews described limitations in the evaluation of the indirect costs of endometriosis.

This review aims to examine and summarize research studies evaluating the costs of endometriosis, focusing on economic evaluations and burden of disease studies, and

including direct and indirect costs. Cost-effectiveness evaluations were reviewed in the context of the most recently published international guidelines.

2. Methods

Relevant studies were obtained by searching the PubMed database and the Cochrane Library, chosen because they hold journals including all disease aspects, and the Econlit database, chosen because it holds journals that are specific to economy. Only full-length articles in English and published between January 2000 and May 2022 were considered. Given the changes in diagnosis and treatment protocols over time, studies published before the year 2000 were considered of limited current relevance. Search terms were: (endometriosis) AND (costs OR cost of illness OR cost analysis OR economic burden). In total, 485 abstracts were obtained in the literature search. After the elimination of duplicates, 289 abstracts were reviewed applying the following inclusion criteria: articles focused on endometriosis, articles analyzing costs of inpatient or outpatient care, or costs of treatment and follow-up, cost of illness studies and cost-effectiveness studies; 32 studies remained to be included in the review (Figure S1). Total costs, costs of primary and secondary care, productivity losses and indirect costs were manually extracted and reported. The included cost-effectiveness studies were from the perspective of the healthcare system. When necessary, cost equivalence in 2022US$ was stated; cost transformation used the index year, adjusting for inflation using the Consumer Price Index.

3. Results of the literature review

3.1 Direct costs of endometriosis

Twenty-one studies describing the direct medical costs of endometriosis were identified in the literature search and included in this review. The economic burden of endometriosis has been primarily estimated from data obtained in retrospective database analyses and patient questionnaires (Table 2). Overall, direct costs have been evaluated in 17 countries in Europe and North America. The distinct settings, subpopulations and specificities found in cost studies hampered the direct comparison of economic data, and it is possible that the differences in the healthcare systems across different countries explain some of the variability in direct costs. Overall, fewer data exists based on primary care settings (general practitioners) compared to secondary healthcare settings (hospitals), and a small number of studies evaluated costs in inpatient and outpatient care separately.

The costs of endometriosis in primary care settings ranged from €171 (2022US$ 320) to US$ 883 (2022US$ 1041) per patient per year in Belgium and Australia, respectively [15,16]. Greater variability was found in secondary care costs, which ranged from US$ 935 (2022US$ 1103) to US$ 13,199 (first post index year, 2022US$ 17,500) per patient per year in Australia and the United States, respectively [16,17]. Additionally, the cost per admission was US$ 39,662 (2022US$ 48,379) between 2014 and 2015 in one study evaluating admission costs in the United States [18]. In terms of temporal trends, two studies described an increasing trend in total secondary care costs, one in Spain between 2014 and 2017 and one in the United States between 2006 and 2015 [18,19].

The total direct medical cost of endometriosis ranged from CA$ 1164 (2022US$ 1459) to US$ 16,573 (2022US$ 20,239) per patient per year in Canada and the United States, respectively [20,21]. Surgical interventions were one of the main cost drivers, increasing 3-fold the total direct medical cost per patient per year, from US$ 6365 (2022US$ 7773)

registered in a non-surgery cohort to US$ 19,203 (2022US$ 23,451) in a surgery cohort [22]. The costliest surgical procedures identified in cost studies were oophorectomy (2022US$ 17,016), excision (2022US$ 4980), cystectomy (2022US$ 2172) and ablation (2022US$ 1588), and laparotomy as a diagnostic procedure (2022$ 9668-13,894) [20,22]. Factors that increased medical costs significantly included surgery, hospitalizations, and infertility treatments.

Diagnostic delays were also associated to increases in direct medical costs: total direct medical costs measured the 5 years before the diagnosis increased from US$ 21,489 (2022US$ 25,885) in patients with delays of less than a year to US$ 34,460 (2022US$ 41,510) in patients with diagnostic delays of 3 to 5 years [23].

The costs of medication were not always disclosed as a standalone item; when reported, drug costs were €117 (2022US$ 219) per patient per year in Austria, €190 (2022US$ 246) in Sweden, €191 (2022US$ 358) in Belgium 2009 and €320 (2022US$ 246) in a multi-center study in ten European countries [15,24-26]. In addition, several studies investigated the additional costs associated to opioid usage in patients with endometriosis in the United States, with the highest costs found in patients that were prescribed opioids both before and after diagnosis [27-29]. Finally, the cost of complementary therapies was often not covered by public healthcare systems, despite being described as a significant economic burden for patients, including expenses in physiotherapy, mental health specialists and naturopaths [30].

3.2 Cost-effectiveness studies

Several diagnostic and treatment strategies have been evaluated in an effort to establish more efficient and cost-effective approaches (Table 3). Eight cost-effectiveness studies were identified in the literature search, developed in China, Germany, Japan, Spain, the

United Kingdom and the United States. Seven studies evaluated the cost-effectiveness of treatment strategies, while one study evaluated the cost-effectiveness of early diagnosis strategies. Early physician consultation was cost-effective in patients with dysmenorrhea [31]; the cost-effectiveness of early diagnosis and primary care attention is supported by cost studies, as reported in section 3.1 of this review [23]. In terms of treatment, the recommended approach, including NSAIDs and oral contraceptives, is cost-effective when compared to no hormonal treatment or surgery alone [32,33]. Two cost-effectiveness studies were found evaluating the cost-effectiveness of GnHR- based therapies: one study found elagolix (a GnHR antagonist) to be dominant versus leuprolide acetate (a GnHR agonist) in the treatment of moderate to severe endometriosis pain; a second study supported the cost-effectiveness of GnHR agonist therapies for the prevention of endometriosis recurrence versus conservative surgery only [34,35]. One study found 'no treatment' to be cost-effective versus intramuscular and intrauterine hormones and oral contraceptives to prevent recurrence of endometriosis after conservative surgery in primary care, however, GnRH agonists were not evaluated in this study [36]. In terms of surgical procedures, ultrasound-guided aspiration with ethanol sclerosis was cost-effective when compared with standard surgery for endometriomas [37]. Moreover, ghost ileostomy was found to be cost-effective versus loop ileostomy in patients with deep infiltrating endometriosis of the rectum [38].

3.3 Indirect costs of endometriosis

Eleven studies were identified evaluating the indirect costs of endometriosis. Six studies analyzed the total indirect costs of endometriosis, and 5 studies focused on analyzing the salaries and productivity losses associated to endometriosis (Table 4). Most of the

studies included data from Europe and North America, while evaluations in Argentina, Brazil, Australia and Nigeria were also identified. The indirect costs of endometriosis ranged from CA$ 4043 (2022US$ 4572) in Canada to €7434 (2022US$ 14,079) in Belgium [15,20]. Comparison was established in a 2018 study using a cohort of patients without endometriosis in the United States, where costs of patients with endometriosis were 1.4 times higher than those in patients without endometriosis [21]. In addition, patients receiving surgery for endometriosis registered indirect costs 1.6 times higher than those without surgery [22].

Significant productivity losses were found associated with chronic pain and disability [16,24,39,40]. Total productivity losses ranged from US$ 208 (2022US$ 293) per person per year in Nigeria to US$ 23,712 (2022US$ 33,428) in Italy [39]. The calculation of productivity losses may consider the cost of presenteeism, the time when employees are at work but not working, and absenteeism, consisting of unscheduled absences [41]. One study based on patient surveys in Australia, estimated a cost associated to presenteeism due to endometriosis that reached US$ 6058 per person per year, while the estimated cost of absenteeism was US$ 3647 per person per year [16]. Data obtained in this study indicated that productivity losses associated to pain severity were a major contributor to the total costs of endometriosis [16]. When productivity losses were evaluated before and after surgical treatment, the greatest costs were incurred the 6 months before and following surgery [40]. Finally, one study specifically analyzed the salary of women diagnosed with endometriosis over a 5-year period after diagnosis [40]. In this case, the annual salary of patients diagnosed with endometriosis was lower and experienced a smaller growth versus matched controls; additionally, endometriosis patients registered higher risks of work loss events [42].

4. Discussion

The grave consequences of endometriosis in terms of quality of life and infertility are associated with significant medical and societal costs. The delays in the diagnosis of endometriosis are common and are associated with a worsened quality of life and greater medical costs [23,43]. This review aimed to provide an updated overview of the total burden of endometriosis via the revision of available studies focused on direct and indirect medical costs, and cost-effectiveness studies of new therapies, relying on current guidelines.

In an attempt to shorten diagnosis times and provide a more personalized and multidisciplinary care of the disease, international guidelines advise promoting the diagnosis and management of endometriosis in primary care settings [8]. This study reviewed medical cost evaluations that included both secondary care and primary care centers, providing data for each setting separately. To date, few studies have analyzed the medical costs associated to endometriosis in primary care settings and further data will be necessary to identify any existing trends in the use of primary care resources [21,16,25,26]. Despite limitations, data suggest that the medical costs of endometriosis are principally registered in secondary care settings, where the most expensive admissions are those associated to surgical interventions [22,44]. Surgery alone increased 3-fold direct medical costs per patient and often did not prevent disease recurrence [22]. The different healthcare systems found in different countries may explain some of the variability in direct medical costs, which ranged from 2022US$ 1459 to 2022US$ 20,239 per patient per year [20,21]. Two studies described an increasing trend in secondary care costs over time, however, data should be further analyzed to explore any changes in patients' hospitalization rate versus the rate of outpatient visits

and the implications in terms of cost distribution [18,19]. In this direction, it could be hypothesized that favoring outpatient interventions and shorter hospitals stays could contribute to decreasing the burden of endometriosis from a healthcare perspective, yet current data appears contradictory. Inpatient care costs estimated by Prast et al [24] and Koltermann et al. [44] were five to ten times larger than outpatient costs, whereas As-Sanie et al. [27] and Estes et al. [28] found inpatient care costs to be significantly smaller than outpatient costs.

In parallel, this review included an evaluation of cost-effectiveness studies, which was deemed of relevance when considering the introduction of novel therapies for the management of endometriosis. Emerging pharmacological therapies, including aromatase inhibitors, selective progesterone receptor modulator and GnRH antagonists, may be able to reduce the need for surgical interventions and could have an effect in reducing the total medical costs of the disease, although evidence is limited at this time [8].

Additionally, few studies measured the costs of complementary therapies, including physiotherapy, which are often covered by the patient [30]. The limitations in the access to these therapies via the public healthcare system often represent a source for inequality. Similarly, psychotherapy is generally not offered to these patients despite the higher levels of depression and anxiety documented compared to the general population [45]. The pain, depression and other symptoms associated to endometriosis and the high morbidity found in these patients correlate with significant physical and emotional disability [46,47]. The previously published reviews tackling the burden of endometriosis described a scarcity of indirect cost evaluations, an aspect that has improved over the past years [11,12-14]. Eleven studies were identified at this time

quantifying the indirect costs and productivity losses associated to endometriosis [15,16,20-22,24-26,39,40,42]; these studies included data from a wide range of countries, and found that the indirect costs of endometriosis were significantly larger than costs in patients without the disease [15,20,21]. Surgery was also a determinant factor for indirect costs, with greater indirect costs registered in patients treated with surgery versus patients with no surgical treatment, especially the 6 months prior and after surgery [22,40]. Moreover, substantial productivity losses were associated with chronic pain and disability, ranging from 2022US$ 293 per person per year in Nigeria to 2022US$ 33,428 in Italy [39].

The societal burden of endometriosis is substantial, and data suggests that it also represents a long-term burden at the patient level. In addition to the aforementioned medical costs that are often not covered by the public healthcare system, including physiotherapy and psychotherapy, patients with endometriosis had a lower annual salary and experienced a smaller growth versus matched controls [42]. A similar effect in patients' salary growth has been observed in patients diagnosed with other inflammatory diseases, such as inflammatory bowel disease [48].

Several limitations influenced this review. Firstly, only full-length research studies in English-language were included in this review, relevant data presented in abstracts or other languages might have been excluded. Secondly, although a systematic approach was followed to review relevant publications in the field, limitations associated to the search or inclusion of articles must be considered. Thirly, great disparities exist between data obtained in different countries and using different study settings, including study population, time horizon and data sources, and comparisons should be exercised with caution. Generally, more data is available for Europe and North America, nonetheless,

endometriosis plausibly poses a significant economic burden worldwide. Further research will be needed to fully understand the economic burden of endometriosis, as well as the costs associated to new treatment options.

5. Conclusions

Endometriosis represents a significant burden for healthcare systems and society. Surgery was identified in a number of studies as one of the main cost drivers, presenting an opportunity to reduce medical costs with the introduction of alternative treatments with the capacity to reduce pain and further complications. Further research in new therapies is crucial for improving patients' quality of life and reducing the costs of this disease, while any future updates in national and international guidelines should focus on cutting the time to diagnosis. Additionally, the burden of endometriosis at the patient level should be considered and further analyzed, in terms of costs of complimentary therapies and the reduced salary identified in these patients.

6. Declarations

6.1. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.2. Conflicts of interest

The authors declare that they have no competing interests.

6.3. Availability of data and material

Not applicable.

6.4. Ethics approval and consent to participate

Not applicable.

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8. Tables

Table 1 International and national clinical practice guidelines for endometriosis.

Table 2 Summary of research studies evaluating the direct medical costs of endometriosis.

Table 3 Summary of cost-effectiveness studies of treatment strategies and interventions for endometriosis.

Table 4 Summary of research studies evaluating the indirect costs of endometriosis.

9. Supplementary information

Figure S1 PRISMA flow diagram.

Table 1 International and national clinical practice guidelines for endometriosis.

Society (country, year)	Summary of key recommendations
CNGOF/HAS [4] (France, 2018)	Laparoscopy solely to confirm the diagnosis is not recommended. The choice of treatment should be guided by contraindications, potential adverse effects, existing therapy and the patient's preference. In patients with endometriosis-related pain, a cyclic combined hormonal contraceptive is recommended. Gonadotrophin-releasing hormone agonists alleviate dysmenorrhea and pain but require add-back therapy in the form of concomitant high-dose progestogen and an estrogen.
ESHRE [5] (European consensus, 2022)	Laparoscopy is only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate. Gonadotrophin-releasing hormone agonist treatments are supported as second-line treatment. Postoperative medical treatment may be beneficial for pain management.
NGG [6] (Germany, 2014)	In general, the diagnosis of endometriosis is to be established histologically. Progestins, oral contraceptives or gonadotropin-releasing hormone agonist treatments can be used to reduce symptoms. For primary treatment of ovarian endometriomas, the cyst wall should be removed surgically. Hormonal drug treatment alone is not effective in eliminating an ovarian endometrioma. Complete resection is recommended for deep infiltrating endometriosis.
SOGC [7] (Canada, 2010)	Investigation of suspected endometriosis should include history, physical, and imaging assessments. Routine protein CA-125 testing is not recommended. Combined hormonal contraceptives should be considered as first-line agents. A gonadotropin-releasing hormone agonist can be used as second-line treatment. Surgical management in women with endometriosis-related pain should be reserved for those in whom medical treatment has failed. Surgical treatment of deeply infiltrating endometriosis may require experience with a multidisciplinary approach. Biopsy of endometriosis lesions should be considered to confirm the diagnosis and to rule out underlying malignancy.
WES [8] (Global consensus, 2013)	Endometriosis diagnosis and management should be incorporated into primary health care, offering patients individualized care over a long-term period. Laparoscopic surgical removal of endometriosis is an effective first-line approach for treating pain related to endometriosis. It is recommended to excise lesions, when possible, especially deep endometriotic lesions. The combined oral contraceptive pill is an effective medical treatment to minimize the endometrioma recurrence rate after surgical removal of the cyst.
AETSA [9] (Spain, 2018)	Treatment prescription should be based on symptoms, preferences and priorities of the patient. Laparoscopy is only recommended when symptoms persist, and endometriosis was not diagnosed in preoperative examinations. Long-term NSAIDs treatment is not recommended, and hormonal treatments are preferred. Gonadotropin-releasing hormone agonist or antagonist treatment is not recommended in women under 16 years of age and should be accompanied by additional therapy.

CNGOF/HAS: Collége National des Gynécologues et Obstétriciens Français and French National Authority for Health; ESHRE: European Society of Human Reproduction and Embryology; NGG: National German Guideline (S2k) diagnosis and Treatment of Endometriosis; SOGC: Society of Obstetricians and Gynaecologists of Canada; WES: World Endometriosis Society; AETSA: Evaluación de Tecnologías Sanitarias de Andalucía Consejería de Salud y Familias.

Table 2 Summary of research studies evaluating the direct medical costs of endometriosis.

Study (country, year)	Perspective (index year)	Patient population	Results	Conclusions
Armour et al. [16] (Australia, 2019)	Healthcare system and societal perspective (2017)	Online survey analysis, 340 women.	Primary care: US$ 883 per patient-year Secondary care: US$ 935 per patient-year Out-of-pocket: US$ 822 per patient-year Total: US$ 2640 per patient-year	Priority should be given to improving pain control in women with pelvic pain.
Malik et al. [30] (Australia, 2022)	Healthcare system (2017)	Online cross-sectional questionnaire, 409 women.	*Direct cost* Physiotherapy: $AUD 10,525 per patient 2-month Mental health: $AUD 7555 per patient 2-month Naturopaths: $AUD 7320 per patient 2-month Acupuncturists: $AUD 6587 per patient-month	"The high cost and associations with income and education levels may warrant a change to policy to improve equitable access to these services"
Prast et al. [24] (Austria, 2013)	Healthcare system perspective (2009)	Retrospective questionnaire survey, 73 women.	*Secondary care* Outpatient costs: €327 per patient-year Inpatient costs: €3467 per patient-year Costs of assisted reproduction: €671 per patient-year Drug costs: €117 per patient-year Out-of-pocket costs: €1024 per patient-year Total: €5606 per patient-year	"The question arises as to whether more timely diagnosis, followed by better-targeted treatment, might have the potential to reduce these costs"

Klein et al. [15] (Belgium, 2013)	Healthcare system and societal perspective (2009)	A prospective prevalence-based cost-of-illness study.	*Primary care* €171 per patient-year *Hospitalization* €305 per patient-year *Drug costs* €191 per patient-year *Total direct costs* €2237 per patient-year	"This study showed that direct and indirect costs attributable to endometriosis-associated symptoms are substantial"
Levy et al. [20] (Canada, 2011)	Healthcare system and societal perspective (2009)	Cross-sectional study, 27 women.	*Total direct cost* CA$ 1164 per patient-year CA$ 400 million total per year	"Understanding the interplay between direct costs, lost productivity, and quality of life is critical for accurately identifying and evaluating effective treatments for this condition"
Chen et al. [49] (Canada, 2019)	Healthcare system perspective (2019)	Population-based study, 47,021 women, hospital-based data.	*Secondary care* Uterine endometriosis: US$ 4017 per patient-year Ovarian endometriosis: US$ 3404 per patient-year Other endometriosis: US$ 2422 per patient-year Hysterectomy: US$ 4915 per patient-year Other surgical procedures: US$ 2405 per patient-year Medical procedures: US$ 2101 per patient-year Total cost: US$ 3143 per patient-year up to US$ 147.79 million per year	Uterine endometriosis, hysterectomy and older age presented the highest mean cost per case.
Pynnä et al. [50] (Finland, 2021)	Healthcare system perspective (2013)	Prospective observational study, 311 women.	*Secondary care* Total cost at 6 months: €689 per patient Total cost at 2 years: €2194 per patient	"A majority of direct hospital costs arise over time. This stresses the need for prolonged healthcare management. To control costs, the need for repetitive doctors' appointments, monitoring tests, and ward treatments should be carefully evaluated"

Oppelt et al. [51] (Germany, 2012)	Healthcare payer perspective (2006)	Retrospective database analysis, 20,835 women.	*Secondary care* €3056 per patient-year €40.7 million total per year	"The burden of admissions and the economic impact associated with the inpatients treatment of endometriosis in Germany is substantial"
Koltermann et al. [44] (Germany, 2016)	Healthcare payer perspective (2012)	Retrospective database analysis, 825 women with deep infiltrating endometriosis.	*Outpatient care* All time points: €690 per patient-year Excluding index year (surgery): €656 per patient-year *Inpatient care* All time points: €3553 per patient-year Excluding index year (surgery): €999 per patient-year	"This longitudinal, retrospective claims data analysis shows that costs of deep infiltrating endometriosis patients seem to increase before surgery and reach their highest values in the respective year of surgical treatment of endometriosis"
Darbà et al. [19] (Spain, 2022)	Healthcare system perspective (2018)	Retrospective database analysis, 41,118 patients, hospital-based data.	*Secondary care* Adenomyosis: €3778 per admission Ovarian endometriosis: €3433 per admission Other endometriosis: €4020 per admission Medical procedures: €1774 per admission Surgical procedures: €3822 per admission Total: €3566 per admission	"Older patients, surgical procedures, and lengthier admissions were associated with higher medical costs"
Grundström et al. [25] (Sweden, 2020)	Healthcare system perspective (2019)	Questionnaire, 400 members of the Endometriosis Association and 400 randomly selected women with surgically confirmed endometriosis.	*Primary care* General practitioner: €281 per patient-year *Secondary care* €3696 per patient-year *Drug costs* €190 per patient-year *Total direct costs* €4282 per patient-year	"Our results confirm the substantial negative effect of endometriosis upon women's lives and their relatively high healthcare consumption"

Fuldeore et al. [17] (United states, 2015)	Healthcare payer perspective (2010)	Retrospective case-control study, 37,570 matched pairs of women.	*Secondary care* Endometriosis patients, first post index year: US$ 13,199 per patient-year Controls, first post index year: US$ 3747 per patient-year Difference between groups in the 5 years before diagnosis: US$ 7,028 Difference between groups in the 5 years after diagnosis: US$ 19,277	"Endometriosis poses a significantly high economic burden, both before and after diagnosis. The highest resource utilization and costs experienced by endometriosis patients occur in the first year after diagnosis"
Soliman et al. [22] (United States, 2017)	Healthcare system and societal perspective (2014)	Retrospective cohort study, 124,530 women with endometriosis, 37,106 controls.	*Total direct cost* Surgery cohort: US$ 19,203 per patient-year Non-surgery cohort: US$ 6365 per patient-year	"Regardless of the surgery type, the cost of index surgery contributed substantially to the total healthcare expenditure"
Soliman et al. [21] (United States, 2018)	Healthcare system and societal perspective (2014)	Retrospective cohort study, 113,506 women with endometriosis, 927,599 controls.	*Total direct cost* Endometriosis patients: US$ 16,573 per patient-year Controls: US$ 4733 per patient-year	"Endometriosis patients incurred significantly higher direct and indirect healthcare costs than non-endometriosis patients"
Estes et al. [18] (United states, 2019)	Personal and healthcare payer perspective (2015)	Pool cross-sectional study using data from a National Inpatient Sample, 189,443 inpatient admissions.	*Secondary care* 2006-2007: US$ 22,642 per admission 2010-2011: US$ 30,977 per admission 2014-2015: US$ 39,662 per admission	"The number of inpatient admissions with a primary diagnosis of endometriosis decreased over the past decade, while surgical complications and associated hospital charges increased"
Soliman et al. [52] (United States, 2019)	Healthcare system perspective (2015)	Retrospective cohort study, 15,615 women with endometriosis, 86,829 controls.	*Total direct cost* Endometriosis patients: US$ 13,670 per patient-year Controls: US$ 5780 per patient-year	"Health care costs and resource utilization in all measured categories were higher among endometriosis cases than controls"

As-Sanie et al. [27] (United states, 2020)	Healthcare payer perspective (2015)	Retrospective cohort analysis, 43,516 women, 36,092 with at least one opioid prescription.	*Inpatient care* Opioid group: US$ 7958 per patient-year Non-opioid group: US$ 5113 per patient-year *Outpatient care* Opioid group: US$ 15,153 per patient-year Non-opioid group: US$ 10,249 per patient-year *Drug costs* Opioid group: US$ 6125 per patient-year Non-opioid group: US$ 3103 per patient-year	"Filling an opioid prescription within 1 year after an endometriosis diagnosis was associated with significant excess healthcare burden"
Estes et al. [28] (United states, 2020)	Healthcare payer perspective (2018)	Retrospective database analysis, 85,329 women.	*Outpatient care* Opioid group: US$ 19,309 per patient 24-months Non-opioid group: US$ 12,766 per patient 24-months *Inpatient care* Opioid group: US$ 4705 per patient 24-months Non-opioid group: US$ 3735 per patient 24-months	"This analysis observed significantly higher all-cause healthcare resource utilization and costs for opioid users compared to non-opioid users among patients with newly diagnosed endometriosis"
Estes et al. [29] (United states, 2020)	Healthcare payer perspective (2018)	Retrospective database analysis, 61,019 women.	*Secondary care* High-risk opioid users: US$ 16,377 per patient-year Low-risk opioid users: US$ 13,153 per patient-year Chronic opioid users: US$ 20,930 per patient-year Non-chronic opioid users: US$ 12,272 per patient-year	"This analysis demonstrates significantly higher all-cause and endometriosis-related health care resource utilization and total costs for high-risk opioid users compared to low-risk opioid users among newly diagnosed endometriosis patients over 1 year"

Surrey et al. [23] (United States, 2020)	Healthcare system perspective (2016)	Retrospective database study, 11,793 women.	*Total direct cost 5 years pre-diagnosis* ≤ 1-year diagnostic delay: US$ 21,489 per patient 1-3 years diagnostic delay: US$ 30,030 per patient 3-5 years diagnostic delay: US$ 34,460 per patient	"Patients with endometriosis who had longer diagnostic delays had more pre-diagnosis endometriosis-related symptoms and higher pre-diagnosis healthcare utilization and costs compared with patients who were diagnosed earlier after symptom onset"
Simoens et al. [26] (International, 2012)	Societal perspective (2009)	Questionnaire-based survey, 909 women.	*Primary care* €513 per patient-year *Hospitalization* €547 per patient-year *Drug costs* €320 per patient-year *Total direct cost* €3281 per patient-year	"Our study showed that the economic burden associated with endometriosis treated in referral centers is high and is similar to other chronic diseases"

Table 3 Summary of cost-effectiveness studies of treatment strategies and interventions for endometriosis.

Study (country, year)	Perspective (index year)	Approach and patient population	Study comparison	Results and conclusions
Wu et al. [35] (China, 2018)	Healthcare payer perspective (2015)	Markov model informed by published studies.	Cost-effectiveness of different strategies, including gonadotropin-releasing hormone agonist (GnRH-a) and oral contraceptive therapy, for the prevention of endometriosis recurrence after conservative surgery.	ICER: US$ 6185-6425 for 6-month GnRH-a therapy versus no therapy (WTP: US$ 7400/QALY). Six months of therapy with gonadotropin-releasing hormone agonist can be a highly cost-effective option for the prevention of endometriosis recurrence.
Grand et al. [33] (England, 2019)	National Health Service perspective (2016)	Markov model informed by systematic literature review and expert opinion.	Cost-effectiveness of oral contraceptives versus 'no hormonal treatment' for the treatment of endometriosis-related pain.	Oral contraceptives were dominant versus 'no hormonal treatment' considering any WTP. "The analyses showed that oral contraceptives could be an effective option for the treatment of endometriosis, as this treatment was shown to provide a higher level of QALYs at a lower cost, compared to 'no hormonal treatment'"
Hernández et al. [38] (Germany, 2022)	Healthcare system perspective (2021)	Prospective controlled interventional trial with 54 consecutive patients with deep infiltrating endometriosis of the rectum.	Cost-effectiveness of the ghost ileostomy (GI) procedure in a group of patients after rectal resection for deep infiltrating endometriosis.	ICER not available. "Ghost ileostomy is a cost-effective and safe alternative to loop ileostomy after rectal resection for deep infiltrating endometriosis in cases where it is required"
Arakawa et al. [31] (Japan, 2018)	Healthcare payer perspective (2011)	Markov model based on Japanese patient surveys	Cost-effectiveness of early physician consultation and guideline-based intervention to prevent endometriosis and/or disease progression using oral contraceptive and progestin compared to follow-up of self-care for dysmenorrhea in Japan.	ICER: 115,000 JPY per QALY gained (WTP: 5 million JPY/QALY). "Early physician consultation and guideline-based intervention are more cost-effective than self-care in preventing endometriosis and/or disease progression for patients with dysmenorrhea in Japan"

Garcia-Tejedor et al [37] (Spain, 2020)	Healthcare system perspective (2018)	Prospective, cohort pilot study with 40 patients with suspected ovarian endometrioma identified by ultrasound.	Cost-effectiveness of ultrasound (US)-guided aspiration and ethanol sclerotherapy versus laparoscopic surgery for benign-appearing ovarian endometrioma.	ICER not available. Ethanol sclerotherapy appeared cost-effective and reduced complications in the endometrioma.
Sanghera et al. [36] (United Kingdom, 2016)	Healthcare system perspective (2013)	Markov model informed by a review of existing evidence and clinical input.	Cost-effectiveness of levonorgestrel-releasing intrauterine system, depot-medroxyprogesterone acetate and combined oral contraceptive pill versus 'no treatment' to prevent recurrence of endometriosis after conservative surgery in primary care.	No treatment costed £371.93 and generated 2.27 QALYs. All strategies were more expensive and generated fewer QALYs compared to no treatment. There is currently no evidence to support any treatment being recommended to prevent the recurrence of endometriosis following conservative surgery.
Wang et al. [34] (United States, 2019)	Healthcare payer perspective (2018)	Markov model informed by Phase III elagolix clinical trials and published literature.	Cost–effectiveness of elagolix versus leuprolide acetate in women with moderate to severe endometriosis pain.	Elagolix was dominant versus leuprolide acetate (WTP: US$ 100,000/QALY). "Elagolix (an oral gonadotropin-releasing hormone antagonist) was cost-effective versus leuprolide acetate (gonadotropin-releasing hormone agonist) in the management of moderate to severe endometriosis pain over 1- and 2-year time horizons"
Bohn et al. [32] (United states, 2021)	Healthcare payer perspective (2019)	Cost-effectiveness model using a theoretical study cohort derived from the estimated number of reproductive age (18–45) women with endometriosis-related dysmenorrhea.	Cost effectiveness of sequential medical and surgical therapy for the treatment of endometriosis-related dysmenorrhea.	ICER: US$ 1352 per QALY when using NSAIDs, SARCs or LARCs, surgery versus surgery alone (WTP: US$ 100,000/QALY). NSAIDs, then short-acting reversible contraceptives or long-acting reversible contraceptives followed by surgery was associated with the lowest cost per QALY gained.

ICER: Incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; NSAID: nonsteroidal anti-inflammatory drug; SARC: short-acting reversible contraceptive; LARC: long-acting reversible contraceptive; WTP: willingness-to-pay.

Table 4 Summary of research studies evaluating the indirect costs of endometriosis.

Study (country, year)	Approach and patient population	Results	Conclusions
Armour et al. [16] (Australia, 2019)	Online survey analysis, 340 women (2017 values).	*Productivity losses* Absenteeism: US$ 3647 per patient-year Presenteeism: US$ 6058 per patient-year Total: US$ 17,484 per patient-year	"This research clarifies that endometriosis and chronic pelvic pain have considerable impact for the women affected; the health sector; the wider economy and to carers"
Prast et al. [24] (Austria, 2013)	Retrospective questionnaire survey, 73 women (2009 values).	*Productivity losses* €2106 per patient-year	"There is probably a large potential for reducing indirect costs through timely diagnosis and appropriate treatment, since reducing the stress caused by the disease will also reduce productivity losses"

Simoens et al. [40] (Belgium, 2011)	Longitudinal study, 180 patients (2008 values).	*Productivity losses* 6 months prior to surgery: €1514 per patient 6 months after surgery: €2496 per patient 12 months after surgery: €117 per patient 18 months after surgery €223 per patient 24 months after surgery: €184 per patient	"Results show that the highest non-health-care costs associated with endometriosis are incurred during the 6 months prior to and following surgical treatment"
Klein et al. [15] (Belgium, 2013)	A prospective prevalence-based cost-of-illness study (2009 values).	*Indirect costs* €7434 per patient-year	"Earlier diagnosis and cost-effective treatment of endometriosis may decrease productivity loss, quality of life impairment and healthcare consumption and consequently reduce total costs to patients and society"
Levy et al. [20] (Canada, 2011)	Cross-sectional study, 27 women (2009 values).	*Indirect costs* CA$ 4043 per patient-year CA$ 1391 million total per year	"For some women, surgically confirmed endometriosis has a substantial negative impact that can result in suffering to the individual and her family, and lead to substantial productivity losses"
Grundström et al. [25] (Sweden, 2020)	Questionnaire, 400 members of the Endometriosis Association and to 400 randomly selected women with surgically confirmed endometriosis (2019 values)	*Indirect costs* Under 30 years: €6172 per patient-year 30-39 years: €3553 per patient-year Over 40 years: €4773 per patient-year All ages: €4486 per patient-year	"Our results confirm the substantial negative effect of endometriosis upon women's lives and their relatively high healthcare consumption"
Soliman et al. [22] (United States, 2017)	Retrospective cohort study, 124,530 women with endometriosis, 37,106 controls (2014 values).	*Total indirect cost* Surgery cohort: US$ 8843 per patient-year Non-surgery cohort: US$ 5603 per patient-year	"Endometriosis patients who underwent surgery, compared with endometriosis patients who did not, incurred significantly higher direct costs due to healthcare utilization and indirect costs due to absenteeism or short-term disability"
Soliman et al. [21] (United States, 2018)	Retrospective cohort study, 113,506 women with endometriosis, 927,599 controls (2014 values).	*Total indirect cost* Endometriosis patients: US$ 7146 per patient-year Controls: US$ 4652 per patient-year	"Endometriosis patients incurred significantly higher direct and indirect healthcare costs than non-endometriosis patients"

Estes et al. [42] (United states, 2020)	Retrospective cohort study, 6851 matched pairs (2018 values).	*Annual salary* Endometriosis, year 1: US$ 61,322 per patient Control, year 1: US$ 64,720 per patient Endometriosis, year 5: US$ 68,781 per patient Control, year 5: US$ 75,381 per patient	"Patients with endometriosis experienced lower annual salary and salary growth, as well as higher risks of work loss events, compared with matched controls"
Nnoaham et al. [39] (International, 2011)	Multicenter cross-sectional study with prospective recruitment, 1418 patients (2007 values).	*Productivity losses* From US$ 208 per patient-year in Nigeria to US$ 23,712 in Italy	"Endometriosis impairs health-related quality of life and work productivity across countries and ethnicities, yet women continue to experience diagnostic delays in primary care"
Simoens et al. [26] (International, 2012)	Questionnaire-based survey, 909 women (2009 values).	*Total indirect cost* €7263 per patient-year	"Cost arises predominantly from productivity loss, and is predicted by decreased quality of life"