

# The direct and indirect costs associated with endometriosis: a systematic literature review

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**STUDY QUESTION:** What is the economic burden of endometriosis?

**SUMMARY ANSWER:** The identified studies indicate that there is a significant economic burden associated with endometriosis, as observed by both direct and indirect costs.

**WHAT IS KNOWN ALREADY:** Two previous systematic literature reviews suggested that there were considerable direct costs associated with endometriosis and there was a general lack of measurement of indirect costs.

**STUDY DESIGN, SIZE, DURATION:** We performed a systematic literature review. MEDLINE and EMBASE databases from 2000 to 2013 were searched. The literature search was limited to human studies of patients with endometriosis. Papers in languages other than English were excluded.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Studies reporting direct or indirect costs among patients with endometriosis were considered for inclusion. Direct costs included inpatient, outpatient, surgery, drug and other healthcare service cost. Indirect costs were related to absenteeism and presenteeism (lost productivity at work).

**MAIN RESULTS AND THE ROLE OF CHANCE:** After evaluating the 1396 articles in the search results, 12 primary studies that reported direct or indirect costs associated with endometriosis were identified and included in the data extraction. Three of the studies were conducted in the USA, one study each was conducted in Austria, Belgium, Brazil, Canada, Finland, Germany and Italy, and two studies included data from 10 countries. Significant variability was observed in the reviewed studies in methodology, including data source, cost components considered and study perspective. Estimates of total direct costs ranged from \$1109 per patient per year in Canada to \$12118 per patient per year in the USA. Indirect costs of endometriosis ranged from \$3314 per patient per year in Austria to \$15737 per patient per year in the USA.

**LIMITATIONS, REASONS FOR CAUTION:** The studies identified in the systematic literature review varied greatly by study methodology as well as by country owing to different healthcare systems and costs of healthcare services, which contributed to large variations in the direct and indirect cost estimates.

**WIDER IMPLICATIONS OF THE FINDINGS:** A majority of the studies we found were published after the periods covered in the prior systematic literature reviews, which provided substantial contributions to an understanding of the economic burden of endometriosis, especially in the area of indirect costs. The long-term burden of endometriosis following diagnosis is still under-studied, which is a concern given the chronic nature of the disease and the substantial recurrence of endometriosis symptoms.

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**Key words:** endometriosis / economics / direct costs / indirect costs / healthcare costs / absenteeism / presenteeism

## Introduction

Endometriosis is a common chronic gynecological condition characterized by the growth of endometrial-like tissue in sites outside the uterus, such as the ovaries, Fallopian tubes, pelvis and abdomen (Pren-[tice, 2001](#); [ACOG, 2010](#); [Jacobson et al., 2010](#); [Dunselman et al., 2014](#)). The clinical presentation of endometriosis is highly variable in severity and symptoms, which include dysmenorrhea, chronic non-menstrual pelvic pain, dyspareunia, menorrhagia, lower abdominal pain, subfertility and infertility. The prevalence of endometriosis is estimated to be 6–10% among women in their reproductive years, and one-third to one-half of women with endometriosis have some degree of infertility ([Winkel, 2003](#); [ACOG, 2010](#); [Dunselman et al., 2014](#)). The chronic symptoms of endometriosis can significantly affect patients' physical and emotional well-being and quality of life ([Winkel, 2003](#); [ACOG, 2010](#); [Dunselman et al., 2014](#)).

The symptoms of endometriosis are often nonspecific and can be similar to those induced by other gynecological and gastrointestinal diseases and a definitive diagnosis can only be made on histological examination of surgically removed tissue. These factors make diagnosing endometriosis extremely challenging, particularly in the primary care setting, often resulting in delayed referral and treatment, despite the high prevalence of the disease ([ACOG, 2010](#); [Dunselman et al., 2014](#)). Diagnosis may be delayed up to 10 years from the initial appearance of symptoms ([Greene et al., 2009](#); [Nnoaham et al., 2011](#); [Hudelist et al., 2012](#)).

Treatment options for endometriosis depend on whether the primary goal is the management of endometriosis-associated pain or preserving fertility. Management options for treating endometriosis-associated pain depend on the type and severity of symptoms, as well as an individual patient's age and reproductive plans. For patients who wish to preserve future fertility, pharmacological therapies including nonsteroidal anti-inflammatory drugs, oral contraceptives, progestins, danazol and GnRH agonists, as well as uterus-preserving surgical treatments, such as laparoscopic removal of endometriotic lesions and laparotomy, are potential treatment options. For patients for whom fertility is not a consideration, and for those whose disease is severe and recurrent, hysterectomy with or without bilateral salpingo-oophorectomy is often performed ([ACOG, 2010](#); [Dunselman et al., 2014](#)). Recurrence of endometriosis pain is common after drug therapy or conservative surgery and may occur, albeit infrequently, even after hysterectomy with bilateral salpingo-oophorectomy ([Clayton et al., 1999](#)). Approximately 40–50% of patients experience pain recurrence within 5 years of having laparoscopy ([Valle and Sciarra, 2003](#); [Giudice, 2010](#)). Treatments for endometriosis, such as any invasive procedure, have an inherent risk of complications and can introduce additional discomfort and impairment of daily function for patients.

Direct healthcare costs for managing endometriosis, as well as indirect costs to patients, employers and society due to loss of employment and productivity, are substantial. [Gao et al. \(2006\)](#) conducted a systematic literature review summarizing studies published from 1990 to 2004, and found that the information on the economic burden of endometriosis was limited. However, the limited evidence from the review suggested that there were considerable direct costs associated with endometriosis and there was a general lack of assessment of indirect costs. In another systematic literature review study, summarizing studies published in 1990–2006, [Simoens et al. \(2007\)](#) estimated a total cost of \$22 billion

attributable to endometriosis in the USA in 2002. These estimates were derived from a previous publication from 1995, which reported annual direct costs associated with endometriosis to be \$2801 per patient and annual indirect costs, estimated based on extrapolated productivity loss from hours of lost work, to be \$1023 per patient. However, there is no systematic literature review of more recent studies published since 2006. Given the complexity of the disease, its significant financial impact, and the advancement of surgical procedures, there is a continued need to evaluate and update estimates of the direct and indirect costs associated with endometriosis that reflects the current cost trends for endometriosis. This may help clarify actual disease burden, inform resource allocation, evaluate the costs and benefits of treatments, and improve the efficiency of health service utilization in current and future clinical practice.

Accordingly, this systematic literature review seeks to systematically summarize research studies published from 2000 to 2013 that have evaluated costs associated with endometriosis.

## Methods

### Literature search

A systematic literature search was conducted in MEDLINE and EMBASE databases to identify published studies on the direct and indirect costs of endometriosis. In this systematic literature review, we were only interested in human studies of patients with endometriosis that were primary studies reporting the costs of endometriosis and published in English. The literature search was limited to studies published between 1 January 2000 and 4 November 2013. The methods and perspective employed in this systematic literature review were similar to a parallel study that we conducted for uterine fibroids ([Soliman et al., 2015](#)).

Search terms were developed to capture publications related to endometriosis and costs. The following search terms were used: 'endometriosis, or endometrioses, or endometrioma/endometriomas' and 'cost\$ (\$ for truncation), or cost-of-illness, or burden\$, or burden-of-illness, or economic\$, or absenteeism, or presenteeism, or workplace, or productiv\$, or expenditure\$, or sick leave, or medical leave, or employment, or wage\$, or time loss, or time lost, or income loss, or income lost, or daily activities'. Using these search terms, we searched the titles, abstracts and subject headings present in the databases. In addition, we 'exploded' selected search terms, i.e. 'exp endometriosis', 'exp endometrioses', 'exp endometrioma', 'exp economics' and 'exp cost\$', to capture other potentially relevant search terms.

### Inclusion criteria and study selection

The literature search was limited to human studies of patients with endometriosis that reported primary data on the costs of endometriosis (i.e. costs were not derived from another study). For inclusion in this systematic literature review, one of the following types of costs had to be reported in a study: direct costs (drug costs, surgery costs, medical service costs, and other direct costs) or indirect costs (such as productivity loss). In addition, to reduce issues with language translation, only studies published in English language journals were included.

We excluded studies in which the study population was patients with endometriosis with a specific concurrent comorbidity, studies that were conference proceedings or abstracts, review articles without primary cost data and studies without full text available. Furthermore, we excluded studies that focused only on cost-effectiveness, cost-utility, cost-consequence, cost-minimization and cost-benefit analyses of endometriosis and did not have

primary data on the costs attributable to the disease (i.e. cost values reported or used in the studies were derived from other publications).

All articles identified from the initial MEDLINE and EMBASE search were reviewed in two rounds. In the first round, the study titles and abstracts were independently reviewed by two researchers based on the selection criteria described above. During the second round, full texts of articles retained from the initial round were obtained and reviewed more closely based on the same selection criteria. Review articles and cost-related studies (e.g. cost-effectiveness, cost-utility, cost-consequence, cost-minimization and cost-benefit analyses) were not included in the extraction; however, references cited in these articles were further screened based on the selection criteria, and additional studies that had not appeared in the database search but could meet inclusion criteria were further identified and reviewed.

If there were discrepancies in study selection, the differences were resolved through discussions between the two reviewers. When necessary, a third reviewer was consulted to review the study article independently.

Data extraction

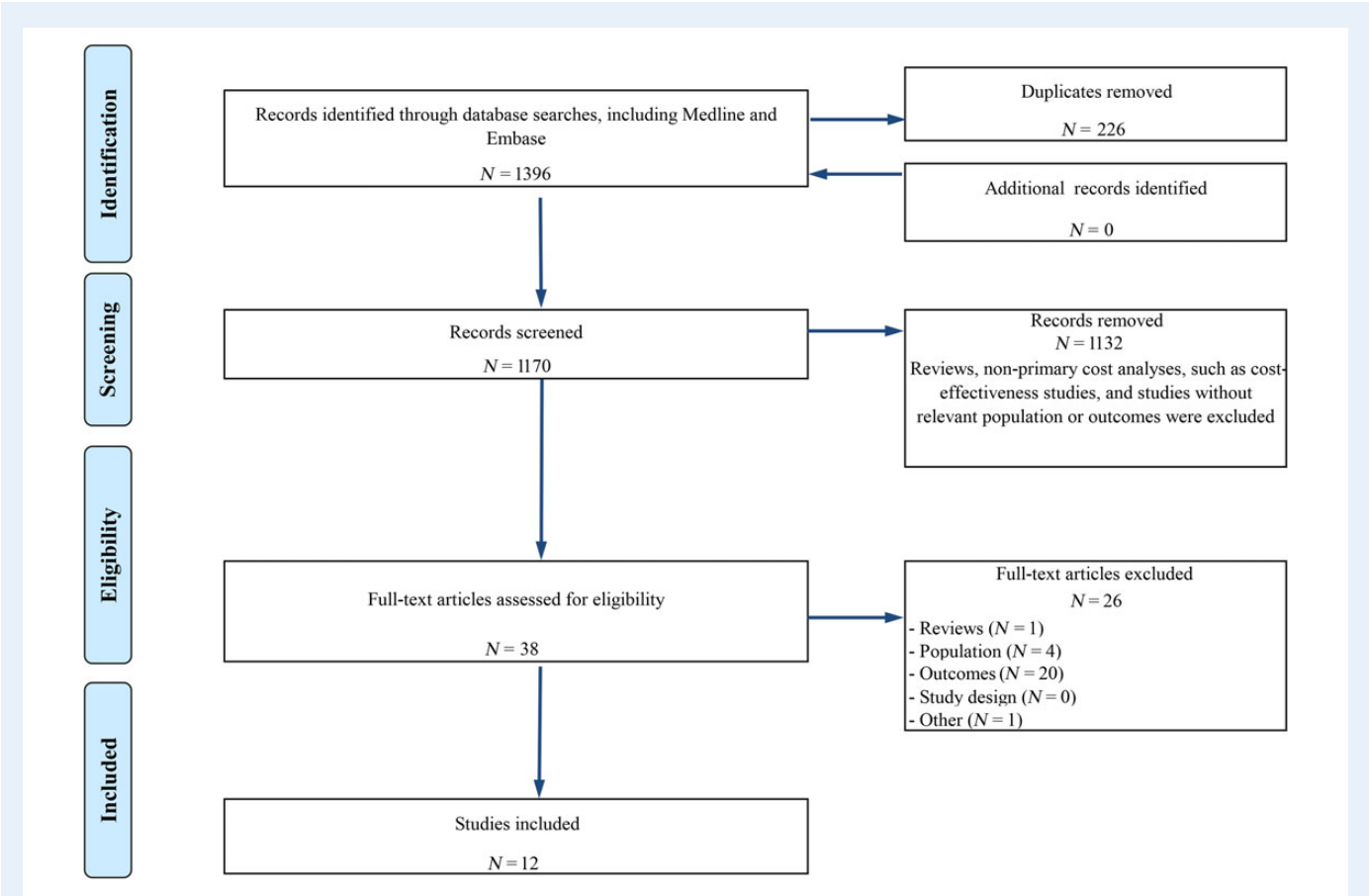
Data were extracted from all selected full-text articles and entered into a data collection form by one researcher. The data entries were audited by another

researcher to ensure accuracy. To evaluate costs across studies, all cost data were converted from the currencies in which they were originally reported to US dollars based on the year in which the cost value was reported. If it was unclear in which year the value was reported, the best available date, such as the year of study publication, was used. Costs were then inflated to 2013 US dollars using the US Medical Care consumer price index (US Bureau of Labor Statistics).

Results

Summary of included studies

The initial search in MEDLINE and EMBASE databases yielded 1396 publications. After removing 226 duplicates, 1170 records were screened against the previously outlined selection criteria in two rounds of reviews. After screening, 12 primary studies that reported direct or indirect costs associated with endometriosis were included and summarized in this systematic literature review. The process of literature review and selection of eligible publications is outlined in Fig. 1.



**Figure 1** Flow diagram for systematic literature review of costs of endometriosis. Notes: (i) Reviews and other cost related non-primary research publications (including cost-effectiveness; cost-utility, cost-consequence, cost-minimization and cost-benefit analyses) with cost information related to endometriosis were reviewed for additional relevant publications. Seven articles were in this category and reviewed for additional relevant publications. These additional articles were articles that were not included in the 1396 articles. (ii) Review articles without primary cost data were excluded. (iii) Studies without endometriosis patients or studies focusing on endometriosis patients with specific comorbidities were excluded. (iv) Studies that did not report any cost information were excluded. (v) Studies that are not primary cost analyses were excluded (e.g. budget impact, cost-effectiveness, cost-consequence, cost-minimization and cost-benefit analyses). (vi) Other exclusion criteria included 'papers in languages other than English were excluded' and 'studies of which the full text was not available were excluded'.

The key characteristics and major findings of the 12 primary studies of the costs of endometriosis are summarized in Table 1. Three of these studies were conducted in the USA (Gao *et al.*, 2006; Mirkin *et al.*, 2007; Fuldeore *et al.*, 2011). One study each was conducted in Austria (Prast *et al.*, 2013), Belgium (Simoens *et al.*, 2011), Brazil (Ikeda *et al.*, 2005), Canada (Levy *et al.*, 2011), Finland (Taipale *et al.*, 2009), Germany (Oppelt *et al.*, 2012) and Italy (Ferrero *et al.*, 2009). Two studies each reported combined data from 10 countries (Nnoaham *et al.*, 2011; Simoens *et al.*, 2012). Simoens *et al.* (2012) combined data collected from Belgium, Denmark, France, Germany, Hungary, Italy, the Netherlands, Switzerland, the UK and the USA. Nnoaham *et al.* (2011) reported data collected from Argentina, Belgium, Brazil, China, England, Ireland, Italy, Nigeria, Spain and the USA.

In addition to the variations in study countries, these studies also differed widely in terms of study methodologies including study populations, data sources and cost measurement perspectives; therefore, direct comparisons between the studies were deemed not appropriate. Several studies captured only women who had undergone surgical procedures to diagnose and treat endometriosis (Ikeda *et al.*, 2005; Taipale *et al.*, 2009; Simoens *et al.*, 2011; Nnoaham *et al.*, 2011; Oppelt *et al.*, 2012), while other studies analyzed all women in databases with a diagnostic code for endometriosis (Gao *et al.*, 2006; Mirkin *et al.*, 2007; Fuldeore *et al.*, 2011; Prast *et al.*, 2013) or used convenience samples (Ferrero *et al.*, 2009; Levy *et al.*, 2011; Simoens *et al.*, 2012) (Table 1). The data sources varied from hospital or clinical databases to survey questionnaires. The study perspectives included societal perspective, national healthcare payer perspective, insurance payer perspective and hospital perspective. Some studies were retrospective analyses of past treatment and cost data (Gao *et al.*, 2006; Mirkin *et al.*, 2007; Fuldeore *et al.*, 2011; Oppelt *et al.*, 2012; Prast *et al.*, 2013), while others prospectively identified women being diagnosed and treated for endometriosis (Ikeda *et al.*, 2005; Ferrero *et al.*, 2009; Taipale *et al.*, 2009; Simoens *et al.*, 2012). Some studies estimated costs of endometriosis by either including claims data with an endometriosis-related diagnostic code or asking the patients and/or physicians directly about endometriosis-related costs (Ikeda *et al.*, 2005; Gao *et al.*, 2006; Ferrero *et al.*, 2009; Fuldeore *et al.*, 2011; Simoens *et al.*, 2011, 2012; Oppelt *et al.*, 2012; Prast *et al.*, 2013), while others assessed the costs of endometriosis by comparing healthcare costs in endometriosis patients with control groups (Mirkin *et al.*, 2007; Nnoaham *et al.*, 2011) (Table 1).

In addition, the scopes of direct costs of healthcare services and indirect costs were defined differently across studies. For example, some studies calculated and summarized the total cost of services during a hospitalization among those with a hospitalization visit, or the costs associated with a surgical procedure, which could be either inpatient or outpatient (Ikeda *et al.*, 2005; Gao *et al.*, 2006; Taipale *et al.*, 2009; Fuldeore *et al.*, 2011; Oppelt *et al.*, 2012). On the other hand, other studies calculated the per patient average costs for all inpatient services required by a group of endometriosis patients within a specified period of time, where not all patients received inpatient services (Mirkin *et al.*, 2007; Simoens *et al.*, 2012; Prast *et al.*, 2013). Furthermore, the unit cost of specific medical services and work productivity loss varied substantially with differences in healthcare system, insurance coverage, cost of healthcare services and cost of living in different study countries, as demonstrated in the summary of cost results below.

## Direct costs of endometriosis

As shown in Table 1, estimates of average total direct costs, including inpatient and outpatient costs, drugs and other healthcare services, ranged from \$1109 per patient per year in Canada (Levy *et al.*, 2011) to \$12118 per patient per year in the USA (Mirkin *et al.*, 2007). Among the studies identified, only Mirkin *et al.* (2007) estimated incremental costs of endometriosis by comparing patients with endometriosis to women without endometriosis. Mirkin *et al.* (2007) estimated the total costs for all inpatient, outpatient and prescription drug services provided in 2003 among patients who were diagnosed with endometriosis from 1999 to 2003. Costs were much higher in the first year following the diagnosis (\$1731 per patient per month) than during the second year following the diagnosis (\$758 per patient per month). The average cost was \$1010 per patient per month among all endometriosis patients included in the study and \$619 per patient per month for matched women without the disease; therefore, the incremental cost attributable to endometriosis was estimated at \$391 per patient per month.

Inpatient costs, which most likely involved surgical procedures, appeared to be an important driver of the direct costs of endometriosis. Prast *et al.* (2013) reported an average inpatient cost of \$5455 per patient per year in Austria, greater than the average reported by Mirkin *et al.* (2007) of \$3931 in the USA. The lowest estimate of the average inpatient cost was \$860 per patient per year based on resource use reported in questionnaires and official price lists in each country and averaged across 10 countries (Belgium, Denmark, France, Germany, Hungary, Italy, the Netherlands, Switzerland, the UK and the USA) (Simoens *et al.*, 2012). However, it should be noted that these estimates were based on either patients in databases with a diagnosis of endometriosis or questionnaires administered to women with a diagnosis of endometriosis. In other words, these average cost estimates included zero Dollars/Euros for women who were not actively seeking or receiving treatment for endometriosis, which could underestimate the inpatient costs of treating endometriosis. The cost per hospitalization is likely to be higher among those with at least one hospital visit. Oppelt *et al.* (2012) estimated an average hospital cost of \$4847 per patient per year in Germany, using data from only women who were admitted for inpatient surgical treatment of endometriosis. Gao *et al.* (2006) reported an estimate of \$18,840 per patient per hospital stay in the USA, but this estimate was derived from hospital charges rather than actual paid costs, and the paid costs would likely be lower than the reported charges. In addition, Gao *et al.* (2006) did not state the proportion of hospitalized patients who underwent surgery. In Finland, Taipale *et al.* (2009) reported a mean hospital cost for endometriosis of \$5322 per patient in a 9-month period, which included 3 months before and 6 months after a hysterectomy; this included all specialty-related costs, including outpatient visits to the hospital.

Four studies specifically examined the costs of surgical procedures. In the USA, the cost per procedure ranged from \$4852 for a diagnostic laparoscopy to \$12894 for an abdominal hysterectomy (Fuldeore *et al.*, 2011). The estimates reported by Fuldeore *et al.* (2011) are lower than those reported by Gao *et al.* (2006). For example, the average cost of an abdominal hysterectomy was \$12894 according to Fuldeore *et al.* (2011), compared with \$18212 and \$21545 (total and subtotal abdominal hysterectomy, respectively) according to Gao *et al.* (2006). Similarly, the cost of a vaginal hysterectomy was \$9694 according to Fuldeore *et al.* (2011), compared with \$19820 (laparoscopically

**Table I** Summary of primary studies on costs of endometriosis published since January 2000

Study	Country/ perspective <sup>a</sup>	Study design and data source	Subjects/controls	Average direct costs <sup>b</sup>	Average indirect costs <sup>b</sup>	Surgical procedure costs <sup>b</sup>
<a href="#">Prast et al. (2013)</a>	Austria/societal	Retrospective patient survey	73 women with endometriosis diagnosis/none	Total direct cost per patient per year (public insurance and out-of-pocket): \$8819.64	Total indirect cost per patient per year (sick leave and unemployment due to endometriosis): \$3314.39	Not reported
<a href="#">Oppelt et al. (2012)</a>	Germany/payer	National inpatient database analysis	21 244 women undergoing surgery to treat endometriosis/none	Total hospital cost per patient per year: \$4846.99 Total indirect and direct cost per patient per year: \$15 635.44	Not reported.	Not reported
<a href="#">Simoens et al. (2012)</a>	10 countries <sup>c</sup> / societal	Prospective patient questionnaire	909 women with endometriosis diagnosis/none	Total direct healthcare cost per patient per year: \$4898.56 Total non-healthcare cost (transportation and support household activity): \$264.04	Total indirect costs of productivity loss per patient per year: \$9910.57	Surgery cost per patient per year: \$1415.08
<a href="#">Fuldeore et al. (2011)</a>	USA/insurance	Retrospective claims database analysis	15 891 women with endometriosis diagnosis/63 564 women without endometriosis matched for age and geography <sup>d</sup>	Not reported	Not reported	(65.5% patients received surgical procedure within 1 year of new endometriosis diagnosis). Cost per surgical procedure: Ranging from \$4852 (diagnostic laparoscopy) to \$12 894 (abdominal hysterectomy) Cost in controls not reported.
<a href="#">Levy et al. (2011)</a>	Canada/societal	Cross-sectional physician and patient questionnaires	27 women with surgically confirmed endometriosis/none	Total direct cost per patient per year: \$1109.45	Total indirect cost per patient per year (lost productivity and leisure time): \$3853.52	Not reported.
<a href="#">Nnoaham et al. (2011)</a>	10 countries <sup>e</sup> / societal	Cross-sectional patient questionnaire	745 women undergoing laparoscopy for endometriosis/673 symptomatic women undergoing laparoscopy or sterilization without endometriosis	Not reported	Absenteeism-related cost per employed woman per week: Range: \$1 (Nigeria) to \$279.63 (Italy). Presenteeism-related cost (reduced productivity at work due to symptoms) per employed woman per week: range: \$3.63 (Nigeria) to \$302.63 (US)	Not reported
<a href="#">Simoens et al. (2011)</a>	Belgium/societal	Longitudinal patient questionnaire	180 women undergoing surgery to treat endometriosis/none	Support for household activities per patient: 6 months before: \$1450.06 6 months after: Mean \$1448.59	Productivity loss per patient: 6 months before surgery: \$2235.64 6 months after surgery: \$3685.70	Not reported
<a href="#">Ferrero et al. (2009)</a>	Italy/not reported	Prospective open-label drug trial	82 women with endometriosis undergoing laparoscopy or laparotomy/none	Drug regimen costs per patient per 6 months: \$13.38 (norethisterone acetate), \$1654.88 (letrozole and norethisterone acetate), \$1705.24 (letrozole, norethisterone acetate, calcium, vitamin D)	Not reported	Not reported



Taipale et al. (2009)	Finland/hospital	Prospective clinical database analysis	20 women undergoing hysterectomy due to endometriosis/317 women undergoing hysterectomy for another benign disease (including benign uterine/ovarian cause, uterovaginal prolapsed, and menorrhagia)	Total hospital cost (surgery, inpatient, ambulatory visits, laboratory, etc.) from 3 months before to 6 months after surgery: \$5321.86 (endometriosis), \$5395.35 (benign uterine/ovarian cause) \$4455.39 (prolapse), \$6072.12 (menorrhagia).	Not reported	Not reported
Mirkin et al. (2007)	USA/payer and patient	Retrospective claims database analysis	13 139 women with endometriosis diagnosis/17 096 average women	Total average direct cost per patient per month: \$1009.83 (endometriosis), \$619.34 (control) Average direct costs per patient per month with endometriosis: 1 year post diagnosis: \$1730.72, 2 years post diagnosis: \$758.09.	Not reported	Not reported
Gao et al. (2006)	USA/payer	National clinical database analysis	Women hospitalized for endometriosis (N not reported)/None	Average total charge per hospital stay: Range from \$16,574.05 (1993) to \$18,839.56 (2002)	Not reported	Cost per surgical procedure: Ranging from \$14,564.73 (vaginal hysterectomy) to \$26,002 (other peritoneal adhesiolysis). Laparoscopy: \$21,268.26.
Ikeda et al. (2005)	Brazil/hospital	Prospective, randomized trial	54 women with endometriosis undergoing laparoscopy/none	Not reported	Not reported	Cost per surgical procedure: \$202.99 (microlaparoscopy under sedation), \$350.46 (microlaparoscopy under general anesthesia), \$388.57 (conventional laparoscopy).

<sup>a</sup>The perspectives of the costs reported in each study were classified as societal, insurance, payer, patient or hospital. Societal perspective included the direct healthcare costs, direct non-healthcare costs and indirect costs for all members of the society. Insurance perspective included amounts paid by the insurance companies. Payer perspective included the costs to the payer or insurance plan. Patient costs included the payer member cost share paid by the patient. Hospital costs included the costs to the hospital.

<sup>b</sup>All costs reported in the studies were adjusted to 2013 US dollar using the US Medical Care consumer price index.

<sup>c</sup>The 10 countries included in the study were: Belgium, Denmark, France, Germany, Hungary, Italy, the Netherlands, Switzerland, the UK and the USA.

<sup>d</sup>Fuldeore et al. (2011) included a matched population control cohort. However, the cohort was used to compare baseline characteristics and surgery rates. Costs were not reported among the population control cohort.

<sup>e</sup>The 10 countries included in the study were: Nigeria, China, Brazil, Argentina, Belgium, Spain, Ireland, England, Italy and the USA.

assisted vaginal hysterectomy) and \$14 565 (other vaginal hysterectomy) according to [Gao et al. \(2006\)](#). The significant difference between the two studies in the USA may be due to the use of charges data in [Gao et al. \(2006\)](#), rather than reimbursed costs as in [Fuldeore et al. \(2011\)](#), and the inclusion of outpatient surgeries in the latter but not the former analyses. While it may be argued that neither charges nor reimbursements represent the true costs of these procedures, we recognize that the costs to the healthcare system are most closely represented by the reimbursements dispersed. In contrast, [Ikeda et al. \(2005\)](#) reported the costs of laparoscopy in Brazil, which ranged from \$203 to \$389. [Simoens et al. \(2012\)](#) reported an average surgery cost (unspecified type) of \$1415 per patient per year across 10 countries.

Most of the estimates for outpatient and pharmacological costs were lower than surgery or inpatient costs. Estimates of outpatient costs ranged from \$123 per patient per year in Canada ([Levy et al., 2011](#)) to \$6299 per patient per year in the USA ([Mirkin et al., 2007](#)). The costs of endometriosis-related pharmacological treatments ranged from \$184 per patient per year in Austria ([Prast et al., 2013](#)) to \$1888 per patient per year in the USA ([Mirkin et al., 2007](#)). A comparative drug trial in Italy reported that the cost of letrozole and norethisterone acetate combination, plus calcium and vitamin D was \$1705 per 6 months ([Ferrero et al., 2009](#)). However, this study focused on a particular drug regimen which is used by patients with pain symptoms caused by rectovaginal endometriosis and not approved for the treatment of endometriosis in the USA ([Ferrero et al., 2009](#)).

## Indirect costs of endometriosis

Indirect costs can be more variable and difficult to quantify than direct costs because of the lack of consistent definitions of components of costs to be considered, lack of definitive documentation of health resource units utilized, reliance on patient recall and variable valuation of productivity ([Segel, 2006](#)). Five studies reported indirect costs of endometriosis (Table I), and all of these studies measured absenteeism due to illness and loss of work productivity ([Levy et al., 2011](#); [Nnoaham et al., 2011](#); [Simoens et al., 2011, 2012](#); [Prast et al., 2013](#)). Additionally, several studies measured other contributors to indirect costs besides absenteeism and the loss of productivity; for example, [Levy et al. \(2011\)](#) calculated indirect costs due to loss of leisure time, and [Prast et al. \(2013\)](#) calculated costs of unemployment due to illness.

[Levy et al. \(2011\)](#) estimated the indirect cost from loss of productivity and leisure time to be \$3854 per patient per year in Canada. [Prast et al. \(2013\)](#) estimated the cost of productivity loss from both sick leave and unemployment due to endometriosis to be \$3314 per patient per year in Austria. The estimated indirect cost across 10 countries was \$9911 per patient per year ([Simoens et al., 2012](#)). In the other 10-country study ([Nnoaham et al., 2011](#)), the average absenteeism-related cost per employed woman ranged from \$52 per patient per year in Nigeria to \$14 541 per patient per year in Italy, and lost productivity at work (i.e. presenteeism) ranged from \$189 per patient per year in Nigeria to \$15 737 per patient per year in the USA. Limited information exists on the productivity losses associated with undergoing a surgical procedure for endometriosis. Among the studies reviewed, only one study looked into such losses among women undergoing surgeries for endometriosis. That study, which included Belgian women, reported a productivity loss of \$2236 per patient in the 6 months before surgery and \$3686 in the 6 months after surgery, decreasing to \$272 per patient during the 18–24

months after surgery ([Simoens et al., 2011](#)). All five studies of the indirect costs of endometriosis reported overall indirect costs over a period of time of illness, and none focused on indirect costs specifically due to a surgical procedure.

One study in Germany ([Oppelt et al., 2012](#)) did not report a specific value for indirect costs, but provided a combined total for direct and indirect costs of \$15 635 per patient per year.

## National economic burden

Taking into account both direct and indirect costs, the annual national economic burden of endometriosis was estimated in several studies, ranging from \$208.26 million in Germany ([Oppelt et al., 2012](#)) and \$516.12 million in Austria ([Prast et al., 2013](#)) to \$1.72 billion in Canada ([Levy et al., 2011](#)). In addition, [Simoens et al. \(2012\)](#) estimated societal annual costs of endometriosis in the following countries: Denmark, \$1.26 billion; Switzerland, \$2.05 billion; Hungary, \$2.52 billion; Belgium, \$2.68 billion; the Netherlands, \$4.09 billion; Italy, \$14.63 billion; France, \$14.95 billion; the UK, \$15.58 billion; Germany, \$19.67 billion and the USA, \$78.05 billion. However, it should be noted that the national economic burden of endometriosis is dependent on the population size, as well as the social and economic context of each country. In addition, the methods for estimating the 'per patient cost', which was used to derive the national burden, differed greatly across studies.

## Discussion

This was a systematic literature review of studies published between 2000 and 2013 that reported primary cost data associated with endometriosis. It provides important additions to the understanding of the economic burden of endometriosis. Two prior reviews on the same topic were published by [Gao et al. \(2006\)](#), which included publications between 1990 and 2004, and by [Simoens et al. \(2007\)](#), which included publications between 1990 and 2006. However, the majority of studies found in the current review was published after 2006 and provide more up-to-date information on the costs of endometriosis. Moreover, this review identified multiple studies reporting indirect costs which were only reported sparsely in the prior reviews (five studies in our review versus two studies in both of the prior reviews). This suggests that indirect costs associated with endometriosis have been examined much more closely in recent years. The current review identified studies from a range of countries (North America, South America, Europe, Asia and Africa) with diverse healthcare systems and socioeconomic statuses. In comparison, the studies reviewed by [Gao et al. \(2006\)](#) were conducted only in North America, European and Asia, while the studies reviewed by [Simoens et al. \(2007\)](#) were conducted in either the USA or the UK. Finally, in contrast with the previous reviews noted above, our review only included primary studies reporting the costs of endometriosis to reflect the real-world burden of endometriosis, and did not include modeling studies or literature reviews summarizing information from primary studies. [Simoens et al. \(2007\)](#) included six modeling studies where costs were estimated using economic models under specific assumptions for a hypothetical cohort of patients with endometriosis, and [Gao et al. \(2006\)](#) included two modeling studies and three prior literature reviews. Therefore, the current review likely provides a more comprehensive, up-to-date summary of the costs of

endometriosis in a real-world setting, reflects a broader and more international perspective and demonstrates the increasing recognition of the significant economic impact of endometriosis across the world.

Of the 12 primary studies included in this systematic literature review, four reported both direct and indirect costs, four reported only direct costs, one reported only indirect costs, two reported only surgery costs and one reported only the sum of direct and indirect costs (Table I). Because these studies were conducted in countries with different structures of healthcare systems, costs of healthcare services, standards of care and living standards, it was difficult to make direct comparisons or to analyze the underlying reasons for the cost differences among countries. Generally, the direct costs of treating endometriosis were higher in the USA than other countries. Total direct costs in the USA were estimated to be \$12 118 per patient per year (Mirkin *et al.*, 2007), compared with total direct costs in other countries, ranging from \$1109 per patient per year in Canada (Levy *et al.*, 2011) to \$8820 per patient per year in Austria (Prast *et al.*, 2013). It should be noted that the lowest estimate of total direct costs was from a Canadian study in which costs were derived from questionnaires that asked physicians and patients to recall previous resource use; the questionnaire was administered to a small sample of 18 physicians and 27 patients and therefore is likely not representative of the general endometriosis population (Levy *et al.*, 2011).

Only a few identified studies measured and reported all components of total direct costs simultaneously (Mirkin *et al.*, 2007; Simoens *et al.*, 2012; Prast *et al.*, 2013); most studies focused on only one or two components, such as surgery, hospitalization or drug costs. Prast *et al.* (2013) reported total direct costs, drug costs, inpatient costs, outpatient costs and other direct costs in Austria based on a patient questionnaire; the estimates were \$8820, \$184, \$5455, \$515 and \$2667 per patient per year, respectively. Simoens *et al.* (2012) also reported all components of total direct costs based on a patient questionnaire in ten countries. The total direct cost was estimated to be \$5163 per woman per year, including \$504 for drug costs, \$860 for inpatient costs, \$808 for outpatient costs, \$1415 for surgery costs and \$1576 for other direct costs per woman per year. The only US study that reported the costs of all components of total direct costs was conducted by Mirkin *et al.* (2007). The estimates for average total direct cost, drug cost, inpatient cost and outpatient cost were \$1010, \$157, \$328 and \$525 per patient per month, respectively. However, the costs were assessed in 2003 and only health plan-allowed charges (sum of net payer cost and member cost share) were assessed. Further studies updating cost figures reported by Mirkin *et al.* (2007) are needed.

Even though the current review did identify multiple publications reporting indirect costs, the indirect cost to patients, employers and society is both under-studied and likely underestimated, particularly in the USA healthcare setting. Analogous to the findings of Simoens *et al.* (2007), in our review we found that indirect costs beyond missed work days and reduced productivity at work, including, but not limited to, unemployment, have not been fully captured and measured. Indirect costs are difficult to quantify, especially for a chronic, complex and recurrent condition like endometriosis that has variable clinical presentations and for which the diagnosis is challenging. All five studies that reported indirect costs relied on patient questionnaires, likely reducing the accuracy of data due to recall bias (Levy *et al.*, 2011; Nnoaham *et al.*, 2011; Simoens *et al.*, 2011, 2012; Prast *et al.*, 2013). In addition, variations in outcome measurements and time frames limit data comparability. For

example, Prast *et al.* (2013) collected missed work days and unemployment due to illness over the course of 1 year. Levy *et al.* (2011) measured missed work, lost leisure time, and missed work for volunteer helpers in the 3 months before surgical diagnosis. Simoens *et al.* (2012) presented time lost from work and productivity decrement at work (presenteeism) in the week prior to survey administration only. We found no US-specific study on the indirect costs of endometriosis published since 2000. As endometriosis occurs predominantly in women in their reproductive years with frequent and debilitating symptoms, the indirect costs of the illness are likely to be large.

The relative magnitude of direct and indirect costs of endometriosis patients is not well characterized as well. Given country-specific and methodological differences, the direct and indirect costs derived from different studies cannot be compared. However, of the four studies which estimated both direct and indirect costs (Levy *et al.*, 2011; Simoens *et al.*, 2011, 2012; Prast *et al.*, 2013), three found higher indirect costs than direct costs (Levy *et al.*, 2011; Simoens *et al.*, 2011, 2012), while only Prast *et al.* (2013) found the direct costs to be higher (Table I). A previous review (Simoens *et al.*, 2007) also showed that the cost of productivity loss was lower than direct healthcare costs; in that study, the indirect costs were extrapolated from estimated hours of missed work and did not cover other potential indirect costs, such as reduced work productivity (presenteeism). It is possible that the indirect costs of endometriosis would be larger than the direct costs if assessment could cover a full range of impairment at work and in daily living.

Methodologically, some of the limitations in the literature highlighted by the prior review (Simoens *et al.*, 2007) have been addressed. For example, recent publications are mostly focusing on costs instead of charges. However, certain limitations in the study design remain in several studies such as small sample sizes and lack of a control group. The small sample sizes of several studies might limit the generalization of study results to all women diagnosed with endometriosis. Six studies included in the review had sample sizes of less than 200 patients (Ikeda *et al.*, 2005; Ferrero *et al.*, 2009; Prast *et al.*, 2013; Taipale *et al.*, 2009; Levy *et al.*, 2011; Simoens *et al.*, 2011). Given the variations in costs and the skewed distributions of cost data, the findings from these studies might not be representative of the overall endometriosis population (Manning and Mullahy, 2001; Simoens *et al.*, 2007). In addition, the lack of control groups in most studies is a significant limitation that could obscure the incremental economic burden of endometriosis. The use of control groups is important in observational studies, as there are many potential confounding factors that could affect the validity of effect estimates. Comparing the costs incurred between a disease-specific population and a matched group of women without the disease could assist in drawing more robust causal relationships between having the disease and incurring a higher economic burden (Lewallen and Courtright, 1998; Akobundu *et al.*, 2006). However, only 4 of the 12 studies included control groups, and only 2 reported costs for control groups (Mirkin *et al.*, 2007; Taipale *et al.*, 2009; Fuldeore *et al.*, 2011; Nnoaham *et al.*, 2011). In particular, Mirkin *et al.* (2007) compared patients with endometriosis with average adult women representing the standard demographic distribution in a typical large insured group: This study showed that endometriosis patients incurred significantly higher healthcare costs than a control of average adult women, with the total average direct cost estimated at \$1010 per patient per month for endometriosis and \$619 for average adult women. In Mirkin *et al.* (2007), the cost of endometriosis patients was estimated using the Medstat Marketscan



Database, whereas the cost for average adult women was estimated using the Milliman's Health Cost Guidelines. The guidelines were developed using insurance data including Medstat MarketScan as well as other data sources to estimate costs for average enrollees in a wide variety of health plans. The differences in data sources may limit the comparison in direct costs between the endometriosis patients and the average adult women. In addition, since the demographics or disease characteristics were not matched between the endometriosis population and the average adult female population, the differences in patient characteristics may further limit the comparison of direct costs between the endometriosis patients and average adult women. [Taipale et al. \(2009\)](#) compared women undergoing hysterectomy due to endometriosis with women undergoing hysterectomy for benign uterine or ovarian causes (e.g. menorrhagia). The study estimated that women undergoing hysterectomy for endometriosis had an average total hospital cost of \$5322 during the 9-month period around the surgery (3 months preceding and 6 months following the operation). This cost was similar to the cost of patients receiving hysterectomy for other reasons (total costs were \$6072 for menorrhagia, \$5395 for benign uterine or ovarian cause and \$4455 for prolapse). Although, the [Taipale et al. \(2009\)](#) study highlighted the high costs for endometriosis patients with hysterectomy, the costs attributable to endometriosis could not be estimated in the absence of a control group without the disease. Future studies comparing endometriosis patients with controls without endometriosis that are matched on demographics and other patient characteristics, including age, race, region, insurance type and the presence of other chronic conditions that are not linked to endometriosis, are necessary to better quantify the costs attributable to endometriosis.

Considering that the diagnosis of endometriosis is often delayed, the burden of undiagnosed, untreated endometriosis remains poorly understood. Previous reviews have recognized the lack of studies examining the costs associated with a delay in the diagnosis of endometriosis ([Gao et al., 2006](#); [Simoens et al., 2007](#)). This continues to be the case, and our review only identified two studies examining costs prior to diagnosis. [Taipale et al. \(2009\)](#) reported substantial hospital costs in the 3 months before surgery, and [Simoens et al. \(2011\)](#) reported that costs associated with support for household activity peaked in the 6 months before surgical procedure. The long-term burden of endometriosis following diagnosis is also under-studied, which is a concern, given the chronic nature of the disease and the substantial recurrence of endometriosis symptoms ([Valle and Sciarra, 2003](#); [Giudice, 2010](#)). We recently completed a *de novo* analysis using medical claims to evaluate the economic burden of endometriosis 5 years before and 5 years after diagnosis, in comparison with a control group of women without endometriosis; the study found that the incremental cost for endometriosis patients compared with controls was \$7028 during the 5 years before diagnosis and \$19 277 during the 5 years following diagnosis ([Fuldeore et al., 2015](#)).

The recent studies identified in this systematic literature review provide estimates of the costs of endometriosis to healthcare systems and society, and demonstrate that the costs associated with endometriosis are substantial. Some specific questions remain unanswered, for example, how direct and indirect costs vary by patient characteristics such as age and previous history of pregnancy, treatment choices and non-healthcare related factors. Additional research is also needed to evaluate how endometriosis costs are affected by disease characteristics, such as endometriosis severity, the extent of growth outside the uterus,

the type and severity of symptoms, pain levels, and the presence of comorbidities that potentially alter treatment patterns and associated costs ([Simoens et al., 2007](#)). Well-designed prospective studies would be well suited to address questions around the impact of disease characteristics and severity. The issue of comorbidities is of particular importance. If the comorbidity can be attributed directly to endometriosis, then the costs associated with that comorbidity should be captured in estimating the total cost of endometriosis. On the other hand, if the comorbidity is simply the serendipitous coexistence of a condition not attributable to endometriosis, then the associated cost should perhaps not be included when determining the cost of endometriosis. Unfortunately, until the pathophysiology of endometriosis is more completely understood, determining the correct linkage between endometriosis and observed comorbidities remains impossible to evaluate completely.

In addition, factors associated with increased economic burden are not very clear in the literature. Out of the 12 articles identified in this systematic literature review, only two studies ([Nnoaham et al., 2011](#); [Simoens et al., 2012](#)) used multivariate analyses to assess the drivers of direct costs and indirect costs. [Nnoaham et al. \(2011\)](#) concluded that pelvic pain and disease severity were the major drivers of work productivity loss associated with endometriosis. [Simoens et al. \(2012\)](#) found that a more severe stage of endometriosis, the presence of pelvic pain symptoms, the presence of infertility, a longer time since diagnosis, a lower age, a lower BMI and a lower number of years since initially seeking medical help were associated with higher direct costs. More studies are required to evaluate the correlates of higher healthcare costs among endometriosis patients.

Finally, a largely untapped area of research that warrants further investigation is the impact of optimized value-based endometriosis care on the overall economic burden of endometriosis. Currently, care modalities for endometriosis patients are still based on suboptimal evidence on the benefits and risks of different medical interventions for the management of endometriosis ([Vercellini et al., 2015](#)). In a recent publication, [Vercellini et al. \(2015\)](#) reviewed this issue and made several recommendations with the goal of establishing value-based care for the screening, diagnosis and management of endometriosis patients. In particular, their suggestions include using non-surgical evidence for diagnosis where feasible, including active comparators in clinical trials of novel therapies, carefully considering the need of surgery in light of benefits, risks, cost-effectiveness and patient preference, taking caution in promoting the screening of all asymptomatic women, and involving patients in the decision-making. Future studies are needed to evaluate the impact of implementing these suggestions on the economic burden of endometriosis.

[Vercellini et al.](#) also underscored the importance of adopting a tripartite approach to 'value-based medicine' that takes benefits, risks and costs of endometriosis care into account. Accordingly, robust estimation of 'value' necessitates high-quality evidence on benefits, risks and costs. This systematic literature review summarizes the current literature on costs and provides directions and recommendations for future studies generating evidence to fully characterize the entire spectrum of the economic burden of endometriosis. Such evidence would be an integral component of estimating the overall value of endometriosis care modalities.

There are several limitations to this systematic literature review. First, we included only studies published in full text. Abstracts and conference proceedings were not considered since the information in those

publications is generally limited and often incomplete. Secondly, no meta-analysis has been carried out to evaluate the economic burden, given the large variations observed in the identified studies.

## Conclusion

These studies identified in this systematic literature review varied greatly by country and study methodology, which contributed to the large variations in reported findings of direct and indirect cost estimates. Despite these and other limitations, the results indicate a substantial economic burden associated with endometriosis, as observed by both direct and indirect costs.

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## Authors' roles

All authors participated in data analysis and interpretation and contributed to the development of the manuscript. The authors maintained control over the final contents of the manuscript and the decision to publish.

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## Conflict of interest

A.M. Soliman is an employee of AbbVie and currently owns AbbVie stocks. H.Y., E.X.D. and C.K. are employees of Analysis Group, Inc., which has received consultancy fees from AbbVie for the conduct of this research. C.W. is a Clinical Professor at the Department Obstetrics and Gynecology at Georgetown University in Washington, DC, USA and has served in a consulting role to AbbVie for this project.

## References

- Akobundu E, Ju J, Blatt L, Mullins CD. Cost-of-illness studies: a review of current methods. *Pharmacoeconomics* 2006;**24**:869–890.
- American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 114: Management of Endometriosis. 2010.
- Chapron C, Querleu D, Bruhat MS, Madelenat P, Fernandez H, Pierre F, Dubuisson JB. Surgical complications of diagnostic and operative gynaecological laparoscopy: a series of 29,966 cases. *Hum Reprod* 1998;**13**:867–872.
- Clayton RD, Hawe JA, Love JC, Wilkinson N, Garry R. Recurrent pain after hysterectomy and bilateral salpingo-oophorectomy for endometriosis: evaluation of laparoscopic excision of residual endometriosis. *BJOG* 1999;**106**:740–744.
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;**29**:400–412.
- Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini R, Remorgio V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in treatment of pain symptoms cause by endometriosis. *Hum Reprod* 2009;**24**:3033–3041.
- Fuldeore M, Chwalisz K, Marx S, Wu N, Boulanger L, Ma L, Lamothe K. Surgical procedures and their cost estimates among women with newly diagnosed endometriosis: a US database study. *J Med Econ* 2011;**14**:115–123.
- Fuldeore M, Yang H, Du EX, Soliman AM, Wu EQ, Winkel CA. Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. *Fertil Steril* 2015;**103**:163–171.
- Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril* 2006;**86**:1561–1572.
- Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010;**362**:2389–2398.
- Greene R, Stratton P, Cleary SD, Ballweg ML, Sinai N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. *Fertil Steril* 2009;**91**:32–39.
- Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, Tamma A, Salzer H. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod* 2012;**27**:3412–3416.
- Ikeda F, Vanni D, Vasconcelos A, Podgaec S, Abrao MS. Microlaparoscopy vs. conventional laparoscopy for the management of early-stage pelvic endometriosis: a comparison. *J Reprod Med* 2005;**50**:771–778.
- Jacobson TZ, Duffy JM, Barlow D, Farquhar C, Koninckx PR, Olive D. Laparoscopic surgery for subfertility associated with endometriosis. *Cochrane Database Syst Rev* 2010;**1**.
- Levy AR, Osenenko KM, Lozano-Ortega G, Sambrook R, Jeddi M, Bélisle S, Reid RL. Economic Burden of Surgically Confirmed Endometriosis in Canada. *J Obstet Gynaecol Can* 2011;**33**:830–837.
- Lewallen S, Courtright P. Epidemiology in practice: case-control studies. *Community Eye Health* 1998;**11**:57.
- Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Econ* 2001;**20**:461–494.
- Maresh MJ, Metcalfe MA, McPherson K, Overton C, Hall V, Hargreaves J, Bridgman S, Dobbins J, Casbard A. The VALUE national hysterectomy study: description of the patients and their surgery. *BJOG* 2002;**109**:302–312.
- Mirkin D, Murphy-Barron C, Iwasaki K. Actuarial analysis of private payer administrative claims data for women with endometriosis. *J Manag Care Pharm* 2007;**13**:262–272.
- Nnoaham KE, Hummelshoj L, Webster P, D'Hooghe T, de Ciccio Nardone F, de Ciccio Nardone C, Jenkinson C, Kennedy SH, Zondervan KT, Study WE. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011;**96**:366–373.
- Oppelt P, Chavtal R, Haas D, Reichert B, Wagner S, Müller A, Lermann JH, Renner SP. Costs of in-patient treatment for endometriosis in Germany 2006: an analysis based on the G-DRG-Coding. *Gynecol Endocrinol* 2012;**28**:903–905.
- Prast J, Oppelt P, Shamiyeh A, Shebl O, Brandes I, Haas D. Costs of endometriosis in Austria: a survey of direct and indirect costs. *Arch Gynecol Obstet* 2013;**288**:569–576.
- Prentice A. Regular review: endometriosis. *BMJ* 2001;**323**:93–95.
- Segel JE. Cost-of-illness studies—a primer. *RTI-UNC Center of Excellence in Health Promotion Economics* 2006:1–39.
- Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. *Hum Reprod Update* 2007;**13**:395–404.
- Simoens S, Meuleman C, D'Hooghe T. Non-health-care costs associated with endometriosis. *Hum Reprod* 2011;**26**:2363–2367.

- Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, Brodsky V, Canis M, Colombo GL, DeLeire T et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centers. *Hum Reprod* 2012;**27**:1292–1299.
- Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, Brodsky V, Canis M, Colombo GL, DeLeire T et al. Correction to Simoens et al. 27 (5): 1292. *Hum Reprod* 2014;**29**:2073.
- Soliman AM, Yang H, Du EX, Kelkar SS, Winkel C. The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013. *Am J Obstet Gynecol* 2015; **213**:141–160.
- Taipale K, Leminen A, Räsänen P, Heikkilä A, Tapper A, Sintonen H, Roine RP. Costs and health-related quality of life effects of hysterectomy in patients with benign uterine disorders. *Acta Obstet Gynecol Scand* 2009;**88**:1402–1410.
- US Bureau of Labor Statistics. Division of Consumer Prices and Price Indexes. Consumer Price Index- All Urban Consumers - US Medical Care, 1982–84. 2013. <http://data.bls.gov/cgi-bin/surveymost?cu>. (6 August 2014, date last accessed).
- Valle RF, Sciarra JJ. Endometriosis: treatment strategies. *Ann N Y Acad Sci* 2003;**997**:229–239.
- Vercellini P, Giudice LC, Evers JL, Abrao MS. Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. *Hum Reprod* 2015;**30**:1996–2004.
- Winkel CA. Evaluation and management of women with endometriosis. *Obstet Gynecol* 2003;**102**:397–408.