

Incremental direct and indirect cost burden attributed to endometriosis surgeries in the United States

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Objective: To compare direct and indirect costs between endometriosis patients who underwent endometriosis-related surgery (surgery cohort) and those who have not received surgery (no-surgery cohort).

Design: Retrospective cohort study.

Setting: Not applicable.

Patient(s): Endometriosis patients (aged 18–49 years) with (n = 124,530) or without (n = 37,106) a claim for endometriosis-related surgery were identified from the Truven Health MarketScan Commercial and Health and Productivity Management databases for 2006–2014.

Intervention(s): Not applicable.

Main Outcome Measure(s): Primary outcomes were healthcare utilization during 12-month pre- and post-index periods, annual direct (healthcare) and indirect (absenteeism and short- and long-term disability) costs during the 12-month post-index period (in 2014 US dollars). Indirect costs were assessed for patients with available productivity data.

Result(s): Patients in the surgery cohort had significantly higher healthcare resource utilization during the post-index period and had mean annual total adjusted post-index direct costs approximately three times the costs among patients in the no-surgery cohort [\$19,203 [SD \$7,133] vs. \$6,365 [SD \$2,364]; average incremental annual direct cost = \$12,838]. The mean cost of surgery (\$7,268 [SD \$7,975]) was the single largest contributor to incremental annual direct cost. Mean estimated annual total indirect costs were \$8,843 (surgery cohort) vs. \$5,603 (no-surgery cohort); average incremental annual indirect cost = \$3,240.

Conclusion(s): 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. Regardless of the surgery type, the cost of index surgery contributed substantially to the total healthcare expenditure. (Fertil Steril® 2017;107:1181–90. ©2017 by American Society for Reproductive Medicine.)

Key Words: Administrative claims database, endometriosis, surgery, work loss

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Endometriosis, a gynecologic disease in which endometrial-like tissue grows outside the uterus and typically accompanied by pelvic

pain and inflammation, afflicts 5%–10% of reproductive-age women in the United States (1). The actual prevalence of endometriosis remains unclear

and is likely underreported owing to diagnostic delay and symptom overlap with other diseases like irritable bowel syndrome, pelvic inflammatory disease, fibromyalgia, and others (2–4). Endometriosis is associated with a significant direct and indirect cost burden among patients (5–7); for example, a recent systematic literature review that examined studies published from 2000 to 2013 estimated the direct costs associated with endometriosis to be \$12,118 per patient per year, and the indirect costs of endometriosis to be \$15,737 per patient per year in the United States (6).

Both pharmacotherapy and surgery are used in clinical practice to manage

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endometriosis (8, 9). For patients who do not respond sufficiently to or are intolerant of pharmacotherapy, surgical interventions are a commonly used and effective management option (8, 10, 11). In women willing to lose fertility, bilateral salpingo-oophorectomy or hysterectomy (with or without oophorectomy) are regarded as the most effective surgical interventions; more conservative procedures can also be used, especially when preservation of fertility is desired (8, 11).

Surgical treatment is a substantial source of costs among endometriosis patients. A multicenter, international, prospective study (7) using European Union data estimated that, on average, 29% of the endometriosis-specific healthcare costs were due to surgery. Another study found that more than 65% of US endometriosis patients underwent surgery within the first year of diagnosis, and the average cost of surgery ranged from \$4,289 for a diagnostic laparoscopy to \$11,397 for abdominal hysterectomy (12).

The present study aims to provide a current evaluation of the cost burden (both direct and indirect) of surgery among endometriosis patients in the US real-world practice. This retrospective analysis estimates the incremental direct and indirect healthcare costs among endometriosis patients who underwent endometriosis-related surgical procedures compared with patients without endometriosis-related surgery. We hypothesized that patients with endometriosis-related surgery incur higher healthcare costs than those who do not undergo surgery.

MATERIALS AND METHODS

Data Source

Data for this retrospective analysis were extracted from the Truven Health MarketScan Commercial Claims and Encounters (Commercial) and the Health and Productivity Management databases for the period of January 1, 2006 through June 30, 2014.

The Commercial database contains information from insurance claims on the inpatient and outpatient healthcare history of approximately 40 million employees, their dependents, and retirees covered under various fee-for-service, preferred provider organizations, and capitated health plans across the United States. The medical and pharmacy claims in MarketScan Research Databases are based on the UB-04 and CMS-1500 health insurance claim forms submitted by providers to the insurance companies of contributing employers and include information on services rendered and associated diagnostic codes, as well as filled pharmacy claims. Claims-based data sets have the advantage of containing relatively comprehensive data on the full spectrum of care a patient receives, with the ability to track very large numbers of patients longitudinally by requiring continuous enrollment during the time of interest. A major limitation of claims-based data is its foundation as a system designed for reimbursement rather than for research purposes. This can result in diagnostic and procedure coding that can contain inaccuracies, difficulty in determining causation, and an absence of data on medical care not subject to insurance reimbursement, such as for over-the-counter medications (13–16). Claims data have been used to

investigate a wide variety of disease areas for decades; more specifically, the MarketScan Commercial database has been successfully used previously to investigate patterns of treatment and costs associated with endometriosis (5, 12, 17).

The Health and Productivity Management database includes information on workplace absenteeism, short-term disability (STD), long-term disability (LTD), and compensations from employer payroll systems and disability case records for a subset of patients in the MarketScan Commercial database for which such information was consistently available for the time period of the study.

The MarketScan Research Databases comprise de-identified administrative healthcare claims data and comply with the US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996.

Study Population

Women aged 18–49 years with a claim for hysterectomy, oophorectomy, laparotomy or laparoscopy, or other endometriosis-related procedure (e.g., ablation/excision/fulguration) between January 1, 2006 and June 30, 2014 with a diagnosis of endometriosis (International Classification of Diseases, Clinical Modification, Ninth Edition [ICD-9-CM], Code 617.x) in a primary or secondary position on a nondiagnostic medical claim on the day of surgery/procedure were identified as the surgery cohort. The date of the surgery was selected as the index date. Female patients in the no-surgery cohort had an endometriosis diagnosis in any position on a nondiagnostic medical claim between January 1, 2006 and June 30, 2014 with no evidence of undergoing any endometriosis-related surgery during the entire study period or preceding the index date; their index date was a randomly assigned date following the first endometriosis diagnosis. All patients across both study cohorts were required to have continuous health plan coverage for 12 months before and after the index date (pre-index and post-index periods). In the no-surgery cohort, the requirement of continuous health plan enrollment, which ensures all of the patient's encounters with the healthcare system that resulted in claims were captured for at least 12 pre-index months, along with the exclusion of patients with evidence of relevant surgical procedures before index, helped to ensure these were endometriosis cases untreated by surgical means in the United States previously (although it does not rule out the chance that some patients who might have received surgery outside of the US healthcare system may be included). Patients with a medical claim indicating a diagnosis of malignant neoplasm of female genitourinary organs (ICD-9-CM: 179.x-184.x) or radical hysterectomy during the 12-month pre-index (baseline) period were excluded from analysis.

Patients in the surgery cohort were further stratified according to the type of index surgery: hysterectomy, oophorectomy, laparotomy, and laparoscopy. A small number of surgery patients with other miscellaneous procedures—excisions, ablation, or fulguration—were excluded from analysis. Patients who underwent multiple procedures on the index date were grouped according to the following hierarchy:

any patient with hysterectomy was classified as “hysterectomy.” Any patient with oophorectomy, except those also undergoing hysterectomy, were classified as oophorectomy patients. Laparotomy patients, either with or without laparoscopy but no other procedure, were classified as laparotomy patients. Finally, those who underwent laparoscopy without any of the previous procedures were classified as laparoscopy patients.

Study Variables

The primary outcome variables were all-cause and endometriosis-related healthcare resource utilization and costs, including costs of surgical treatment, evaluated for the 12-month pre- and post-index periods. Reported costs are total costs that include both plan-paid costs and patient out-of-pocket expenses. Endometriosis-related utilization and expenditures were defined as medical claims with a diagnosis of endometriosis or outpatient pharmacy claims for endometriosis treatment-related drugs (leuprolide, danazol, depot medroxyprogesterone, oral medroxyprogesterone acetate, levonorgestrel implants and intrauterine devices, megestrol acetate, progestin-only oral contraceptive pills, histrelin, goserelin, nafarelin, triptorelin, ganirelix, degarelix, cetrorelix, abarelix, and other oral contraceptive pills; aromatase inhibitors were not included in the analysis) or endometriosis-related surgery (patients with one or more endometriosis-related surgery overall, and stratified by surgery type into laparotomy, laparoscopy, hysterectomy, oophorectomy). Direct healthcare utilization and expenditures were reported for the following categories: inpatient, emergency room (ER), and outpatient services including obstetrics/gynecology (OB/GYN) visits and outpatient prescriptions. The Medical Care component of the United States Department of Labor’s Bureau of Labor Statistics Consumer Price Index (18) was used to adjust all currency amounts into year 2014 US dollars.

Productivity loss measured by proportion of patients with eligibility/claims for absenteeism (absence from work), STD and LTD, number of days lost, and the associated indirect costs in the post-index period were compared between surgery and no-surgery cohorts. The time loss (measured in days) was monetized by applying an average daily wage to the data. Average daily wage was calculated using the age and geographic region-adjusted wage rate from the US Bureau of Labor Statistics for year 2010. Because STD/LTD benefits do not normally replace full wages, 70% of the average daily wage was captured as expenditure incurred owing to STD/LTD (19, 20).

Other study parameters measured were patient demographic and clinical characteristics in the pre-index period. Demographics consisted of age, geographic region (US Census division), urbanicity (urban, rural, other/unknown), health plan type, and index year; all evaluated on index date. Clinical characteristics included the computed Deyo Charlson Comorbidity Index (CCI) (21), the prevalence of comorbid conditions (identified by ICD-9-CM codes), or evidence of pregnancy (as indicated by relevant ICD-9-CM diagnosis or Current Procedural Terminology codes). Baseline medication utilization, identified by Healthcare Common Procedure Cod-

ing System codes and National Drug Codes, was also summarized and compared between the study cohorts.

Statistical Analysis

Descriptive statistics were used to compare demographic and clinical characteristics, medication utilization, healthcare utilization, and costs between surgery and no-surgery cohorts. Continuous variables were summarized as means and SDs. Categorical variables were summarized as counts and percentages. Statistical comparisons between the two study cohorts were performed using analysis of variance and *t* tests for continuous variables and χ^2 test for categorical variables. A *P* value of $<.05$ was defined a priori as statistically significant.

Multivariate generalized linear regression models (with a log link function and γ error distribution) were used to estimate the incremental direct and indirect costs among patients in the surgery cohort in comparison with patients in the no-surgery cohort. To account for potential baseline differences between the surgery and no-surgery cohorts, regression models controlled for demographic characteristics (age, geographic region, and health plan type) and clinical differences (CCI and baseline comorbidities), as well as pre-index total healthcare costs of both study cohorts. To allow for straightforward interpretation of results, the recycled prediction method (22) was used to generate predicted mean cost differences between the study cohorts. Statistical significance was set at the a priori level of $P<.05$. A similar research design and analytic approach were used in a separate study that examined the incremental direct and indirect cost burden of endometriosis in the United States. Results of that study will be reported elsewhere (unpublished results).

RESULTS

Study Sample

The final study sample included 124,530 endometriosis patients who underwent endometriosis-related surgery and 37,106 women with no claims for any endometriosis-related surgery between January 1, 2006 and June 30, 2014.

Patient Characteristics

Baseline demographic and clinical characteristics stratified by cohort are presented in Table 1. Mean (SD) CCI scores in the pre-index period were 0.21 (0.63) for both cohorts. More than half of the patients in the surgery cohort had a hysterectomy procedure as their qualifying surgery (53%). Women in both cohorts had similar rates of comorbidities. Overall, a significantly higher proportion of patients in the surgery cohort (80.3%) had gynecologic comorbidities compared with those in the no-surgery cohort (37.3%, $P<.0001$). Opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and hormonal contraceptives were commonly used medications during the pre-index period, with higher prescriptions claims in the surgery cohort compared with the no-surgery cohort for all except hormonal contraceptives.

TABLE 1

Patient characteristics.			
Characteristic	Surgery cohort (n = 124,530)	No-surgery cohort (n = 37,106)	P value
Age (y), mean (SD)	38.28 (7.34)	37.99 (7.44)	< .0001
Age group (y)			< .0001
18–24	6,416 (5.2)	2,267 (6.1)	
25–29	10,374 (8.3)	2,856 (7.7)	
30–34	19,516 (15.7)	6,190 (16.7)	
35–39	26,736 (21.5)	8,287 (22.3)	
40–44	32,276 (25.9)	9,100 (24.5)	
45–49	29,212 (23.5)	8,406 (22.7)	
Population density			< .0001
Urban	101,164 (81.2)	31,891 (86.0)	
Rural	22,142 (17.8)	4,696 (12.7)	
Unknown	1,224 (1.0)	519 (1.4)	
Geographic region			< .0001
Northeast	14,334 (11.5)	7,423 (20.0)	
North Central	29,644 (23.8)	8,161 (22.0)	
South	59,120 (47.5)	13,635 (36.8)	
West	20,150 (16.2)	7,317 (19.7)	
Unknown	1,282 (1.0)	570 (1.5)	
Health plan type			< .0001
Comprehensive	1,878 (1.5)	432 (1.2)	
EPO	1,497 (1.2)	529 (1.4)	
HMO	20,642 (16.6)	5,606 (15.1)	
POS	10,181 (8.2)	2,748 (7.4)	
PPO	75,307 (60.5)	22,204 (59.8)	
POS with capitation	694 (0.6)	262 (0.7)	
CDHP	6,559 (5.3)	2,588 (7.0)	
HDHP	3,065 (2.5)	1,498 (4.0)	
Unknown	4,707 (3.8)	1,239 (3.3)	
Qualifying surgery			
Hysterectomy	66,062 (53.0)	n.a.	
Laparoscopy	51,668 (41.5)	n.a.	
Laparotomy	3,898 (3.1)	n.a.	
Oophorectomy	2,231 (1.8)	n.a.	
Deyo CCI, mean (SD)	0.21 (0.63)	0.21 (0.63)	.11
Comorbid conditions			
Abdominal/pelvic pain	32,960 (26.5)	6,793 (18.3)	< .0001
Acute coronary syndrome	1,081 (0.9)	283 (0.8)	.051
Anal or rectal pain	485 (0.4)	134 (0.4)	.437
Anxiety	10,194 (8.2)	3,712 (10.0)	< .0001
Asthma	6,851 (5.5)	2,329 (6.3)	< .0001
Bladder pain	174 (0.1)	62 (0.2)	.225
COPD	3,317 (2.7)	983 (2.6)	.879
Depression	12,119 (9.7)	3,967 (10.7)	< .0001
Diabetes	4,364 (3.5)	1,189 (3.2)	.0053
Heart failure	210 (0.2)	76 (0.2)	.145
Hyperlipidemia	7,095 (5.7)	2,116 (5.7)	.969
Hypertension	14,736 (11.8)	3,669 (9.9)	< .0001
Irritable bowel syndrome	2,975 (2.4)	891 (2.4)	.892
Migraine	8,895 (7.1)	2,704 (7.3)	.344
Osteoarthritis	2,673 (2.1)	904 (2.4)	.0009
Osteoporosis	198 (0.2)	109 (0.3)	< .0001
Pelvic peritoneal adhesions	1,901 (1.5)	281 (0.8)	< .0001
Upper respiratory infections	38,596 (31.0)	11,120 (30.0)	.0002
Comorbid conditions, gynecologic			
Any gynecologic comorbidity listed below	100,045 (80.3)	13,844 (37.3)	< .0001
Dyspareunia	5,761 (4.6)	567 (1.5)	< .0001
Dysmenorrhea	22,422 (18.0)	2,247 (6.1)	< .0001
Excessive or frequent menstruation	35,598 (28.6)	3,576 (9.6)	< .0001
Metrorrhagia	5,549 (4.5)	696 (1.9)	< .0001
Ovarian cysts	26,790 (21.5)	2,939 (7.9)	< .0001
Unspecified symptoms of female genital organs	41,302 (33.2)	5,005 (13.5)	< .0001
Uterine fibroids	27,216 (21.9)	2,699 (7.3)	< .0001
Vaginitis	9,495 (7.6)	2,647 (7.1)	.0016

Soliman. Cost burden of endometriosis surgery. *Fertil Steril* 2017.

TABLE 1

Characteristic	Surgery cohort (n = 124,530)	No-surgery cohort (n = 37,106)	P value
Continued.			
Reproductive claims			
Infertility	8,026 (6.4)	1,804 (4.9)	< .0001
Fertility treatments	5,661 (4.5)	2,025 (5.5)	< .0001
Pregnancy/delivery	5,371 (4.3)	3,808 (10.3)	< .0001
Medications			
Antidepressants	62,334 (50.1)	16,253 (43.8)	< .0001
Estrogen/progestin oral contraceptives	50,304 (40.4)	17,633 (47.5)	< .0001
NSAIDs	95,332 (76.6)	24,074 (64.9)	< .0001
Opioids	118,011 (94.8)	28,288 (76.2)	< .0001

Note: Values are number (percentage) unless otherwise noted. Demographic characteristics and qualifying surgery measured at index date. Clinical characteristics measured over 12-month pre-index baseline period. CCI = Charlson Comorbidity Index; CDHP = consumer-driven health plan; COPD = chronic obstructive pulmonary disease; EPO = exclusive provider organization; HDHP = high deductible health plan; HMO = health maintenance organization; n.a. = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs; POS = point of service; PPO = preferred provider organization.

Soliman. Cost burden of endometriosis surgery. *Fertil Steril* 2017.

Healthcare Utilization and Costs

With few exceptions, endometriosis patients with surgery used significantly more healthcare services in the 12 months after surgery than those without surgery. In nearly every category analyzed (inpatient admissions, ER visits, physician office visits, specialist OB/GYN visits, and outpatient prescription claims), the surgery cohort had a larger percentage of patients with a relevant claim, a larger mean number of relevant claims, or both (Table 2). Exceptions to this included proportion of patients with a physician office visit, which was similarly high in both cohorts (95% in both), and proportion of patients with a specialist OB/GYN visit (53% in both cohorts). The trend was reversed in the case of outpatient prescription claims, for which the no-surgery cohort had both a greater percentage of patients with claims and a higher mean number of prescriptions per patients. For information on pre-index utilization, see Supplemental Figure 1 (available online).

Overall, annual all-cause expenditures were significantly higher in the surgery cohort compared with the no-surgery cohort during the post-index period (\$18,881 vs. \$7,013; $P < .0001$), whereas the opposite was true during the pre-index period (\$6,841 vs. \$8,247; $P < .0001$) (Fig. 1A). For surgery patients the major drivers of higher all-cause costs were inpatient admissions (68.8%) and pharmacy claims (20.7%), with a lower proportion driven by outpatient office (5.3%) or emergency room visits (9.6%). Similarly, the surgery cohort incurred significantly higher endometriosis-related expenditures than their no-surgery counterparts (\$8,415 vs. \$275; Fig. 1B), with index surgery costs accounting for the majority, but not all, of the difference.

Among the endometriosis patients who underwent surgery, the costs of the qualifying surgical event were highest for those who underwent oophorectomy (\$12,794) and lowest for laparoscopy (\$3,422; Table 2). As described in the section on the study population, these groups may also have secondary procedures performed in conjunction with the index surgery (except for the laparoscopy subcohort, which was defined as a single-procedure cohort). Costs for patients

who received only a single procedure on index are also given in Table 2.

By type of surgery, the total healthcare costs in the 12 months following the surgery ranged from \$17,133 to \$23,813, and endometriosis-related costs ranged from \$7,678 to \$12,878, with the highest cost incurred by patients who underwent oophorectomy and the least cost by those who underwent laparoscopy (Fig. 2A). The differences in the total annual direct costs between each of the surgery subcohorts and the no-surgery cohort ranged from \$10,120 for the least invasive procedure (laparoscopy) to \$16,800 for oophorectomy.

Work Loss and Indirect Costs

Although the proportion of patients with absence claims in the post-index period was the same across both cohorts, the average number of absent days was higher for the surgery cohort than for the no-surgery cohort, resulting in higher average costs of work loss due to absence (\$6,237 vs. \$4,781; $P < .0001$; Table 2). The proportion of patients with STD claims, days of STD claimed, and the associated costs were significantly higher in the surgery cohort compared with the no-surgery cohort (\$2,379 vs. \$597; $P < .0001$; Table 2). Among surgery patients the vast majority (93.8%) of those with an STD claim had a claim within 30 days after index—very proximal to the surgery date. The rates of LTD were low in both cohorts, with a similar mean number of LTD work days lost in the surgery cohort and the no-surgery cohort (Table 2).

By type of surgery, indirect costs due to short-term disability were highest among oophorectomy patients, whereas indirect costs due to absence were highest among hysterectomy patients (Fig. 2B).

Multivariate Adjusted Direct and Indirect Healthcare Costs

Endometriosis patients who have undergone surgery had a statistically significant incremental adjusted direct and

TABLE 2

Utilization and costs during 12-month follow-up.

Parameter	Surgery cohort (n = 124,530)	No-surgery cohort (n = 37,106)	P value
Healthcare utilization, all-cause			
Patients with inpatient admission, n (%)	53,948 (43)	3,205 (9)	< .0001
Admissions per patient, mean (SD)	0.49 (0.64)	0.11 (0.43)	< .0001
Patients with ER visit, n (%)	35,546 (29)	9,744 (26)	< .0001
ER visits per patient, mean (SD)	0.52 (1.37)	0.50 (1.46)	.010
Patients with physician office visit, n (%)	117,983 (95)	35,203 (95)	.330
Physician office visits per patient, mean (SD)	7.0 (6.6)	7.2 (7.4)	< .0001
Patients with OB/GYN specialist visit, n (%)	66,368 (53)	19,765 (53)	.920
OB/GYN office visits per patient, mean (SD)	1.4 (2.6)	1.1 (1.9)	< .0001
Patients with outpatient prescription claim, n (%)	120,445 (97)	33,770 (91)	< .0001
Prescriptions per patient, mean (SD)	20.6 (20.5)	17.2 (20.1)	< .0001
Healthcare utilization, endometriosis-related			
Patients with inpatient admission, n (%)	33,658 (27)	80 (<1)	< .0001
Admissions per patient, mean (SD)	0.27 (.45)	0.002 (.05)	< .0001
Patients with ER visit, n (%)	2,096 (1.7)	208 (<1)	< .0001
ER visits per patient, mean (SD)	0.02 (0.17)	0.01 (0.19)	< .0001
Patients with physician office visit, n (%)	20,089 (16)	4,385 (12)	< .0001
Physician office visits per patient, mean (SD)	0.35 (1.13)	0.21 (0.870)	< .0001
Patients with OB/GYN specialist visit, n (%)	13,732 (11)	2,829 (7.6)	< .0001
OB/GYN office visits per patient, mean (SD)	0.21 (0.82)	0.12 (0.52)	< .0001
Patients with outpatient prescription claim, n (%)	27,967 (23)	11,807 (32)	< .0001
Prescriptions per patient, mean (SD)	1.1 (2.7)	1.8 (3.6)	< .0001
Healthcare costs (\$)			
All-cause, mean (SD)	18,881 (18,708)	7,103 (18,038)	< .0001
Endometriosis-related, mean (SD)	8,417 (8,943)	275 (1,558)	< .0001
Cost of qualifying surgical event, mean (SD)	7,268 (7,975)	n.a.	
Hysterectomy (n = 66,062), mean (SD)	9,955 (8,659)	n.a.	
Laparoscopy (n = 51,668), mean (SD)	3,422 (3,936)	n.a.	
Laparotomy (n = 3,898), mean (SD)	8,592 (10,085)	n.a.	
Oophorectomy (n = 2,231), mean (SD)	12,794 (12,299)	n.a.	
Single procedure only at index			
Hysterectomy (n = 46,936), mean (SD)	8,954 (7,923)	n.a.	
Laparoscopy ^a (n = 51,668), mean (SD)	3,422 (3,936)	n.a.	
Laparotomy (n = 2,107), mean (SD)	10,413 ^b (11,328)	n.a.	
Oophorectomy (n = 1,071), mean (SD)	11,962 (10,304)	n.a.	
Work loss			
Patients with absence data, n (%)	1,559 (1.3)	368 (1.0)	< .0001
Patients with absence claim, n (%)	1,110 (71.2)	262 (71.2)	.999
Absence days, mean (SD)	33.84 (23.76)	26.67 (17.83)	< .0001
Patients with STD data, n (%)	9,483 (7.6)	2,448 (6.6)	< .0001
Patients with STD claim, n (%)	4,479 (47.2)	229 (9.4)	< .0001
STD days, mean (SD)	18.94 (26.95)	4.95 (21.46)	< .0001
Patients with LTD data, n (%)	7,490 (6.0)	2,175 (5.9)	.275
Patients with LTD claim, n (%)	41 (0.5)	7 (0.3)	.188
LTD days, mean (SD)	0.46 (8.73)	0.31 (8.37)	.505
Indirect costs due to work loss (\$)			
Absence, mean (SD)	6,237 (4,745)	4,781 (3,335)	< .0001
STD, mean (SD)	2,379 (3,457)	597 (2,639)	< .0001
LTD, mean (SD)	60 (1,194)	40 (1,091)	.517

Note: All costs are estimated as 2014 US dollars.

^a As described in the text, the primary laparoscopy cohort is already defined as having a single-procedure only as a qualifying event.

^b Patients with a laparotomy claims but no laparoscopy claim on index were markedly more likely to have an inpatient procedure (69% inpatient) compared with the more inclusive cohort as a whole (47% inpatient), which can account for the increased cost.

Soliman. Cost burden of endometriosis surgery. *Fertil Steril* 2017.

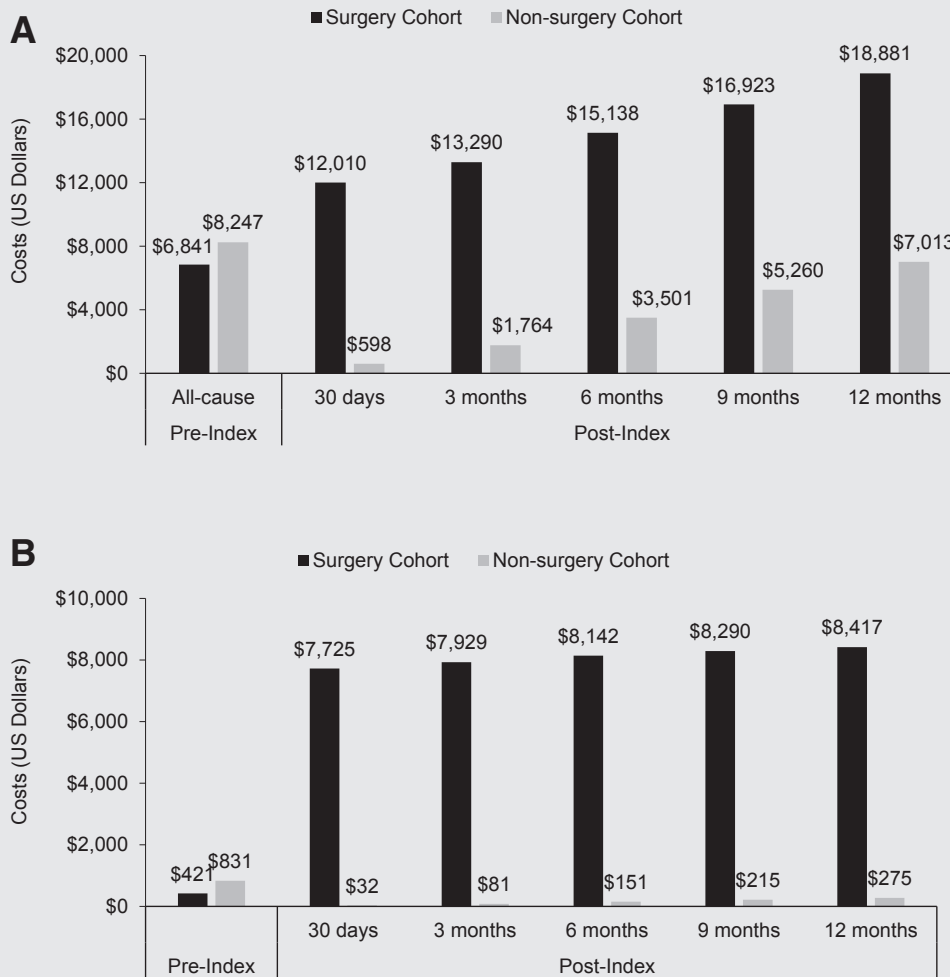
indirect cost burden compared with endometriosis patients who did not receive surgery. The mean adjusted annual incremental direct healthcare costs were \$12,838 for endometriosis patients with surgery compared to endometriosis patients without surgery ($P < .001$; Supplemental Table 1). The mean adjusted incremental costs related to absenteeism and STD compared with the no-surgery controls were \$1,155, and \$1,885, respectively (both $P < .001$; Supplemental Table 1). Two-part models were used for estimating STD regression

models because of the large number of zero costs that were observed in the analytic sample (23). The overall incidence and associated costs were very low for LTD and hence were not examined in a separate multivariate model.

DISCUSSION

This study is the first study to simultaneously assess both direct and indirect costs associated with endometriosis

FIGURE 1



All costs are estimated as per 2014 US Dollars
 All p<0.0001 for Surgery Cohort vs. No-surgery cohort

Healthcare costs in the pre- and post-index periods. Costs in the post-index period are cumulative from the index date to the period shown. (A) All-cause healthcare costs. (B) Endometriosis-related healthcare costs.

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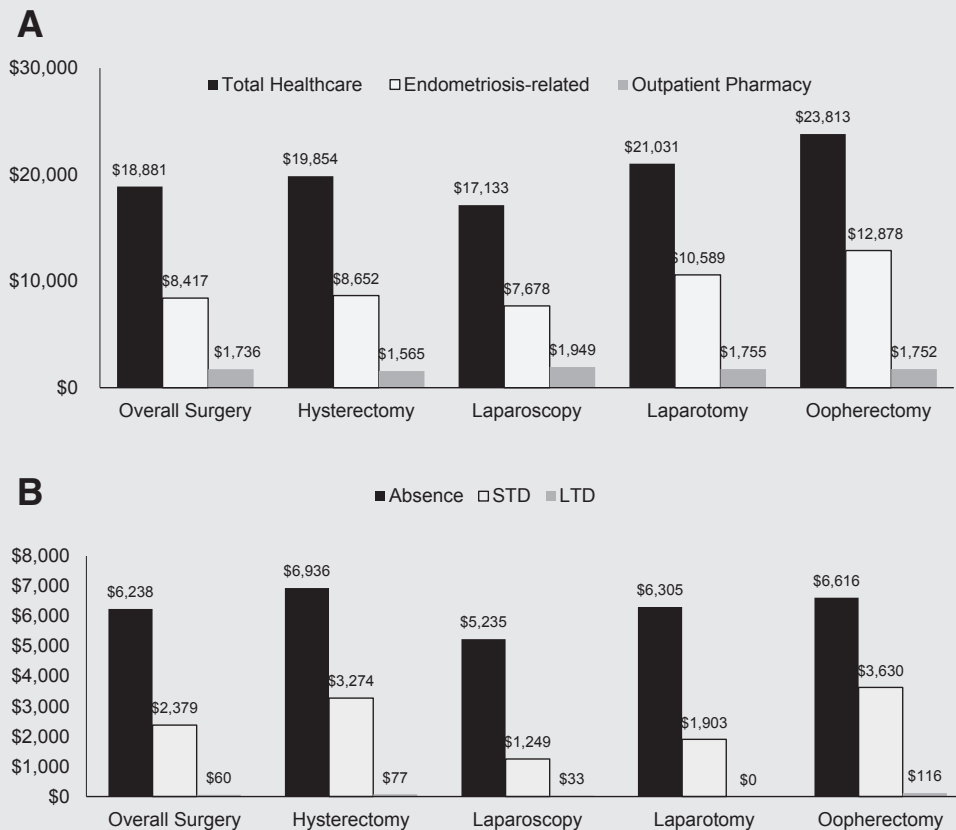
surgeries in the United States. This analysis showed that the direct healthcare costs for surgery among endometriosis patients, measured 12 months after endometriosis diagnosis, were significantly higher than those for patients who did not undergo any endometriosis-related surgery. Similarly, work loss due to absence and STD and associated indirect costs were higher in the surgery cohort.

The relative magnitude of burden (direct and indirect) due to surgery in patients with endometriosis remains highly elusive. Although some researchers have assessed both direct healthcare costs and indirect costs associated with endometriosis in the United States (4, 6, 7), there are currently no studies that have quantified both direct and indirect healthcare costs associated with surgery in endometriosis patients in the United States. The present study showed that endometriosis patients who underwent surgery

incurred significantly higher healthcare costs compared with those who did not undergo any surgery, with the adjusted mean total direct cost estimated at \$19,203 per patient per year for an endometriosis patient who has undergone surgery and \$6,365 per patient per year for a patient with no surgery.

Overall, surgery (accounting for 87% of endometriosis-related costs) was the key driver of the endometriosis-related costs incurred by the patients during follow-up, of which oophorectomy was the most expensive procedure. Similar to our study, other research has shown that surgery costs account for a large portion of the overall cost for endometriosis patients (5-7, 12, 17). The hysterectomy costs, direct and indirect, are comparable to those reported in an analysis of surgical interventions for women with abnormal uterine bleeding (24).

FIGURE 2



All costs are estimated as per 2014 US Dollars.
STD, Short-Term Disability; LTD, Long-Term-Disability

Costs in the post-index period by type of surgery. (A) Healthcare costs by type of surgery in the post-index period. (B) Indirect costs by type of surgery in the post-index period.

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When adjusted for inflation, the estimates of costs for the qualifying surgery we found seem to indicate a trend toward lower costs over time as part of the changing landscape of gynecologic surgical care. An earlier study by Gao et al. (3) estimated the costs of surgical procedures to range between \$14,896, for nonlaparoscopic vaginal hysterectomy up to \$26,593 for “other peritoneal adhesiolysis” (all costs here and below are inflation-adjusted by the medical component of the U.S. consumer price index (CPI-M) to 2014 US dollars). The costs of the surgical procedures in the present analysis are more comparable overall to more recent estimates from Fuldeore et al. (12), but there is still a trend for lower costs for most procedures. Fuldeore et al. found the cost for abdominal hysterectomy to be \$13,211 and for vaginal hysterectomy to be \$9,932, compared with the present finding of the surgical cost for hysterectomy (using the single-procedure costs) to be \$8,954 (which is a composite of vaginal, abdominal, and laparoscopic hysterectomy approaches). The observed reductions in the cost of a hysterectomy procedure could be attributed to the strong trend toward outpatient hysterectomy proced-

ures instead of inpatient procedures (25). The cost of laparoscopy was 32% lower in the present analysis than in the Fuldeore et al. study as well (\$4,972 vs. \$3,387), whereas the cost of laparotomy was similar (3% lower, \$9,045 vs. \$8,754), and oophorectomy was somewhat more expensive (\$11,690 vs. \$13,309, a 13% increase).

Endometriosis-related surgery was associated with considerable indirect costs as well. Although previous studies have estimated indirect costs in the United States due to absenteeism and productivity loss in patients diagnosed with endometriosis, no previous studies have examined the incremental effect of surgery on indirect costs. We found that the indirect costs for endometriosis patients with surgery (due to absenteeism, including STD and LTD) were significantly higher, with 7.1 and 13.9 additional days of absence and STD across all patients, leading to increased average annual costs of \$1,457 and \$1,782, per patient, respectively (all $P < .001$). This should be considered a conservative estimate of the incremental indirect costs, because costs due to reduced on-the-job productivity (“presenteeism”) are not

measured. Previous work indicates that presenteeism may comprise a majority of productivity losses due to endometriosis (7, 26).

A notable strength of our study is that it included a large, representative cohort of endometriosis patients and described both their direct and indirect healthcare costs. Additionally, the present real-world assessment provides an update to prior cost estimates that captures practices of surgical interventions among endometriosis patients in the United States, which will help provide more useful estimates for examining the cost effectiveness of surgical treatment of endometriosis compared with the other treatment modalities, such as pharmacotherapy. Finally, the present analysis provides an adjusted estimate of cost differences, using multivariate regression modeling that controlled for potential confounding effects of observed differences in patient characteristics like demographics, comorbidities, and prior healthcare costs between the two study cohorts.

Nonetheless, this study has limitations, some of which are due to utilizing an administrative claims database for research. Any endometriosis-related surgery that did not have an endometriosis diagnosis recorded on the same day as the procedure would not have been captured using our methodology and thus was not used to estimate cost of surgeries or endometriosis-related costs. Similarly, the exact reason for each surgical procedure could not be fully ascertained from the claims data (thus, we required a record of an endometriosis diagnosis code on the procedure day to help overcome this limitation). No specific information on the endometriosis-associated pain levels or the American Society for Reproductive Medicine stage of endometriosis was available from the claims data as well. Pain levels and disease stage would impact the likelihood that a patient would undergo a surgery and thus could have affected patients' assignment into the surgery cohort. In addition, claims data do not contain histopathologic results, which could be used to confirm the endometriosis diagnosis. Any medical care that did not result in a reimbursed claim, such as the use of over-the-counter medications, was not captured in the data. Common to all studies that utilize data on commercially insured populations only, the caveat that our results may not be fully applicable to patients who are insured through mechanisms other than commercial insurance (e.g., Medicaid, self-insured, or uninsured) would apply as well.

Owing to the observational nature of this study, bias arising from nonrandom patient assignment/exposure to endometriosis surgeries could not be entirely ruled out. To address this, the multivariable analyses corrected for potential confounders that were measured in the claims data (e.g., age and geographic region). Unobservable factors may have affected surgery choice and associated outcomes like physicians' preference for surgical management vs. medical management approaches, as well as patients' preferences for undergoing a surgical treatment.

The method of diagnosis, which may have differed between the cohorts, was not identified in this study. Surgical diagnosis is often considered the gold standard of endometriosis diagnostic testing (27, 28), although close to half of

women diagnosed with endometriosis are diagnosed nonsurgically (29, 30), and some diagnoses may represent suspected rather than confirmed endometriosis. In our sample, patients in the no-surgery cohort are likely to have been diagnosed nonsurgically. Further research would be required to clarify whether there is a relationship between method of diagnosis and subsequent costs in endometriosis.

One last limitation to note was due to the length of the pre-index period. In the present study design the no-surgery cohort consisted of patients without evidence of surgery for at least a 12-month pre-index period. However, this does not preclude the chance that those women might have received an endometriosis-related surgery earlier than the prescribed 12-month pre-index period. Future studies with a longer pre-index lookup period would be needed to examine this possibility.

Despite limitations, this study was unique in that it evaluated a large sample of patients from a large commercial insurance database and provides an update on direct and indirect healthcare costs associated with undergoing an endometriosis-related surgery. In addition, because the commercial database includes adult endometriosis patients treated by clinicians across all US geographic regions and covered under various health plans, the findings of this study reflect the cost burden trends for surgery among endometriosis patients in a real-world setting.

In conclusion, the results from this analysis showed that, after multivariate adjustment, endometriosis patients who underwent surgery had significantly higher healthcare resource utilization that translated to substantial direct and indirect cost burden compared with patients without surgery. This study suggests that the prevalence of endometriosis and the need for treatment, along with the related procedures, exert a significant burden on the individual, healthcare system, and society as a whole.

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SUPPLEMENTAL TABLE 1

Multivariable analysis of costs per patient during 12-month follow-up.

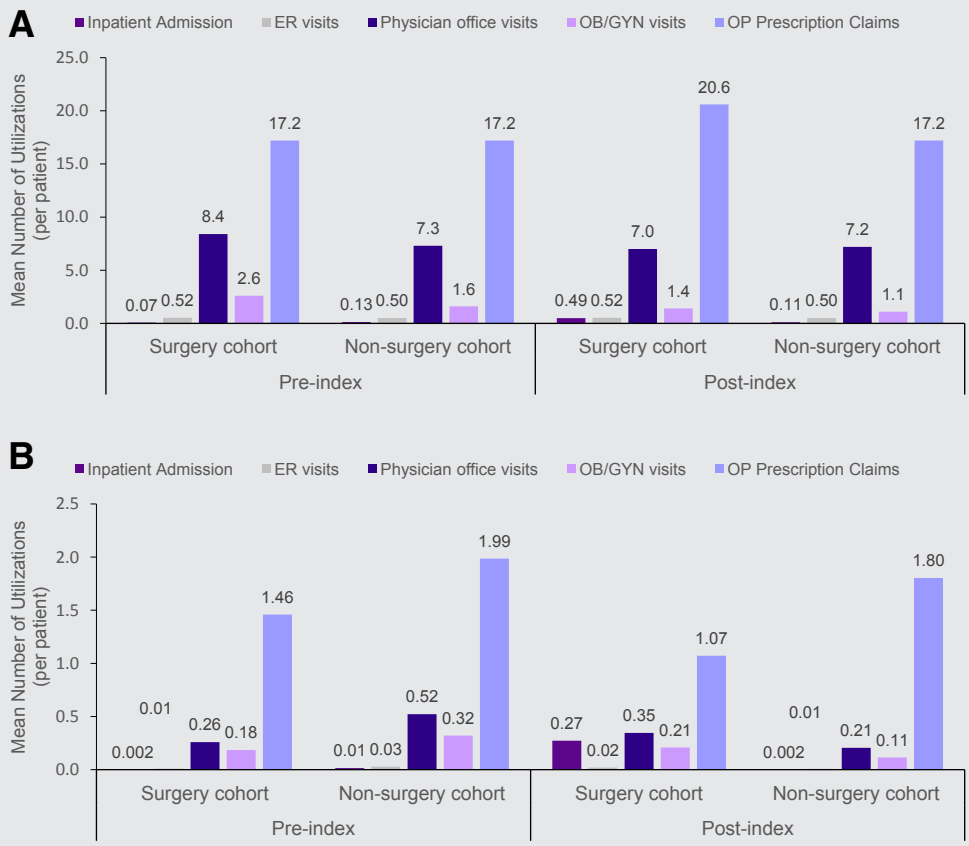
Factor	Surgery cohort	No-surgery cohort	Incremental cost
Total healthcare costs (\$)	19,203 (7,134); n = 124,530	6,365 (2,364); n = 37,106	12,838
Indirect costs (\$)			
Absence	6,177 (1,756); n = 1,559	5,022 (1,428); n = 368	1,155
Short-term disability ^a	2,439 (1,264); n = 9,483	553 (287); n = 2,448	1,885

Note: Values are mean (SD) and n. All costs are estimated as 2014 US dollars. All cohort differences are significant, $P < .001$.

^a Owing to very low incidence and associated costs, long-term disability was not examined in a separate multivariate model.

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SUPPLEMENTAL FIGURE 1



All $p < 0.0001$ for Surgery Cohort vs. No-surgery cohort; except for all-cause pre-index OP prescription claims ($p = 0.98$) and all-cause post-index ER visits ($p = 0.01$) for Surgery Cohort vs. No-surgery cohort

ER, Emergency Room; OB/GYN, Obstetrician/gynecologist; OP, Outpatient

Healthcare utilization in the pre- and post-index periods. (A) All-cause healthcare utilization. (B) Endometriosis-related healthcare utilization.

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