ENDOMETRIOSIS HISTORY AND PRESCRIPTION MEDICATION USAGE AMONG REPRODUCTIVE-AGED WOMEN IN NHANES 1999-2006

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ABSTRACT

Endometriosis is a gynecologic, chronic inflammatory condition characterized by the presence of tissue histologically resembling endometrial glands and stroma outside of the uterus. The condition can be associated with substantial symptoms and a range of comorbidities. The economic burden of endometriosis symptom and comorbidity pharmaceutical management has been examined in a limited number of studies using insurance claims data; no studies to our knowledge have captured the clinical complexity of the condition using information on the number and types of prescription medications in the general population. I examined the history of endometriosis diagnosis and current prescription medication use in a cross-sectional analysis of U.S. individuals ages 20-54 years using National Health and Nutrition Examination Survey (NHANES) data from years 1999 to 2006 (unweighted n=5,550). History of endometriosis diagnosis and number of current prescription medications were collected by self-report. Prescription number was categorized as ≥2 prescriptions (vs. <2) within 30 days of the NHANES interview, and polypharmacy was defined as ≥5 prescriptions (vs. <5). I conducted log-binomial regression to estimate the prevalence ratios (PRs) and 95% confidence intervals (CIs) for the relationship between endometriosis history and prescription medication use, adjusting for age, education, insurance status, body mass index, and smoking, and accounting for the complex survey sampling design. Prevalence of endometriosis diagnosis history, current use of ≥2 prescriptions, and polypharmacy were 9%, 32%, and 8% respectively. Those with a history of endometriosis diagnosis (vs. without) had a 40% greater prevalence of taking ≥2 prescription medications (PR 1.4, 95% CI: 1.3, 1.7). I observed a stronger association with polypharmacy use (PR 1.9, 95% CI: 1.3, 2.7). My results suggest endometriosis is associated with greater prescription medication use, highlighting the clinical complexity of the condition and the multiple medications that may be needed to manage symptoms and comorbidities.

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INTRODUCTION

Endometriosis is a chronic inflammatory condition characterized by the presence of tissue histologically similar to the endometrium growing outside of the uterus (Zondervan et al., 2018). It affects approximately 6-10% of reproductive-age women (Falcone & Flyckt, 2018). However, the true prevalence of endometriosis is unknown, given that the condition can only be definitively diagnosed by surgical visualization of endometriotic lesions typically through laparoscopy (Dunselman et al., 2014). Symptoms of endometriosis can be substantial and include cyclic and acyclic pelvic pain; pain with urination, bowel movements, and/or intercourse; as well as fatigue and infertility (Zondervan et al., 2020, Carlyle et al., 2020). In addition, some data suggest that endometriosis commonly co-occurs with other conditions that also can have an adverse impact on well-being, such as fibromyalgia, migraines, depression, anxiety, rheumatoid arthritis, asthma, thyroid conditions, and cardiovascular disease (Kvaskoff et al., 2017; Poppe et al., 2007; Zondervan et al., 2020). Both the symptoms of endometriosis and associated comorbidities can negatively affect quality of life (Nnoaham et al., 2011) – to the extent that the burden of endometriosis can be comparable to that of other chronic conditions such as diabetes (Simoens et al., 2012).

There is no current cure for endometriosis. Treatment focuses on disease suppression and amelioration of symptoms, such as the surgical excision of lesions, hormonal therapies, and pain management (Carey et al., 2017; Carlyle et al., 2020). Pharmaceutical management is also central to care, with the selection of prescription medications being unique and varying across individuals (Gambone et al., 2002). Despite this, few studies have evaluated the impact of endometriosis on prescription medication use. The prescribing of high numbers of prescription medications can present challenges with treatment regimen adherence and drug-drug interactions, and the total costs can incur financial burden. Although these burdens of polypharmacy have been studied with respect to multimorbidity in geriatric populations (Muth et al., 2019), reproductive-aged individuals have been less commonly studied. The few studies that have

been conducted with respect to reproductive-age participants used insurance claim data to evaluate prescription medication costs, reporting higher costs for those with endometriosis (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015). Although these findings are important and shed light on the burden of endometriosis, it is unclear whether the higher costs are driven by many prescription medications or a few expensive medications. In addition, those studies were limited to those who were insured, excluding those who may be uninsured or have inconsistent insurance coverage. Thus, the focus on cost alone may not fully capture the complex clinical picture of endometriosis, including its associated symptoms and co-occurring comorbidities, and its burden in the general population. This may be captured, however, by considering the number and types of prescription medications taken using publicly available data of the U.S. population. Hence, the purpose of the present study is to investigate whether history of endometriosis diagnosis is associated with increased prescription medication use in a nationally representative sample of U.S. reproductive-age individuals. I also explored whether specific therapeutic categories of prescription medications are more frequently prescribed to those with a history of endometriosis diagnosis compared to those without the condition.

METHODS

Study design and population

I conducted a cross-sectional study using de-identified, publicly available data from the National Health and Nutrition Examination Survey (NHANES) across four data cycles from years 1999-2006 (1999-2000, 2001-2002, 2003-2004, and 2005-2006 cycles). NHANES is a nationally representative survey of the non-institutionalized United States population conducted by the Centers for Disease Control and Prevention (CDC) to evaluate the health status of adults and children in the U.S. population (NCHS, 1999). The major components of NHANES include an in-person interview and Mobile Examination Center (MEC) examination, which collects information on demographics, reproductive health, prescription medication use, health-related behaviors, and medical conditions. Participants of all ages are selected using a complex population-based over-sampling design. This sampling design is done to obtain greater representation of subgroups less frequently represented in the U.S. population. These subgroups include Black Americans, Hispanics, persons over age 60, and low-income whites. The four NHANES cycles from 1999-2006, in total, consisted of 41,474 participants.

For the present analyses, I restricted the study population to female participants (ages 20-54 years at the time of NHANES interview) for whom information was available on both endometriosis diagnosis history as well as prescription medication use. Information collected by the field interviewer during the in-person interview on gender was limited to male or female; participants were only directly asked their gender "if not obvious" to the field interviewer (NCHS, 1999). Therefore, I used gender-inclusive language when describing study participants (Rioux et al., 2022). I included participants regardless of menopausal, hysterectomy, and bilateral oophorectomy status at the time of NHANES interview to minimize selection bias. Endometriosis is associated with an earlier age at menopause (Pokoradi et al., 2011) and pharmaceutical management of endometriosis-related symptoms can induce menopausal symptoms (Dunselman et al., 2014). Endometriosis is also associated with surgical menopause from undergoing hysterectomy and/or bilateral oophorectomy (Fedele et al., 2005). Thus, given the cross-sectional study

design and median of 10 years between endometriosis diagnosis and NHANES interview in the study population (described below), the exclusion of participants with a history of natural or surgical menopause could remove from the study population those with a history of endometriosis diagnosis who also may use a greater number of prescription medications. A total of 5,550 participants met the eligibility criteria and were included in the present analyses (Figure 1).

History of endometriosis diagnosis

Data on the exposure of interest in the present analyses, history of endometriosis diagnosis, was collected among female participants ages 20-54 years using the Reproductive Health Questionnaire as part of the MEC examination. During the interview, participants were asked, "Has a doctor or other health professional ever told you that you had endometriosis?" Using the responses to this question, we created a binary variable for endometriosis diagnosis history (yes, no); we coded the responses of "don't know" or "refused" as missing. If a participant responded yes, they were additionally asked for their age at diagnosis.

Prescription medication use

The outcome of interest, the number of prescription medications, was ascertained during the in-person interview using the Prescription Medications Questionnaire. Participants were asked the question: "In the past month, have you used or taken a medication for which a prescription is needed?" Participants who answered yes to this question were then asked to show the NHANES interviewer the containers for each medication; for each participant, information on the standard generic ingredient names were collected in addition to the total number of prescriptions for each participant. Since the total number of prescriptions was only collected among participants reporting prescription medication use, I created a composite variable that also included participants who reported not taking any prescription medications (coded as using 0 prescription medications). I coded the responses of "don't know" or "refused" as missing. I

categorized the total number of prescriptions as a binary variable using the cut point of two prescription medications (<2, ≥2 prescription medications). I selected the cut point of two prescription medications using the median number of medications among those taking prescription medications in the study population given the absence of data in the literature for reproductive-age women. I also considered the outcome of polypharmacy, which is defined as five or more prescription medications, using a binary variable (<5, ≥5 prescription medications) (Guillot et al., 2020).

In addition to the number of prescription medications, for use in an exploratory analysis, I considered the therapeutic classification of each medication prescribed. Each generic drug ingredient name recorded in the Prescription Medication Questionnaire was assigned a specific generic drug code. In the NHANES Drug Information dataset, each generic drug code was linked to the corresponding therapeutic category using the Multum Lexicon Therapeutic Classification scheme, a three-level nested system (NCHS, 1999). For the present analyses, we used data on Therapeutic Category 1, Level 2. For example, the three-level classification scheme for a common antidepressant medication, escitalopram, is psychotherapeutic agent [Level 1], antidepressant [Level 2], SSRI antidepressant [Level 3].

Covariates

In NHANES, a number of questionnaires are administered to participants to collect data on a range of factors. Data on age and educational attainment were available from the Demographics Questionnaire whereas data on body mass index were collected by measurement of participant weight and height. The Smoking and Tobacco Use Questionnaire ascertained data on smoking status and insurance coverage data were attained through the Health Insurance Questionnaire. History of diabetes and diagnosis of hypertension, thyroid problems, and asthma were ascertained using the Diabetes Questionnaire and the Medical Conditions Questionnaire, respectively. The Miscellaneous Pain Questionnaire collected data on history of severe migraines as well as history of chronic pain. Information on migraine and chronic pain history was limited to three NHANES data cycles from years 1999-2000, 2001-2002, and 2003-2004. The

Depression Screener Questionnaire from the 2005-2006 NHANES cycle was used to evaluate depression symptoms. A score ≥10 was categorized as moderate to severe depression symptoms and a score <10 was categorized as none to mild depression (Manea et al., 2012). Information on history of depression was limited to one NHANES data cycle from years 2005-2006.

Statistical analyses

I used descriptive statistics to compare sociodemographic and health-related characteristics between those with and without a history of endometriosis diagnosis. I examined the association between history of endometriosis diagnosis and prevalence of two or more prescription medications using log-binomial regression to estimate the prevalence ratios (PRs) and 95% confidence intervals (CIs). I used the same approach to examine the association between history of endometriosis diagnosis and prevalence of polypharmacy (≥5 prescription medications). I applied appropriate weights during the analysis to account for the complex survey sampling design within NHANES (NCHS, 1999). In all analyses, I adjusted for age (continuous) at time of NHANES interview. I selected covariates *a priori* based on established associations with endometriosis and polypharmacy medication use (Eisenberg et al, 2022; Fuldeore et al., 2015). In the multivariable-adjusted model, in addition to age, I adjusted for educational attainment (high school graduate or general equivalency diploma (GED) or less, some college or other post-secondary education, college graduate or more), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), and smoking status (never, former, current < 20 cigarettes per day, current ≥20 cigarettes per day).

I explored whether specific therapeutic categories of prescription medications were more frequently prescribed to those with a history of endometriosis diagnosis compared to those without the diagnosis using descriptive statistics. Although data were available on 20 Therapeutic Category 1, Level 2 categories, I explored the therapeutic medication categories for which 250 or more prescriptions were reported in the study sample. Given the primary outcome defined as ≥2 prescription medications, I also

descriptively evaluated the frequency of using ≥2 prescription medications from the same therapeutic category (e.g., ≥2 analgesic medications) and the use of combinations of two prescriptions for which 250 or more prescriptions were reported.

I conducted three sensitivity analyses. First, I repeated the main analyses excluding participants who were menopausal or who had a history of hysterectomy and/or bilateral oophorectomy at the time of NHANES interview. Specifically, I restricted the study population to those who were premenopausal at the time of NHANES interview (unweighted n = 4,453), defined as having an intact uterus, at least one ovary, and menses within the past 12 months. Participants with an intact uterus and at least one ovary who did not have menses within the past 12 months due to current or recent pregnancy, or due to medical treatment that resulted in amenorrhea were also considered premenopausal. I conducted this sensitivity analysis to increase the ability of my study to detect an association between endometriosis diagnosis history and prescription medication use as premenopausal individuals actively experiencing endometriosis symptoms may require more pharmaceutical symptom management than postmenopausal individuals with a history of endometriosis diagnosis. The severity of endometriosis symptoms requiring pharmaceutical management typically decreases during menopause as a result of diminished endogenous estrogen levels (Bulun et al., 2019). Additionally, menopausal hormonal therapy increases, with use of exogenous estrogen and progesterone preparations to manage symptoms of menopause (Armeni et al., 2021). Thus, prescription medications captured among postmenopausal participants may include those used to manage menopausal-related symptoms as opposed to endometriosis symptoms. In this sensitivity analysis, I considered both outcomes of two or more prescription medications and polypharmacy.

Second, I conducted a sensitivity analysis considering time since endometriosis diagnosis. A longer time between initial symptom presentation and diagnosis has been associated with higher pharmacy costs (Surrey et al., 2018). This data in conjunction with the average delay of 7-10 years between symptom onset and endometriosis diagnosis (Seear, 2009) suggests that individuals with endometriosis may use

more prescription medications closer to the time of endometriosis diagnosis to manage symptoms. Alternatively, it is possible that a longer time between endometriosis diagnosis and NHANES interview could allow for more pharmaceutical treatment options to be implemented, and for additional comorbidities to be diagnosed, also requiring pharmaceutical management (Surrey et al., 2018). To explore both hypotheses, I used available data on age at endometriosis diagnosis and age at NHANES interview to create a variable capturing time since endometriosis diagnosis. I categorized the variable as no endometriosis, ≤10 years since endometriosis diagnosis, and >10 years since endometriosis diagnosis. For this variable, I selected 10 years as the cut point given the median of 10 years between age at endometriosis diagnosis and age at NHANES interview in the study population. Time since endometriosis diagnosis was evaluated in relation to use of two or more prescription medications as well as polypharmacy.

Third, I repeated the main analyses additionally adjusting for history for at least one of the following comorbidities: diabetes, hypertension, thyroid problems, asthma, severe migraines within three months of NHANES interview, chronic pain, and history of moderate to severe depression. This sensitivity analysis was conducted to evaluate the association between endometriosis diagnosis history and prescription medication use, separate from comorbidities that can co-occur with endometriosis.

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) and Stata statistical software (version 15.1; StataCorp, College Station, TX). This project was determined not to involve human subjects by the Human Research Protection Program at Michigan State University.

RESULTS

In the study population, the weighted prevalence of endometriosis diagnosis history was 9% (unweighted n = 380). Participants reporting a history of endometriosis diagnosis, compared to those without such a history, tended to be older (ages 40-49), non-Hispanic White, and more frequently reporting completing high school, and having insurance coverage (Table 1). In addition, endometriosis cases tended to report currently smoking, being menopausal, and having a history of hysterectomy and/or bilateral oophorectomy than non-cases. Those with and without a history of endometriosis diagnosis were similar with regard to alcohol consumption, BMI, age at menarche, and parity. As for comorbidities, participants with a history of endometriosis diagnosis more frequently reported a history of hypertension, thyroid problems, asthma, migraines, chronic pain, and moderate to severe depression compared to those without a history of endometriosis diagnosis.

In the study population, the median number of prescriptions used in the past 30 days was 0 (IQR 0-2). The weighted prevalence of using ≥2 prescriptions and ≥5 prescriptions (polypharmacy) were 32% and 8%, respectively. I observed that nearly half (49%, weighted prevalence) of those with a history of endometriosis diagnosis reported using ≥2 prescription medications than 24% (weighted prevalence) of those without the condition. After multivariable adjustment, a history of endometriosis diagnosis was associated with a 40% increased prevalence of taking ≥2 prescription medications (PR 1.4, 95% CI: 1.3, 1.7) (Table 2). The magnitude of the association was stronger when evaluating history of endometriosis diagnosis in relation to polypharmacy; 15% (weighted prevalence) of those with a history of endometriosis diagnosis reported using ≥5 prescription medications compared to 6% (weighted prevalence) without a history of endometriosis diagnosis. Participants with a history of endometriosis diagnosis had a 90% increased prevalence of taking ≥5 prescription medications compared to those without a history of endometriosis diagnosis (PR 1.9, 95% CI 1.3, 2.7) (Table 3).

In my exploratory analyses of the most prevalent therapeutic categories of prescription medication use,

the top five most prevalent therapeutic prescription categories in the study population were analgesics, sex hormones, antidepressants, antidiabetic agents, and thyroid hormones. I observed that participants with a history of endometriosis diagnosis more frequently reported using analgesics, sex hormones, and antidepressants compared to participants without a history of endometriosis diagnosis (Figure 2). In contrast, endometriosis cases less frequently reported using antidiabetic agents and thyroid hormones than participants without a history of endometriosis diagnosis.

In my exploratory analysis investigating the frequency of using ≥2 prescription medications from the same therapeutic category, I observed that those with a history of endometriosis diagnosis more frequently used ≥2 analgesics, ≥2 antidepressants, and ≥2 sex hormones compared to participants without a history of endometriosis diagnosis (Figure 3). On the other hand, participants without a history of endometriosis diagnosis more frequently reported use of ≥2 antidiabetic agents than endometriosis cases. When I examined the use of combinations of two prescriptions for which 250 or more prescriptions were reported (analgesics, sex hormones, antidepressants, antidiabetic agents, and thyroid hormones), the most frequently reported combinations of therapeutic categories of two prescription medications in the study population were analgesics and sex hormones (weighted prevalence 2.4%), sex hormones and antidepressants (weighted prevalence 2.3%), and analgesics and antidepressants (weighted prevalence 2.9%). Participants with a history of endometriosis diagnosis, compared to those without such a history, reported a higher prevalence of combined analgesic and sex hormone prescription medication use (7.6% vs. 1.9%), combined sex hormone and antidepressant prescription medication use (7.0% vs. 1.9%), and combined analgesic and antidepressant prescription medication use (4.9% vs. 2.7%) (Figure 4).

In my sensitivity analysis restricting the study population to premenopausal participants, I observed a similar result to that of the main analysis for the association between history of endometriosis diagnosis and use of ≥2 prescriptions (adjusted PR 1.4, 95% CI: 1.1, 1.7) (Supplemental Table 1). However, the association between endometriosis diagnosis history and polypharmacy among premenopausal

participants was attenuated compared to that observed in the main results (adjusted PR 1.4, 95% CI: 0.7, 2.7) (Supplemental Table 2). This is likely due to small cell sizes among the participants with a history of endometriosis diagnosis (unweighted n = 197); 14 participants reported use of ≥5 prescription medications.

As for my sensitivity analysis considering time since endometriosis diagnosis, I observed similar associations for ≤10 years since endometriosis diagnosis and ≥2 prescription medications (aPR 1.4, 95% CI: 1.2, 1.7) and >10 years since endometriosis diagnosis and ≥2 prescription medications (aPR 1.5, 95% CI: 1.2, 1.8) (Supplemental Table 3). However, when I considered the outcome of polypharmacy, the association between >10 years since endometriosis diagnosis and polypharmacy (aPR 2.0, 95% CI: 1.3, 3.1) was stronger in magnitude than the association between ≤10 years since endometriosis diagnosis and polypharmacy (aPR 1.7, 95% CI: 1.1, 2.7) (Supplemental Table 4).

When I evaluated the association between endometriosis diagnosis history and prescription medication use additionally adjusting for the presence of one or more comorbidities of diabetes, hypertension, asthma, thyroid problems, as expected, compared to the results obtained in the main analyses, the associations were attenuated. The adjusted prevalence ratios for the associations between endometriosis diagnosis history and use of ≥2 prescription medications and ≥5 prescription medications in the past 30 days were 1.3 (95% CI: 1.2, 1.5) (Supplemental Table 5) and 1.6 (95% CI: 1.2, 2.2) (Supplemental Table 6), respectively. The association between endometriosis diagnosis history and use of ≥2 prescription medications was also attenuated after adjusting for presence of chronic pain and migraines in addition to the above comorbidities in cycles 1999-2004 for which data were available. There was no attenuation after adjusting for the presence of diabetes, hypertension, asthma, thyroid problems, or depression using data from 2005-2006. I observed an attenuation when considering polypharmacy, after adjusting for covariates with data available from 1999-2004 and 2005-2006; however, the estimates were accompanied by wide confidence intervals due to small cell sizes.

DISCUSSION

In the present analysis, I observed that a history of endometriosis diagnosis was associated with an increased prevalence of using ≥2 prescription medications within 30 days of NHANES interview, with nearly half (49%) of those with a history of endometriosis diagnosis using ≥2 prescription medications in comparison to 24% of those without the condition. The magnitude of the association was stronger when I considered polypharmacy (taking ≥5 prescription medications).

An increased prevalence of using ≥2 prescription medications with a history of endometriosis diagnosis is plausible. Given that there is no cure for endometriosis, pharmaceutical management is central to care and focuses on minimizing endometrial lesion growth and managing symptoms, particularly pain symptoms that can be substantial (Zondervan et al., 2020; Carlyle et al., 2020). Endometriosis is a multifactorial condition, and pain can arise from inflammation stimulated by an altered hormonal milieu. Growth of endometriotic lesions stimulates an inflammatory response that is associated with neuropathic pain, resulting in a complex pain response that can interact with the central nervous system leading to chronic pain (Carey et al., 2017; Carlyle et al., 2020). Thus, first line prescription medication treatment options consist of non-steroidal anti-inflammatory agents and/or acetaminophen to treat inflammatory pain. Neuroleptic agents such as gabapentin, pregabalin, and tricyclic antidepressants can be used to target neuropathic pain (Carlyle et al., 2020). Continuous low dose combined oral contraceptives are also a first line treatment used to decrease estrogen-induced inflammation (Carlyle et al., 2020). Gonadotrophin-releasing hormone (GnRH) agonists/antagonists produce a hypoestrogenic state to manage moderate-to-severe endometriosis pain when first-line treatments are ineffective; however, they produce menopause-like side effects (Carlyle et al., 2020). In addition to pain symptoms, endometriosis is associated with comorbidities that may also require pharmaceutical intervention. Some data suggest that endometriosis commonly co-occurs with pain conditions such as fibromyalgia and migraines, mental health conditions such as depression and anxiety, immunologic conditions such as rheumatoid arthritis and asthma, autoimmune thyroid conditions, as well as cardiovascular disease (Kvaskoff et al., 2017; Poppe et al.,

2007; Zondervan et al., 2020). Hence, a range of prescription medications may be used to manage endometriosis-related pain and associated comorbidities.

My results are consistent with the few studies that have examined endometriosis diagnosis history and prescription medication use (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015). Unlike my study that evaluated the number of prescription medications, prior studies focused on the financial costs of prescription medication use due to endometriosis (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015). All three reported higher annual prescription costs and cumulative pharmacy spending among those with endometriosis compared to those without the condition (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015).

In my exploratory analysis, the top five most prevalent therapeutic prescription medication categories identified were analgesics, sex hormones, antidepressants, antidiabetic agents, and thyroid hormones. Compared to those without a history of endometriosis diagnosis, those with a history of the condition more frequently reported using prescription medications and their combinations in the therapeutic categories of analgesics, sex hormones, and antidepressants. These prescription medication therapeutic categories align with the first and second line of pharmaceutical management of endometriosis-related pain. They also correspond with the comorbidities that appear to co-occur with endometriosis. The most frequent therapeutic prescription medication categories identified in my study were similar to those reported in a case-control study conducted in Israel (Eisenberg et al., 2022). That study reported higher prescription utilization for oral contraceptive medications, pain medications, and antidepressants for endometriosis cases compared to controls (Eisenberg et al., 2022).

My study had several limitations. First, the information on the outcome of interest, number of prescription medications was collected using participant self-report. The possibility exists that participants may not remember all prescription medications they are taking, resulting in missed medications. However, this

concern is likely minimal since participants were asked about recently used medications (in the past 30 days) and showed the NHANES interviewer the containers for each medication. This approach to ascertaining prescription medications had the benefit of capturing prescription medications actually taken by the participants. This contrasts with prior studies using prescription claims data where it is possible that filled prescriptions were never taken by the participant (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015).

Second, I relied on self-report to ascertain information on the exposure of interest, history of endometriosis diagnosis. Among those categorized as not having a history of endometriosis diagnosis, there is the potential for undiagnosed disease. However, the misclassification of endometriosis diagnosis history is likely to be minimal given the low estimated prevalence of endometriosis (around 10%). Even in the presence of non-differential misclassification, which I would expect may attenuate the observed association, I was able to detect an association between endometriosis diagnosis history and prevalence of the number of prescription medications used.

Third, in NHANES, data were not collected on endometriosis symptom severity. This information would have allowed me to understand whether prescription medications were specifically used to manage endometriosis-related symptoms or co-occurring comorbidities. I attempted to disentangle these reasons for prescription medication use in two ways. I conducted a sensitivity analysis adjusting for comorbidities. After adjustment, I continued to observe a 30% and 60% increase in prevalence of using ≥2 and ≥5 prescription medications, respectively, in the past month. This suggests that comorbidities do not appear to explain the entire association between endometriosis diagnosis history and prescription medication use. I also conducted a sensitivity analysis evaluating time since endometriosis diagnosis in relation to the number of prescription medications used. I hypothesized that increased prescription medication use immediately following diagnosis may indicate pharmaceutical management of endometriosis-related symptoms, whereas increased prescription use more than a decade after diagnosis

may indicate pharmaceutical management of comorbidities. However, I observed similar associations for ≤10 and >10 years since endometriosis diagnosis in relation to use of ≥2 prescription medications. My results differed from those of two other studies conducted in the U.S.; a case-control study observed the greatest difference in mean annual prescription costs between endometriosis cases and controls in the first year following endometriosis diagnosis (Fuldeore et al., 2015) whereas a cohort study reported that cumulative pharmacy spending increased with years following diagnosis (Epstein et al., 2017). The discrepancy in results across studies could be due to study design differences in the ascertainment of prescription medication use and the approach used to identify those with an endometriosis diagnosis. Further investigation of the contribution of endometriosis-related symptoms and co-occurring comorbidities to prescription medication use is warranted.

The key strength of the present study was the use of population-based data representative of the U.S. population. Not only are the results generalizable in the U.S., but the study population also included individuals regardless of insurance status. This is in contrast to the prior studies using prescription claim databases that have been limited to insured individuals (Eisenberg et al., 2022; Epstein et al., 2017; Fuldeore et al., 2015). The inclusion of individuals who may not have consistent insurance coverage and access to care allowed us to quantify the extent of the burden of endometriosis on health, as indicated by current prescription medication use. The burden appears to be considerable, with nearly half of those with endometriosis using ≥2 prescription medications and 15% using ≥5 prescription medications. Furthermore, the associations I observed among NHANES participants ages 20-54 years regardless of menopausal status also persisted in analyses restricted to premenopausal participants of the same age. This highlights the adverse impact of endometriosis on overall health in a relatively young population during the reproductive years.

In the present study, I asked a novel question using publicly available data to move the field of endometriosis research forward. Although the results from prior studies have been important in shedding

light on the burden of endometriosis from the economic perspective in terms of pharmaceutical costs, I was able to further contribute information on the number and types of prescription medications used. In doing so, my results underscore the health burden of endometriosis due to the complexity of the condition and associated comorbidities. Quantifying the health burden of endometriosis is critical for a condition that historically has had a long diagnostic delay, ranging from 4 to 11 years, between symptom onset and diagnosis (Agarwal et al., 2019), with patients commonly reporting that they were told “nothing was wrong” when they first visited a physician for endometriosis (Ballweg, 2004) and had symptoms normalized. Recognizing the impact of endometriosis on overall health is needed to improve both public awareness and healthcare provider knowledge.

CONCLUSION

In a cross-sectional study representative of the U.S. population, a history of endometriosis diagnosis was associated with an increased prevalence of using multiple prescription medications. The commonly reported therapeutic categories of prescription medications were consistent with the management of endometriosis-related pain and comorbidities. These results highlight the health burden of endometriosis, a clinically complex condition, requiring multiple prescription medications for management.

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APPENDIX A

TABLES

Table 1. Sociodemographic and health-related characteristics by history of endometriosis diagnosis among participants ages 20-54 years, National Health and Nutrition Examination Survey, 1999-2006 (N = 5,550)[a].

	History of endometriosis diagnosis			
	Yes (n=380)[a]		No (n= 5,170)[a]	
Participant characteristics at NHANES interview	n[a]	(%)[b]	n[a]	(%)[b]
Age, years				
20-29	52	(10)	1,816	(27)
30-39	120	(30)	1,439	(28)
40-49	143	(44)	1,317	(30)
50-54	65	(16)	598	(14)
Race/Ethnicity				
Mexican American	30	(2)	1,284	(8)
Other Hispanic	7	(2)	264	(6)
Non-Hispanic White	261	(84)	2,305	(68)
Non-Hispanic Black	67	(8)	1,079	(12)
Other/More than one race	15	(4)	238	(6)
Education				
<HS graduate	48	(11)	1,295	(16)
HS graduate	101	(31)	1,139	(23)
Some college or associate degree	133	(33)	1,616	(34)
College graduate or above	98	(25)	1,115	(27)
Missing	0		5	
Insurance coverage				
No	55	(14)	1,219	(19)
Yes	323	(86)	3,906	(81)
Missing	2		45	
Smoking status				
Never	200	(49)	3,241	(58)
Former	67	(18)	829	(18)
Current, <20 cigs/day	61	(18)	753	(15)
Current, ≥20 cigs/day	52	(15)	337	(9)

Table 1. (cont'd)

Missing	0		10	
Alcohol consumption				
Never	41	(9)	976	(15)
Former	81	(20)	1,091	(18)
Current	258	(71)	3,101	(67)
Missing	0		2	
BMI (kg/m^2)[c]				
<25.0	133	(39)	1,769	(41)
25.0-<30.0	106	(27)	1,458	(26)
≥30.0	139	(34)	1,887	(33)
Missing	2		56	
Age at menarche (years)				
≤10	42	(11)	471	(8)
11	56	(15)	685	(13)
12	110	(29)	1,372	(27)
13	90	(25)	1,246	(27)
≥14	76	(20)	1,304	(25)
Missing	6		92	
Number of live births				
0	100	(25)	1,301	(28)
1	88	(21)	1,074	(18)
2	99	(30)	1,312	(28)
≥3	93	(24)	1,483	(26)
Menopausal status				
No	227	(56)	4,328	(81)
Yes	151	(44)	811	(19)
Missing	2		31	
History of hysterectomy				
No	228	(56)	4,776	(91)
Yes	152	(44)	389	(9)
Missing	0		5	
History of bilateral oophorectomy				
No	279	(71)	5,001	(96)

Table 1. (cont'd)

Yes	101	(29)	156	(4)
Missing	0		13	
History of diabetes				
No	363	(97)	4,891	(95)
Yes	17	(3)	277	(5)
Missing	0		2	
History of hypertension				
No	280	(78)	4,275	(83)
Yes	100	(22)	871	(17)
Missing	0		24	
History of thyroid problems				
No	332	(85)	4,763	(91)
Yes	48	(15)	395	(9)
Missing	0		12	
History of asthma				
No	292	(77)	4,475	(85)
Yes	88	(23)	694	(15)
Missing	0		1	
History of severe migraines in past 3 months[d]				
No	158	(55)	2,568	(68)
Yes	118	(45)	1,233	(32)
Missing	0		3	
History of chronic pain[d]				
No	198	(72)	3,292	(85)
Yes	78	(28)	507	(15)
Missing	0		5	
History of depression[e]				
None to mild	70	(69)	1,023	(76)
Moderate to severe	34	(31)	338	(24)
Missing	0		5	

Abbreviations: HS, high school; BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.
[a]Unweighted sample size.
[b]Weighted percent accounting for complex survey sampling design.

Table 1 (cont'd)
[c]Using height and weight measured during NHANES mobile exam component.
[d]Using data available from 1999-2004 cycles (endometriosis diagnosis history, n = 276; without endometriosis diagnosis history, n = 3,804).
[e]Using data available from 2005-2006 cycle (endometriosis diagnosis history, n = 104; without endometriosis diagnosis history, n = 1,366).

Table 2. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and prescription drug use among participants ages 20-54 years (N = 5,550)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]			
	≥2 (n = 1418)[a] n[a] (%)[c]	**<2 (n = 4132)[a] n[a] (%)[c]**	**Age-adjusted PR (95% CI)[d]**	**Multivariable-adjusted PR (95% CI)[e]**
History of endometriosis diagnosis				
No	1233 (86)	3937 (93)	1.0	1.0
Yes	185 (14)	195 (7)	1.5 (1.3, 1.7)	1.4 (1.3, 1.7)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Adjusted for age (continuous).
[e]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Table 3. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and polypharmacy among participants ages 20-54 years (N = 5,550)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]			
	≥5 (n = 341)[a]	**<5 (n = 5209)[a]**	**Age-adjusted**	**Multivariable-adjusted**
	n[a] (%)[c]	**n[a] (%)[c]**	**aPR (95% CI)[d]**	**aPR (95% CI)[e]**
History of endometriosis diagnosis				
No	285 (81)	4885 (92)	1.0	1.0
Yes	56 (19)	324 (8)	2.0 (1.4, 2.7)	1.9 (1.3, 2.7)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Adjusted for age (continuous).
[e]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

APPENDIX B

FIGURES

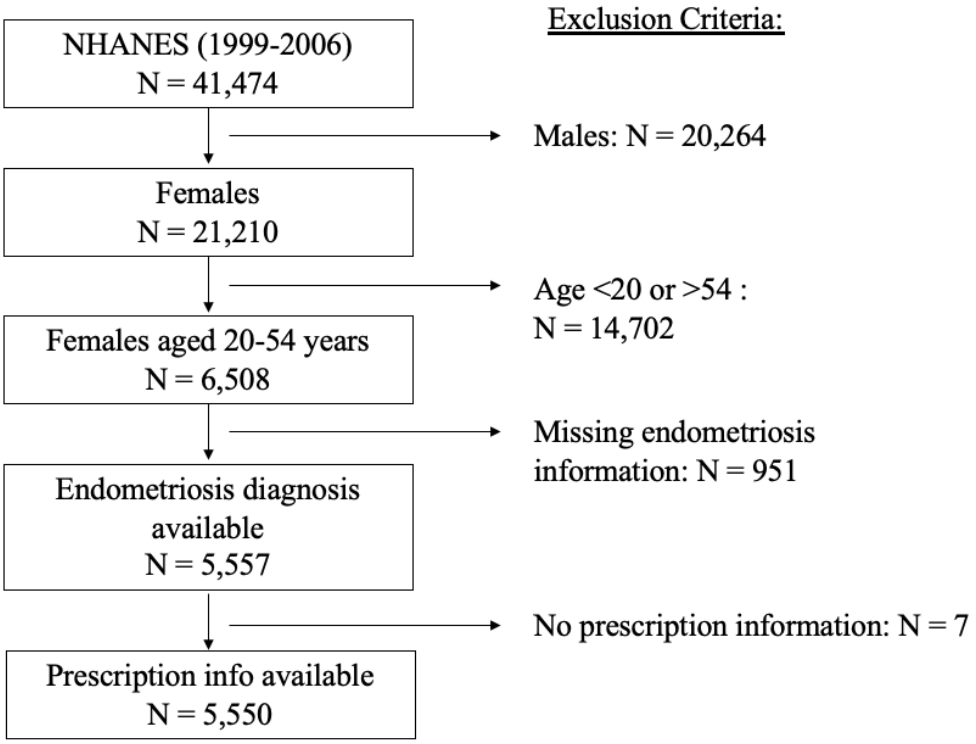


Figure 1. Eligibility criteria to restrict study population to reproductive-age females (ages 20-54 years) with endometriosis diagnosis information and prescription medication information available among participants in National Health and Nutrition Examination Survey, 1999-2006.

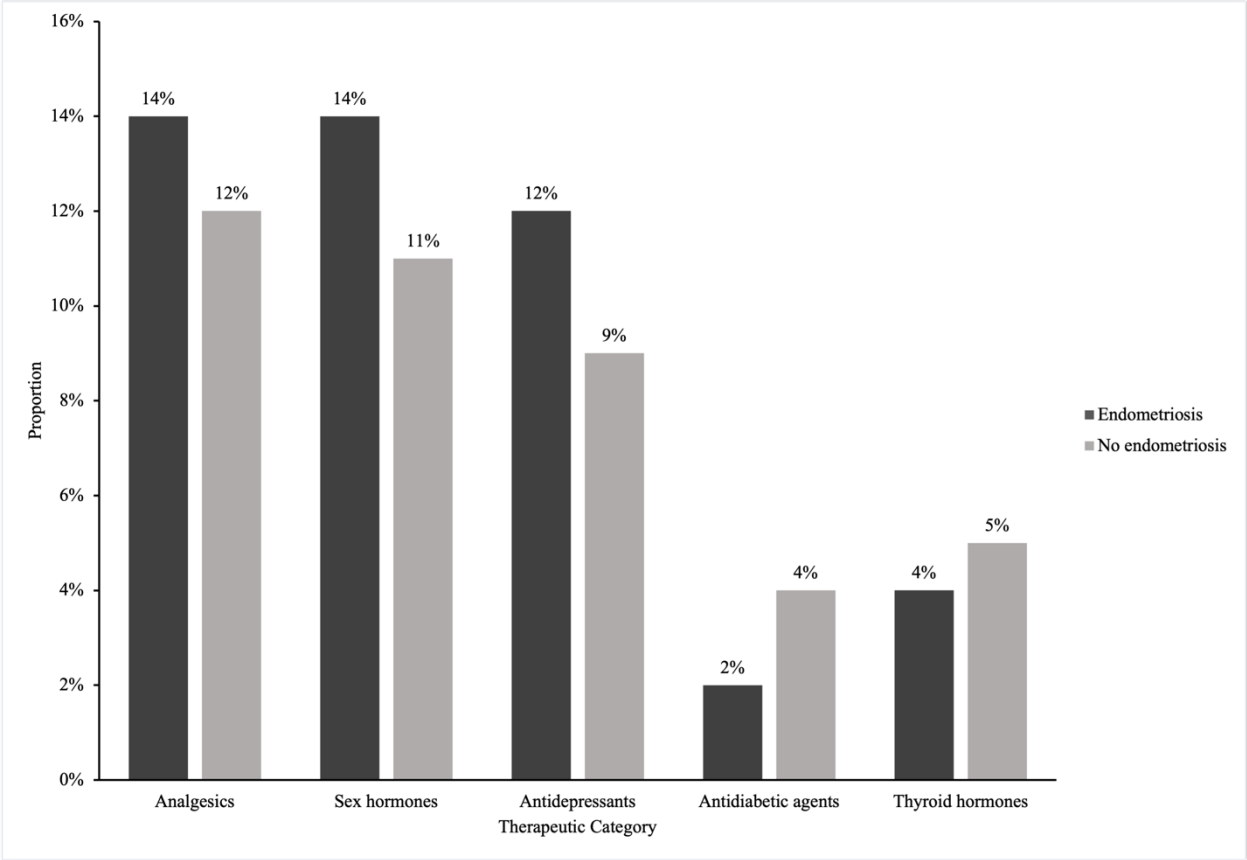


Figure 2. Weighted proportion of top prescription medication therapeutic categories by history of endometriosis diagnosis among participants ages 20-54 years (N = 5,550), National Health and Nutrition Examination Survey, 1999-2006.

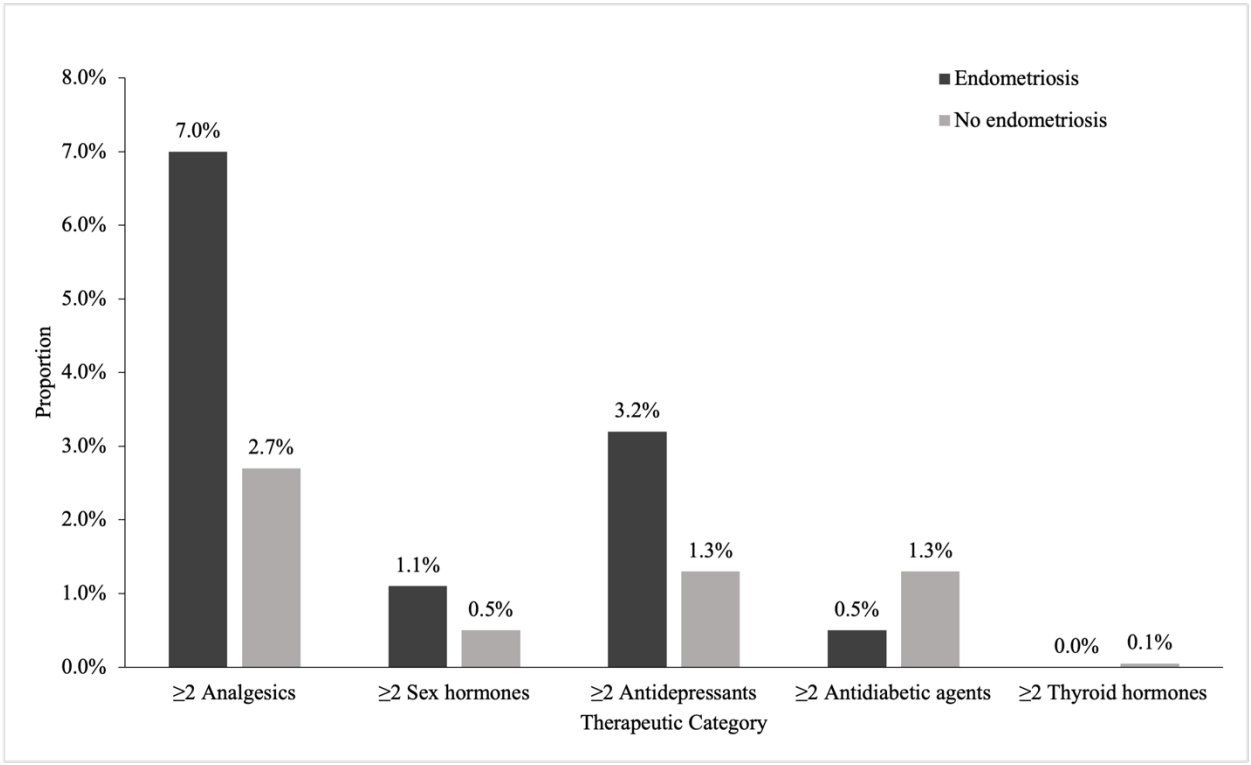
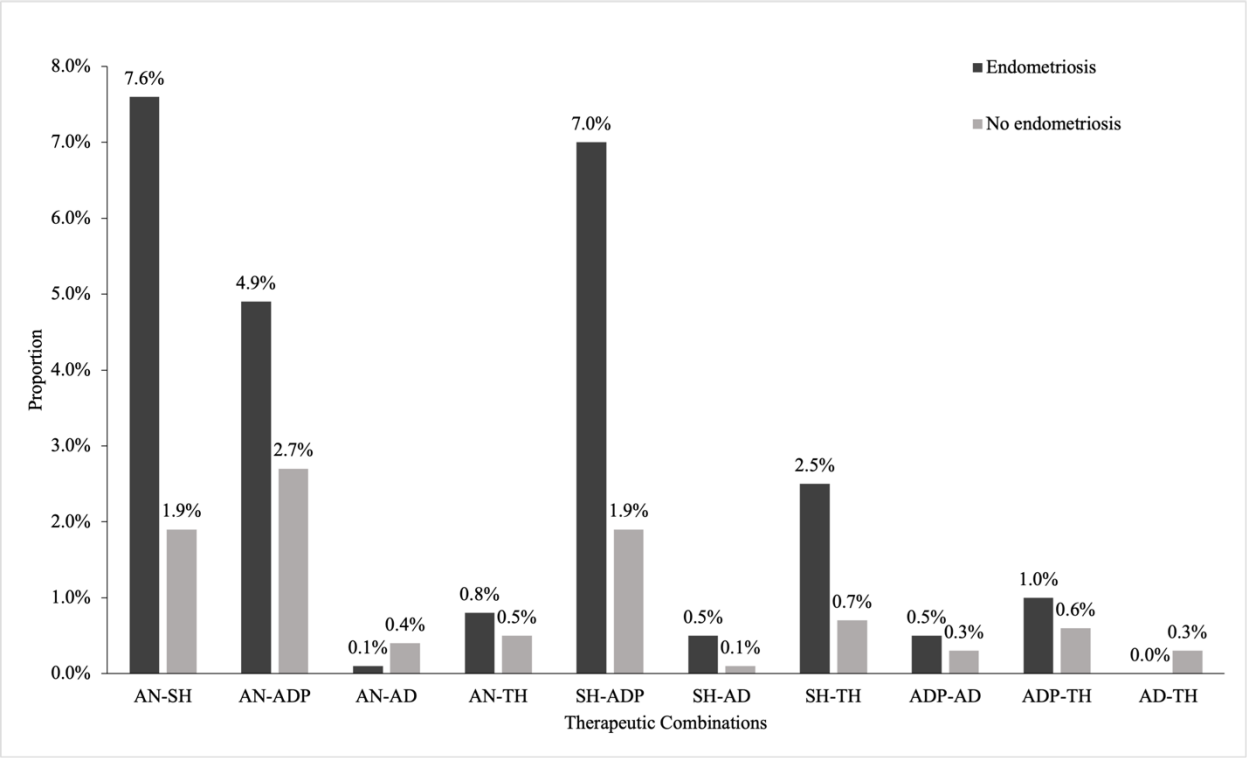


Figure 3. Weighted proportion of ≥2 prescription medications from the same therapeutic category considering the top 5 most frequently reported therapeutic categories used in combination by history of endometriosis diagnosis among participants ages 20-54 years (N = 5,550), National Health and Nutrition Examination Survey, 1999-2006.



Abbreviations: AD, antidiabetic agents; ADP, antidepressants; AN, analgesics; SH, sex hormones; TH, thyroid hormones

Figure 4. Weighted proportion of use of combinations of two prescription medications from the top 5 most frequently reported therapeutic categories by history of endometriosis diagnosis among participants ages 20-54 years (N = 5,550) National Health and Nutrition Examination Survey, 1999-2006.

APPENDIX C

SUPPLEMENTAL TABLES

Supplemental Table 1. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and prescription drug use among premenopausal participants[a] ages 20-54 years (N = 4,453)[b], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[c]			
	≥2 (n= 878)[b] **n[b] (%)[d]**	**<2 (n= 3575)[b]** **n[b] (%)[d]**	**Age-adjusted PR (95% CI)[e]**	**Multivariable-adjusted PR (95% CI)[f]**
History of endometriosis diagnosis				
No	807 (91)	3,449 (95)	1.0	1.0
Yes	71 (9)	126 (5)	1.5 (1.2, 1.9)	1.4 (1.1, 1.7)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Premenopausal defined as having an intact uterus, at least one ovary, and menses in the past year, or reason for missing menses is due to pregnancy or medical treatments.
[b]Unweighted sample size.
[c]At the time of NHANES interview.
[d]Weighted percent accounting for complex survey sampling design.
[e]Adjusted for age(continuous).
[f]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Supplemental Table 2. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and polypharmacy among premenopausal participants[a] ages 20-54 years (N = 4,453)[b], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[c]			
	≥5 (n = 161)[b]	<5 (n = 4,292)[b]	Age-adjusted	Multivariable-adjusted
	n[b] (%)[d]	n[b](%)[d]	PR (95% CI)[e]	PR (95% CI)[f]
History of endometriosis diagnosis				
No	147 (90)	4,109 (95)	1.0	1.0
Yes	14 (10)	183 (5)	1.6 (0.9, 3.1)	1.4 (0.7, 2.7)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Premenopausal defined as having an intact uterus, at least one ovary, and menses in the past year or reason for missing menses is due to pregnancy or medical treatments.
[b]Unweighted sample size.
[c]At the time of NHANES interview.
[d]Weighted percent accounting for complex survey sampling design.
[e]Adjusted for age (continuous).
[f]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Supplemental Table 3. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis considering years since diagnosis and prescription drug use among participants ages 20-54 years (N = 5,545)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]			
	≥2 (n = 1,417)[a]	**<2 (n = 3,128)[a]**	**Age-adjusted**	**Multivariable-adjusted**
	n[a] (%)[c]	**n[a] (%)[c]**	**PR (95% CI)[d]**	**PR (95% CI)[e]**
History of endometriosis diagnosis				
No	1,233 (86)	3,937 (94)	1.0	1.0
Yes, ≤10 years since diagnosis	83 (6)	118 (3)	1.5 (1.2, 1.8)	1.4 (1.2, 1.7)
Yes, >10 years since diagnosis	101 (8)	73 (3)	1.6 (1.3, 1.9)	1.5 (1.2, 1.8)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Adjusted for age (continuous).
[e]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Supplemental Table 4. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis considering years since diagnosis and polypharmacy among participants ages 20-54 years (N = 5,545)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]			
	≥5 (n = 3,41)[a]	**<5 (n = 5,204)[a]**	**Age-adjusted**	**Multivariable-adjusted**
	n[a] (%)[c]	**n (%)[c]**	**PR (95% CI)[d]**	**PR (95% CI)[e]**
History of endometriosis diagnosis				
No	285 (81)	4,885 (92)	1.0	1.0
Yes, ≤10 years since diagnosis	22 (7)	179 (4)	2.0 (1.3, 3.3)	1.7 (1.1, 2.7)
Yes, >10 years since diagnosis	34 (12)	140 (4)	2.0 (1.3, 3.0)	2.0 (1.3, 3.1)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Adjusted for age (continuous).
[e]Adjusted for age (continuous), education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Supplemental Table 5. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and prescription drug use among participants ages 20-54 years (N = 5,550)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]				
	≥2 (n = 1,418)[a] n[a] (%)[c]	<2 (n = 4,132)[a] n[a] (%)[c]	Model 1[g] PR (95% CI)	Model 2[h] PR (95% CI)	Model 3[i] PR (95% CI)
1999-2006[d]					
History of endometriosis diagnosis					
No	1,233 (86)	3,937 (93)	1.0	1.0	1.0
Yes	185 (14)	195 (7)	1.5 (1.3, 1.7)	1.4 (1.2, 1.6)	1.3 (1.2, 1.5)
1999-2004[e]					
History of endometriosis diagnosis					
No	907 (86)	2,897 (93)	1.0	1.0	1.0
Yes	128 (14)	148 (7)	1.4 (1.2, 1.7)	1.3 (1.1, 1.4)	1.2 (1.1, 1.4)
2005-2006[f]					
History of endometriosis diagnosis					
No	326 (83)	1,040 (94)	1.0	1.0	1.0
Yes	57 (17)	47 (6)	1.8 (1.4, 2.2)	1.5 (1.2, 1.8)	1.4 (1.1, 1.8)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Information available for diabetes, hypertension, asthma, and thyroid problems.
[e]Information available for diabetes, hypertension, asthma, thyroid problems, migraines, and chronic pain.
[f]Information available for diabetes, hypertension, asthma, thyroid problems, and depression.
[g]Model 1: Adjusted for age (continuous).
[h]Model 2: Adjusted for Model 1 covariates and history of at least 1 comorbidity.
[i]Model 3: Adjusted for Model 2 covariates and education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).

Supplemental Table 6. Adjusted prevalence ratios and 95% confidence intervals for the association between history of endometriosis diagnosis and polypharmacy among participants ages 20-54 years (N = 5,550)[a], National Health and Nutrition Examination Survey, 1999-2006.

	Number of prescriptions[b]				
	≥5 (n = 341)[a]	**<5 (n = 5,209)[a]**	**Model 1[g]**	**Model 2[h]**	**Model 3[i]**
	n[a] (%)[c]	**n[a] (%)[c]**	**PR (95% CI)**	**PR (95% CI)**	**PR (95% CI)**
1999-2006[d]					
History of endometriosis diagnosis					
No	285 (81)	4,885 (92)	1.0	1.0	1.0
Yes	56 (19)	324 (8)	2.0 (1.4, 2.7)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)
1999-2004[e]					
History of endometriosis diagnosis					
No	206 (82)	3,598 (92)	1.0	1.0	1.0
Yes	39 (18)	237 (8)	1.8 (1.2,2.8)	1.5 (1.0, 2.3)	1.5 (1.0, 2.3)
2005-2006[f]					
History of endometriosis diagnosis					
No	79 (78)	1,287 (92)	1.0	1.0	1.0
Yes	17 (22)	87 (8)	2.3 (1.2, 4.3)	1.7 (0.9, 3.0)	1.7 (0.9, 3.1)

Abbreviations: CI, confidence interval; PR, prevalence ratio.
[a]Unweighted sample size.
[b]At the time of NHANES interview.
[c]Weighted percent accounting for complex survey sampling design.
[d]Information available on diabetes, hypertension, asthma, and thyroid problems.
[e]Information available on diabetes, hypertension, asthma, thyroid problems, migraines, and chronic pain.
[f]Information available on diabetes, hypertension, asthma, thyroid problems, and depression.
[g]Model 1: Adjusted for age (continuous).
[h]Model 2: Adjusted for Model 1 covariates and history of at least 1 comorbidity.
[i]Model 3: Adjusted for Model 2 covariates and education (≤ high school, some college or associate degree, college graduate or above), insurance coverage (yes, no), body mass index (<25.0, 25.0-<30, ≥30 kg/m^2), smoking (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day).