Reviewed Preprint
v1 • March 12, 2025
Not revised

Reviewed Preprint
v2 • June 9, 2026
Revised by authors

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Competing interests: No competing interests declared

Reviewing editor: Daria Lizneva, Icahn School of Medicine at Mount Sinai, United States

Understanding Pain in Polycystic Ovary Syndrome: Health Risks and Treatment Effectiveness

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eLife Assessment

This study presents **valuable** findings on the high prevalence of pain in women with polycystic ovary syndrome and its association with distinct future health risks across different racial groups. The evidence supporting the conclusions is **compelling**, utilizing a massive global dataset and rigorous propensity score matching to identify pain as a critical, yet underexplored, clinical marker. The work will be of interest to reproductive endocrinologists, medical biologists, and clinicians involved in the diagnosis and management of polycystic ovary syndrome.

https://doi.org/10.7554/eLife.103875.2.sa3

Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in women, often accompanied by various symptoms including significant pain, such as dysmenorrhea, abdominal, and pelvic pain, which remains underexplored. This retrospective study examines electronic health records (EHR) data to assess the prevalence of pain in women with PCOS. Conducted on January 2026, using data from 120 Health Care Organizations within the TriNetX Global Network, the study involved 103,675,738 women from diverse racial backgrounds. The analysis focused on the prevalence of pain among women with PCOS, both overall and in those prescribed PCOS-related medications. Relative risk ratios (RR) were calculated for future health outcomes and stratified by self-reported race. The study found that 20.67% of women with PCOS experienced pain, with the highest prevalence among Black or African American (32.70%) and White (30.78%) populations. Both the PCOS and PCOS and Pain cohorts exhibited increased RR for various health conditions, with significant differences noted across racial groups for infertility, ovarian cysts, obesity, and respiratory diseases. Additionally, women with PCOS who were treated with PCOS-related medications showed a decrease in pain diagnoses following treatment. In conclusion, this study highlights the critical need to address pain in the diagnosis and management of PCOS due to its significant impact on patient health outcomes.

Impact Statement

Insufficient data exist on the prevalence of pain in women with a PCOS diagnosis, and its associations with future health outcomes. Among, 597,638 women with PCOS in the TriNextX Global Network, 20.67% have dysmenorrhea, abdominal, and pelvic pain. Women with PCOS and Pain are at increased risk for developing ovarian cysts, infertility, T2D, and fatty liver disease and are at further risk when stratified by self-reported race groups.

Introduction

According to the World Health Organization (WHO), polycystic ovary syndrome (PCOS) affects approximately 8-13% of women of reproductive age, with an alarming 70% of affected individuals remaining undiagnosed globally (Organization, 28 June 2023). The assessment of PCOS has been substantiated by multiple guidelines (Azziz et al., 2016; Teede et al., 2010) and has undergone refinement since its initial description by Stein and Leventhal in 1935 (Stein & Leventhal, 1935). Standard diagnostic criteria have evolved through international efforts, including conferences convened by the National Institutes of Health (NIH) in 1990 (Zawadri, 1992), the ESHRE/ASRM-sponsored PCOS consensus workshop group in Rotterdam in 2003 and 2004 (ESHRE & Group, 2004), and the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome in 2018, most recently updated in 2023 (Mousa & Tay, 2023; Teede et al., 2018).

Recommendations for assessing PCOS encompass a multifaceted approach, including the evaluation of irregular menstrual cycles, ovulatory dysfunction, biochemical and clinical hyperandrogenism, ultrasound findings, serum Anti-Mullerian Hormone (AMH) levels, and various other factors such as ethnic disparities, cardiovascular disease risk, menopausal status, impaired glucose tolerance, and risk of type 2 diabetes mellitus (T2DM) (Mousa & Tay, 2023; Teede et al., 2018). Additionally, screening and managing psychological manifestations, implementing lifestyle interventions, and adhering to pharmacological treatment principles are integral aspects of PCOS management (Mousa & Tay, 2023; Teede et al., 2018). While the diagnostic criteria for PCOS primarily focus on reproductive and metabolic manifestations, the substantial burden of pain experienced among women with PCOS is a critical factor that warrants effective prevention and management of the disease.

The assessment of pain in PCOS necessitates a multidimensional approach, incorporating self-reported scales, clinical evaluation, and possibly imaging techniques to elucidate the underlying etiology and severity. Several commonly utilized assessment tools incorporate evaluations of pain among women with PCOS. The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ), developed by Cronin et al. in 1998, assesses various domains, including painful menstrual cycles (Cronin et al., 1998). Additionally, the SF-36 scale, examines eight dimensions of health, including bodily pain (McHorney et al., 1993). Women with PCOS across diverse demographic backgrounds have consistently reported lower SF-36 scores, specifically in the domain of bodily pain (Drosdzol et al., 2007; Elsenbruch et al., 2003; Hahn et al., 2005; Li et al., 2011). Furthermore, the Menorrhagia Outcomes Questionnaire, developed by Lamping et al. in 1998, evaluates both heavy menstrual bleeding (HMB) and the associated pain (Lamping et al., 1998). Despite the validation of these instruments, they may not comprehensively capture key symptoms expressed by patients with PCOS, especially those related to dysmenorrhea, abdominal, or pelvic pain. Insufficient data exist to highlight the prevalence of pain reported by women both before and after a PCOS diagnosis, as well as any associations between this pain and the condition itself and its long-term effects. To address this gap in research, we propose an investigation utilizing health records to shed light on this underexplored aspect of PCOS.

Electronic health records (EHRs) have become indispensable for managing vast amounts of clinical data, including patient demographics, medical history, medications, allergies, laboratory test results, vital signs, and imaging reports, as well as genetic information obtained from patient genomes when available. Given that EHRs contain comprehensive information about patient care, including the progression of signs and symptoms, severity, comorbidities, and treatments, they provide invaluable resources for conducting large-scale retrospective studies. EHR-based studies have been particularly valuable in assessing the prevalence of conditions that are often underdiagnosed or misdiagnosed in women (Kruse et al., 2018; Maletzky et al., 2022; Penrod et al., 2023). The temporal aspect of clinical events, such as the onset of symptoms, treatment administration, and follow-up visits, can also be mined from EHRs, providing crucial insights into disease trajectories and treatment efficacy (Zhao et al., 2017).

Pain, particularly in the context of PCOS, remains an underexplored area of research. By leveraging EHR data we can identify women with PCOS who have reported dysmenorrhea, abdominal, and pelvic pain. The objective of this research is to use EHR and look at longitudinal data retrospectively to determine the pain reported by women with PCOS and to compare this to women without PCOS. The primary hypothesis of this study is that women with PCOS experience a higher prevalence to pain (including dysmenorrhea, abdominal pain, and pelvic pain) compared to women without PCOS, and this prevalence varies by racial groups. The hypothesis aims to investigate the prevalence of pain in women with and without pain. Our approach will provide insights into the relationship between pain symptoms and PCOS contributing to a better understanding of the condition and potentially improving patient care.

Methods

Study Design

The data used in this study was collected on January 9th, 2026, from the TriNetX Global Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 1196,361,552 million patients from 172 healthcare organizations in 19 different countries. TriNetX has a rigorous quality control pipeline which can be found in the platforms, documentation. Briefly, EHR data is received from HCOs in CSV format. TriNetX maps the data to a standard and controlled set of clinical terminology. Demographics data are mapped to HL7 administrative standards, diagnoses are represented by ICD codes, procedures are represented by ICD and CPT codes, and medications are mapped to RxNorm ingredients. The data is then transformed into a proprietary data format. Data cleaning is performed and records that don't meet the TriNetX quality standards are excluded. Quality checks are done for formatting and records with missing required data are excluded. TriNetX does not impute or estimate clinical values to fill gaps in patients' records and there is no guarantee of data completeness.

Cohort Definitions

A retrospective cohort analysis was conducted for patients with PCOS and patients with PCOS and Pain. Patients who were identified as cases (met inclusion and exclusion criteria) were compared to their respective controls. Description of inclusion and exclusion criteria for each cohort can be found in Table 1 – Figure supplement 1.

For the PCOS cohort, PCOS was defined as either having a PCOS diagnosis (ICD-10-CM E28.2), or an irregular menstruation (ICD-10-CM N92.6) and hirsutism (ICD-10-CM L68.0) diagnosis, or an irregular menstruation (ICD-10-CM N92.6) and androgen excess (ICD-10-CM E28.1) diagnosis. PCOS controls were defined as having a physical examination (ICD-10-CM Z00.0) and none of the PCOS case criteria. PCOS participants also had to satisfy stringent exclusion criteria to avoid confounders. Exclusion criteria for PCOS consisted of Maternal care for benign tumor of corpus uteri (ICD-10-CM O34.1), Leiomyoma of uterus (ICD-10-CM D25), endometriosis (ICD-10-CM N80), Polyp of corpus uteri (ICD-10-CM N84.0), female pelvic inflammatory disease unspecified (ICD-10-CM N73.9), hypothyroidism (ICD-10-CM E03.8, E03.9), hyperprolactinemia (ICD-10-CM E22.1), and adrenal hyperplasia (ICD-10-CM E27.8, Q89.1). Description of inclusion and exclusion criteria for each cohort can be found in Table 1 - Figure supplement 1.

For the PCOS and Pain cohort, PCOS was defined the same as above. PCOS and Pain cases were defined as patients with a PCOS case as well as being diagnosed for either abdominal and pelvic pain (ICD-10-CM R10) or dysmenorrhea (ICD-10-CM N94.6) ± three months from their first PCOS diagnosis. PCOS and Pain controls were defined as patients with PCOS but no pain diagnoses. Description of inclusion and exclusion criteria for each cohort can be found in Table 1 - Figure supplement 1.

To compare cohorts (cases / controls), the first documented encounter or PCOS (case / controls) or PCOS and Pain (case / controls) was defined as an "index event" in TriNetX. Index events are the specific dates a patient satisfies all selected cohort criteria. Baseline characteristics are all assessed

before the index event while all health outcomes are assessed *after* the index event. Figure 1 - Figure supplement 2 shows a graphical representation of this relationship among index events and outcomes specified in this study.

Propensity Score Matching

The TriNetX platform uses a cohort matching method called 1:1 propensity score matching (Austin, 2011). For each cohort analysis, cases were matched on the following criteria: age at the index event, self-reported race, overweight, obesity, and other hyperalimentation (ICD-10-CM E65-E69) status, type 2 diabetes mellitus (T2D) (ICD-10-CM E11) status, essential (primary) hypertension (ICD-10-CM I10) status, and hyperlipidemia, unspecified (ICD-10-CM E78.5) status. Baseline conditions were assessed up to one day before the index event. Figure 1 shows the number of patients in each case and control cohort both at baseline and after propensity score matching.

Future Health Outcomes

For each of the cohorts listed above, we calculated relative risk ratios (RR) with 95% confidence intervals for 11 future health outcomes: abdominal and pelvic pain (R10) or dysmenorrhea (N94.6), female infertility (ICD-10-CM N97), noninflammatory disorders of ovary, fallopian tube and broad ligament (ICD-10-CM N83), obesity (ICD-10-CM E65-E68), Type 2 Diabetes (ICD-10-CM E11), depressive episode (ICD-10-CM F32), other anxiety disorders (F41), gastro-esophageal reflux disease (GERD) (ICD-10-CM K21), nonalcoholic steatohepatitis (ICD-10-CM K75.81) or fatty liver, not elsewhere classified (ICD-10-CM K76.0), chronic kidney disease (ICD-10-CM N18), and essential hypertension (ICD-10-CM I10). The RR for future health outcomes was calculated on participants who satisfied the 1:1 propensity score matching criteria (above). Differences in relative risks were calculated for significance by calculating the difference of two estimates (Altman & Bland, 2003). Future health outcomes were only considered if their first occurrence was at least 3 months after the index event. Figure 1 shows the health outcomes assessed after 1:1 propensity score matching (Austin, 2011; Guo & Fraser, 2014; Haukoos & Lewis, 2015). These analyses were done within the TriNetX platform, and no individual-level data was extracted from the platform.

Self-Reported Race Stratified Sub-Analysis

We did a follow-up analysis looking at health outcomes for patients with PCOS and PCOS and Pain compared to matched controls stratified by self-reported race and ethnicity. The following race categories are present in the TriNetX platform: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other, White, and Unknown Race. For our analysis, we included the following four race categories: Asian, Black or African American, and Other (American Indian or Alaskan Native or Native Hawaiian or Other Pacific Islander, or Other), and White (Figure 2 - Figure supplement 3). Due to the small population sizes of American Indian or Alaskan Native or Native Hawaiian or Other Pacific Islander, or Other, we decided to combine these four self-reported race groups together into one “Other” population. For the PCOS and Pain cohorts, we looked at ovarian cysts, infertility, obesity, T2D, depression, anxiety, GERD, pharyngitis, essential hypertension, liver disease, and kidney disease stratified by self-reported race (Figure 2 - Figure supplement 3).

PCOS Medication Sub-Analysis

We performed a follow-up analysis looking at the number of patients with PCOS who were documented as having pain before being prescribed three common PCOS medications (systemic contraceptives (VA: HS200), metformin (RxNorm 6809), or spironolactone (RxNorm 9997)) as shown in Figure 3 - Figure supplement 4. Three cohorts were created on January 16th, 2026, in the TriNetX Global Network. There were approximately 190,888,407 million patients from 170 healthcare organizations in 19 different countries. Patients were included if they had a PCOS diagnosis (described above) *and* 1) ever had a systemic contraceptives prescription but not a metformin or spironolactone prescription, 2) ever had a metformin prescription but not a systemic contraceptives or spironolactone prescription, and 3) ever had a spironolactone but not a

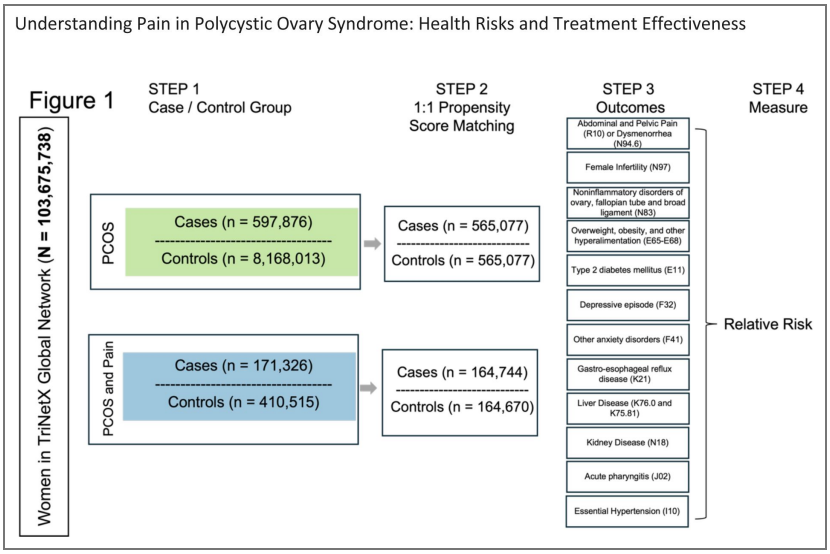


Figure 1. **Analysis pipeline.**

Analysis pipeline to calculate relative risk ratios (RR) for future health outcomes in PCOS (green) and PCOS and Pain (blue) cohorts for the 103,675,738 women queried. STEP 1 shows the number of women in the case and controls for both the PCOS (green) and PCOS and Pain (blue) cohorts. STEP 2 shows the number of cases and controls after 1:1 propensity score matching. STEP 3 shows the different future health conditions that were considered for future health outcomes. STEP 4 shows that the final step is calculating the relative risk for the future health outcomes.

systemic contraceptives or metformin prescription. For patients with PCOS, we counted the number of participants who had a diagnosis code for either dysmenorrhea or abdominal and pelvic pain before the index event. The index event was defined as a participant having a PCOS diagnosis and a medication prescription at the same time. We then counted the number of patients with PCOS who reported either dysmenorrhea or abdominal and pelvic pain after the index event. We further compared the change in prevalence before and after the indexed event.

Results

Demographics of Women with PCOS in the TriNetX Global Network

We first identified participants with PCOS and associated comorbidities. The demographics and characteristics of both the PCOS and non-PCOS cohorts are detailed in Table 2 - Figure supplement 5. We queried the 103,675,738 women of any age from 172 Health Care Organizations (HCOs) in the TriNetX Global Network for PCOS and associated comorbidities. After applying stringent inclusion/exclusion criteria for PCOS and subsequent controls (see Methods) we found a 5.6% (n = 576,077) prevalence of PCOS at an average age of 28.1 (SD ± 9.04) in this population. When we stratified the PCOS participants in 10-year age groups, we observe that the majority of PCOS patients are either 21-30 years old (30.46%) or 31-40 years old (38.42%) (Figure 4 – Figure supplement 7). Of those participants with PCOS, 4.85%, 13.15%, 23.32%, and 58.68% self-identified as Asian, Black or African American, Other, or White respectively (Table 2 - Figure supplement 5).

We then examined the prevalence of PCOS-associated comorbidities represented in the PCOS cohort. We observed that 16.28% of patient with PCOS had a diagnosis code for obesity, 5.93% had a diagnosis code for essential hypertension, 3.51% had a diagnosis code for T2D, and 2.96% had a diagnosis code for hyperlipidemia (Table 2 - Figure supplement 5). We also investigated the prevalence of other women's health conditions related to PCOS such as infertility and ovarian cysts. Table 2 - Figure supplement 5 shows that women with PCOS had a 2.34% prevalence of infertility and a 3.92% prevalence of ovarian cysts.

Since many women with PCOS are prescribed medications to help manage symptoms associated with the condition, we aimed to gain a deeper understanding of the prevalence of PCOS-prescribed medications in the PCOS cohort. We found that 14.88% of the PCOS cohort were prescribed systemic oral contraceptives, 6.82% were prescribed metformin, and 3.15% were prescribed spironolactone (Table 2 - Figure supplement 5).

A focus of our paper is understanding the impact pain has on women with PCOS; therefore, we looked at the prevalence of both dysmenorrhea and abdominal and pelvic pain. We observed that overall, there was a 20.67% prevalence of pain (2.85% prevalence of dysmenorrhea, 17.82% prevalence of abdominal or pelvic pain) (Table 2 - Figure supplement 5).

Demographics of Women with PCOS and Pain in the TriNetX Global Network

As noted above, 20.67% of women with PCOS also had a pain diagnosis, encompassing either dysmenorrhea or pelvic and abdominal pain. We first examined the demographics of the study participants using data from the TriNetX Global Network. Table 3 - Figure supplement 6 shows the comprehensive demographic results, highlighting the distribution of pain diagnoses for age, race, and other relevant demographic factors. This table provides a clear view of the demographic characteristics and their potential influence on the prevalence of pain among individuals with PCOS. Similar to the PCOS cohort, participants with PCOS and Pain had an average age of 28.5 (SD ± 8.78) with the majority of participants being between 21-30 years old (32.74%) or 31-40 years old (38.97%). Interestingly, the prevalence of PCOS and Pain was slightly higher at these ages compared to the prevalence of PCOS alone (Figure 4 – Figure supplement 7). Among the women with PCOS and Pain, 3.58% women were Asian, 14.54% Black or African America, 20.63% categorized as Other, and 61.25% self-reported as White (Table 3 - Figure supplement 6). However, when we looked at the prevalence of PCOS and Pain compared to controls (PCOS

without pain) within a self-reported race group, we observed that the highest prevalence of PCOS and Pain was 48.11% in the Black or African American population followed by 44.76% in the Other population and 43.84% in the White population, and 27.20% in the Asian population. (Table 4 - Figure supplement 8). With respect to PCOS comorbidities, the cohort of individuals with both PCOS and Pain exhibited a higher prevalence of comorbid conditions compared to the entire population of individuals with PCOS. Specifically, 33.88% of PCOS and Pain participants had an obesity diagnosis, 12.43% had an essential hypertension diagnosis, 7.84% had a T2D diagnosis, and 7.39% had a hyperlipidemia diagnosis. These high prevalences represent a respective increase of 16.28%, 5.93%, 3.52%, and 2.96% compared to all participants with PCOS. Notably, as illustrated in Figure 2, there is at least a two-fold increase in the prevalence of each comorbid condition among those with both PCOS and Pain. This substantial increase highlights the heightened risk and burden of comorbidities within the PCOS and Pain cohort.

We observed a similar trend with respect to two diseases affecting women with PCOS. We see a 2-fold increase in the prevalence of infertility (5.92%) and ovarian cysts (10.65%) in the PCOS and Pain cohort when we compared to the PCOS cohort as shown in Figure 2. Further, there is at least a 2-fold increase in prescriptions for all three common PCOS symptom-management medications in PCOS and Pain cohort compared to PCOS cohort (Figure 2). **Risk of Future Health Outcomes for all PCOS vs. PCOS and Pain**

Given that PCOS symptoms first manifest in puberty and during reproductive years, we aimed to assess the risk for patients with PCOS, and those with both PCOS and Pain, developing future health outcomes. The risk (%) for the future health outcomes assessed in this study can be found in the risk column of Table 5 – Figure supplement 9. To start, we see that 21% of women with PCOS overall were at risk for a future diagnosis of Pain (abdominal and pelvic pain or dysmenorrhea). Of the comorbidities of PCOS, obesity, T2D, and essential hypertension had 20.7%, 5.1%, and 7.7% increased risk in the PCOS overall cohort and 20.4%, 5.2%, and 8.2% increased risk in the PCOS and Pain cohort respectively. Liver disease and kidney disease, which are on the rise in PCOS patients, were found to have a 4.0% and 0.7% increased risk in the PCOS cohort and at 5.4% and 0.9% increased risk in the PCOS and Pain cohort. The “Explore Outcome” feature on the TriNetX platform revealed that anxiety, depression, gastroesophageal reflux disease (GERD), and acute pharyngitis were the most common future health outcomes for women diagnosed with PCOS and Pain. When we looked at risk for these future health outcomes, we observed that 17.1%, 11.5%, 10.5%, 10.0% of patients with PCOS and 20.1%, 13.7%, 13.5%, 13.3% of patients with PCOS and Pain were at risk of developing anxiety, depression, acute pharyngitis, and GERD respectively. Overall, besides obesity, patients with PCOS and Pain showed a higher risk for the investigated future health outcomes than PCOS alone. We explore the relationship of future health outcome risk further in the results below.

Relative Risk of Future Health Outcomes for all PCOS vs. PCOS and Pain

Given that PCOS symptoms first manifest in puberty and during reproductive years, we aimed to assess the relative risk for patients with PCOS, and those with both PCOS and Pain, developing future health outcomes. We calculated the RR for matched PCOS patient cohorts with their respective controls and PCOS and Pain patient cohorts with their respective controls (see Methods). Results are visualized in Figure 3 and cohorts counts, RRs, and p-values for differences in risk ratios are provided in Table 5 - Figure supplement 9.

Figure 2. Prevalence of conditions and medications associated with PCOS and Pain.

Barplots show the prevalence (%) (left y-axis) of different diseases associated with PCOS (green) and PCOS and Pain (blue) (x-axis). Purple line indicates the prevalence fold-change between the PCOS and PCOS and Pain cohorts (right y-axis).

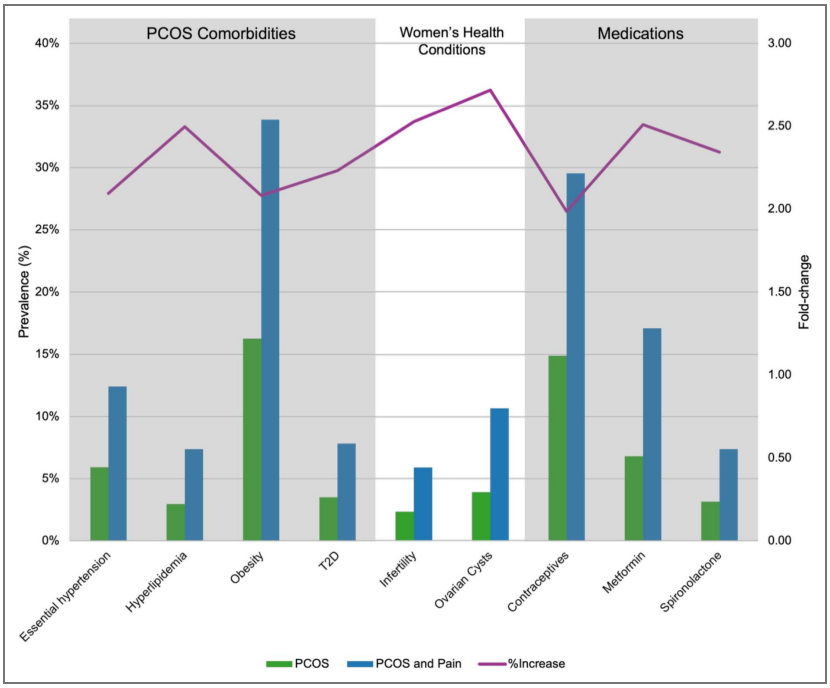
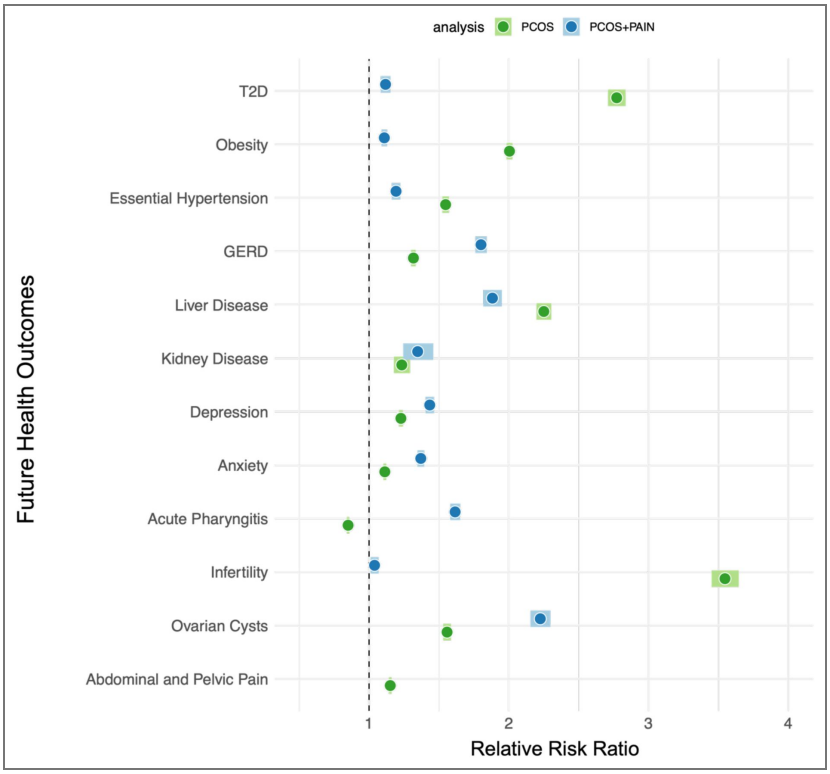


Figure 3. Relative risk ratios for future health outcomes associated with PCOS and Pain.

Relative risk ratios (RR) (x-axis) for future health outcomes (y-axis) for both PCOS (green) and PCOS and Pain (blue) cohorts. Darker hued circles indicate RR, while lighter hued boxes indicate the 95% confidence intervals. The black dashed line is set 1 and is the threshold for RR, where > 1 is increased RR and < 1 is decreased RR.



In Figure 3, we see the RR for both participants within the PCOS cohort (green) for 12 health outcomes and PCOS and Pain cohort (blue) for 11 health outcomes. Aside from acute pharyngitis, the PCOS cohort has significantly increased risk for developing the following future health outcomes compared to matched controls: T2D, obesity, essential hypertension, GERD, liver disease, kidney disease, depression, anxiety, infertility, ovarian cysts, and pain. The PCOS and Pain cohort meanwhile has significantly increased risk for developing all of the following future health outcomes compared to their matched controls: T2D, obesity, essential hypertension, GERD, kidney disease, depression, anxiety, acute pharyngitis, infertility, ovarian cysts, and pain.

While almost all of the RR are increased for case cohorts compared to match controls, a few results stand out as being particularly interesting. Infertility, for example, a common complication associated with PCOS, has a RR of 3.55 (95% CI 3.45-3.64) in PCOS cases overall. Meanwhile, the RR for a future outcome of infertility for women with PCOS and Pain is a near-insignificant 1.04 (95% CI 1.04-1.07). This difference in relative risks has a p-value of 6.04E-820 (Table 5 - Figure supplement 9). On the other hand, ovarian cysts have a RR of 1.56 (95% CI 1.53-1.59) in PCOS cases overall, but an even higher RR in PCOS and Pain cases (RR=2.23, 95% CI 2.16-2.30). This relative risk difference is also statistically significant (p-value = 2.24E-36) (Table 5 - Figure supplement 9). In GERD, depression, anxiety, and acute pharyngitis all had higher RRs in PCOS and Pain cases vs. controls compared to PCOS cohort cases compared to controls (Figure 3, Table 5 - Figure supplement 9). We see that GERD, acute pharyngitis, depression, and anxiety are 1.80 (95% CI 1.76-1.84), 1.62 (95% CI 1.58-1.65), 1.43 (95% CI 1.40-1.47), and 1.37 (95% CI 1.35-1.39) in the PCOS and Pain cohort compared to 1.32 (95% CI 1.30-1.33), 0.85 (95% CI 0.84-0.86), 1.23 (95% CI 1.21-1.24) and 1.11 (95% CI 1.10-1.12) in the entire PCOS cohort at statistical significance (Figure 3, Table 5 - Figure supplement 9).

PCOS and PCOS and Pain cohorts were at comparable increased risk for developing future kidney disease. The RR of the PCOS cohort was 1.23 (95% CI 1.18-1.29) while the RR for the PCOS and Pain cohort was 1.35 (95% CI 1.24-1.46) (Figure 3). The relative risk difference was not statistically significant (p-value = 6.64E-02) (Table 5 - Figure supplement 9).

Obesity, T2D, essential hypertension, and liver disease had increased risk for the PCOS cohort compared to the PCOS and Pain cohort. T2D had a RR of 2.77 (95% CI 2.71-2.84) in the PCOS cohort compared to 1.12 (95% CI 1.08-1.15) in the PCOS in Pain cohort. Obesity had a RR of 2.00 (95% CI 1.98-2.03) in the PCOS cohort compared to 1.11 (95% CI 1.09-1.13) in the PCOS and Pain cohort. Meanwhile, the RR for liver disease was 2.25 (95% CI 2.20-2.30) in the PCOS cohort compared to 1.89 (95% CI 1.82-1.95) in the PCOS and Pain cohort. Finally, essential hypertension had a RR of 1.55 (95% CI 1.52-1.57) in the PCOS cohort and 1.19 (95% CI 1.16-1.22) in the PCOS and Pain cohort (Figure 3). All relative risk differences were statistically significant (Table 5 - Figure supplement 9).

Relative Risk of Future Health Outcomes Stratified by Self-Reported Race

Since we were interested in the impact of Pain for women with PCOS, we next investigated if there were any race-specific risks (self-reported from EHR) for these outcomes. We stratified the PCOS and Pain case and control cohorts by self-reported race and calculated RR for the same 11 future health outcomes (methods) discussed above. Figure 4(A-K) shows the RR for each of the 11 future health outcomes in the Asian (orange), Black or African American (yellow), Other (red), and White (purple) PCOS and Pain cohorts. We observed significant race-specific differences in RR for a number of future health outcomes. Figure 4A shows that infertility has increased RR in the Other cohort (RR = 1.35, 95% CI 1.18-1.54) and Black or African American (RR = 1.23, 95% CI 1.13-1.34). Both the Other and Black or African American PCOS and Pain cohorts had significantly increased risk when compared to the Asian and White cohorts (adjusted p-value ≤ 0.005) (Figure 4A, Table 6 - Figure supplement 10, Table 7 - Figure supplement 11). Ovarian cysts had increased RR across Asian (RR = 1.63, 95% CI 1.35-1.98), Black or African American (RR = 2.28, 95% CI 2.11-2.47), Other (RR = 2.31, 95% CI 2.06-2.60), and White (RR = 2.15, 95% CI 2.06-2.23) PCOS and Pain cohorts. However, there was a significantly increased RR for ovarian cysts in the Other, Black

of African American, and White PCOS and Pain cohorts compared to the Asian PCOS and Pain cohort (adjusted p-value ≤ 0.05) (Figure 4B). Meanwhile, while all self-reported race cohorts show at least a 1.42 increased RR for depression, there was a significantly increased RR in Black or African American and Other PCOS and Pain cohorts compared to White PCOS and Pain cohorts (adjusted p-value ≤ 0.05) (Figure 4F). Interestingly, the Asian PCOS and Pain cohort had a decreased RR (RR = 0.8, 95% CI 0.51-1.27) for kidney disease compared to an increased RR in the Black or African American (RR = 1.53, 95% CI 1.45-1.61), Other (RR = 1.58, 95% CI 1.39-1.46), and White (RR = 1.42, 95% CI 1.39-1.46) PCOS and Pain cohorts (Figure 4I). Moreover, here was a significant increased RR for kidney disease in the White PCOS and Pain cohort compared to the Asian PCOS and Pain cohort (adjusted p-value ≤ 0.05) (Figure 4I). None of the PCOS and Pain self-reported race cohorts showed notable RR for the future health outcomes of T2D, Obesity, or Essential Hypertension (Figure 4C-E). On the other hand, all PCOS and Pain self-reported race groups had increased RR for anxiety (RR at least 1.36, 95% CI 1.33-1.39), GERD (RR at least 1.69, 95% CI 1.59-1.78), and acute pharyngitis (RR at least 1.48, 95% CI 1.30-1.69) (Figure 4 G, J, K).

Medications Prescribed to Patients with PCOS May Modify Pain Prevalence

Since women with PCOS are often prescribed medications to help their PCOS symptoms, we aimed to investigate if there were any changes in the pain diagnoses after being prescribed systemic contraceptives (COCPs), metformin, or spironolactone. For patients with PCOS who were prescribed each of the three medications exclusively, we calculated the percent who reported dysmenorrhea or abdominal and pelvic pain both before and after the prescription (see Methods). We found that there were 118,144 women with PCOS who were prescribed systemic contraceptives, 65,162 prescribed metformin, and 15,460 prescribed spironolactone. The prevalence of abdominal and pelvic pain diagnosis was 6-8x greater than that of a dysmenorrhea diagnosis for PCOS participants before they were prescribed PCOS-related medications (Figure 5).

Oftentimes, women with PCOS are prescribed COCPs, metformin, and spironolactone to manage their symptoms. We observed that women with PCOS had prescriptions for COCPs 17.8% of the time, metformin 10.3% of the time and spironolactone 2.3% of the time. As can be observed in Figure 5, participants with PCOS reported abdominal and pelvic pain at a prevalence of 31.8%, 24.8%, and 26.3% respectively before their first prescription of COCPs, metformin, and spironolactone. At least 3 months after being prescribed a PCOS-associated medication, we observe a significant reduction in the prevalence of abdominal and pelvic pain. Spironolactone shows the largest reduction of pain prevalence with a –9.1% reduction of pain diagnosis after prescription compared to before, followed by COCPs (−6.3%) and metformin (−5.3%). Similar results are observed for dysmenorrhea. While lower overall, there was also a decreased prevalence of pain for all three medications, the prevalence for dysmenorrhea was 9.4%, 3.6% and 4.3% for participants with PCOS prescribed COCPs, metformin, and spironolactone respectively. Unlike with abdominal and pelvic pain, COCP prescriptions were associated with the largest decrease in dysmenorrhea prevalence (−3.8%), followed by spironolactone (−2.6%), and (−1.6%).

Discussion

Polycystic ovary syndrome is the most prevalent endocrine disorder among women (Mousa & Tay, 2023; Walters et al., 2018). Diagnosis and treatment plans are customized based on the symptoms presented by women. However, an important yet often overlooked variable is pain, which may manifest as dysmenorrhea, abdominal, or pelvic pain. The use of EHR data has facilitated access to patient records containing longitudinal clinical information, utilizing the readily available International Classification of Diseases (ICD) codes (Wu et al., 2016). Our study aimed to elucidate the prevalence and impact of pain among individuals with PCOS, as well as to investigate the relative risk of future health outcomes and the effectiveness of commonly prescribed medications on pain. Firstly, we observed a significantly higher prevalence of pain among women with PCOS compared to those without the condition. Specifically, 20.67% of women

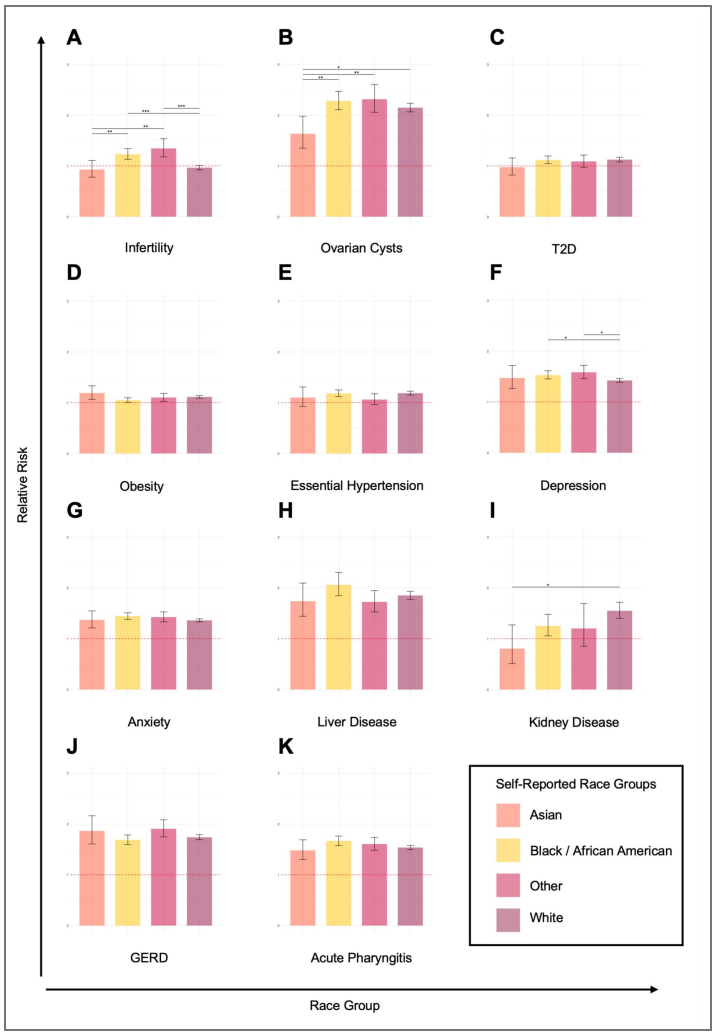


Figure 4. Self-reported race-stratified relative risk ratios for future health outcomes (A–K).

Relative risk ratios (RR) for future health outcomes (y-axis) stratified by self-reported race. Colors represent different self-reported race groups (x-axis): Asian (orange), Black or African American (yellow), Other (red), White (purple). Error bars represent the 95% confidence intervals. Significant differences between RR are represented by asterisks (*), where p-value ≤ 0.05 = *, p-value ≤ 0.005 = **, p-value ≤ 0.0005 = ***, and p-value ≤ 0.00005 = ****. Red dashed lines is set 1 and is the threshold for RR, where > 1 is increased RR and < 1 is decreased RR.

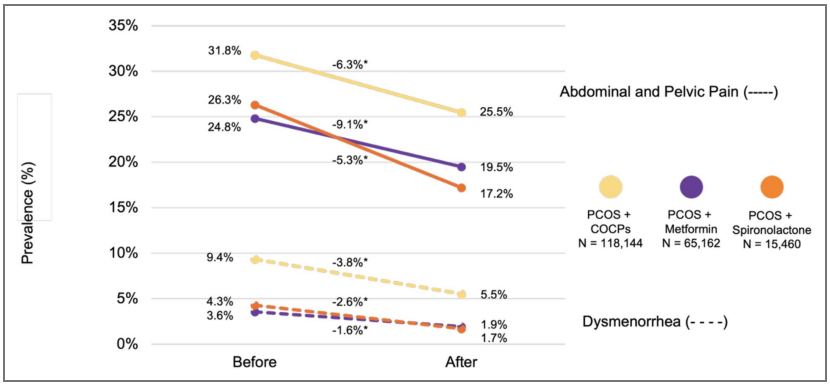


Figure 5. Prevalence of Pain for women with PCOS before and after medications.

Prevalence (%) changes (y-axis) of pain for women with PCOS cohort before and after prescription of COCPs (yellow), metformin (purple), and spironolactone (orange) (x-axis). Analysis was done separately for abdominal and pelvic pain (solid lines) and dysmenorrhea (dashed lines).

with PCOS reported experiencing pain, compared to 15.7% in the non-PCOS cohort. This increased prevalence reveals the substantial burden of pain as a symptom of PCOS, which often goes underreported and undertreated. Our demographic analysis of women with PCOS and Pain also revealed a difference in diagnosis of pain across self-reported race groups and was especially high in the Black or African American population (32.7%) and White population (30.78%). These findings suggest that pain is a significant symptom of PCOS that can vary across different demographic groups. The high prevalence of pain underscores the need for healthcare clinicians to routinely assess and address pain in the management of PCOS, particularly in racially diverse populations. The diversity in pain perception and reporting among different racial groups can be influenced by a variety of factors, including genetic differences, cultural attitude towards pain, access to healthcare, and socioeconomic status. Women of different racial groups often experience different severities in pain (Portenoy et al., 2004). This can lead to disparities in pain management and treatment outcomes (Campbell & Edwards, 2012; Jamieson & Steege, 1996). Additionally, cultural differences may also affect how individuals report pain and their willingness to seek medical help (Hadjiconstantinou et al., 2017).

PCOS manifests with many other concomitant conditions (Anagnostis et al., 2018; Asuncion et al., 2000; Balen et al., 2016; Escobar-Morreale et al., 2011; Hadjiconstantinou et al., 2017; Kitzinger & Willmott, 2002; Patel, 2018). Our study revealed that women with PCOS and Pain have at least a 2-fold increased prevalence of other health conditions at baseline compared to women with PCOS in general. The prevalence of obesity in the PCOS and Pain cohort was 33.88% compared to a 14.63% prevalence in the entire PCOS cohort. Excess abdominal visceral fat is well-documented to increase inflammation (Després, 2012) and PCOS is considered a pro-inflammatory condition linked with cardiovascular disease (CVD) and T2D. This inflammation, in turn, can underlie obesity, CVD, and insulin resistance (IR) (Abraham Gnanadass et al., 2021; Osborn & Olefsky, 2012). Our data show that 12.43% of patients with PCOS and Pain also had a diagnosis for essential hypertension and 7.84% of PCOS and Pain patients had a T2D diagnosis. These results underscore the health challenges faced by individuals dealing with both PCOS and Pain issues necessitating treatment approaches that address both the syndrome itself and its accompanying symptoms.

Women with PCOS are significantly at risk for future health outcomes such as infertility, T2D, coronary heart disease, dyslipidemia, depression, non-alcoholic fatty liver disease, and obstructive sleep (Anagnostis et al., 2018; Ávila et al., 2014; Chaudhuri, 2023; McGowan, 2011; Patel, 2018; Zore et al., 2017). Our results also highlight specific risks for different subgroups (PCOS overall and PCOS and Pain). In the overall PCOS cohort, the highest future health outcome risks are for infertility (RR = 3.54) and T2D (RR = 2.77). However, in patients with PCOS and Pain, the highest risks are for ovarian cysts (RR = 2.23). Ovarian cysts are a hallmark feature of polycystic ovarian morphology (PCOM), which is caused by immature/arrested follicles that do not ovulate and cause a “string of pearls” appearance and enlarging of the ovaries (Adashi et al., 2023; Tsilchorozidou et al., 2004). Ovarian cysts have long been disputed by the PCOS research community as not being associated with PCOS and therefore, not being associated with pain. However, the magnitude of this risk as shown in our results underscores the importance of regular monitoring and appropriate management strategies for patients presenting with both PCOS and pain symptoms. Liver disease had high and comparable RR in both cohorts with overall PCOS (RR = 2.23) and PCOS and Pain (RR = 1.89). PCOS is known to be linked with non-alcoholic fatty liver disease (NAFLD) (Butt & Devi, 2024; Kumarendran et al., 2018; Torres & Harrison, 2016). This association between PCOS and pain and liver disease may be explained by the shared metabolic disturbances common to both PCOS and NAFLD, such as insulin resistance and dyslipidemia (Georgescu, 2022; Qu et al., 2013; Torres & Harrison, 2016). The presence of chronic pain could potentially exacerbate these metabolic imbalances through various mechanisms, including altered stress responses and lifestyle factors (Kivimäki et al., 2023). These findings suggest that patients with PCOS who also experience chronic pain may represent a distinct phenotype with unique risk profiles. In contrast, women with PCOS without documented pain demonstrated higher relative risks for infertility, obesity, and T2D, suggesting a more metabolically driven PCOS phenotype. The differing RR patterns between PCOS with and without

pain may therefore reflect heterogeneity in underlying pathophysiology, symptom recognition, or healthcare utilization. Further longitudinal and mechanistic studies will be needed to better understand these distinct clinical trajectories. Additionally, the increased risk for future health conditions in the PCOS and Pain cohort also suggest that pain may be an important marker for identifying individuals at risk of developing future health outcomes, necessitating more vigilant monitoring and proactive intervention.

Women with PCOS had a higher future risk of depression (RR=1.23) and anxiety (RR=1.11). These associations were substantially stronger in the PCOS and Pain cohort (depression RR=1.43; anxiety RR=1.37). This pattern aligns with prior evidence and supports routine mental health screening as part of PCOS care (Teede et al., 2018; Teede et al., 2023). Clinically, the higher RR estimates in the pain-enriched PCOS subgroup can be supported by the understanding that persistent pain associated with PCOS (dysmenorrhea, abdominal and pelvic pain), which can amplify stress, sleep disruption, and functional impairment, all of which can worsen mood and anxiety and increase healthcare contacts where these diagnoses are captured (O'Brien & Bosak, 2025; Sai & Mahaparale, 2024). We also observed increased future GERD risk in the PCOS overall cohort (RR=1.32), with a marked elevation in the PCOS and Pain cohort (RR=1.80). The increased RR for GERD in women with PCOS and PCOS and Pain supports the established model that obesity and central adiposity in PCOS, particularly in those with pain, is a factor for GERD and its complications (Hampel et al., 2005). Finally, acute pharyngitis showed increased risk specifically in the PCOS and Pain cohort (RR=1.62). This may reflect reflux-related upper airway irritation (laryngopharyngeal reflux), which has been linked to chronic pharyngitis-type presentations, as well as utilization/coding effects in a subgroup of PCOS patients with more frequent clinical encounters (Cui et al., 2024).

Lastly, our analysis explored the impact of common PCOS medications on pain management. We found that prescriptions for COCPs, metformin, and spironolactone are associated with a reduction in reported pain symptoms. Specifically, individuals who received these medications showed a 5.00% average decreased prevalence of pain diagnoses after treatment, suggesting that these medications may also manage pain symptoms in individuals with PCOS. A recent publication looked at the association of PCOS-related medications with adverse drug reactions (ADRs) for women with PCOS and found that metformin and COCPs was significantly associated with abdominal pain (Sidra et al., 2019). However, this study did not measure the association of ADRs with pain before and after the prescription of PCOS medication. Our results offer insights for application showing that efficient pharmacological management of PCOS symptoms can also help alleviate associated pain. Additionally, the efficacy of these medications in reducing pain, specifically spironolactone and COCPs, which are prescribed in PCOS for their antiandrogenic effects, may suggest hyperandrogenism to be a contributor to increased pain in PCOS, and a potential target for addressing pain in PCOS. Furthermore, the advantages of these treatments may be beneficial, not just in managing typical PCOS symptoms, but also in tackling the significant burden of pain experienced by many women with PCOS, highlighting a valuable role in drug repurposing.

Our study has limitations that need to be considered when interpreting the results. Firstly, relying on ICD codes to identify pain and other health outcomes may not capture the range of experiences and clinical intricacies. While these codes offer an approach to data collection, they might not fully reflect variations in pain severity or the personal experiences of those, with PCOS (Kataria & Ravindran, 2020). Although extensive, the use of EHR data may still contain gaps or discrepancies that could impact the accuracy of our results (Madden et al., 2016). Furthermore, since this study is observational, by nature it cannot establish a causal relationship between PCOS, pain, and future health outcomes. Moreover, the demographic variations observed—especially the higher occurrence of pain among individuals—could be influenced by socio-economic factors, access to healthcare, nutrition, and other unmeasured variables. In addition, self-reported race was not captured the same globally as it is not a variable that is coded by HCOs world-wide. Lastly,

TriNetX captures only medication prescriptions, which does not allow our analysis to consider adherence issues, dosage differences, or concurrent treatments that may influence the outcomes observed.

We were unable to evaluate the use of analgesics or anti-inflammatory medications, as over-the-counter pain medications commonly used for dysmenorrhea and pelvic pain are not consistently captured within the TriNextX electronic health record system. This limitation prevents the assessment of how pain-specific treatments may influence reported pain outcomes.

Future research should focus on overcoming these limitations through studies with detailed clinical assessments and a broader range of demographic and socio-economic factors.

Conclusion

Various pain subtypes can profoundly affect the daily lives of PCOS patients. Due to limited research in clinical and laboratory settings, the effects and underlying mechanisms of pain remain unclear. Our study highlights the significant prevalence and impact of pain in women with PCOS, revealing critical differences across racial groups and underscoring the heightened risk for future health complications in those experiencing pain. These findings emphasize the importance of comprehensive pain assessment, management and inclusion as guidelines in the standard care of PCOS, with a particular focus on addressing racial disparities. Additionally, the observed effectiveness of medications such as systemic oral contraceptives, metformin, and spironolactone in reducing pain symptoms provide valuable insights for clinical practice, suggesting that these treatments can offer dual benefits in managing both PCOS and associated pain. Dysmenorrhea, abdominal, and pelvic pain are common experiences in women with PCOS, in the absence of pelvic-related conditions that can contribute to this type of pain, such as pelvic inflammatory disease, endometriosis, and fibroids. It is crucial to distinguish between pain originating from PCOS and Pain arising from comorbidities to ensure appropriate management and targeted treatment strategies for improving the quality of life in affected individuals.

Supplemental Materials

	PCOS	No PCOS
Inclusion	Female	Female
	PCOS Diagnosis (ICD 10 Code E28.2)	
	Irregular menstruation (ICD 10 Code N92.6) and Hirsutism (ICD 10 Code L68.0) or Irregular menstruation (ICD 10 Code N92.6) and Androgen Excess (ICD 10 Code)	
Exclusion	Endometriosis (ICD 10 Code N80)	PCOS Diagnosis (ICD 10 Code E28.2)
	Uterine Fibroids (ICD 10 Code D25, O34.1, O34.11, O34.10)	Irregular menstruation (ICD 10 Code N92.6) and Hirsutism (ICD 10 Code L68.0)
	Polyp of corpus uteri (ICD 10 Code N84.0)	Irregular menstruation (ICD 10 Code N92.6) and Androgen Excess
	Pelvic Inflammation (ICD 10 Code N73.9)	Endometriosis (ICD 10 Code N80), Uterine Fibroids (ICD 10 Code D25, O34.1), Polyp of corpus uteri (ICD 10 Code N84.0), Pelvic Inflammation (ICD 10 Code N73.9) , Hypothyroidism (ICD 10 Code E03.8, E03.9), Hyperprolactinemia (ICD 10 Code E22.1), Adrenal hyperplasia (ICD 10 Code E27.8, Q89.1)
	PCOS and Pain	PCOS
Inclusion	Female	Female
	PCOS Diagnosis (ICD 10 Code E28.2)	PCOS Diagnosis (ICD 10 Code E28.2)
	Irregular menstruation (ICD 10 Code N92.6) and Hirsutism (ICD 10 Code L68.0) or Irregular menstruation (ICD 10 Code N92.6) and Androgen Excess (ICD 10 Code)	Irregular menstruation (ICD 10 Code N92.6) and Hirsutism (ICD 10 Code L68.0) or Irregular menstruation (ICD 10 Code N92.6) and Androgen Excess (ICD 10 Code)
	Abdominal and pelvic pain (ICD Code 10 R10) or dysmenorrhea (ICD Code 10 N94.6)	
Exclusion	Endometriosis (ICD 10 Code N80), Uterine Fibroids (ICD 10 Code D25, O34.1, O34.11, O34.10), Hypothyroidism (ICD 10 Code E03.8, E03.9), Pelvic Inflammation (ICD 10 Code N73.9), Hyperprolactinemia (ICD 10 Code E22.1), Adrenal hyperplasia (ICD 10 Code E27.8, Q89.1), Polyp of corpus uteri (ICD 10 Code N84.0)	Endometriosis (ICD 10 Code N80), Uterine Fibroids (ICD 10 Code D25, O34.1, O34.11, O34.10), Hypothyroidism (ICD 10 Code E03.8, E03.9), Pelvic Inflammation (ICD 10 Code N73.9), Hyperprolactinemia (ICD 10 Code E22.1), Adrenal hyperplasia (ICD 10 Code E27.8, Q89.1), Polyp of corpus uteri (ICD 10 Code N84.0)
		Abdominal and pelvic pain (ICD Code 10 R10) or dysmenorrhea (ICD Code 10 N94.6)

Table 1 – Figure Supplement 1. **Inclusion and exclusion criteria for PCOS (top) and PCOS and Pain (bottom) cases and control cohorts.**

Figure 1 – Figure Supplement 2. Index Events for Women in TriNetX.

Schematic representing how events were indexed in TriNetX for both the PCOS (green) and PCOS and Pain (blue) cohorts.

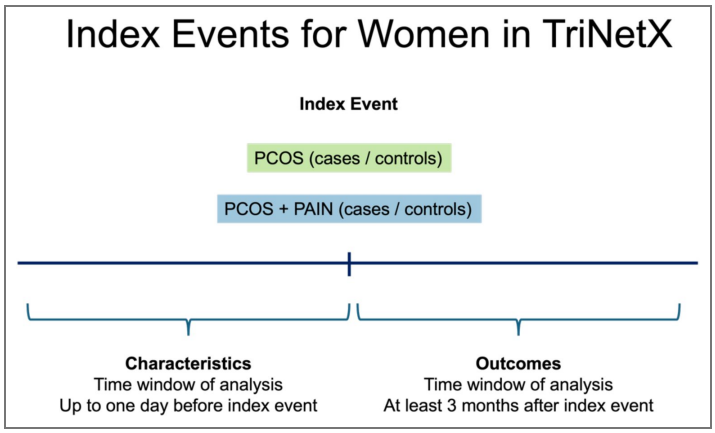


Figure 2 – Figure Supplement 3. Analysis pipeline for self-reported race groups.

Self-reported race-stratified TriNetX relative risk ratio analysis pipeline for future health outcomes in PCOS and Pain cohorts. Colors represent different self-reported race groups: Asian (orange), Black or African American (yellow), Other (red), White (purple).

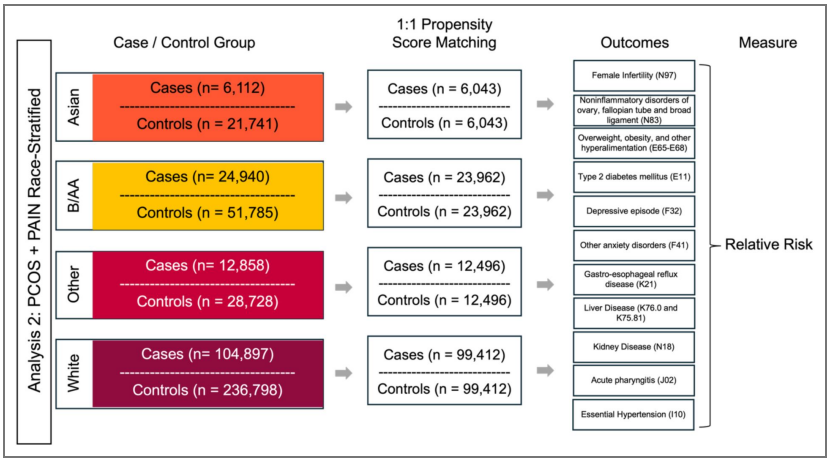
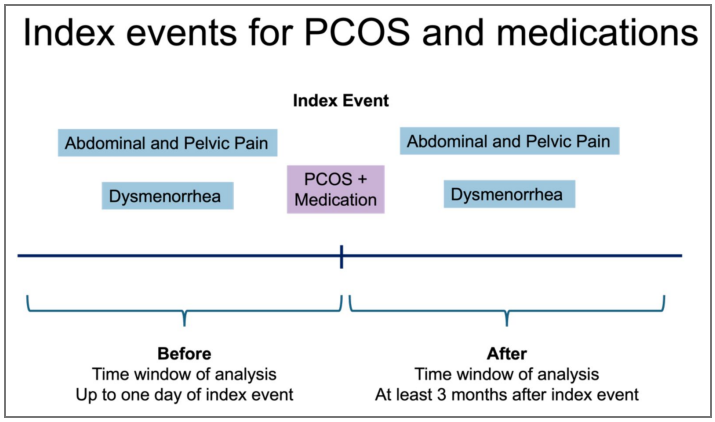


Figure 3 – Figure Supplement 4. Index events for PCOS and medications.

Schematic representing how the PCOS and medication events were indexed in TriNetX for both abdominal and pelvic pain and dysmenorrhea.



		Before						After					
Characteristic ID	Characteristic Name	PCOS	% PCOS	No PCOS	% No PCOS	p-value	SD	PCOS	% PCOS	No PCOS	% No PCOS	p-value	SD
	Total	576876		8168013				565077		565077			
AI	Age at Index	28.13 (± 9.04)		43.31 (± 20.07)				28.15 (± 9.03)		28.16 (± 9.04)		2.86E-01	0.00201
1002-5	American Indian or Alaska Native	2843	0.50 %	22878	0.29%	0.00E+00	0.03479	2843	0.50 %	1692	0.30%	0.00E+00	0.03222
2028-9	Asian	27410	4.85 %	318481	3.97%	0.00E+00	0.04296	27397	4.85 %	27951	4.95%	1.57E-02	0.00454
2054-5	Black or African American	74376	13.15%	940271	11.71%	0.00E+00	0.04380	74335	13.16%	74972	13.27%	7.68E-02	0.00333
2076-8	Native Hawaiian or Other Pacific Islander	2810	0.50 %	22962	0.29%	0.00E+00	0.03380	2810	0.50 %	1704	0.30%	0.00E+00	0.03104
2131-1	Other Race	35155	6.22 %	386380	4.81%	0.00E+00	0.06161	35070	6.21 %	34717	6.14%	1.68E-01	0.00260
UNK	Unknown Race	91101	16.11%	1792170	22.31%	0.00E+00	0.15797	91100	16.12%	92810	16.42%	1.31E-05	0.00820
2106-3	White	331862	58.68%	4549060	56.64%	0.00E+00	0.04137	331522	58.67%	331231	58.62%	5.78E-01	0.00105
	Other	131909	23%	2224390	28%			131823	23%	130923	23%		

Supplemental Table 2. Demographic results for PCOS case and control cohorts before and after 1:1 propensity score matching.

For each cohort analysis, cases were matched on the following criteria: age at the index event, self-reported race, overweight, obesity, and other hyperalimentation (ICD-10-CM E65-E69) status, type 2 diabetes mellitus (T2D) (ICD-10-CM E11) status, essential (primary) hypertension (ICD-10-CM I10) status, and hyperlipidemia, unspecified (ICD-10-CM E78.5) status. Baseline conditions were assessed up to one day before the index event.

Supplemental Table 2. (continued)

2186-5	Not Hispanic or Latino	356042	62.95%	4273952	53.21%	0.00E+00	0.198447	355745	62.96%	315837	55.89%	0.00E+00	0.144199
UN	Unknown Ethnicity	141799	25.07%	3286982	40.92%	0.00E+00	0.341983	141761	25.09%	201808	35.71%	0.00E+00	0.232572
2135-2	Hispanic or Latino	67716	11.97%	471268	5.87%	0.00E+00	0.215461	67571	11.96%	47432	8.39%	0.00E+00	0.118087
E65-E68	Overweight, obesity and other hyperalimentation	92042	16.28%	718866	8.95%	0.00E+00	0.22199	91562	16.20%	91393	16.17%	6.66E-01	0.00081
I10	Essential (primary) hypertension	33561	5.93%	1233003	15.35%	0.00E+00	0.30898	33554	5.94%	33531	5.93%	9.27E-01	0.00017
E11	Type 2 diabetes mellitus	19880	3.52%	442620	5.51%	0.00E+00	0.09624	19847	3.51%	20462	3.62%	1.81E-03	0.00587
E78.5	Hyperlipidemia, unspecified	16734	2.96%	737752	9.19%	0.00E+00	0.26295	16733	2.96%	16355	2.89%	3.49E-02	0.00397
R10	Abdominal and pelvic pain	100807	17.82%	1122832	13.98%	0.00E+00	0.10530	100661	17.81%	99781	17.66%	3.02E-02	0.00408
N94.6	Dysmenorrhea, unspecified	16107	2.85%	137898	1.72%	0.00E+00	0.07580	16070	2.84%	18870	3.34%	0.00E+00	0.02863
N97	Female infertility	13244	2.34%	34447	0.43%	0.00E+00	0.16421	13241	2.34%	4333	0.77%	0.00E+00	0.12767
N83	Noninflammatory disorders of ovary, fallopian tube and broad ligament	22160	3.92%	138266	1.72%	0.00E+00	0.13300	22144	3.92%	15098	2.67%	0.00E+00	0.06989
HS200	CONTRACEPTIVES,SYSTEMIC	84147	14.88%	651819	8.12%	0.00E+00	0.21324	84076	14.88%	91954	16.27%	0.00E+00	0.03845
6809	metformin	38551	6.82%	260773	3.25%	0.00E+00	0.16386	38506	6.81%	14589	2.58%	0.00E+00	0.20104
9997	spironolactone	17819	3.15%	103247	1.29%	0.00E+00	0.12691	17813	3.15%	7063	1.25%	0.00E+00	0.12994

Table 3 - Figure Supplement 6. Demographic and baseline characteristics for PCOS and Pain case and control cohorts before and after 1:1 propensity score matching.

For each cohort analysis, cases were matched on the following criteria: age at the index event, self-reported race, overweight, obesity, and other hyperalimentation (ICD-10-CM E65-E69) status, type 2 diabetes mellitus (T2D) (ICD-10-CM E11) status, essential (primary) hypertension (ICD-10-CM I10) status, and hyperlipidemia, unspecified (ICD-10-CM E78.5) status. Baseline conditions were assessed up to one day before the index event.

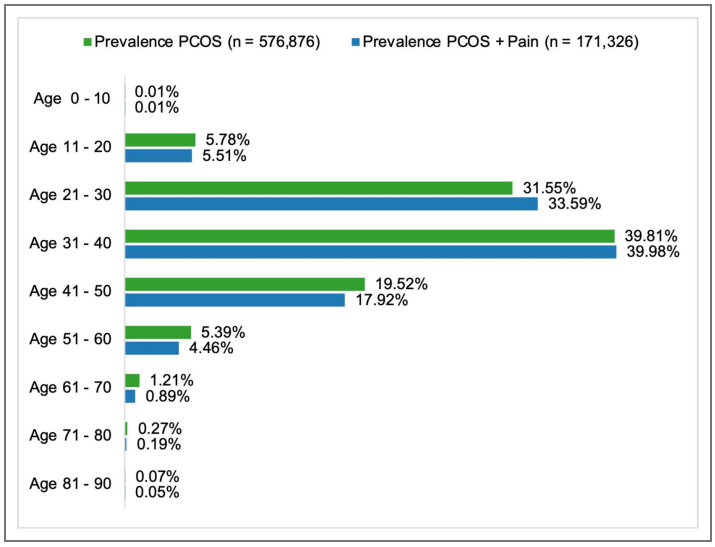
		Before						After					
Characteristic ID	Characteristic Name	PCOS + Pain	% PCOS + Pain	PCOS - Pain	% PCOS - Pain	p-value	SD	PCOS + Pain	% PCOS + Pain	PCOS - Pain	% PCOS - Pain	p-value	SD
	Total	171326		410515				164744		164744			
AI	Age at Index	28.53 (± 28.53)		28.41 (± 9.20)	100 %	3.08E-06	0.0136	28.39 (± 8.81)		28.40 (± 9.03)	100 %	8.48E-01	0.00067
1002-5	American Indian or Alaska Native	950	0.56 %	1931	0.48 %	1.34E-04	0.0109	933	0.57 %	740	0.45 %	2.24E-06	0.01649
2028-9	Asian	6075	3.58 %	21499	5.36 %	0.00E+00	0.0862	6044	3.67 %	5969	3.63 %	4.86E-01	0.00243
2054-5	Black or African American	24692	14.55%	50827	12.67%	0.00E+00	0.0548	23657	14.37%	25050	15.21%	8.05E-12	0.02383
2076-8	Native Hawaiian or Other Pacific Islander	937	0.55 %	1927	0.48 %	4.57E-04	0.0100	928	0.56 %	756	0.46 %	2.64E-05	0.01465
2131-1	Other Race	10935	6.44 %	24595	6.13 %	8.34E-06	0.0128	10637	6.46 %	10595	6.43 %	7.66E-01	0.00104
UNK	Unknown Race	22174	13.06%	69034	17.21%	0.00E+00	0.1158	22043	13.39%	22107	13.43%	7.43E-01	0.00114
2106-3	White	104003	61.26%	231439	57.68%	0.00E+00	0.0730	100428	60.99%	99453	60.40%	5.04E-04	0.01212
	Other	34996	21%	97487	24%			34541	21%	34198	21%		
2186-5	Not Hispanic or Latino	109689	64.59%	250682	62.40%	0	0.045	105912	64.29%	106378	64.57%	0.08991917	0.0059
UN	Unknown Ethnicity	36480	21.48%	106152	26.43%	0	0.116	35807	21.74%	38637	23.45%	4.4381E-32	0.0411
2135-2	Hispanic or Latino	23662	13.93%	44881	11.17%	0	0.083	23025	13.98%	19729	11.98%	0	0.0596
E65-E68	Overweight, obesity and other hyperalimentation	57508	33.88%	58705	14.63%	0.00E+00	0.4608	52443	31.85%	52512	31.89%	7.96E-01	0.00090
I10	Essential (primary) hypertension	21094	12.43%	20962	5.22 %	0.00E+00	0.2559	17411	10.57%	17868	10.85%	1.00E-02	0.00897
E11	Type 2 diabetes mellitus	13316	7.84 %	12421	3.10 %	0.00E+00	0.2100	10826	6.57 %	10529	6.39 %	3.56E-02	0.00732
E78.5	Hyperlipidemia, unspecified	12548	7.39 %	10765	2.68 %	0.00E+00	0.2165	9994	6.07 %	9648	5.86 %	1.09E-02	0.00887
R10	Abdominal and pelvic pain	73588	43.35%	38148	9.51 %	0.00E+00	0.8310	71136	43.20%	20710	12.58%	0.00E+00	0.72651
N94.6	Dysmenorrhea, unspecified	12010	7.07 %	5391	1.34 %	0.00E+00	0.2884	11704	7.11 %	2977	1.81 %	0.00E+00	0.25894

Table 3 - Figure Supplement 6. (continued)

N97	Female infertility	10047	5.92 %	9443	2.35 %	0.00E+00	0.1798	9689	5.88 %	4305	2.61 %	0.00E+00	0.16263
N83	Noninflammatory disorders of ovary, fallopian tube and broad ligament	18080	10.65%	9851	2.46 %	0.00E+00	0.3358	17401	10.57%	5146	3.13 %	0.00E+00	0.29795
HS200	CONTRACEPTIVES,SYSTEMIC	50158	29.55%	54520	13.59%	0.00E+00	0.3955	48365	29.37%	26568	16.13%	0.00E+00	0.31975
6809	metformin	29039	17.11%	26583	6.63 %	0.00E+00	0.3284	26679	16.20%	14735	8.95 %	0.00E+00	0.22008
9997	spironolactone	12536	7.38 %	12620	3.15 %	0.00E+00	0.1907	11780	7.15 %	5889	3.58 %	0.00E+00	0.15927

Figure 4 – Figure Supplement 7. Age-stratified Prevalence of PCOS and PCOS and Pain.

Bar plots show the prevalence (%) of overall PCOS (green) and PCOS and Pain (blue) stratified by 10-year age groups. The total number of women with PCOS is 576,876 and the total number of women with PCOS and Pain is 171,326.



Supplemental Table 4 – Figure Supplement 8. Counts and prevalence (%) of PCOS cases and controls for self-reported race groups.

Self-reported race group	PCOS	No PCOS	Prevalence (%)
Asian	4810	16345	22.74%
Black or African American	16887	35703	32.11%
Other	25909	78786	24.75%
White	87077	196103	30.75%

Outcomes	Cohort Name	Patients in Cohort	Patients with Outcome	Risk (%)	Relative Risk Ratio (RR)	95% CI (Lower)	95% CI (Upper)	P-value
Abdominal and Pelvic Pain	PCOS + Pain	0	0		NA	NA	NA	NA
Abdominal and Pelvic Pain	PCOS - Pain	141399	13599	9.6%				
Abdominal and Pelvic Pain	PCOS Overall	412548	86597	21.0%	1.15	1.14	1.16	
Abdominal and Pelvic Pain	PCOS Controls	434896	79269	18.2%				
Acute Pharyngitis	PCOS + Pain	129728	17522	13.5%	1.62	1.58	1.65	**1.64e-397**
Acute Pharyngitis	PCOS - Pain	144688	12096	8.4%				
Acute Pharyngitis	PCOS Overall	499241	52252	10.5%	0.85	0.84	0.86	
Acute Pharyngitis	PCOS Controls	478551	58938	12.3%				
Anxiety	PCOS + Pain	110687	22193	20.1%	1.37	1.35	1.39	**2.33E-11**
Anxiety	PCOS - Pain	127316	18631	14.6%				
Anxiety	PCOS Overall	446953	76641	17.1%	1.11	1.10	1.12	
Anxiety	PCOS Controls	446119	68745	15.4%				
Depression	PCOS + Pain	124618	17015	13.7%	1.43	1.40	1.47	**1.72E-05**
Depression	PCOS - Pain	137978	13136	9.5%				
Depression	PCOS Overall	480632	55085	11.5%	1.23	1.21	1.24	
Depression	PCOS Controls	487289	45485	9.3%				
Essential Hypertension	PCOS + Pain	143081	11675	8.2%	1.19	1.16	1.22	**4.96E-56**

Supplemental Table 5 - Figure Supplement 9. Relative risk ratios (RR) for PCOS and PCOS and Pain cases and control cohorts.

Significant differences in RR between PCOS and PCOS and Pain cohorts are bolded.

Supplemental Table 5 - Figure Supplement 9. (continued)

Essential Hypertension	PCOS - Pain	140519	9611	6.8%				
Essential Hypertension	PCOS Overall	507320	39064	7.7%	1.55	1.52	1.57	
Essential Hypertension	PCOS Controls	522019	25971	5.0%				
GERD	PCOS + Pain	130549	17386	13.3%	1.80	1.76	1.84	
GERD	PCOS - Pain	147029	10873	7.4%				**2.52E-48**
GERD	PCOS Overall	506269	50438	10.0%	1.32	1.30	1.33	
GERD	PCOS Controls	516304	39041	7.6%				
Infertility	PCOS + Pain	164744	9358	5.7%	1.04	1.01	1.07	
Infertility	PCOS - Pain	164744	9005	5.5%				**6.04e-820**
Infertility	PCOS Overall	530186	22014	4.2%	3.55	3.45	3.64	
Infertility	PCOS Controls	559224	6548	1.2%				
Kidney Disease	PCOS + Pain	163279	1409	0.9%	1.35	1.24	1.46	
Kidney Disease	PCOS - Pain	163529	1047	0.6%				6.64E-02
Kidney Disease	PCOS Overall	561790	3884	0.7%	1.23	1.18	1.29	
Kidney Disease	PCOS Controls	561941	3148	0.6%				
Liver Disease	PCOS + Pain	153385	8287	5.4%	1.88	1.82	1.95	
Liver Disease	PCOS - Pain	159449	4576	2.9%				**1.35E-23**
Liver Disease	PCOS Overall	548043	21676	4.0%	2.25	2.20	2.30	
Liver Disease	PCOS Controls	557915	9806	1.8%				
Obesity	PCOS + Pain	99165	20223	20.4%	1.11	1.09	1.13	**2.07e-506**
Obesity	PCOS - Pain	92475	17003	18.4%				
Obesity	PCOS Overall	391393	80997	20.7%	2.00	1.98	2.03	
Obesity	PCOS Controls	444137	45849	10.3%				
Ovarian Cysts	PCOS + Pain	138617	10601	7.6%	2.23	2.16	2.30	
Ovarian Cysts	PCOS - Pain	156505	5379	3.4%				**2.24E-36**
Ovarian Cysts	PCOS Overall	527152	29047	5.5%	1.56	1.53	1.59	
Ovarian Cysts	PCOS Controls	547043	19347	3.5%				
T2D	PCOS + Pain	150919	7882	5.2%	1.12	1.08	1.15	
T2D	PCOS - Pain	149586	6989	4.7%				**4.28e-453**
T2D	PCOS Overall	528769	27124	5.1%	2.77	2.71	2.84	
T2D	PCOS Controls	541299	10018	1.9%				

Outcomes	RR	95 % CI Lower	95 % CI Upper	RACE
Acute Pharyngitis	1.48116696	1.29900096	1.68887908	Asian
Acute Pharyngitis	1.66642937	1.57489338	1.76328562	B/AA
Acute Pharyngitis	1.60569876	1.48306611	1.73847174	Other
Acute Pharyngitis	1.53787092	1.49711267	1.57973878	White
Anxiety	1.37047289	1.21289211	1.5485268	Asian
Anxiety	1.44386081	1.38026336	1.5103886	B/AA
Anxiety	1.42629925	1.3311973	1.52819537	Other
Anxiety	1.36169361	1.33334855	1.39064125	White
Depression	1.47187919	1.26181799	1.71691033	Asian
Depression	1.53080853	1.45255841	1.61327403	B/AA
Depression	1.58435711	1.4575857	1.72215428	Other
Depression	1.42379325	1.38739798	1.46114328	White
Essential Hypertension	1.10175221	0.92689833	1.30959124	Asian
Essential Hypertension	1.18313939	1.11944727	1.25045534	B/AA
Essential Hypertension	1.06165101	0.96025234	1.17375696	Other
Essential Hypertension	1.18741942	1.1492195	1.22688909	White
GERD	1.86396399	1.60692434	2.16211906	Asian
GERD	1.68644514	1.59424661	1.78397571	B/AA
GERD	1.9067563	1.74527112	2.08318328	Other
GERD	1.73962561	1.69145936	1.78916345	White
Infertility	0.92789088	0.77790505	1.10679508	Asian
Infertility	1.22993058	1.12907207	1.33979864	B/AA
Infertility	1.34484386	1.17822233	1.53502863	Other
Infertility	0.96529958	0.92097876	1.01175329	White
Kidney Disease	0.80568333	0.51015392	1.27241132	Asian
Kidney Disease	1.25078401	1.05720935	1.47980213	B/AA

Supplemental Table 6 - Figure Supplement 10. Relative risk ratios (RR) for race-stratified PCOS and Pain cohorts.

Kidney Disease	1.20232146	0.85431738	1.69208415	Other
Kidney Disease	1.55051184	1.3989211	1.71852934	White
Liver Disease	1.7390311	1.44298843	2.09580973	Asian
Liver Disease	2.06281014	1.84566266	2.30550564	B/AA
Liver Disease	1.72535256	1.52806526	1.94811147	Other
Liver Disease	1.85267848	1.77495717	1.93380302	White
Obesity	1.19010005	1.06383317	1.33135362	Asian
Obesity	1.04902361	1.00414517	1.09590781	B/AA
Obesity	1.10151702	1.02825194	1.1800024	Other
Obesity	1.11370946	1.08908507	1.13889061	White
Ovarian Cysts	1.63305195	1.34853662	1.97759455	Asian
Ovarian Cysts	2.27846823	2.10514611	2.46606041	B/AA
Ovarian Cysts	2.31263825	2.05642382	2.600775	Other
Ovarian Cysts	2.14690293	2.06404786	2.23308397	White
T2D	0.97408555	0.82056074	1.15633444	Asian
T2D	1.11663425	1.04370298	1.19466177	B/AA
T2D	1.08770207	0.97431501	1.21428468	Other
T2D	1.12329217	1.07820896	1.17026043	White

Supplemental Table 6 - Figure Supplement 10. (continued)

Future Health Outcome	Group 1	Group 2	Z	P	P(BH)
Acute Pharyngitis	Asian	B/AA	-1.6166987	0.10594334	0.31783001
Acute Pharyngitis	Asian	Other	-1.0314123	0.3023475	0.46968711
Acute Pharyngitis	Asian	White	-0.5496948	0.58252871	0.58252871
Acute Pharyngitis	B/AA	Other	0.74639393	0.45542949	0.54651538
Acute Pharyngitis	B/AA	White	2.5154627	0.01188763	0.07132575
Acute Pharyngitis	Other	White	1.00868706	0.31312474	0.46968711
Anxiety	Asian	B/AA	-0.7853388	0.43225496	0.86450992
Anxiety	Asian	Other	-0.5578196	0.57696755	0.86545132
Anxiety	Asian	White	0.10162617	0.91905341	0.91905341
Anxiety	B/AA	Other	0.29106415	0.77100226	0.91905341
Anxiety	B/AA	White	2.30990701	0.0208933	0.12535982
Anxiety	Other	White	1.25941664	0.20787988	0.62363965
Depression	Asian	B/AA	-0.4729643	0.63623868	0.676734
Depression	Asian	Other	-0.8241903	0.40983142	0.676734
Depression	Asian	White	0.41692399	0.676734	0.676734
Depression	B/AA	Other	-0.6839542	0.49400409	0.676734
Depression	B/AA	White	2.42762719	0.01519796	**0.04940984**
Depression	Other	White	2.39833165	0.01646995	**0.04940984**
Essential Hypertension	Asian	B/AA	-0.7698166	0.44140868	0.66211302
Essential Hypertension	Asian	Other	0.36361672	0.71614424	0.85937309
Essential Hypertension	Asian	White	-0.8344677	0.4040175	0.66211302
Essential Hypertension	B/AA	Other	1.8526185	0.06393706	0.19181118
Essential Hypertension	B/AA	White	-0.1101123	0.91232028	0.91232028
Essential Hypertension	Other	White	-2.0784656	0.0376665	0.19181118
GERD	Asian	B/AA	1.23623073	0.21637281	0.43274562
GERD	Asian	Other	-0.2575035	0.79679012	0.79679012

Supplemental Table 7 - Figure Supplement 11. Significance for relative risk ratios for each self-reported race combination.

Both P-value (P) and adjusted p-values using Benjamini-Hochberg (P(BH)) are reported. Significant differences in RR between self-reported race groups are bolded.

Supplemental Table 7 - Figure Supplement 11. (continued)

GERD	Asian	White	0.89599097	0.37025759	0.4443091
GERD	B/AA	Other	-2.2953454	0.02171334	0.13028004
GERD	B/AA	White	-0.9683209	0.33288412	0.4443091
GERD	Other	White	1.93661501	0.05279242	0.15837727
Infertility	Asian	B/AA	-2.8183597	0.00482697	**0.00724046**
Infertility	Asian	Other	-3.3001771	0.00096624	**0.00193248**
Infertility	Asian	White	-0.4245574	0.67115934	0.67115934
Infertility	B/AA	Other	-1.111312	0.26643407	0.31972089
Infertility	B/AA	White	4.86428327	1.15E-06	**6.89E-06**
Infertility	Other	White	4.62996514	3.66E-06	**1.10E-05**
Kidney Disease	Asian	B/AA	-1.7704376	0.07665427	0.15330853
Kidney Disease	Asian	Other	-1.3750696	0.16910986	0.20293183
Kidney Disease	Asian	White	-2.7392558	0.00615784	**0.03694707**
Kidney Disease	B/AA	Other	0.2033752	0.83884178	0.83884178
Kidney Disease	B/AA	White	-2.1359645	0.03268231	0.09804693
Kidney Disease	Other	White	-1.3968767	0.16245065	0.20293183
Liver Disease	Asian	B/AA	-1.5404237	0.12345711	0.24691422
Liver Disease	Asian	Other	0.06951799	0.94457731	0.94457731
Liver Disease	Asian	White	-0.6480213	0.51697119	0.62036542
Liver Disease	B/AA	Other	2.12621006	0.03348577	0.20091464
Liver Disease	B/AA	White	1.76655909	0.0773021	0.23190629
Liver Disease	Other	White	-1.083748	0.27847656	0.41771484
Obesity	Asian	B/AA	2.05439618	0.03993736	0.11981209
Obesity	Asian	Other	1.15206197	0.24929561	0.30666863
Obesity	Asian	White	1.13695477	0.25555719	0.30666863
Obesity	B/AA	Other	-1.1736814	0.24052266	0.30666863
Obesity	B/AA	White	-2.3881842	0.01693185	0.10159113
Obesity	Other	White	-0.2981351	0.76560009	0.76560009
Ovarian Cysts	Asian	B/AA	-3.1514691	0.00162451	**0.00717584**
Ovarian Cysts	Asian	Other	-3.0366859	0.00239195	**0.00717584**
Ovarian Cysts	Asian	White	-2.7436718	0.00607562	**0.01215125**
Ovarian Cysts	B/AA	Other	-0.2060601	0.83674398	0.83674398
Ovarian Cysts	B/AA	White	1.31921453	0.1870974	0.2806461
Ovarian Cysts	Other	White	1.17691992	0.23922747	0.28707296
T2D	Asian	B/AA	-1.4522022	0.1464454	0.43933621
T2D	Asian	Other	-1.0609978	0.28869092	0.57738184
T2D	Asian	White	-1.5841392	0.11316204	0.43933621
T2D	B/AA	Other	0.39837874	0.69035103	0.82842123
T2D	B/AA	White	-0.147501	0.88273658	0.88273658
T2D	Other	White	-0.5372402	0.59110168	0.82842123

Data availability

All summary-level data has all been included in this manuscript.

Acknowledgements

We would like to acknowledge the patients in the TriNetX Global Network without whom this work would not be possible.

Additional information

Disclosure

AI Generative (ChatGPT) was used as a language editing tool.

Funding

Tess Cherlin was supported by NIH | National Institute of General Medical Sciences (NIGMS) (grant # K12GM081259 (HHS))

Authors' Contributions

SSV, SO, and KS conceived and supervised the study. TC and SSV designed the methods. TC and SS performed the analysis. TC analyzed the data and designed the figures. SM and TC wrote the manuscript. All authors interpreted the results. All authors read, edited, and approved the final manuscript.

Compliance with Ethical Standards

Not Applicable

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References

Abraham Gnanadass S, Divakar Prabhu Y, Valsala Gopalakrishnan A (2021) Association of metabolic and inflammatory markers with polycystic ovarian syndrome (PCOS): an update. *Archives of Gynecology and Obstetrics* **303**:631-643 https://doi.org/10.1007/s00404-020-05951-2 | PubMed

Adashi EY, Cibula D, Peterson M, Azziz R (2023) The polycystic ovary syndrome: the first 150 years of study. *F&S Reports* **4**:2-18 https://doi.org/10.1016/j.xfre.2022.12.002 | PubMed

Anagnostis P, Tarlatzis BC, Kauffman RP (2018) Polycystic ovarian syndrome (PCOS): Long-term metabolic consequences. *Metabolism* **86**:33-43 https://doi.org/10.1016/j.metabol.2017.09.016 | PubMed

Asuncion M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HcF (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *The Journal of Clinical Endocrinology & Metabolism* **85**:2434-2438 https://doi.org/10.1210/jcem.85.7.6682 | PubMed

Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research* **46**:399-424 https://doi.org/10.1080/00273171.2011.568786 | PubMed

Ávila MAPd, Bruno RV, Barbosa FC, Andrade FCd, Nardi AE (2014) Polycystic ovary syndrome: implications of metabolic dysfunction. *Revista do Colégio Brasileiro de Cirurgiões* **41**:106-110 https://doi.org/10.1590/s0100-69912014000200006 | PubMed

Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, Lizneva D, Natterson-Horowtiz B, Teede HJ, Yildiz BO (2016) Polycystic ovary syndrome. *Nature Reviews Disease Primers* **2**:16057 https://doi.org/10.1038/nrdp.2016.57 | PubMed

Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H (2016) The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Human reproduction update* **22**:687-708 https://doi.org/10.1093/humupd/dmw025 | PubMed

Butt AS, Devi J (2024) Polycystic ovary syndrome and nonalcoholic fatty liver disease. In: Rehman R, Sheikh A (Eds). *Polycystic Ovary Syndrome* Elsevier. pp. 92-99 https://doi.org/10.1016/b978-0-323-87932-3.00021-9

Campbell CM, Edwards RR (2012) Ethnic differences in pain and pain management. *Pain management* **2**:219-230 https://doi.org/10.2217/pmt.12.7 | PubMed

Chaudhuri A (2023) Polycystic ovary syndrome: Causes, symptoms, pathophysiology, and remedies. *Obesity Medicine* **39**:100480 https://doi.org/10.1016/j.obmed.2023.100480

Cronin L, Guyatt G, Griffith L, Wong E, Azziz R, Futterweit W, Cook D, Dunaif A (1998) Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *The Journal of Clinical Endocrinology & Metabolism* **83**:1976-1987 https://doi.org/10.1210/jcem.83.6.4990 | PubMed

Cui N, Dai T, Liu Y, Wang Y-Y, Lin J-Y, Zheng Q-F, Zhu D-D, Zhu X-W (2024) Laryngopharyngeal reflux disease: Updated examination of mechanisms, pathophysiology, treatment, and association with gastroesophageal reflux disease. *World journal of gastroenterology* **30**:2209 https://doi.org/10.3748/wjg.v30.i16.2209 | PubMed

Després J-P (2012) Abdominal obesity and cardiovascular disease: is inflammation the missing link?. *Canadian Journal of Cardiology* **28**:642-652 https://doi.org/10.1016/j.cjca.2012.06.004 | PubMed

Drosdzol A, Skrzypulec V, Mazur B, Pawlińska-Chmara R (2007) Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. *Folia histochemica et cytobiologica* **45**:93-97 https://doi.org/10.2478/4495 | PubMed

Elsenbruch S, Hahn S, Kowalsky D, Öffner AH, Schedlowski M, Mann K, Janssen OE (2003) Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism* **88**:5801-5807 https://doi.org/10.1210/jc.2003-030562 | PubMed

Escobar-Morreale HF, Luque-Ramírez M, González F (2011) Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertility and sterility* **95**:1048-1058.e1042 https://doi.org/10.1016/j.fertnstert.2010.11.036 | PubMed

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and sterility* **81**:19-25 https://doi.org/10.1016/j.fertnstert.2003.10.004

Georgescu CE (2022) Polycystic ovary syndrome and nonalcoholic fatty liver disease. In: Diamanti-Kandarakis E (Ed). *Polycystic Ovary Syndrome* Elsevier. pp. 187-216 https://doi.org/10.1016/b978-0-12-823045-9.00007-9

Hadjiconstantinou M, Mani H, Patel N, Levy M, Davies M, Khunti K, Stone M (2017) Understanding and supporting women with polycystic ovary syndrome: a qualitative study in an ethnically diverse UK sample. *Endocrine connections* **6**:323-330 https://doi.org/10.1530/ec-17-0053 | PubMed

Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, Kimmig R, Benson S, Balamitsa E, Elsenbruch S (2005) Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *European journal of endocrinology* **153**:853-860 https://doi.org/10.1530/eje.1.02024 | PubMed

Hampel H, Abraham NS, El-Serag HB (2005) Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Annals of internal medicine* **143**:199-211 https://doi.org/10.7326/0003-4819-143-3-200508020-00006 | PubMed

Jamieson DJ, Steege JF (1996) The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. *Obstetrics & Gynecology* **87**:55-58 https://doi.org/10.1016/0029-7844(95)00360-6 | PubMed

Kataria S, Ravindran V (2020) Electronic health records: a critical appraisal of strengths and limitations. *Journal of the Royal College of Physicians of Edinburgh* **50**:262-268 https://doi.org/10.4997/jrcpe.2020.309 | PubMed

Kitzinger C, Willmott J (2002) 'The thief of womanhood': women's experience of polycystic ovarian syndrome. *Social science & medicine* **54**:349-361 https://doi.org/10.1016/s0277-9536(01)00034-x | PubMed

Kivimäki M, Bartolomucci A, Kawachi I (2023) The multiple roles of life stress in metabolic disorders. *Nature Reviews Endocrinology* **19**:10-27 https://doi.org/10.1038/s41574-022-00746-8 | PubMed

Kruse CS, Stein A, Thomas H, Kaur H (2018) The use of electronic health records to support population health: a systematic review of the literature. *Journal of medical systems* **42**:214 https://doi.org/10.1007/s10916-018-1075-6 | PubMed

Kumarendran B, O'Reilly MW, Manolopoulos KN, Toulis KA, Gokhale KM, Sitch AJ, Wijeyaratne CN, Coomarasamy A, Arlt W, Nirantharakumar K (2018) Polycystic ovary syndrome, androgen excess, and the risk of nonalcoholic fatty liver disease in women: a longitudinal study based on a United Kingdom primary care database. *PLoS medicine* **15**:e1002542 https://doi.org/10.1371/journal.pmed.1002542 | PubMed

Lamping DL, Rowe P, Clarke A, Black N, Lessof L (1998) Development and validation of the menorrhagia outcomes questionnaire. *BJOG: An International Journal of Obstetrics & Gynaecology* **105**:766-779 https://doi.org/10.1111/j.1471-0528.1998.tb10209.x | PubMed

Li Y, Li Y, Ng EHY, Stener-Victorin E, Hou L, Wu T, Han F, Wu X (2011) Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertility and sterility* **96**:452-458 https://doi.org/10.1016/j.fertnstert.2011.05.072 | PubMed

Madden JM, Lakoma MD, Rusinak D, Lu CY, Soumerai SB (2016) Missing clinical and behavioral health data in a large electronic health record (EHR) system. *Journal of the American Medical Informatics Association* **23**:1143-1149 https://doi.org/10.1093/jamia/ocw021 | PubMed

Maletzky A, Böck C, Tschoellitsch T, Roland T, Ludwig H, Thumfart S, Giretzlehner M, Hochreiter S, Meier J (2022) Lifting hospital electronic health record data treasures: challenges and opportunities. *JMIR Medical Informatics* **10**:e38557 https://doi.org/10.2196/38557 | PubMed

McGowan MP (2011) Polycystic ovary syndrome: a common endocrine disorder and risk factor for vascular disease. *Current treatment options in cardiovascular medicine* **13**:289-301 https://doi.org/10.1007/s11936-011-0130-0 | PubMed

McHorney CA, Ware Johne J, Anastasiae R (1993) The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical care* **31**:247-263 https://doi.org/10.1097/00005650-199303000-00006 | PubMed

Mousa A, Tay CT (2023) Technical Report for the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome: 2023 Update. Monash Centre for Health Research & Implementation.

O'Brien K, Bosak C (2025) Primary Dysmenorrhea. In: *Medicinal Cannabis in Women's Health: An Evidence-Based Clinician's Guide* Springer. pp. 215-244 https://doi.org/10.1007/978-3-032-01737-6_6

World Health Organization (2023) Polycystic ovary syndrome. World Health Organization.

Osborn O, Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. *Nature medicine* **18**:363-374 https://doi.org/10.1038/nm.2627 | PubMed

Patel S (2018) Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. *The Journal of steroid biochemistry and molecular biology* **182**:27-36 https://doi.org/10.1016/j.jsbmb.2018.04.008 | PubMed

Penrod N, Okeh C, Velez Edwards DR, Barnhart K, Senapati S, Verma SS (2023) Leveraging electronic health record data for endometriosis research. *Frontiers in Digital Health* **5**:1150687 https://doi.org/10.3389/fdgth.2023.1150687 | PubMed

Portenoy RK, Ugarte C, Fuller I, Haas G (2004) Population-based survey of pain in the United States: differences among white, African American, and Hispanic subjects. *The journal of pain* **5**:317-328 https://doi.org/10.1016/j.jpain.2004.05.005 | PubMed

Qu Z, Zhu Y, Jiang J, Shi Y, Chen Z (2013) The clinical characteristics and etiological study of nonalcoholic fatty liver disease in Chinese women with PCOS. *Iranian journal of reproductive medicine* **11**:725 PubMed

Sai B, Mahaparale S (2024) Review on various disorders of the female reproductive system. *Indian J. Applied & Pure Bio.* **39**:1547-1556

Sidra S, Tariq MH, Farrukh MJ, Mohsin M (2019) Evaluation of clinical manifestations, health risks, and quality of life among women with polycystic ovary syndrome. *PloS one* **14**:e0223329 https://doi.org/10.1371/journal.pone.0223329 | PubMed

Stein IF, Leventhal ML (1935) Amenorrhea associated with bilateral polycystic ovaries. *American journal of obstetrics and gynecology* **29**:181-191 https://doi.org/10.1016/S0002-9378(15)30642-6

Teede H, Deeks A, Moran L (2010) Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Medicine* **8**:41 https://doi.org/10.1186/1741-7015-8-41 | PubMed

Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ (2018) Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human reproduction* **33**:1602-1618 https://doi.org/10.1093/humrep/dey256 | PubMed

Teede HJ, Tay CT, Laven JJ, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, Redman LM, Boyle JA (2023) Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *European journal of endocrinology* **189**:G43-G64 https://doi.org/10.1093/ejendo/lvad096 | PubMed

Torres DM, Harrison SA (2016) Nonalcoholic Fatty Liver Disease: Clinical Features, Disease Modifiers, and Natural History. *Alcoholic and Non-Alcoholic Fatty Liver Disease: Bench to Bedside* 183-194 https://doi.org/10.1007/978-3-319-20538-0_9

Tsilchorozidou T, Overton C, Conway GS (2004) The pathophysiology of polycystic ovary syndrome. *Clinical endocrinology* **60**:1-17 https://doi.org/10.1046/j.1365-2265.2003.01842.x | PubMed

Walters KA, Gilchrist RB, Ledger WL, Teede HJ, Handelsman DJ, Campbell RE (2018) New perspectives on the pathogenesis of PCOS: neuroendocrine origins. *Trends in Endocrinology & Metabolism* **29**:841-852 https://doi.org/10.1016/j.tem.2018.08.005 | PubMed

Wu P-Y, Cheng C-W, Kaddi CD, Venugopalan J, Hoffman R, Wang MD (2016) –Omic and electronic health record big data analytics for precision medicine. *IEEE Transactions on Biomedical Engineering* **64**:263-273 https://doi.org/10.1109/tbme.2016.2573285 | PubMed

Zawadri J (1992) Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. Polycystic ovary syndrome. Current issues in endocrinology and metabolism..

Zhao J, Papapetrou P, Asker L, Boström H (2017) Learning from heterogeneous temporal data in electronic health records. *Journal of biomedical informatics* **65**:105-119 https://doi.org/10.1016/j.jbi.2016.11.006 | PubMed

Zore T, Joshi NV, Lizneva D, Azziz R (2017) Polycystic ovarian syndrome: long-term health consequences. Seminars in Reproductive Medicine.

Peer reviews

Reviewer #1 (Public review):

Summary:

This retrospective study provides a new data regarding the prevalence of pain in women with PCOS and its relationship with health outcomes. Using data from electronic health records (EHR), the authors found a significantly higher prevalence of pain among women with PCOS compared to those without the condition: 19.21% of women with PCOS versus 15.8% in non-PCOS women. The highest prevalence of pain was conducted among Black or African American (32.11%) and White (30.75%) populations. Besides, women with PCOS and pain have at least a 2-fold increased prevalence of obesity (34.68%) at baseline compared to women with PCOS in general (16.11%). Also, women with PCOS had the highest risk for infertility and T2D, but women with PCOS and pain had higher risks for ovarian cysts and liver disease. Regarding these results, authors suggested the critical need to address pain in the diagnosis and management of PCOS due to its significant impact on patient health outcomes.

Strengths:

The problem of pain assessment in PCOS patients is well described and authors provided a clear rationale selection of the retrospective design to investigate this problem.

A large number of analyzed patient's records (76,859,666 women) and its uniformity increases the power of the study. Using the Propensity Score Matching makes possible to reduce the heterogeneity of the compared cohorts and influence of comorbid conditions.

Analysis in different ethnic cohorts provides actual and necessary data regarding the prevalence of pain and its relationship with different health conditions that will be helpful for clinicians to make a diagnosis and manage the PCOS in women of different ethnicity.

Assessment of risk of different health conditions as including PCOS-associated pathology as other common groups of diseases in PCOS women with or without pain allows to differentiate the risk of comorbid conditions depending on the presence of one symptom (pelvic or abdominal pain, dysmenorrhea).

Weaknesses:

The significant weakness of the study is the absence of Latin American cohort. Probably the White cohort includes Latin Americans or others, but results of the study cannot be extrapolated to particular White ethnicities.

Comments on revised version:

At present, I have no questions or recommendations for the authors, as they have exhaustively addressed the previous comments and incorporated the necessary corrections.

https://doi.org/10.7554/eLife.103875.2.sa2

Reviewer #2 (Public review):

Summary:

The study offers a thorough analysis of the prevalence of pain in women with polycystic ovary syndrome (PCOS) and its associations with health outcomes across various racial groups. Furthermore, the research investigates the prevalence of PCOS and pain among

different racial demographics, as well as the increased risk of developing various conditions in comparison to individuals who have PCOS alone.

Strengths:

The study emphasizes pain as a significant comorbidity of PCOS, an area that is critically underexplored in existing literature. The findings regarding the increased prevalence of some of the diseases in the PCOS + pain group provide valuable direction for future research and clinical care. I believe physicians should incorporate pain score assessments into their clinical practice to improve patients' quality of life and raise awareness about pain management. If future research focuses on the mechanisms of pain, it would provide a better understanding of pain and allow for a focus on the underlying causes rather than just symptomatic management. The study also highlights the association between PCOS+pain and various comorbidities, such as obesity, hypertension, and type 2 diabetes, as well as conditions like infertility and ovarian cysts, offering a holistic view of the burden of PCOS.

Weaknesses:

Due to the nature of retrospective design, some data may not be readily available in the EHR system. Diagnosis of PCOS, pain is based on ICD codes, which may lead to misclassification and may not capture symptom severity or patient-reported experiences.

https://doi.org/10.7554/eLife.103875.2.sa1

Author response:

The following is the authors' response to the original reviews.

> ***Public Reviews:***
>
> ***Reviewer #1 (Public review):***
>
> *Summary:*
>
> *This retrospective study provides new data regarding the prevalence of pain in women with PCOS and its relationship with health outcomes. Using data from electronic health records (EHR), the authors found a significantly higher prevalence of pain among women with PCOS compared to those without the condition: 19.21% of women with PCOS versus 15.8% in non-PCOS women. The highest prevalence of pain was conducted among Black or African American (32.11%) and White (30.75%) populations. Besides, women with PCOS and pain have at least a 2-fold increased prevalence of obesity (34.68%) at baseline compared to women with PCOS in general (16.11%). Also, women with PCOS had the highest risk for infertility and T2D, but women with PCOS and pain had higher risks for ovarian cysts and liver disease. Regarding these results, the authors suggested the critical need to address pain in the diagnosis and management of PCOS due to its significant impact on patient health outcomes.*
>
> *Strengths:*
>
> *(1) The problem of pain assessment in PCOS patients is well described and the authors provided a clear rationale selection of the retrospective design to investigate this problem.*
>
> *(2) A large number of analyzed patient records (76,859,666 women) and their uniformity increases the power of the study. Using the Propensity Score Matching makes it possible to reduce the heterogeneity of the compared cohorts and the influence of comorbid conditions.*

> *(3) Analysis in different ethnic cohorts provides actual and necessary data regarding the prevalence of pain and its relationship with different health conditions that will be helpful for clinicians to make a diagnosis and manage PCOS in women of different ethnicities.*
>
> *(4) Assessment of the risk of different health conditions including PCOS-associated pathology as other common groups of diseases in PCOS women with or without pain allows to differentiate the risk of comorbid conditions depending on the presence of one symptom (pelvic or abdominal pain, dysmenorrhea).*

We would like to thank the Reviewer for their positive feedback on this manuscript. Pain assessment in women with PCOS is of paramount interest and because of a gap in this research area, we are trying to address it.

> *Weaknesses:*
>
> *(1) Although the paper has strengths in methodology and data analysis, it also has some weaknesses. The lack of a hypothesis doesn't allow us to evaluate the aim and significance of this study.*

We would like to thank the Reviewer for their valuable feedback regarding the hypothesis of this study. We understand that the hypothesis may not have been written clearly under the objectives and we have corrected this in the formal revision.

The primary hypothesis of this study is that women with PCOS experience a higher prevalence to pain (including dysmenorrhea, abdominal pain and pelvic pain) compared to women without PCOS, and this prevalence varies by racial groups. Our hypothesis aims to explore the relationship between PCOS and pain, the associated health risks, and the potential racial disparities in pain prevalence and long-term health outcomes. Additionally, we seek to assess the effect of treatment on reducing pain symptoms in women with PCOS. This study not only examines the immediate burden of pain but also investigates its long-term consequences, including risks of infertility, obesity, and type 2 diabetes.

To enhance clarity for readers, we explicitly stated this hypothesis in the revised manuscript and have ensured that its connection to the study's objectives is clearly articulated. We appreciate the Reviewer's insights and have incorporated these refinements to strengthen the manuscript.

> *(2) The exclusion criteria don't include conditions, that can lead to symptoms similar to PCOS: thyroid diseases, hyperprolactinemia, and congenital adrenal hyperplasia. Thyroid status is not being taken into account in the criteria for matching. All these conditions could occur as on prevalence results as on risk assessment.*

We would like to thank the Reviewer for highlighting the need to include these additional conditions that mimic PCOS. After excluding hypothyroidism, hyperprolactinemia, and adrenal hyperplasia from the PCOS and PCOS and pain cohorts, we observed that 7,690 patients (1.65%) with PCOS and 1,854 patients (1.36%) with PCOS were removed. Based on this observation, we added these three conditions to our exclusion criteria and reran all our analysis for disease for our resubmission. The manuscript, figures, and tables have been updated to reflect these exclusions. Additionally, we have added rationale for excluding these conditions to the Discussion. With these major changes to the analysis, we aim to improve transparency and provide more accurate results and precise interpretations of our findings to the field.

> *(3) The significant weakness of the study is the absence of a Latin American cohort. Probably the White cohort includes Latin Americans or others, but the results of the study*

> *cannot be extrapolated to particular White ethnicities.*

We appreciate the Reviewer's suggestion to include Latin American cohorts in this study. The TriNetX platform has both self-reported race and ethnicity demographic information. In Table 3 - Figure Supplement 5 and Table 4 - Figure Supplement 6 we include baseline demographic information for both race (Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other, White, and Unknown Race) and ethnicity (Not Hispanic or Latino, Unknown, and Hispanic or Latino). In this paper we focused our future health outcome sub-analysis on four self-reported race groups: Asian, Black or African American, Other (Native Hawaiian or Other Pacific Islander, Other, Unknown Race), and White. We agree that including Latin American cohorts in the analysis is essential to better understand the health disparities affecting this population. Future work to better define Latin American cohorts in EHR data would significantly aid our ability to investigate this further.

> *(4) The authors didn't provide sufficient rationale for future health outcomes and this list didn't include diseases of the digestive system or disorders of thyroid glands, which can also cause abdominal pain.*

We appreciate the Reviewer comment and concern regarding additional rationale for future health outcomes. We originally chose to investigate general future health outcomes like disease of the digestive system, circulatory system, etc. These disease groups were selected based on being general and having high prevalence as future health outcomes for patients with PCOS and Pain.

Our initial results highlight the prevalence of disorders of the digestive system (Figure 2). However, after considering the Reviewers comments and to further strengthen our analysis, we included the most prevalent digestive system disorder in our relative risk (RR) analysis. Gastro-esophageal reflux disease (GERD) was identified as the most prevalent future digestive condition for women with PCOS and Pain (13.5%). There was also a 10.5% prevalence in women with PCOS overall.

We were not able to include the same analysis for thyroid dysfunctions as this condition is a part of our exclusion criterion. These updates have been incorporated into the revised manuscript to ensure clarity and completeness.

> ***Reviewer #2 (Public review):***
>
> *Summary:*
>
> *The study offers a thorough analysis of the prevalence of pain in women with polycystic ovary syndrome (PCOS) and its associations with health outcomes across various racial groups. Furthermore, the research investigates the prevalence of PCOS and pain among different racial demographics, as well as the increased risk of developing various conditions in comparison to individuals who have PCOS alone.*
>
> *Strengths:*
>
> *The study emphasizes pain as a significant comorbidity of PCOS, an area that is critically underexplored in existing literature. The findings regarding the increased prevalence of some of the diseases in the PCOS + pain group provide valuable direction for future research and clinical care. I believe physicians should incorporate pain score assessments into their clinical practice to improve patient's quality of life and raise awareness about pain management. If future research focuses on the mechanisms of pain, it would provide a better understanding of pain and allow for a focus on the underlying causes rather than just symptomatic management. The study also highlights the association between PCOS+pain and various comorbidities, such as obesity,*

> *hypertension, and type 2 diabetes, as well as conditions like infertility and ovarian cysts, offering a holistic view of the burden of PCOS.*

We sincerely appreciate the Reviewer's insightful comments. We hope that our findings will encourage further research on the occurrence of pain in women with PCOS and that others will replicate our results to strengthen the evidence in this area. As noted in our introduction, there are currently no standardized abdominal pain score assessments specifically for women with PCOS. We hope that the findings from this study will contribute to efforts toward developing a standardized pain assessment for the PCOS community. In the meantime, further research across more diverse populations will be essential to build a more comprehensive understanding of this issue.

> *Weaknesses:*
>
> *Due to the nature of the retrospective study, some data may not be readily available in the system. Instead of simply categorizing participants based on whether they experience pain, it would be more useful to employ a pain scale or questionnaire to better understand the severity and type of patients' pain. This approach would allow for a more thorough analysis of pain improvement following treatment with the three widely used medications for PCOS. Additionally, it would be beneficial for the authors to specify subtypes of the disease rather than generalizing conditions, such as mentioning specific digestive system disorders or mental health disorders. The lack of detailed analysis of specific disorders limits the depth of the findings. This may cause authors to make incorrect conclusions.*

We appreciate the Reviewer for highlighting the importance of categorizing pain levels experienced by women with PCOS. However, there is currently no standardized pain assessment for abdominal pain, and therefore more research is required before such a classification can be made. Additionally, the electronic health record data we leveraged via the TriNextX platform does not include any pain scale data from unstructured notes. Despite these limitations, this study is an important step toward recognizing abdominal and pelvic pain in women with PCOS. Our findings indicate that women with PCOS report abdominal pain independent of digestive conditions such as irritable bowel syndrome— a condition often associated with pain in this population.

We would like to thank the Reviewer for their thoughtful comment with respect to subtyping future health outcomes. To get at the most impactful future health outcomes affecting women with PCOS and Pain, we have included the top 5 most prevalent health outcomes associated with PCOS and Pain. Specifically, we included analysis for anxiety disorder, depressive episodes, essential hypertension, Gastro-esophageal reflux disease (GERD), and acute pharyngitis. We observed that 17.1%, 11.5%, 10.5%, 10.0% of patients with PCOS and 20.1%, 13.7%, 13.5%, 13.3% of patients with PCOS and Pain were at risk of developing anxiety, depression, acute pharyngitis, and GERD respectively. For our revision, we have included these 5 conditions in our PCOS, PCOS and Pain and self-reported race-stratified future health outcome relative risk (RR) analyses. The revised manuscript, figures, and tables all reflect these changes.

> ***Recommendations for the authors:***
>
> ***Reviewer #1 (Recommendations for the authors):***
>
> *(1) I highly recommend checking all papers and supplements for misprints. There are a lot of missing spaces in the Introduction.*

We would like to thank the Reviewer for bringing this to our attention. We have carefully reviewed the manuscript and all supplementary materials and corrected formatting issues,

including missing spaces and typographical errors throughout the Introduction and the rest of the document.

> *(2) Supplementary Table 3: numbers from the first line in "%No PCOS" should be in "No PCOS"?*

We thank the Reviewer for bringing this error to our attention. We have identified the source of the problem and values have been added to the appropriate column.

> *(3) Why for the matching authors use the categorical data for overweight/obesity and not the entire values? There are different stages of obesity that can be predominant in different cohorts and contribute to the results.*

We would like to thank the Reviewer for their insightful question. While TriNetX does have some BMI values for patient participants, this data is not included for all patients. For example, only 29-30% of women in the PCOS control and case cohorts have BMI recorded. Therefore, we focused on ICD codes for obesity instead to include as much data as possible.

> *(4) What criteria were being used to determine hyperlipidemia and obesity? Were these criteria equal for all patients, or did they depend on ethnicity?*

We would like to apologize to the Reviewer for any confusion. The criteria to determine hyperlipidemia and obesity are ICD-10-CM codes as recorded in the TriNetX platform. The ICD-10-CM codes for obesity are E65-E68 and the ICD-10-CM code for hyperlipidemia is E78.5. Please also see the Methods section of this manuscript where all the ICD-10-CM codes are described.

> *(5) The section material and methods should provide information regarding quality assurance checks and any steps to eliminate data suspected to be unreliable or invalid, to process missing data, consisting of data or claim duplicates. If quality assurance of data hadn't been conducted, it should have been noticed in the study limitations.*

We thank the Reviewer for this suggestion. We have revised the Methods section to explicitly describe the data quality assurance procedures inherent to the TriNetX platform. Specifically, we clarified that TriNetX applies standardized data mapping to controlled clinical terminologies (ICD, CPT, RxNorm), performs automated quality checks and excludes records that do not meet platform-defined standards.

> *(6) It's not clear why the authors didn't include in the analysis the information regarding taking painkillers or anti-inflammatory drugs by patients. Maybe there is no such data in EHR. However, if the patient has some chronic inflammatory or autoimmune disease, she should be prescribed medication. I recommend specifying this issue in the section Material and Methods and/or study limitations.*

We would like to thank the Reviewer for this important suggestion. We have now clarified this point in the limitations section of the discussion. Specifically, we added text explaining that over-the-counter analgesics and anti-inflammatory medications are not reliably captured by EHR or within the TriNetX platform and therefore could not be evaluated in our analysis.

> *(7) The authors should provide the Table or complete Supplementary Tables 2 and 3 with the parameters of patients used for matching.*

We apologize to the Reviewer for any confusion. The parameters used for propensity score matching are described fully in the Methods section of the paper. Table 2 – Figure Supplement 5 and Table 3 – Figure supplement 6 display baseline characteristics for patients before and after the 1:1 propensity score matching using these parameters. We have now also

added the propensity score matching parameters to the table descriptions to provide fluidity and further clarification.

> *(8) The authors found out that women with PCOS and pain have higher RR for ovary cysts and liver diseases compared to women with PCOS who have higher RR for infertility, obesity, and T2D. Discussion includes thoughts regarding a higher risk of ovary cysts and liver disease in women with PCOS and pain, but there is not any suggestion as to why women with PCOS and without pain have a higher risk of infertility, obesity, and T2D. If there is no data explaining this phenomenon, I recommend noting the need for additional research.*

We would like to thank the Revier for this helpful feedback. The Discussion section now includes deeper insights into the pathophysiology behind the two distinct PCOS phenotypes (PCOS overall vs. PCOS and Pain) and their differing risk profiles for future health outcomes. Specifically, we note that while women with PCOS overall may be more metabolically driven (higher risk of infertility, obesity, and T2D), women with PCOS and Pain show a higher risk of ovarian cysts and liver disease. We clarify that these findings are observational and hypothesis-generating and emphasize the need for future longitudinal and mechanistic studies.

> *(9) The authors suggested that systematic contraceptives, metformin, or spironolactone reduce pain in PCOS women. The reduction is significant, but the number of patients with beneficial effects is low (2.5-7.5%). Is it enough to recommend prescribing this medication not only for PCOS treatment but against pain?*

We thank the Reviewer for this important comment. We agree that although the reduction in pain diagnoses following treatment with COCPs, metformin, or spironolactone was statistically significant, the absolute proportion of patients experiencing benefit was modest. Our intention was not to recommend prescribing these medications solely for pain management, but rather to highlight that standard PCOS therapies may have additional benefits in reducing pain symptoms. We have clarified this point in the Discussion to emphasize that these findings are observational and hypothesis-generating, and that prospective studies are needed before these medications can be considered specifically for pain management in PCOS.

> ***Reviewer #2 (Recommendations for the authors):***
>
> *(1) Including a subtype analysis of specific diseases on digestive, respiratory, and mental health diseases rather than generalizing the system will enhance the content.*

We would like to thank the Reviewer for this helpful suggestion. In the revised manuscript, instead of the generalized disease systems we previously reported on, we have included analysis for the top 5 most prevalent conditions. Specifically, we included analysis for anxiety disorder, depressive episodes, essential hypertension, Gastro-esophageal reflux disease (GERD), and acute pharyngitis. We observed that 17.1%, 11.5%, 10.5%, 10.0% of patients with PCOS and 20.1%, 13.7%, 13.5%, 13.3% of patients with PCOS and Pain were at risk of developing anxiety, depression, acute pharyngitis, and GERD respectively.

> *(2) Including the prevalence of dysmenorrhea among healthy populations would allow readers to better compare its impact on the lives of individuals with PCOS.*

We would like to apologize to the Reviewer for any confusion. The prevalence of dysmenorrhea for cases and control cohorts can be found in Table 2 – Figure Supplement 5 and Table 3 – Figure Supplement 6 before and after propensity score matching.

> *(3) Introducing an analysis of age subgroups will provide readers with a clearer understanding of the prevalence of pain and specific diseases across different age*

> *groups.*

We would like to thank the Reviewer for this helpful suggestion. For this revision, we did a sub-analysis to explore the prevalence of PCOS and PCOS and Pain stratified by 10-year age groups. A barplot of these results can be found in Figure 4 - Figure Supplement 7.

Thank you again to the Reviewers for the positive and constructive feedback for this manuscript. We have made the appropriate edits and changes to the final revisions of the manuscript.

https://doi.org/10.7554/eLife.103875.2.sa0