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Clinical Research Article

Rising Incidence, Health Resource Utilization, and Costs of Polycystic Ovary Syndrome in the United Kingdom

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Abstract

Context: Trends in incidence of polycystic ovary syndrome (PCOS) and effects on health resource utilization are unclear.

Objective: To describe trends in prevalence and incidence of PCOS in the United Kingdom. To establish healthcare resource use and associated costs.

Methods: Data were extracted from the Clinical Practice Research Datalink Aurum and Hospital Episode Statistics databases. Point prevalence and incidence were calculated (2004-2020). Patients with PCOS were matched to controls (1:1) by age, body mass index, and primary care practice. Primary care contacts were assigned an average cost and prescription items assigned a net ingredient cost. Inpatient admissions and outpatient consultations were processed into healthcare resource groups and costed to the national tariff.

Results: PCOS incidence increased from 1.22 per 1000 person years in 2004 to 1.77 (2012) and 2.20 (2019). Point prevalence increased from 1.02% (2004) to 2.2% (2012) and 3.5% (2020), and was highest in Asians. Mean contacts per person year (ppy) for patients with PCOS vs controls were 0.48 vs 0.29 for inpatients ($P < .001$), 3.81 vs 2.15 for outpatients ($P < .001$), and 6.43 vs 4.68 ($P < .001$) for primary care. Mean healthcare costs (ppy) were £837 vs £493 ($P < .001$) for inpatients, £444 vs £253 ($P < .001$) for outpatients, £157 vs £112 for primary care, and £109 vs £83 ($P < .001$) for primary care prescriptions. Total healthcare contacts ppy were 10.72 vs 7.11 ($P < .001$) and total associated costs £1546 vs £940 ($P < .001$).

Conclusion: The incidence of PCOS has risen significantly. Health resource utilization and costs of PCOS are significantly greater than controls.

Key Words: polycystic ovary syndrome, incidence, prevalence, costs and cost analysis, health resources, ethnicity

Abbreviations: BMI, body mass index; CPRD, Clinical Practice Research Datalink; CRR, cost rate ratio; GBD, Global Burden of Diseases Injuries and Risk Factors Study; HES, Hospital Episode Statistics; HRG, healthcare resource group; IRR, incidence rate ratio; IMD, Index of Multiple Deprivation; ONS, Office for National Statistics; PCOS, polycystic ovary syndrome; pkpy, per 1000 patient years; ppy, per person year.

Polycystic ovary syndrome (PCOS) is a common endocrine condition characterized by hyperandrogenism, menstrual disturbance, and subfertility. In addition to its reproductive sequelae, PCOS is associated with an increased risk of several comorbidities that impact across the lifespan (1). These include an increased risk of type 2 diabetes (2) and cardiovascular events (3), adverse mental health outcomes (4), and impaired quality of life (5). Variation in presentation and care often results in delayed or missed diagnosis, with international surveys reporting high patient dissatisfaction (6). These factors are likely to impact significantly on healthcare resource utilization and economic burden, although previous data are sparse.

Azziz et al estimated the mean annual cost of the diagnostic evaluation of PCOS to be $93 million in 2014 US dollars (7). Treatment costs were estimated as $622 million for hirsutism, $1.35 billion for hormonal treatment of menstrual dysfunction, and $533 million for infertility care (7). The group extended these analyses to estimate annual costs of PCOS-associated type 2 diabetes and stroke as $1.5 and $2.4 billion in 2020 US dollars, respectively (8). Additional direct healthcare annual costs for anxiety, depression, and eating disorders in PCOS were recently estimated as over $4 billion (9), suggesting that the total direct healthcare economic burden currently exceeds $15 billion (9). However, there are few data of the economic impact of PCOS outside the United States. Ding et al estimated the burden of disease attributable to PCOS-associated type 2 diabetes as £237 million in 2014 pounds Sterling (10), but this study relied on Bayesian modeling to estimate costs and, to our knowledge, no study has estimated PCOS-associated costs based on directly observed data.

A rise in the prevalence and incidence of PCOS may also be expected to increase healthcare burden. Previous prevalence estimates have varied widely, in part related to differences in classification, in addition to variation in recruitment, sampling methods, and ethnicity. Using Rotterdam criteria, the international PCOS guideline systematic review and meta-analysis estimated a pooled prevalence among adult females of 11.77% (5). However, prevalence estimates in routine healthcare settings are usually significantly lower, likely attributable to reduced diagnostic awareness. In contrast to

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prevalence, the data on incidence of PCOS are more limited, although secular trends in weight gain (11) and improved awareness of the condition as a result of advocacy and guideline development might both be expected to contribute to an increase.

Understanding the burden of PCOS has the potential to provide policymakers and research funders with real-world evidence-based information with which to make informed decisions about healthcare resource allocation. We therefore sought to establish the current burden of PCOS on the healthcare system in the United Kingdom, analyzing secular trends in prevalence and incidence in addition to the impact on health resource utilization and associated costs.

Materials and Methods

The study was conducted using the Clinical Practice Research Datalink (CPRD) primary care (Aurum) and linked Hospital Episode Statistics (HES) datasets. The CPRD Aurum database is a longitudinal, anonymized, research database derived from 1489 primary care practices in England. CPRD Aurum contains records for 41 million patients and is representative of the English population in terms of age, sex, ethnicity, and deprivation (12-14). Around 70% of practices engage in a linkage scheme, wherein their patient records are linked with various data sources. This includes integration with the HES data set, detailing both inpatient and outpatient interactions across National Health Service hospitals in the United Kingdom. Additionally, patient records are linked to the Office for National Statistics (ONS) mortality data set.

CPRD Aurum captures diagnostic information through both SNOMED CT (UK edition) and the Read code classification, a standard in UK primary-care practices. Diagnoses within HES and ONS data are reported using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) classification. Surgical procedures documented in HES employ the OPCS Classification of Interventions and Procedures version 4 (OPCS-4) classification.

Patient Selection

Two cohorts were created: initially a prevalent cohort was selected comprising all females with a diagnosis of PCOS recorded in either the Aurum primary care or HES admitted patient care datasets who were registered between January 1, 2004, and December 31, 2021. Patients were required to be flagged by CPRD as being of an acceptable research quality (12) and eligible for HES linkage. If the patients were ≥18 years old at diagnosis, the index date was defined as the earliest of first diagnosis date or January 1, 2004. If the patients were <18 years old at diagnosis, the index date was defined as the latest of the first day of the year they turned 18 years old or January 1, 2004.

The prevalent cohort was then filtered to create the incident cohort. In addition to the eligibility requirements in the prevalent cohort, patients needed to have been ≥18 years old on their first diagnosis and must have had a minimum "wash-in" of 90 days from the registration date to first diagnosis. Index date was set as their first diagnosis of PCOS. The age limit of ≥18 years was chosen due to the challenges of establishing a diagnosis of PCOS in adolescence (5).

Patients with PCOS from the incident cohort were then matched 1:1 to a control from all females in CPRD who were flagged as being of acceptable research quality, HES eligible, and with no history of PCOS. The matching criteria were age, primary care practice and body mass index (BMI) category (Underweight: BMI <18.5 kg/m^2, Healthy: BMI 18.5-<25 kg/m^2, Overweight: BMI 25 -<30 kg/m^2, Obese Class I: BMI 30 -<40 kg/m^2, Obese Class II: BMI ≥40 kg/m^2, and Missing). All controls were required to be registered at the time of their matched case's index date and were then followed up until the earliest of end of CPRD follow-up, end of HES follow-up (October 31, 2020), or death date.

Incidence and Prevalence

Incidence and prevalence were reported between 2004-2019 and 2004-2020, respectively. Patients were included in the numerator for incidence in the respective year if they had their first PCOS diagnosis at age ≥18 years and 90 days after their registration start date. For prevalence, patients were included in the numerator if they had a diagnosis of PCOS before the midpoint (30 June) of the respective year and were a registered patient. Age-standardized prevalence estimates for the most recent year of data were generated to account for differences in the demographic profile in CPRD with that of the United Kingdom as measured by the ONS population estimates (15). As well as assessing rates for the total population, incidence and prevalence estimates were also stratified by ethnicity, practice level Index of Multiple Deprivation (IMD) quintiles and age group.

Healthcare Resource Use

Patients' health care contacts were costed and analyzed during the selected study period. This study focused on the primary care setting (general practitioner contacts and prescriptions) and the secondary care setting of inpatient admission and outpatient attendances. Primary care contacts were classified according to the combination of staff role and consultation type. Costs were derived from the Unit Costs of Health and Social Care 2020 based on mapping tables derived internally for previous CPRD studies (16). Primary care contacts specifically related to PCOS were defined by those contacts for which a SNOMED code for PCOS was recorded on the same consultation.

Inpatient admissions were ascertained from the HES admitted patient care dataset and described by number, length of stay, and cost. Healthcare resource groups (HRGs) were assigned to each inpatient admission and processed using HRG 4 grouper software (National Casemix Office, Winchester, UK). The allocated HRG was then linked to the 2020 National Tariff adjusting for the nature of the admission (elective admissions vs emergency) and excess length of stay. Admissions were classified as primarily related to PCOS where a diagnosis code relating to PCOS was recorded as the first diagnosis.

Outpatient appointments were collated from the HES outpatient dataset described by specialty and processed using HRG 4 grouper software. The allocated HRG was then linked to the 2019 National Tariff. PCOS-specific appointments were defined where a first diagnosis code was recorded as a PCOS event.

In addition, where possible, disease-related contacts were assessed for each of PCOS, anxiety/depression, and type 2 diabetes using a combination of SNOMED and Read codes for the data captured in primary care, and ICD-10 codes in primary diagnoses for data captured in secondary care. We

were unable to assess the impact of contacts for fertility due to restrictions around coding of sensitive data (17).

For women with PCOS, the age-standardized cost estimates were calculated for 2019 (the most recent full year of data), to adjust for demographic differences in CPRD in comparison to the UK population as reported by ONS (15).

Statistical Analysis

For the incident cohort, baseline characteristics at index date were derived and compared with matched controls using univariate statistics (t test for continuous variables and chi-square tests for categorical variables).

Crude resource use and cost rates were calculated for the unmatched cases and matched cases and controls for each contact type (all clinical contacts, primary care, inpatient, outpatient, and prescriptions) and reported per person years (ppy). Resource use was compared between matched cases and controls using an unadjusted Poisson regression model, and costs were compared using an unadjusted Gamma regression model. Incident and cost rate ratios (CCRs) are presented along with 95% CIs and *P* values. For the adjusted models the following covariates were included (all were available and tested for inclusion in each model): age, BMI category, smoking status, alcohol status, prior type 2 diabetes, baseline morbidity (represented by the Charlson index), and systolic and diastolic blood pressure. The statistical significance threshold was set to a *P* value of less than .05, and 95% CIs were given for estimates.

CPRD data are obtained under license from the UK Medicines and Healthcare products Regulatory Agency. This study received ethics approval from the CPRD Research Data Governance committee (RDG Numbers 22_001922, 22_001774).

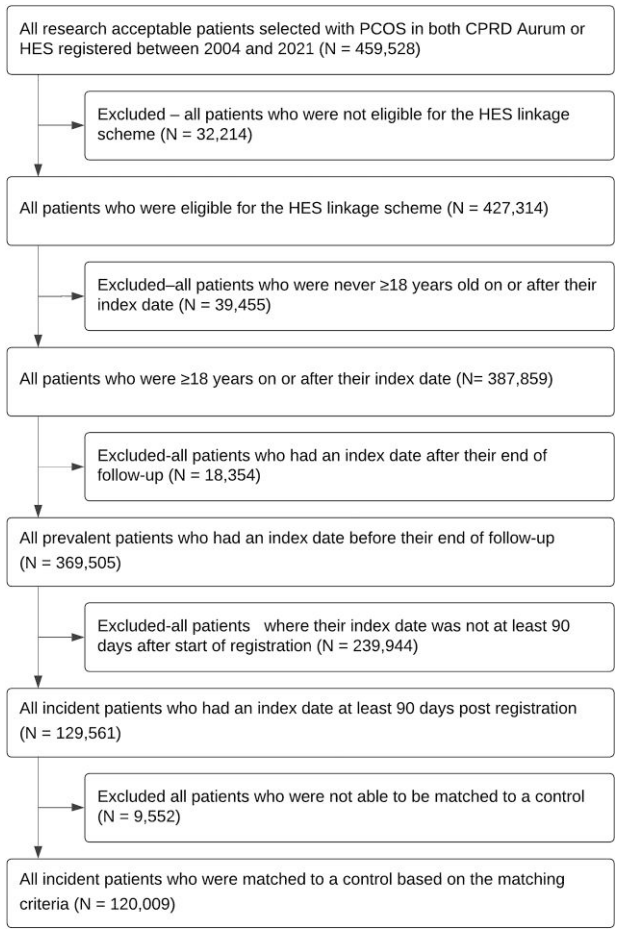


Figure 1. Attrition chart for identification of the polycystic ovary syndrome (PCOS) cohort.

Results

Patient Selection and Baseline Characteristics

Of females registered within the CPRD Aurum dataset between 2004 and 2021, 459 528 had a diagnosis of PCOS recorded in either the HES or Aurum databases. Following application of the additional inclusion and exclusion criteria, 369 505 (80.4%) patients formed the prevalent cohort (Fig. 1). Of these, 129 561 (35%) patients were classified as an incident case, 120 009 of whom were matched to a control. Table 1 shows the baseline characteristics of the study population. Mean age at recorded first diagnosis of PCOS was 27.27 years (6.90). A significantly higher proportion of women with PCOS had type 2 diabetes at index date (2.9% vs 1.3%). The Charlson comorbidity index was also significantly higher in women with PCOS than in controls (0.39 vs 0.31).

Incidence and Prevalence

Figure 2A shows the incidence of PCOS in adult women between 2004 and 2019. Over the study period there was a gradual increase in the incidence of PCOS from 1.22 per 1000 patient years (pkpy) in 2004 to 1.77 pkpy in 2012 and 2.20 pkpy in 2019. A similar pattern was observed for prevalence (Fig. 2B), with point prevalence increasing from 1.02% in 2004 to 2.18% in 2012 and 3.48% in 2020. The estimated age-standardized prevalence of PCOS was 3.3% in 2020. Table 2 shows the incidence and prevalence of PCOS stratified by ethnicity in 2019, using the highest-level ethnicity categorization in ONS ("Asian," "Black," "Mixed," "White," "Other"). Prevalence and incidence rates were highest among patients of Asian ethnicity, with an incidence rate ratio (IRR) of 2.47 (95% CI 2.42; 2.51) when compared with the "White" category. Table 2 also displays the incidence and prevalence aggregated by IMD quintiles. The most deprived areas showed higher rates for both incidence and prevalence than the least deprived (fourth IMD quintile, IRR = 1.37, 1.35-1.40), When categorized by age group, the highest incidence was observed in early adulthood (Fig. 3A), especially in 18- to 19-year-olds (11.46 pkpy). Prevalence was highest in women in their 30s (Fig. 3B).

Healthcare Resource Utilization and Costs

Females with PCOS had significantly increased health care contacts per person year (ppy) compared with controls (Table 3). Overall, there were 10.72 healthcare contacts ppy for cases vs 7.11 for controls ($P < .001$) and respective costs of £1546 ppy vs £940 ($P < .001$). This difference was apparent across all healthcare settings: 6.43 ppy vs 4.68 ppy for primary care contacts ($P < .001$), 0.48 ppy vs 0.29 ppy for inpatient admissions ($P < .001$), and 3.81 ppy vs 2.15 ppy for outpatient appointments ($P < .001$). The respective costs were also significantly greater for PCOS vs controls: £157 ppy compared with £112 ppy ($P < .001$) in primary care, £837 ppy vs £493 ppy in inpatients, ($P < .001$), and

Table 1. Baseline characteristics of incident unmatched cases, matched cases, and their respective matched controls

Characteristic	Unmatched	Matched		*P* value
	Cases (n = 129 561)	Cases (n = 120 009)	Controls (n = 120 009)	
Age, mean (SD)	27.18 (6.95)	27.27 (6.90)	27.27 (6.90)	1.0
BMI, median (LQ-UQ)	27.12 (22.66-33.40)	26.63 (22.50-32.47)	26.32 (22.30-31.81)	<.001
Missing	47 831 (36.9%)	45 825 (38.2%)	45 825 (38.2%)	
BMI category				1.0
Underweight (<18.5 kg/m^2)	2470 (1.9%)	1936 (1.6%)	1936 (1.6%)	
Healthy (18.5-24.9 kg/m^2)	29 491 (22.8%)	28 578 (23.8%)	28 578 (23.8%)	
Overweight (25-29.9 kg/m^2)	18 984 (14.7%)	17 956 (15.0%)	17 956 (15.0%)	
Obese Class I (30-39.9 kg/m^2)	23 612 (18.2%)	21 504 (17.9%)	21 504 (17.9%)	
Obese Class II (≥40 kg/m^2)	7173 (5.5%)	4210 (3.5%)	4210 (3.5%)	
Missing	47 831 (37.0%)	45 825 (38.2%)	45 825 (38.2%)	
Alcohol status				<.001
Current drinker	63 762 (49.2%)	58 342 (48.6%)	59 177 (49.3%)	
Ex-drinker	2249 (1.7%)	1855 (1.5%)	2073 (1.7%)	
Missing	49 064 (37.9%)	48 163 (40.1%)	45 373 (37.8%)	
Nondrinker	14 486 (11.2%)	11 649 (9.7%)	13 386 (11.2%)	
Smoking status				<.001
Current smoker	29 055 (22.4%)	26 714 (22.2%)	25 872 (21.6%)	
Ex-smoker	31 784 (24.5%)	29 610 (24.7%)	27 916 (23.3%)	
Missing	3351 (2.6%)	3094 (2.6%)	6098 (5.1%)	
Nonsmoker	65 371 (50.5%)	60 591 (50.5%)	60 123 (50.1%)	
Charlson comorbidity index, mean (SD)	0.40 (0.76)	0.39 (0.76)	0.31 (0.66)	<.001
Systolic blood pressure category				<.001
<120 mmHg	42 081 (32.5%)	39 348 (32.8%)	35 753 (29.8%)	
120-139 mmHg	33 595 (25.9%)	30 712 (25.6%)	27 508 (22.9%)	
>139 mmHg	4618 (3.6%)	4062 (3.4%)	3038 (2.5%)	
Missing	49 267 (38%)	45 887 (38.2%)	53 710 (44.8%)	
Diastolic blood pressure category				<.001
<80 mmHg	53 513 (41.3%)	49 894 (41.6%)	47 490 (39.6%)	
80-90 mmHg	21 780 (16.8)	19 807 (16.5%)	15 996 (13.3%)	
>89 mmHg	5001 (3.9%)	4421 (3.7%)	2813 (2.3%)	
Missing	49 267 (38%)	45 887 (38.2%)	53 710 (44.8%)	
Prior type 2 diabetes	3864 (3.0%)	3500 (2.9%)	1572 (1.3%)	<.001
Prior anxiety/depression	5907 (4.9%)	5751 (4.8%)	4423 (3.9%)	<.001
Ethnicity				<.001
Asian	17 297 (13.4%)	16 111 (13.4%)	12 378 (10.3%)	
Black	6859 (5.3%)	6347 (5.3%)	7120 (5.9%)	
Mixed	2944 (2.3%)	2735 (2.3%)	2561 (2.1%)	
Other	2275 (1.8%)	2124 (1.8%)	2017 (1.7%)	
White	76 295 (58.9%)	70 655 (58.9%)	71 311 (59.4%)	
Not specified	23 891 (18.4%)	22 037 (18.4%)	24 622 (20.5%)	
Index of Multiple Deprivation				1.0
1st quintile	18 034 (13.9%)	16 779 (14.0%)	16 779 (14.0%)	
2nd quintile	19 565 (15.1%)	18 180 (15.1%)	18 180 (15.1%)	
3rd quintile	26 052 (20.1%)	23 985 (20.0%)	23 985 (20.0%)	
4th quintile	32 835 (25.3%)	30 568 (25.5%)	30 568 (25.5%)	
5th quintile	33 075 (25.5%)	30 497 (25.4%)	30 497 (25.4%)	

Abbreviations: BMI, body mass index; LQ, lower quartile; UQ, upper quartile.

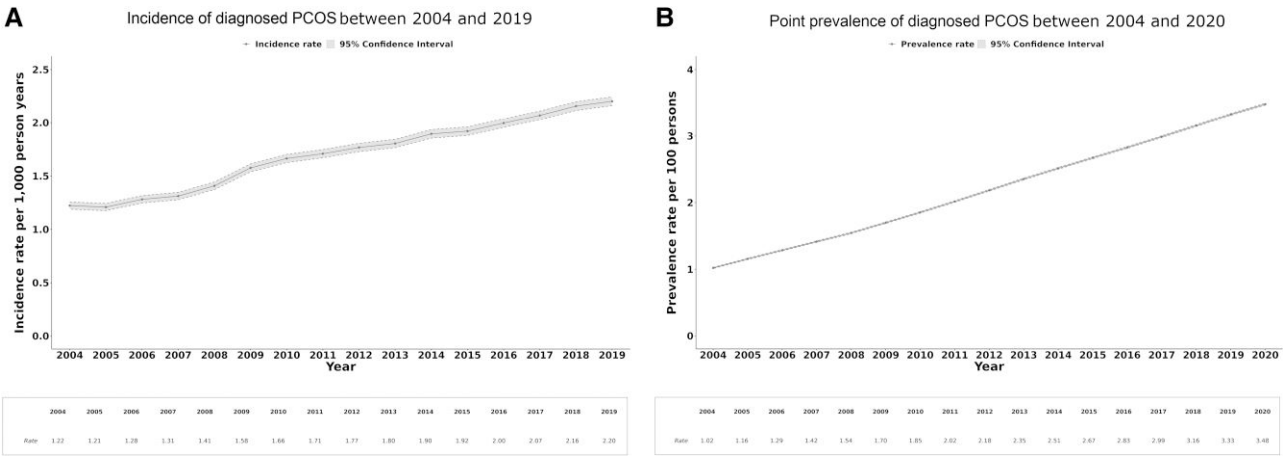


Figure 2. (A) Incidence and (B) point prevalence of diagnosed PCOS in the United Kingdom.

Table 2. Incidence and prevalence of PCOS stratified by ethnicity and Index of multiple deprivation in 2019

	2019		IRR
	Prevalence per 100 persons	Incidence per 1000 person years	
Ethnicity[a]			
Asian	5.21 (5.14-5.27)	3.98 (3.78-4.18)	2.47 (2.42-2.51)
Black	3.94 (3.86-4.03)	2.87 (2.64-3.12)	1.76 (1.72-1.81)
Mixed	4.66 (4.52-4.81)	3.75 (3.32-4.21)	2.31 (2.22-2.4)
Not specified	2.54 (2.50-2.57)	2.42 (2.30-2.54)	0.99 (0.97-1.00)
Other	3.95 (3.81-4.10)	4.11 (3.63-4.63)	2.33 (2.23-2.43)
White	3.18 (3.16-3.20)	1.86 (1.81-1.90)	
IMD quintile[b]			
1st	3.31 (3.27-3.34)	1.79 (1.70-1.88)	
2nd	3.18 (3.15-3.22)	1.93 (1.84-2.03)	1.07 (1.05-1.09)
3rd	3.23 (3.20-3.26)	2.05 (1.97-2.14)	1.15 (1.13-1.17)
4th	3.43 (3.39-3.46)	2.54 (2.45-2.64)	1.37 (1.35-1.40)
5th	3.44 (3.41-3.48)	2.53 (2.43-2.62)	1.36 (1.33-1.38)

Abbreviations: IRR, Incidence rate ratio; IMD, Index of Multiple Deprivation.
[a]Reference = White.
[b]Reference = 1st quintile.

£444 ppy vs £253 ppy in outpatients ($P < .001$). The number of prescriptions administered in primary care were significantly higher in patients with PCOS (12.25 ppy vs 9.35 ppy, $P < .001$) than in controls, as were the respective costs (£109 ppy vs £83 ppy; $P < .001$).

Table 3 also shows the utilization of disease-specific resources in women with PCOS. These showed elevated contact rates for both anxiety/depression and type 2 diabetes compared with their matched controls across all healthcare settings. Anxiety/depression contacts in women with PCOS were 0.39 ppy vs 0.29 ppy (£111 ppy vs £61 ppy, respectively) and type 2 diabetes contacts were 0.06 ppy vs 0.03 ppy (£100 ppy vs £53 ppy). When only assessing women with PCOS, the PCOS-related contacts were 0.35 ppy with an attributable cost of £214.

In 2019 women with PCOS had a total cost of £1447 ppy. The estimated age-standardized cost of treating women with PCOS in the UK was £1 221 005 928 in 2019. Of this 12.3% was attributable directly to PCOS, 12.2% to anxiety/depression and 3.6% to type 2 diabetes.

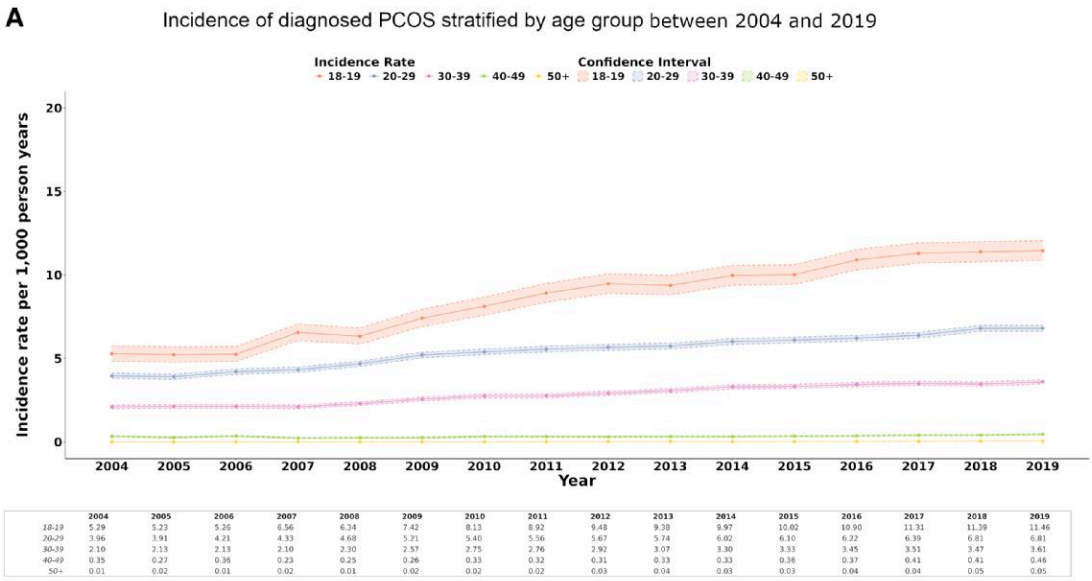
Health Resource Utilization Generalized Linear Models

Table 4 reports the adjusted IRRs and CRR from the matched cohort. The adjusted IRR for all contacts showed that women with PCOS had 1.39 times more contacts compared to their matched controls with a respective CRR of 2.32 ($P < .001$). In primary care, women with PCOS were shown to have 1.29 times more contacts than controls and a CRR of 1.64 ($P < .001$). The adjusted IRR for prescriptions administered in the primary care setting showed women with PCOS had a higher frequency of prescription than controls (1.20, $P < .001$) and the CRR showed similar results (cost ratio = 1.48, $P < .001$). Inpatient admissions were more frequent in women with PCOS (adjusted IRR = 1.24) than in controls (adjusted CRR = 2.97, 95% CI: 2.77-3.18, $P < .001$). Outpatient admissions were more frequent in women with PCOS with an adjusted IRR of 1.52 and a respective CRR of 1.90 ($P < .001$).

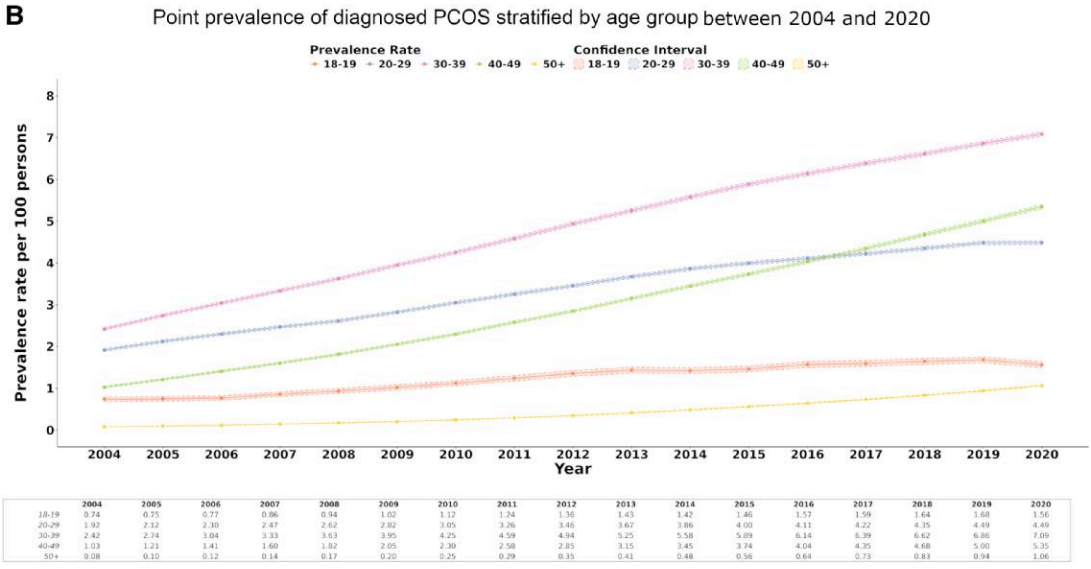
Discussion

In this large analysis of real-world electronic health record data, we demonstrated a significant increase in incidence and prevalence of PCOS over the last 2 decades in the United Kingdom. Healthcare contacts and associated costs were also significantly higher across all healthcare settings for patients with PCOS than matched controls. These findings confirm a rising economic burden of PCOS and reinforce the need for improved resource allocation and research funding for this underserved population.

The reported prevalence of PCOS is highly variable, in part due to differences in diagnostic criteria, with higher rates reported for Rotterdam compared to National Institutes of Health or Androgen Excess-PCOS Society criteria (18). A limitation of our work is that we were unable to explore the criteria used to establish a diagnosis of PCOS, but we presume that this was largely made in accordance with the Rotterdam criteria, which have been used widely in the United Kingdom and internationally since the original European Society of Human Reproduction and Embryology/American Society



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
18-19	5.29	5.23	5.26	6.56	6.34	7.42	8.13	8.92	9.48	9.38	9.97	10.02	10.90	11.31	11.39	11.46
20-29	3.96	3.91	4.21	4.33	4.68	5.21	5.40	5.56	5.67	5.74	6.02	6.10	6.22	6.39	6.81	6.81
30-39	2.10	2.13	2.13	2.10	2.30	2.57	2.75	2.76	2.92	3.07	3.30	3.33	3.45	3.51	3.47	3.61
40-49	0.35	0.27	0.36	0.23	0.25	0.26	0.33	0.32	0.31	0.33	0.33	0.36	0.37	0.41	0.41	0.46
50+	0.01	0.02	0.01	0.02	0.01	0.02	0.02	0.02	0.03	0.04	0.03	0.03	0.04	0.04	0.05	0.05



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
18-19	0.74	0.75	0.77	0.86	0.94	1.02	1.12	1.24	1.36	1.43	1.42	1.46	1.57	1.59	1.64	1.68	1.56
20-29	1.92	2.12	2.30	2.47	2.62	2.82	3.05	3.26	3.46	3.67	3.86	4.00	4.11	4.22	4.35	4.49	4.49
30-39	2.42	2.74	3.04	3.33	3.63	3.95	4.25	4.59	4.94	5.25	5.58	5.89	6.14	6.39	6.62	6.86	7.09
40-49	1.03	1.21	1.41	1.60	1.82	2.05	2.30	2.58	2.85	3.15	3.45	3.74	4.04	4.35	4.68	5.00	5.35
50+	0.08	0.10	0.12	0.14	0.17	0.20	0.25	0.29	0.35	0.41	0.48	0.56	0.64	0.73	0.83	0.94	1.06

Figure 3. (A) Incidence and (B) point prevalence of diagnosed PCOS in the United Kingdom stratified by age group.

for Reproductive Medicine consensus statement (19). Prevalence may also vary according to sampling method, with lower rates reported in studies such as ours where diagnosis is captured from electronic databases or health insurance claim data rather than direct assessments (20-22). In an analysis of the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) database, the global age-standardized point-prevalence rate for PCOS in 2019 was estimated as 1677 per 100 000 (1.7%) (23). However, the GBD database uses a variety of data sources that include unpublished and published scientific literature, survey data, and disease registries. In a previous UK study based on primary care data, Ding et al estimated an overall prevalence of PCOS of 2.27% in 2014 (24). This is not dissimilar to our findings, albeit that they included "probable" cases in addition to those with a confirmed diagnosis. Although our data confirm a rise in prevalence of a recorded diagnosis of PCOS, suggesting a possible improvement in diagnostic awareness over time, the true prevalence is likely to be much higher. Based on Rotterdam criteria, the 2023 evidence-based international guideline reported a prevalence of 10% to 13% in a systematic review of 81 studies undertaken in unselected, community-based populations (5). Improved education is therefore still needed to improve the gaps that are apparent in physician knowledge (25).

In contrast to prevalence, fewer studies have examined the incidence of PCOS. Liu et al compared estimated age-standardized incidence rates of PCOS in the GBD database across 194 countries and territories in 2017 (26). They reported a global age-standardized incidence rate of 82.44 per 100 000 population among women of reproductive age, representing a 4.5% increase since 2007. Safiri et al also used the GBD database to report an estimated annual global PCOS incidence of 59.8 per 100 000 (0.06%) in 2019, representing a more marked 29.5% increase since 1990 (23). Differences in data sources and methodologies used in modeling are likely to account for these discrepancies. Safiri et al found that incidence was highest in the high-income

Table 3. Healthcare costs and contacts rates per person year in unmatched cases, matched cases, and their respective matched controls split by contact type

Contact type			Unmatched	Matched		
			Cases	Cases	Controls	*P* value
	Any diagnosis	Contacts	6 216 503	5 970 659	3 223 759	
		Contacts, ppy	10.27	10.72	7.11	<.001
All contacts		Total cost £	902 221 930	861 481 594	426 121 657	
		Total cost £, ppy	1490	1546	940	<.001
	PCOS	Contacts	214 085	206 717		
		Contacts, ppy	0.35	0.37		
		Total cost £	129 398 636	124 985 420		
		Total cost £, ppy	214	224		
	Anxiety/Depression	Contacts	223 228	216 030	130 331	
		Contacts, ppy	0.37	0.39	0.29	<.001
		Total cost £	64 443 331	62 118 261	27 885 100	
		Total cost £, ppy	106	111	61	<.001
	Type 2 Diabetes	Contacts	33 013	31 782	13 196	
		Contacts, ppy	0.05	0.06	0.03	<.001
		Total cost £	57 875 882	55 800 246	23 999 440	
		Total cost £, ppy	96	100	53	<.001
Primary care	Any diagnosis	Contacts	3 707 728	3 580 172	2 120 603	
		Contacts, ppy	6.12	6.43	4.68	<.001
		Total cost £	90 881 535	87 695 767	50 711 006	
		Total cost £, ppy	150	157	112	<.001
	PCOS	Contacts	153 463	148 077		
		Contacts, ppy	0.25	0.27		
		Total cost £	4 366 035	4 208 629		
		Total cost £, ppy	7	8		
	Anxiety/Depression	Contacts	183 798	178 098	114 313	
		Contacts, ppy	0.30	0.32	0.25	<.001
		Total cost £	5 266 318	5 100 598	3 258 010	
		Total cost £, ppy	8.69	9.15	7.18	<.001
	Type 2 diabetes	Contacts	22 292	21 741	10 837	
		Contacts, ppy	0.04	0.04	0.02	<.001
		Total cost £	430 701	419 722	205 330	
		Total cost £, ppy	0.71	0.75	0.45	<.001
Prescription	All prescriptions	Prescriptions	7 058 940	6 822 211	4 237 965	
		Prescriptions, ppy	11.65	12.25	9.35	<.001
		Total cost £	62 935 362	60 671 828	37 428 325	
		Total cost £, ppy	104	109	83	<.001
Inpatient	Any diagnosis	Admissions	282 229	269 143	129 434	
		Admissions, ppy	0.47	0.48	0.29	<.001
		Length of stay	422 720	402 811	191 400	
		Length of stay, ppy	0.70	0.72	0.42	<.001
		Total cost £	488 905 627	480 786 306	223 410 574	
		Total cost £, ppy	807	837	493	<.001
	PCOS	Admissions	59 653	57 688		
		Admissions, ppy	0.10	0.10		
		Length of stay	144 901	140 102		
		Length of stay, ppy	0.24	0.25		
		Total cost £	124 910 346	120 656 176		
		Total cost £, ppy	206	216		
	Anxiety/Depression	Admissions	30 603	29 650	12 847	
		Admissions, ppy	0.05	0.05	0.03	<.001
		Length of stay	100 220	95 600	44 582	
		Length of stay, ppy	0.17	0.17	0.10	<.001
		Total cost £	57 431 815	55 367 392	23 791 309	
		Total cost £, ppy	94.78	99	52	<.001
	Type 2 diabetes	Admissions	10 613	9935	2331	
		Admissions, ppy	0.02	0.02	0.01	<.001
		Length of stay	81 909	74 948	14 761	
		Length of stay, ppy	0.14	0.13	0.03	<.001
		Total cost £	21 019 545	19 501 443	4 260 302	
		Total cost £, ppy	35	35	9	<.001
Outpatient	Any diagnosis	Attendances	2 226 546	2 121 344	973 722	
		Attendances, ppy	3.68	3.81	2.15	<.001
		Total cost £	259 499 406	255 565 036	114 571 752	
		Total cost £, ppy	428	444	253	<.001
	PCOS	Attendances	969	952		
		Attendances, ppy	<0.01	<0.01		
		Total cost £	122 255	120 615		
		Total cost £, ppy	<1	<1		

(*continued*)

Table 3. Continued

Contact type			Unmatched	Matched		
			Cases	Cases	Controls	*P* value
	Anxiety/Depression	Attendances	8827	8282	3171	
		Attendances, ppy	0.01	0.01	0.01	<.001
		Total cost £	1 745 198	1 650 271	835 781	
		Total cost £, ppy	2.88	2.96	1.84	<.001
	Type 2 diabetes	Attendances	108	106	28	
		Attendances, ppy	<0.01	<0.01	<0.01	.003
		Total cost £	13 366	13 132	2801	
		Total cost £, ppy	0.02	0.02	0.01	.003

Abbreviations: PCOS, polycystic ovary syndrome; ppy, per person year.

Table 4. Unadjusted and adjusted generalized linear models comparing all healthcare contacts and costs between matched cases and controls

	Unadjusted				Adjusted			
	IRR	SD	95% CI	*P* value	IRR	SD	95% CI	*P* value
Contacts								
All contacts	1.48	0.0007	1.48-1.48	<.001	1.39	0.0008	1.39-1.39	<.001
Primary care	1.34	0.0008	1.34-1.35	<.001	1.29	0.0010	1.29-1.29	<.001
Prescription	1.31	0.0006	1.31-1.31	<.001	1.20	0.0007	1.20-1.20	<.001
Inpatient	1.27	0.0026	1.26-1.28	<.001	1.24	0.0032	1.23-1.24	<.001
Outpatient	1.67	0.0012	1.66-1.67	<.001	1.52	0.0014	1.52-1.53	<.001
	CRR				CRR			
Costs								
All contacts	2.47	0.0196	2.38-2.57	<.001	2.32	0.0237	2.21-2.43	<.001
Primary care	1.71	0.0064	1.69-1.74	<.001	1.64	0.0074	1.61-1.66	<.001
Prescription	1.50	0.0189	1.45-1.56	<.001	1.48	0.0240	1.42-1.56	<.001
Inpatient	2.97	0.0278	2.82-3.14	<.001	2.97	0.0345	2.77-3.18	<.001
Outpatient	1.91	0.0133	1.86-1.96	<.001	1.90	0.0164	1.84-1.97	<.001

Adjusted covariates: Body mass index category, systolic blood pressure category, smoking status, alcohol status, Charlson index, prior type 2 diabetes.
Abbreviations: CRR, cost rate ratio; IRR, incidence rate ratio.

Asia-Pacific region, Australasia, and Western Europe, with age-standardized rates of 221.7, 198.4, and 149.7 per 100 000, respectively (23). These rates are similar to our observation of an incidence of 2.2 per 1000 person years in 2019. In contrast, the largest increases in incidence since 1990 were observed in lower income economies, notably the Maldives, Equatorial Guinea, and Myanmar (23). Globalization, urbanization, and adoption of a Western diet might explain some of these differences, since excess weight is known to unmask and exacerbate many of the component features of PCOS (1). Indeed, Health Survey for England data confirm a significant rise in the prevalence of obesity in women over our study timeframe (27), suggesting that weight gain may be contributing to the rise in PCOS diagnosis. Similar rises in the incidence of prediabetes over this time period (28) highlight the importance of weight gain as a shared risk factor in these metabolic disorders, with the higher prevalence (Table 1) and consultation rates (Table 3) for a diagnosis of type 2 diabetes consistent with our previous observations (2). However, while we recognize that even small changes in BMI might lead to significant effects at a population level, we speculate that increased diagnostic awareness may also account for the observed rise in prevalence and incidence. Indeed, it is noticeable that incidence was found to have risen most steeply in our study in 2007/2008, at a time when widespread adoption of the Rotterdam criteria, leading to an expanded PCOS case definition, had likely embedded into routine clinical practice. Safiri et al found that the highest annual incidence rate was in adolescents aged 15 to 19 years (23). While we intentionally excluded patients diagnosed with PCOS before 18 years in our study because of the diagnostic challenges at this age (5), we too noted the highest incidence rates in young women. This suggests that adolescence and young adulthood may be key life stages for prevention, early diagnosis, and therapeutic intervention. We also found significant differences in prevalence according to ethnicity, with the highest rates among patients of Asian ethnicity, followed by "Mixed," "Black," "Other," and "White." The 2023 International guidelines also found some evidence of a higher prevalence in Southeast Asian and Eastern Mediterranean regions, albeit that the evidence was considered low quality (5). A limitation of our work is that we were unable to categorize ethnicity beyond the highest-level ethnicity categorization in CPRD Aurum, which describes Asian ethnicity in its broadest sense. Nevertheless, we consider our observation of a higher prevalence in Asian, Black, and mixed ethnicity patients an important one, especially since cardiometabolic risk may be higher in such groups (29). We also found a higher incidence of a recorded diagnosis of PCOS among patients whose general

practice was located in areas with a higher IMD. Although we were limited to practice-level rather than patient-level analyses, our observations align with previous data that have shown an association of deprivation with both PCOS prevalence (30) and risk of cardiovascular events (3). These observations imply that interventions to reduce disease burden should be targeted to the most socially and materially deprived.

Healthcare contacts were significantly increased across all healthcare settings in women with PCOS compared with matched controls. Patients with PCOS are faced with a number of difficulties in establishing a timely diagnosis (6) and the many comorbidities that impact negatively upon their overall wellbeing and quality of life (1, 5). In a cross-sectional study using an online questionnaire, Gibson-Helm et al found that more than a third of patients had their diagnosis delayed by more than 2 years, with almost half needing to see 3 or more health professionals before a diagnosis was made (6). Where possible, we examined condition-related contacts, finding an excess contact rate and associated costs for type 2 diabetes and anxiety/depression across all healthcare settings. A limitation of our study is that we were unable to undertake a similar analysis for fertility due to restrictions on recording of potentially sensitive data (17). International surveys have shown that concerns around weight, menstrual irregularity, fertility, and hirsutism are the commonest patient priorities (6). These factors are likely to have accounted for many of the excess consultations, in addition to the excess risk of adverse mental health outcomes and impaired health-related quality of life that we and others have previously reported (4, 5, 9, 31). Not only do these findings reinforce the potential value of recently developed educational resources for health professionals (32) and for women with PCOS (33) in improving the diagnostic and treatment experience, but they also highlight the need for better models of patient care. To date there has been limited progress in establishing evidence-based integrated models of care in PCOS (34) despite evidence from other chronic diseases of a benefit in improving outcomes (35, 36) and cost-effectiveness (37).

Our finding of an increased cost of treatment is consistent with data from the United States, which estimate that the current direct total healthcare cost of PCOS is in excess of $15 billion dollars (7-9). Yadav et al estimated that approximately 29.5% of these costs in the United States are attributable to the treatment of reproductive aspects (including hirsutism, infertility, and menstrual dysfunction), 28% to treatment of mental health disorders (anxiety, depression, and eating disorders), 15% to obstetric aspects, and 26% to type 2 diabetes or stroke (9). In contrast, the costs of the initial diagnostic workup were comparatively low (only 1.1% of the total), suggesting that a thorough initial evaluation may be a clinically effective and cost-effective measure in reducing later morbidity (9). Our observations provide the first international health economic perspective and suggest that the costs of PCOS are consistently high regardless of the underlying model of healthcare. In the United Kingdom, Ding et al estimated that the costs of treating type 2 diabetes associated with PCOS were £237 million in 2014 (10). We have added to their findings by calculating total costs and by using directly observed data rather than estimates based on modeling, finding that the age-standardized cost of treating patients with PCOS in the United Kingdom was in excess of £1.2 billion in 2019. However, our study was limited to the measurement of direct health-related costs only. This approach is likely to significantly underestimate the true economic burden because the costs of assessment and treatment undertaken in the private sector were not captured. Furthermore, our study was not designed to measure the intangible costs (related to reduced quality of life) or indirect costs (due to reduced work productivity) associated with PCOS, which are both likely to be considerable. Indeed, Liu et al estimated that in 2017 PCOS accounted globally for 0.43 million disability-adjusted life years, a time-based measure combining years of life lost due to premature mortality and time lived in states of less than full health (26).

Our study has several strengths and limitations. Strengths include the large sample size, population setting, controlled design, and calculations based on directly observed data. However, our study has several limitations, including coding imperfections and missing data that are common to all datasets which are based in routine clinical practice. In particular, BMI was missing in a third of cases, although we compensated for this by modeling BMI as a categorical variable. Studies are also needed to estimate costs of treatment in the private health sector in addition to estimates of intangible and indirect costs.

In conclusion, we report a rising incidence and prevalence of a recorded diagnosis of PCOS in the United Kingdom over the last 2 decades and confirm that healthcare resource utilization and costs are significantly higher than in matched controls. Our data emphasize the importance of recognizing PCOS as a public health priority and underscore the need for greater investment and research funding for this historically under-resourced disorder.

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Disclosures

The authors declare no conflict of interest.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. CPRD data are available upon application after ISAC approval through a licensed organization (Human Data Sciences). Source data are not publicly available. This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. HES data—Copyright © (2023), reused with the permission of The Health & Social Care Information Centre. All rights reserved. The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.html.

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