Polycystic ovary syndrome is associated with adverse mental health and neurodevelopmental outcomes

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Abstract

Context

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and subfertility but the effects on mental health and child neurodevelopment are unclear.

Objectives

To determine if (i) there is an association between PCOS and psychiatric outcomes, and (ii) whether rates of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are higher in children of mothers with PCOS.

Design

Data were extracted from the Clinical Practice Research Datalink. Patients with PCOS were matched to two control sets (1:1) by age, BMI and primary care practice. Control set 2 was additionally matched on prior mental health status. Primary outcomes were the incidence of depression, anxiety and bipolar disorder. Secondary outcomes were the prevalence of ADHD or ASD in the children.

Results

16,986 eligible patients were identified; 16,938 and 16,355 were matched to control sets 1 and 2 respectively. Compared to control set 1, baseline prevalence was 23.1% versus 19.3% for depression, 11.5% versus 9.3% for anxiety and 3.2% versus 1.5% for bipolar disorder ($p<0.001$). The hazard ratio for time to each endpoint was 1.26 (95% CI 1.19-1.32), 1.20 (1.11-1.29) and 1.21 (1.03-1.42) for set 1, and 1.38 (1.30-1.45), 1.39 (1.29-1.51) and 1.44 (1.21-1.71) for set 2. The odds ratios for ASD and ADHD in children were 1.54 (1.12-2.11) and 1.64 (1.16-2.33) for set 1, and 1.76 (1.27-2.46) and 1.34 (0.96-1.89) for set 2.

Conclusions

PCOS is associated with psychiatric morbidity and increased risk of ADHD and ASD in their children. Screening for mental health disorders should be considered during assessment.

Précis

Analysis of 17,000 patients with PCOS and controls found an increased incidence of psychiatric morbidity in women with PCOS, and increased risk of autism spectrum disorder and ADHD in their children.

Introduction

Polycystic Ovary Syndrome is the commonest endocrine condition affecting young women, and is characterized by hyperandrogenism, menstrual disturbance and subfertility. In addition to its well-recognized reproductive sequelae (1), PCOS is now established as a metabolic disorder underpinned by insulin resistance and leading to an increased risk of type 2 diabetes (2).

The cutaneous manifestations of hyperandrogenism, including hirsutism, acne and scalp hair loss, are emotionally distressing (3, 4), and could contribute to an increased prevalence of depression and anxiety in this population (5-8). Comorbid mental health disorders have also been shown to contribute to impaired quality of life in PCOS (9). However, it is difficult to establish how many of these outcomes are attributable to PCOS *per se*, and how many to obesity, which is common in this patient group and itself associated with adverse mental health outcomes, including depression (10) and anxiety (11). This risk of depression may be particularly increased in patients with metabolically unhealthy obesity, which is characterized by insulin resistance and abdominal adiposity (12), compared to metabolically healthy weight-matched controls (13, 14). Furthermore, in community-based studies, the association between obesity and depression appears stronger for women compared to men (15). This association may be bi-directional: in longitudinal studies obesity increases the risk of a subsequent diagnosis of depressive disorder, whilst depression at baseline in turn increases the odds for developing obesity (16). This latter risk appears to be particularly high for adolescent females (16).

Whilst previous studies have focused on the risk of depressive disorder and anxiety in patients with PCOS, hyperandrogenism may also influence the risk of other mental health disorders including schizophrenia (17). However, a recent population-based cohort study failed to demonstrate an increased risk of developing schizophrenia (or bipolar disorder) in women with PCOS, although an increased risk of depressive disorder, anxiety disorder and sleep disorder was confirmed (18). Other studies have shown that the risk of eating disorder, notably binge-eating disorder, may be increased in women with PCOS (19, 20). Attention deficit hyperactivity disorder (ADHD) has also been shown to associate with hyperandrogenism (21) and obesity in adults (22), albeit that the latter effect size is moderate,

More recently, these studies have been extended to examine the influence of intra-uterine androgen exposure on neurodevelopmental outcomes in the children of mothers with PCOS. Brain development is influenced significantly by exposure to androgens during early gestation. Female rhesus monkeys exposed *in utero* to androgens show increased male-type behavior (23) whilst both attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder is more likely to be diagnosed in males than females (24, 25). These observations suggest that ADHD and ASD may be influenced by prenatal androgen exposure. One small case-control study has suggested that women with PCOS may have higher scores on ADHD symptoms on self-report scales (26) whilst we have recently shown that white matter microstructure is altered in young women with PCOS (27). Most recently, Kosidou *et al*, in a matched case-control study, found that maternal PCOS increased the odds of ASD in the children by 59%, which was further exacerbated by concomitant obesity (28). These studies require confirmation but suggest that PCOS may represent a novel risk-state for later life neurodevelopmental disorders.

Although these observations suggest that PCOS may be associated with several adverse mental health outcomes, many studies are limited by a failure to match for obesity (a potential major confounder), small sample sizes, cross-sectional study designs and assessment of psychiatric morbidity using rating scales, rather than formal diagnosis by a psychiatrist or other clinician. In light of these uncertainties, we sought to establish the relative risks of major mental health outcomes (depressive disorder, anxiety, bipolar disorder, schizophrenia, eating disorder, ADHD and ASD) for patients with PCOS, and neurodevelopmental disorders (ASD and ADHD) in children born to mothers with PCOS.

Materials and Methods

The study employed a retrospective cohort design using data from the Clinical Practice Research Datalink (CPRD), a longitudinal, anonymized research database collected from 674 primary care practices in the United Kingdom. The CPRD contains records for over 11 million patients and is representative of the UK population in terms of age and sex (29). Approximately 60% of practices participate in a linkage scheme, by which their patient records are linked to other data sources, including the Hospital Episode Statistics (HES) dataset, which provides data on all inpatient and outpatient contacts occurring within National Health Service hospitals in England, and the Office for National Statistics (ONS) mortality dataset. Diagnostic information in the CPRD primary-care dataset is recorded using the Read code classification, a UK primary-care practice standard. HES inpatient data are recorded using the ICD-10 classification.

Patient selection and matching of controls

The study was conducted using data from CPRD's primary-care (GOLD) and linked HES data sets. The study population were those patients flagged by CPRD as being of an acceptable research quality. Patients with a diagnosis of PCOS recorded in the primary care dataset using the Read code classification (C164.00, C164.12, C165.00) from 2000 to 2014 were selected. The earliest diagnosis date was selected as the index date. A minimum "wash-in" period of 6 months from the patient's practice registration date to index date was used to maximize the likelihood that the case represented an incident case.

Patients identified with PCOS were matched at a ratio of 1:1 to two sets of non-PCOS controls. This was to allow for the baseline prevalence of the selected outcomes for patients with PCOS to be calculated relative to non-PCOS controls using matching criteria 1. Matching criteria 2 allowed for patients to be matched on mental health history to identify the incidence of outcomes following PCOS diagnosis. For control set 1, cases with PCOS were matched to controls with no history of PCOS; the controls took the index date of the case. All controls were required to have at least a 6-month wash-in period from registration at the practice to the case index date. Controls were matched by age (± 2 years), BMI category (<25 kg/m^2, 25-30 kg/m^2, >30 kg/m^2) and primary care practice. The same matching criteria were applied to control set 2, who were additionally matched for a history of prior mental health disorder (depression, anxiety, bipolar disorder, schizophrenia, eating disorder, autism, ADHD). Controls could appear in both sets. Mental health disorders were defined by the Read code

classification or 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) classification (Supplementary appendix 1).

Endpoints

Primary outcomes were the incidence of depressive disorder, anxiety, bipolar disorder, schizophrenia, eating disorder, ADHD and autism spectrum disorder in cases and controls. Secondary outcomes were the prevalence of ADHD or autism spectrum disorder in the children of mothers with PCOS. Children were identified via the mother-baby link generated within CPRD which links mothers with their children. To maximize patient numbers, births both before and after index date were included in this study.

Data analysis

Baseline characteristics between cases and controls were compared using univariate statistics (t-test for continuous variables and χ^2 for categorical variables). Crude rates of progression to each outcome were presented and time to each endpoint was analyzed using Cox proportional hazard models (CPHM). The Cox models included the following covariates (all were available and tested for inclusion in each model): age, BMI, smoking status, baseline morbidity represented by the Charlson index (30), total number of contacts with the general practitioner in the year before index date that is regarded as a proxy for general morbidity, and deprivation based on quintiles of Index of Multiple Deprivation (IMD). The IMD is an area-based measure of social and material deprivation based upon various criteria including income and education. Covariates were entered into each model if they were significant in that model. Threshold statistical significance was $p \leq 0.05$, and 95% confidence intervals (CI) were given for hazard ratios (HR).

Multivariate logistic regression was used to examine the association of PCOS status with risk of autism spectrum disorder and ADHD in the children.

A sensitivity analysis exploring the association of bipolar disorder with PCOS was undertaken, excluding cases who had been treated with valproate therapy prior to index date.

Studies using CPRD are covered by ethics approval granted by Trent Multicentre Research Ethics Committee (Reference 05/MRE04/87). CPRD Independent Scientific Advisory Committee approval was granted for this study (ISAC 16-249).

Results

89,732 patients with PCOS were initially identified. After application of the inclusion/exclusion criteria, 16,986 patients remained eligible for matching with control subjects (figure 1). 16,938 (99.7%) and 16,355 (96.3%) patients could be matched with controls for control sets 1 and 2 respectively.

Baseline characteristics

The baseline characteristics of patients with PCOS and controls are shown in tables 1 and 2 respectively for control sets 1 and 2. For control set 1, median follow-up was 3.87 years (interquartile range (IQR) 1.80-7.25) for cases and 2.81 years (IQR 1.20-5.80) for controls. For control set 2, median follow-up was 3.88 years (IQR 1.81-7.26) for cases and 3.07 years (IQR 1.32-6.70) for controls. In both control sets, there were significant differences between cases and controls. Patients with PCOS had increased primary care contacts in the year prior to index date (median 6.0 contacts versus 4.0 for both control sets), and an increased proportion of patients classified with extreme obesity (6.7% vs 3.9% in control set 1 and 6.3% vs 3.8% in control set 2). In addition, there were significant differences in smoking status, alcohol history and systolic and diastolic blood pressure.

Prevalence of mental health disorders

In control set 1, 3,912 (23.1%) patients with PCOS had previously been diagnosed with depression compared to 3,272 (19.32%) of controls ($p<0.00001$) (Supplementary appendix 2). A prior diagnosis of anxiety was also higher in patients with PCOS (n=1,956, 11.55%) compared to controls (n=1,579, 9.32%) ($p<0.00001$). There was also a significant increase in the recorded diagnosis of bipolar disorder (PCOS 535 (3.16%) vs 384 (1.45%) controls, $p<0.00001$). Prior diagnosis of eating disorder for patients with PCOS was higher (n=262, 1.55%) than controls (n=175, 1.03%) ($p=0.00003$). In the sensitivity analysis excluding pairs of cases and controls where either had been treated with valproate therapy prior to index date, the rate of bipolar disorder remained significantly greater for patients with PCOS (526 (3.14%) versus 375 (1.45%); $p <0.00001$).

There were no significant differences in the prevalence of schizophrenia, autism spectrum disorder or ADHD between cases and controls (Supplementary appendix 2).

Incidence of mental health disorders

For control set 1 the rate of depression following index date was 42.62 per 1,000 patient years (pky) for patients with PCOS compared with 34.46 pky for controls. The respective figures for anxiety, bipolar disorder and eating disorder were 21.99 pky versus 17.61 pky, 4.83 pky versus 3.64 pky, and 7.57 pky versus 4.36 pky (Table 3). For control set 2 the rates were 41.66 pky versus 26.66 pky for depression, 21.33 pky versus 12.64 pky for anxiety, 4.42 pky versus 2.48 pky for bipolar disorder, and 7.40 pky versus 3.95 pky for eating diosorder.

Hazard ratios for mental health disorders

Time to event for depression and anxiety for both control sets are shown in the Kaplan-Meier curves in figure 2. After adjusting for demographic and morbidity indicators in the Cox proportional hazards model, the hazard ratios for patients with PCOS compared to controls in control set 1 were 1.26 (95% CI 1.19-1.32) for depression, 1.20 (95% CI 1.11-1.29) for anxiety, 1.21 (95% CI 1.03 – 1.42) for bipolar disorder and 1.37 (95% CI 1.05-1.81) for eating disorder. For control set 2 the hazard ratios were 1.38 (95% CI 1.30-1.45) for depression, 1.39 (95% CI 1.29-1.51) for anxiety and 1.54 (95% CI 1.16-2.05) for eating disorder. Due to model violations it was not possible to calculate the hazard ratio for bipolar disorder (Table 3).

In the sensitivity analysis excluding cases who had been treated with valproate therapy prior to index date the HR for cases to controls for bipolar disorder was 1.21 (95% CI 1.03-1.42) for control set 1 and 1.45 (95% CI 1.21-1.73) for control set 2.

ADHD and Autism Spectrum Disorder in children of patients with PCOS

In control set 1 there were 8,962 children born to patients with PCOS compared to 8,885 born to the controls. The respective rate of ADHD was 4.81 pky versus 3.32 pky with an odds ratio of 1.64 (95% CI 1.16-2.33). The rate of ASD was 5.82 pky versus 3.92 pky; odds ratio 1.54 (95% CI 1.12-2.11). In control set 2, there were 8,695 births to women with PCOS and 8,973 to controls. The rate of ADHD was 6.00 pky versus 3.54 pky; odds ratio 1.75 (1.27 – 2.46) and the rate of ASD was 4.44 pky versus 3.90 pky; odds ratio 1.34 (95% CI 0.96-1.89) (Table 4).

Discussion

In this large retrospective database analysis we have reported a significantly increased prevalence of depression, anxiety, bipolar disorder and eating disorder at the time of diagnosis with PCOS compared to matched controls. There was no difference in rates of clinically recorded ASD, ADHD or schizophrenia, though the background rate of these conditions resulted in the study being under-powered for these conditions. The incidence of these conditions following index date was also increased for patients with PCOS. In addition, we have reported increased rates of ASD and ADHD in the children of women with PCOS compared with controls.

Our findings of an increased prevalence of depression and anxiety in women with PCOS are consistent with a number of cross-sectional studies using screening tools such as the Beck Depression/Anxiety Inventory or the Hospital Anxiety and Depression Scale (HADS). This risk is maintained even when only moderate-to-severe symptoms are considered and when the diagnosis is made by a psychiatrist (31, 32). We also observed an increased incidence of depression and anxiety when we matched patients and controls for a prior history of mental health disorder. Similarly increased risks of developing depression and anxiety with time have been found in Taiwanese (17) and Australian (33) patients with PCOS.

A number of potential mechanisms may be in operation. Obesity, which is itself associated with depression and anxiety (9, 10), is a common co-morbidity in women with PCOS and could explain some of this risk. However, in a systematic review and meta-analysis of cross-sectional studies (32), the increased odds of depressive and anxiety symptoms persisted even when subjects with PCOS were matched on BMI with controls, indicating that factors other than obesity must be contributing. Hyperandrogenism is a hallmark of PCOS and may lead to the emotionally distressing symptoms of hirsutism and acne. High patient-rated Ferriman-Gallwey scores, as a measure of hirsutism, have been associated with higher HADS depression and anxiety scores in women presenting to dermatology clinics for hair removal (34). Ferriman-Gallwey scores were also increased in PCOS subjects with anxiety and depression symptoms, and free testosterone levels were higher in women with PCOS and anxiety compared to those with no anxiety (32). However, the relationship between androgen levels and affective symptoms may not be so clear-cut since others have shown an association of *lower* testosterone and androgen metabolite concentrations with worse self-reported depression symptoms in women with PCOS (35). Increased changes in testosterone concentrations across the

perimenopause have also been associated with depression (36, 37). Fertility may be another major concern for women with PCOS, although depression and anxiety scores remain higher than controls in studies where this has been accounted for (32, 38). Of interest, insulin resistance has also been proposed as a potential mechanism by which depression and anxiety might be increased in PCOS. Insulin resistance, a characteristic of both lean and overweight patients with PCOS, shows a bidirectional relationship with depression in the general population (39) whilst in a recent study of PCOS subjects, insulin resistance was associated with depression risk independently of age, BMI, ethnicity and exercise (40).

In contrast to depression and anxiety, only a few studies have examined the risk of other psychiatric disorders in women with PCOS. However, two population-based studies have shown that the risk of mental health disorders in PCOS may be broader than previously recognized, with increased odds of bipolar disorder, schizophrenia, personality disorders, autism spectrum disorder, bulimia and tics, in addition to depression and anxiety (17, 41). Whilst we were underpowered to show an effect of PCOS on autism spectrum disorder, ADHD and schizophrenia, we did confirm an increased prevalence and incidence of bipolar disorder compared to matched controls. Valproate therapy could, at least in part, explain this association since symptoms compatible with PCOS have been reported in women treated for bipolar disorder with valproate (42). However, other studies have shown that symptoms pre-date treatment (43). Furthermore, in keeping with another registry study (41) we found that this association, although slightly attenuated, persisted when excluding subjects treated with valproate before diagnosis. The prevalence and incidence of eating disorder was also higher in patients with PCOS. This is in keeping with other studies (19, 20), which have shown an association of binge-eating with menstrual dysfunction (44), and a higher rate of eating disorders in women with PCOS especially in the presence of concurrent anxiety (20).

Since the intra-uterine environment is known to be important in regulating child neurodevelopment, we were also keen to examine the effect of maternal PCOS status (and potential hyperandrogenism) on the risk of neurodevelopmental disorders in their children. Our linkage analysis found an increased risk of a recorded diagnosis of ASD and ADHD in children born to mothers with PCOS. This is in agreement with the observations of Kosidou *et al* (25, 45), who reported respectively increased risks of 59% and 42%, of a similar magnitude to our data. They have recently extended their observations in relation to ASD to report an increased risk in mothers with a diagnosis of hirsutism (46). These data support the view that increased

exposure to androgens *in utero* might adversely influence brain development. Indeed, intra-amniotic Δ4 sex-steroid levels, including testosterone and androstenedione, were found to be higher in mothers of children who subsequently developed ASD than those who did not (47). PCOS might expose the developing fetus to excess androgens since women with PCOS show increased circulating androgen levels during gestation and have greater placental androgenic capacity (48-50). Prenatal androgen exposure might increase ASD and ADHD risk through effects on dendritic morphology, neuronal density, abnormal synapse function and morphology (51, 52). In this regard, our recent findings of altered white matter microstructure in women with PCOS, notably in androgen-sensitive areas such as the corpus callosum (27), are intriguing and merit further investigation. Maternal androgen excess might also predispose to anxiety in the children of mothers with PCOS: in a rodent model, prenatal androgen exposure resulted in increased anxiety-like behavior in offspring, mediated via androgen receptor activation in the amygdala and accompanied by changes in serotonergic and GABAergic genes in the amygdala and hippocampus (53).

Whilst environmental influences such as androgen exposure may go some way to explaining the effects of PCOS on mental health risk, other explanations for these findings also merit consideration. In a nationwide Swedish registry study, Cesta *et al* found a higher risk for a range of psychiatric disorders not only in PCOS subjects but also in their siblings (41). Endocrine disturbances could account for these findings since nearly 50% of sisters of women with PCOS are hyperandrogenic (54) whilst their brothers also have alterations in gonadotropin and steroidogenic hormone secretion (55). Alternatively, shared familial factors between PCOS and psychiatric disorders may exist, including a common genetic predisposition as well as shared psychosocial factors in childhood.

Our study has a number of strengths, especially the large, population-based sample and adjustment for a number of potential confounders. However, our study also has limitations. As with all database studies, there is the possibility of confounding and bias that should be considered when interpreting these results. Patients with PCOS had significantly increased primary care contacts in the 12 months prior to baseline (6 versus 4 in both control sets). This may be due to consultations relating to symptoms and investigations relevant to the PCOS diagnosis, but they may also relate to the prevalence of other conditions which may be associated with other health-related morbidities.

Observation bias may also be a factor in these results, as patients with increased contacts with health professionals necessitated by the presence of a condition such as PCOS have increased chance of other conditions such as depression and anxiety being diagnosed and recorded within the dataset. We deliberately used a broad range of codes to determine depression and anxiety as there is evidence that over the study time period there has been a shift in primary care such that the recording of clinical diagnoses of depression has reduced whilst the recording of depressive symptoms has increased. Overall, however, the combined rate for the incidence of diagnoses and symptoms has remained relatively stable (56). It is possible, however, that some symptom terms such as 'Feeling depressed' may be less indicative of clinically relevant depression than diagnosis terms such as 'Chronic depression'. Whilst there may be some ambiguity surrounding depression and anxiety this is less likely for bipolar disorder which was increased in the population with PCOS compared with controls.

There was significant missing data in this study. Body mass index was not available for over 50% of cases although obesity is known to be associated with depression and anxiety (9, 10) and also with PCOS. To compensate for this we modelled BMI as a categorical variable with missing included as a category, but it should be considered that different levels of BMI within the 'missing' category could partially explain some of the observed results in this study.

In conclusion, our study confirms that women with PCOS are at increased risk of being diagnosed with depression, anxiety, bipolar disorder and eating disorder, and that their children are at increased risk of a diagnosis of autism spectrum disorder and ADHD. Our data support international guidelines which recommend screening for mental health disorders as part of the comprehensive clinical care for women with this condition (57, 58). Further research is critical in understanding the mechanisms by which these risks arise in order to optimise interventions to reduce psychiatric morbidity.

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Tables and figures

Table 1 *Baseline characteristics for women with PCOS and matched controls – control set 1*

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Baseline Characteristics	Case		Control		p-value
Total, n (%)	16,938	100.00	16,938	100.00	
Age (years), mean, SD	26.90	7.20	27.01	7.36	0.1983
Follow-up (years), median, LQ-UQ	3.87	1.80 - 7.25	2.81	1.20 - 5.80	<0.0001
Observation period pre-index (years), median, LQ-UQ	4.33	1.90 - 9.10	3.32	1.48 - 7.59	<0.0001
Primary care contact in prior year, median, LQ-UQ	6	3 - 9	4	1 - 7	<0.0001
BMI (kg/m^2), mean, SD	29.86	7.86	28.99	7.01	<0.0001
BMI (kg/m^2)					<0.0001
Underweight, (<20), n(%)	653	3.86	663	3.91	
Normal, (20-24), n(%)	1,652	9.75	1,683	9.94	
Overweight, (>24-29), n(%)	1,885	11.13	1,938	11.44	
Obesity, (>29-39), n(%)	2,955	17.45	3,335	19.69	
Extreme Obesity, (>39), n(%)	1,133	6.69	659	3.89	
Missing, n(%)	8,660	51.13	8,660	51.13	
Smoking					<0.0001
Never, n(%)	10,540	62.23	10,333	61	
Prior, n(%)	2,934	17.32	2,559	15.11	
Current, n(%)	4,394	25.94	4,918	29.04	
Missing, n(%)	174	1.03	727	4.29	
Alcohol					<0.0001
Never, n(%)	3,525	20.81	3,181	18.78	
Prior, n(%)	240	1.42	229	1.35	
Current, n(%)	9,713	57.34	9,812	57.93	
Missing, n(%)	3,460	20.43	3,716	21.94	
Diastolic BP					<0.0001
Diastolic BP (mmHg), mean, SD	74.97	9.82	73.52	9.55	<0.0001
<80, n(%)	6,128	36.18	6,878	40.61	
80-89,n(%)	2,913	17.2	2,783	16.43	
>89, n(%)	697	4.12	468	2.76	
Missing, n(%)	7,200	42.51	6,809	40.2	
Systolic BP					<0.0001
Systolic BP (mmHg), mean, SD	118.78	13.78	117.89	13.26	<0.0001
<120, n(%)	4,782	28.23	5,201	30.71	
120-139, (%)	4,170	24.62	4,286	25.3	
>139, n(%)	786	4.64	642	3.79	
Missing, n(%)	7,200	42.51	6,809	40.2	

668 **Table 2** *Baseline characteristics for women with PCOS and matched controls – control set 2*

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Baseline Characteristics	Case		Control		p-value
Total, n(%)	16,355	100.00	16,355	100.00	
Age (years), mean, SD	26.93	7.21	27	7.37	0.3997
Follow-up (years), median, LQ-UQ	3.88	1.81 - 7.26	3.07	1.32 - 6.70	<0.0001
Observation period pre-index (years), median, LQ-UQ	4.30	1.89 - 9.05	3.67	1.63 - 8.13	<0.0001
Primary care contact in prior year, median, LQ-UQ	6	3 - 9	4	1 - 7	<0.0001
BMI (kg/m^2), mean, SD	29.68	7.83	28.84	7.07	<0.0001
BMI (kg/m^2)					<0.0001
Underweight, (<20), n(%)	632	3.86	664	4.06	
Normal, (20-24), n(%)	1,600	9.78	1,594	9.75	
Overweight, (>24-29), n(%)	1,789	10.94	1,842	11.26	
Obesity, (>29-39), n(%)	2,721	16.64	3,052	18.66	
Extreme Obesity, (>39), n(%)	1,027	6.28	617	3.77	
Missing, n(%)	8,586	52.5	8,586	52.5	
Smoking					<0.0001
Never, n(%)	10,051	61.46	10,231	62.56	
Prior, n(%)	2,459	15.04	2,970	18.16	
Current, n(%)	4,185	25.59	4,652	28.44	
Missing, n(%)	170	1.04	749	4.58	
Alcohol					<0.0001
Never, n(%)	3,403	20.81	3,052	18.66	
Prior, n(%)	218	1.33	237	1.45	
Current, n(%)	9,378	57.34	9,342	57.12	
Missing, n(%)	3,356	20.52	3,724	22.77	
Diastolic BP					<0.0001
Diastolic BP (mmHg), mean, SD	74.9	9.82	73.27	9.58	<0.0001
<80, n(%)	5,887	36	6,765	41.36	
80-89,n(%)	2,773	16.96	2,496	15.26	
>89, n(%)	652	3.99	464	2.84	
Missing, n(%)	7,043	43.06	6,630	40.54	
Systolic BP					<0.0001
Systolic BP (mmHg), mean, SD	118.71	13.78	117.85	13.06	<0.0001
<120, n(%)	4,576	27.98	4,999	30.57	
120-139, (%)	3,991	24.4	4,110	25.13	
>139, n(%)	745	4.56	616	3.77	
Missing, n(%)	7,043	43.06	6,630	40.54	

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Table 3 *Number, crude rates and associated hazard ratios for depression, anxiety and bipolar disorder in women with PCOS and matched controls*

	Cases		Controls		Hazard Ratio (CI)	p-value
	Number	**(Rate pky)**	**Number**	**(Rate pky)**		
Control set 1	16,938		16,938			
Depression	3,545	42.62	2,327	34.46	1.26 (1.19 – 1.32)	<0.00001
Anxiety	1,829	21.99	1,189	17.61	1.20 (1.11 – 1.29)	<0.00001
Bipolar Disorder	402	4.83	246	3.64	1.21 (1.03 – 1.42)	0.02126
Autism	14	0.83	16	0.94		
ADHD	13	0.77	11	0.65		
Schizophrenia	22	1.30	9	0.53		
Eating Disorder	125	7.57	72	4.36	1.37 (1.05 – 1.81)	0.02283
Control set 2	16,355		16,355			
Depression	3,353	41.66	2,146	26.66	1.38 (1.30 – 1.45)	<0.00001
Anxiety	1,717	21.33	1,017	12.64	1.39 (1.29 – 1.51)	<0.00001
Bipolar Disorder	356	4.42	200	2.48		
Autism	9	0.55	3	0.18		
ADHD	8	0.49	6	0.37		
Schizophrenia	10	0.61	6	0.37		
Eating Disorder	118	7.40	63	3.95	1.54 (1.16 - 2.05)	0.00256

pky: per 1,000 person years

Table 4 *Number, rate and odds ratio of ADHD and autism in the children of mothers with PCOS and matched controls*

Mental Health Disorder	Cases		Controls		Odds Ratio (CI)	p-value
	Number	(Rate pky)	Number	(Rate pky)		
Control set 1	8,962		8,885			
ADHD	81	4.81	56	3.32	1.64 (1.16 – 2.33)	0.00526
Autism	98	5.82	67	3.98	1.54 (1.12 – 2.11)	0.00068
Control set 2	8,695		8,973			
ADHD	74	4.44	65	3.90	1.34 (0.96 – 1.89)	0.08708
Autism	95	6.00	59	3.54	1.75 (1.27 – 2.46)	0.00080

pky: per 1,000 person years

Figure 1 *Attrition chart for identification of pool of patients with PCOS*

Figure 2 | *Kaplan-Meier curves showing time to depression and anxiety for patients with PCOS compared to matched controls.*