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

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11

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31

32 **Abstract**

33

34 **Context**

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

37

38 **Objectives**

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

42

43 **Design**

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

49

50 **Results**

51 16,986 eligible patients were identified; 16,938 and 16,355 were matched to control sets 1 and  
52 2 respectively. Compared to control set 1, baseline prevalence was 23.1% versus 19.3% for  
53 depression, 11.5% versus 9.3% for anxiety and 3.2% versus 1.5% for bipolar disorder  
54 ( $p < 0.001$ ). The hazard ratio for time to each endpoint was 1.26 (95% CI 1.19-1.32), 1.20 (1.11-  
55 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)  
56 for set 2. The odds ratios for ASD and ADHD in children were 1.54 (1.12-2.11) and 1.64 (1.16-  
57 2.33) for set 1, and 1.76 (1.27-2.46) and 1.34 (0.96-1.89) for set 2.

58

59 **Conclusions**

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

62 **Précis**

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

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96 **Introduction**

97 Polycystic Ovary Syndrome is the commonest endocrine condition affecting young women,  
98 and is characterized by hyperandrogenism, menstrual disturbance and subfertility. In addition  
99 to its well-recognized reproductive sequelae (1), PCOS is now established as a metabolic  
100 disorder underpinned by insulin resistance and leading to an increased risk of type 2 diabetes  
101 (2).

102  
103 The cutaneous manifestations of hyperandrogenism, including hirsutism, acne and scalp hair  
104 loss, are emotionally distressing (3, 4), and could contribute to an increased prevalence of  
105 depression and anxiety in this population (5-8). Comorbid mental health disorders have also  
106 been shown to contribute to impaired quality of life in PCOS (9). However, it is difficult to  
107 establish how many of these outcomes are attributable to PCOS *per se*, and how many to  
108 obesity, which is common in this patient group and itself associated with adverse mental health  
109 outcomes, including depression (10) and anxiety (11). This risk of depression may be  
110 particularly increased in patients with metabolically unhealthy obesity, which is characterized  
111 by insulin resistance and abdominal adiposity (12), compared to metabolically healthy weight-  
112 matched controls (13, 14). Furthermore, in community-based studies, the association between  
113 obesity and depression appears stronger for women compared to men (15). This association  
114 may be bi-directional: in longitudinal studies obesity increases the risk of a subsequent  
115 diagnosis of depressive disorder, whilst depression at baseline in turn increases the odds for  
116 developing obesity (16). This latter risk appears to be particularly high for adolescent females  
117 (16).

118  
119 Whilst previous studies have focused on the risk of depressive disorder and anxiety in patients  
120 with PCOS, hyperandrogenism may also influence the risk of other mental health disorders  
121 including schizophrenia (17). However, a recent population-based cohort study failed to  
122 demonstrate an increased risk of developing schizophrenia (or bipolar disorder) in women with  
123 PCOS, although an increased risk of depressive disorder, anxiety disorder and sleep disorder  
124 was confirmed (18). Other studies have shown that the risk of eating disorder, notably binge-  
125 eating disorder, may be increased in women with PCOS (19, 20). Attention deficit  
126 hyperactivity disorder (ADHD) has also been shown to associate with hyperandrogenism (21)  
127 and obesity in adults (22), albeit that the latter effect size is moderate,

128

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

142

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

151

152 **Materials and Methods**

153 The study employed a retrospective cohort design using data from the Clinical Practice  
154 Research Datalink (CPRD), a longitudinal, anonymized research database collected from 674  
155 primary care practices in the United Kingdom. The CPRD contains records for over 11 million  
156 patients and is representative of the UK population in terms of age and sex (29). Approximately  
157 60% of practices participate in a linkage scheme, by which their patient records are linked to  
158 other data sources, including the Hospital Episode Statistics (HES) dataset, which provides  
159 data on all inpatient and outpatient contacts occurring within National Health Service hospitals  
160 in England, and the Office for National Statistics (ONS) mortality dataset. Diagnostic  
161 information in the CPRD primary-care dataset is recorded using the Read code classification,  
162 a UK primary-care practice standard. HES inpatient data are recorded using the ICD-10  
163 classification.

164

165 *Patient selection and matching of controls*

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

173

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

186 classification or 10<sup>th</sup> revision of the International Statistical Classification of Diseases and  
187 Related Health Problems (ICD-10) classification (Supplementary appendix 1).

188

### 189 *Endpoints*

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

196

### 197 *Data analysis*

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

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

212

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

215

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

219



220 **Results**

221

222 89,732 patients with PCOS were initially identified. After application of the  
223 inclusion/exclusion criteria, 16,986 patients remained eligible for matching with control  
224 subjects (figure 1). 16,938 (99.7%) and 16,355 (96.3%) patients could be matched with controls  
225 for control sets 1 and 2 respectively.

226

227 *Baseline characteristics*

228 The baseline characteristics of patients with PCOS and controls are shown in tables 1 and 2  
229 respectively for control sets 1 and 2. For control set 1, median follow-up was 3.87 years  
230 (interquartile range (IQR) 1.80-7.25) for cases and 2.81 years (IQR 1.20-5.80) for controls. For  
231 control set 2, median follow-up was 3.88 years (IQR 1.81-7.26) for cases and 3.07 years (IQR  
232 1.32-6.70) for controls. In both control sets, there were significant differences between cases  
233 and controls. Patients with PCOS had increased primary care contacts in the year prior to index  
234 date (median 6.0 contacts versus 4.0 for both control sets), and an increased proportion of  
235 patients classified with extreme obesity (6.7% vs 3.9% in control set 1 and 6.3% vs 3.8% in  
236 control set 2). In addition, there were significant differences in smoking status, alcohol history  
237 and systolic and diastolic blood pressure.

238

239 *Prevalence of mental health disorders*

240 In control set 1, 3,912 (23.1%) patients with PCOS had previously been diagnosed with  
241 depression compared to 3,272 (19.32%) of controls ( $p < 0.00001$ ) (Supplementary appendix  
242 2). A prior diagnosis of anxiety was also higher in patients with PCOS ( $n=1,956$ , 11.55%)  
243 compared to controls ( $n=1,579$ , 9.32%) ( $p < 0.00001$ ). There was also a significant increase in  
244 the recorded diagnosis of bipolar disorder (PCOS 535 (3.16%) vs 384 (1.45%) controls,  
245  $p < 0.00001$ ). Prior diagnosis of eating disorder for patients with PCOS was higher ( $n=262$ ,  
246 1.55%) than controls ( $n=175$ , 1.03%) ( $p=0.00003$ ). In the sensitivity analysis excluding pairs  
247 of cases and controls where either had been treated with valproate therapy prior to index date,  
248 the rate of bipolar disorder remained significantly greater for patients with PCOS (526  
249 (3.14%) versus 375 (1.45%);  $p < 0.00001$ ).

250

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

253

254 *Incidence of mental health disorders*

255 For control set 1 the rate of depression following index date was 42.62 per 1,000 patient years  
256 (pky) for patients with PCOS compared with 34.46 pky for controls. The respective figures for  
257 anxiety, bipolar disorder and eating disorder were 21.99 pky versus 17.61 pky, 4.83 pky versus  
258 3.64 pky, and 7.57 pky versus 4.36 pky (Table 3). For control set 2 the rates were 41.66 pky  
259 versus 26.66 pky for depression, 21.33 pky versus 12.64 pky for anxiety, 4.42 pky versus 2.48  
260 pky for bipolar disorder, and 7.40 pky versus 3.95 pky for eating disorder.

261

262

263 *Hazard ratios for mental health disorders*

264 Time to event for depression and anxiety for both control sets are shown in the Kaplan-Meier  
265 curves in figure 2. After adjusting for demographic and morbidity indicators in the Cox  
266 proportional hazards model, the hazard ratios for patients with PCOS compared to controls in  
267 control set 1 were 1.26 (95% CI 1.19-1.32) for depression, 1.20 (95% CI 1.11-1.29) for anxiety,  
268 1.21 (95% CI 1.03 – 1.42) for bipolar disorder and 1.37 (95% CI 1.05-1.81) for eating disorder.  
269 For control set 2 the hazard ratios were 1.38 (95% CI 1.30-1.45) for depression, 1.39 (95% CI  
270 1.29-1.51) for anxiety and 1.54 (95% CI 1.16-2.05) for eating disorder. Due to model violations  
271 it was not possible to calculate the hazard ratio for bipolar disorder (Table 3).

272

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

276

277 *ADHD and Autism Spectrum Disorder in children of patients with PCOS*

278 In control set 1 there were 8,962 children born to patients with PCOS compared to 8,885 born  
279 to the controls. The respective rate of ADHD was 4.81 pky versus 3.32 pky with an odds ratio  
280 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  
281 (95% CI 1.12-2.11). In control set 2, there were 8,695 births to women with PCOS and 8,973  
282 to controls. The rate of ADHD was 6.00 pky versus 3.54 pky; odds ratio 1.75 (1.27 – 2.46) and  
283 the rate of ASD was 4.44 pky versus 3.90 pky; odds ratio 1.34 (95% CI 0.96-1.89) (Table 4).

284

285

286 **Discussion**

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

295  
296 Our findings of an increased prevalence of depression and anxiety in women with PCOS are  
297 consistent with a number of cross-sectional studies using screening tools such as the Beck  
298 Depression/Anxiety Inventory or the Hospital Anxiety and Depression Scale (HADS). This  
299 risk is maintained even when only moderate-to-severe symptoms are considered and when the  
300 diagnosis is made by a psychiatrist (31, 32). We also observed an increased incidence of  
301 depression and anxiety when we matched patients and controls for a prior history of mental  
302 health disorder. Similarly increased risks of developing depression and anxiety with time have  
303 been found in Taiwanese (17) and Australian (33) patients with PCOS.

304  
305 A number of potential mechanisms may be in operation. Obesity, which is itself associated  
306 with depression and anxiety (9, 10), is a common co-morbidity in women with PCOS and could  
307 explain some of this risk. However, in a systematic review and meta-analysis of cross-sectional  
308 studies (32), the increased odds of depressive and anxiety symptoms persisted even when  
309 subjects with PCOS were matched on BMI with controls, indicating that factors other than  
310 obesity must be contributing. Hyperandrogenism is a hallmark of PCOS and may lead to the  
311 emotionally distressing symptoms of hirsutism and acne. High patient-rated Ferriman-Gallwey  
312 scores, as a measure of hirsutism, have been associated with higher HADS depression and  
313 anxiety scores in women presenting to dermatology clinics for hair removal (34). Ferriman-  
314 Gallwey scores were also increased in PCOS subjects with anxiety and depression symptoms,  
315 and free testosterone levels were higher in women with PCOS and anxiety compared to those  
316 with no anxiety (32). However, the relationship between androgen levels and affective  
317 symptoms may not be so clear-cut since others have shown an association of *lower* testosterone  
318 and androgen metabolite concentrations with worse self-reported depression symptoms in  
319 women with PCOS (35). Increased changes in testosterone concentrations across the

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

328

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

345

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

354 exposure to androgens *in utero* might adversely influence brain development. Indeed, intra-  
355 amniotic  $\Delta 4$  sex-steroid levels, including testosterone and androstenedione, were found to be  
356 higher in mothers of children who subsequently developed ASD than those who did not (47).  
357 PCOS might expose the developing fetus to excess androgens since women with PCOS show  
358 increased circulating androgen levels during gestation and have greater placental androgenic  
359 capacity (48-50). Prenatal androgen exposure might increase ASD and ADHD risk through  
360 effects on dendritic morphology, neuronal density, abnormal synapse function and morphology  
361 (51, 52). In this regard, our recent findings of altered white matter microstructure in women  
362 with PCOS, notably in androgen-sensitive areas such as the corpus callosum (27), are  
363 intriguing and merit further investigation. Maternal androgen excess might also predispose to  
364 anxiety in the children of mothers with PCOS: in a rodent model, prenatal androgen exposure  
365 resulted in increased anxiety-like behavior in offspring, mediated via androgen receptor  
366 activation in the amygdala and accompanied by changes in serotonergic and GABAergic genes  
367 in the amygdala and hippocampus (53).

368

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

378

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

387

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

400

401 There was significant missing data in this study. Body mass index was not available for over  
402 50% of cases although obesity is known to be associated with depression and anxiety (9, 10)  
403 and also with PCOS. To compensate for this we modelled BMI as a categorical variable with  
404 missing included as a category, but it should be considered that different levels of BMI within  
405 the 'missing' category could partially explain some of the observed results in this study.

406

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

414

415

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417

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664 **Tables and figures**

665  
666 **Table 1** *Baseline characteristics for women with PCOS and matched controls – control set 1*

<b>Baseline Characteristics</b>	<b>Case</b>		<b>Control</b>		<b>p-value</b>
<b>Total, n (%)</b>	16,938	100.00	16,938	100.00	
<b>Age (years), mean, SD</b>	26.90	7.20	27.01	7.36	0.1983
<b>Follow-up (years), median, LQ-UQ</b>	3.87	1.80 - 7.25	2.81	1.20 - 5.80	<0.0001
<b>Observation period pre-index (years), median, LQ-UQ</b>	4.33	1.90 - 9.10	3.32	1.48 - 7.59	<0.0001
<b>Primary care contact in prior year, median, LQ-UQ</b>	6	3 - 9	4	1 - 7	<0.0001
<b>BMI (kg/m<sup>2</sup>), mean, SD</b>	29.86	7.86	28.99	7.01	<0.0001
<b>BMI (kg/m<sup>2</sup>)</b>					<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	
<b>Smoking</b>					<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	
<b>Alcohol</b>					<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	
<b>Diastolic BP</b>					<0.0001
<b>Diastolic BP (mmHg), mean, SD</b>	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	
<b>Systolic BP</b>					<0.0001
<b>Systolic BP (mmHg), mean, SD</b>	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	

<b>Baseline Characteristics</b>	<b>Case</b>		<b>Control</b>		<b>p-value</b>
<b>Total, n(%)</b>	16,355	100.00	16,355	100.00	
<b>Age (years), mean, SD</b>	26.93	7.21	27	7.37	0.3997
<b>Follow-up (years), median, LQ-UQ</b>	3.88	1.81 - 7.26	3.07	1.32 - 6.70	<0.0001
<b>Observation period pre-index (years), median, LQ-UQ</b>	4.30	1.89 - 9.05	3.67	1.63 - 8.13	<0.0001
<b>Primary care contact in prior year, median, LQ-UQ</b>	6	3 - 9	4	1 - 7	<0.0001
<b>BMI (kg/m<sup>2</sup>), mean, SD</b>	29.68	7.83	28.84	7.07	<0.0001
<b>BMI (kg/m<sup>2</sup>)</b>					<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	
<b>Smoking</b>					<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	
<b>Alcohol</b>					<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	
<b>Diastolic BP</b>					<0.0001
<b>Diastolic BP (mmHg), mean, SD</b>	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	
<b>Systolic BP</b>					<0.0001
<b>Systolic BP (mmHg), mean, SD</b>	118.71	13.78	117.85	13.06	<0.0001
<120, n(%)	4,576	27.98	4,999	30.57	
120-139, n(%)	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	

**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)		
<b>Control set 1</b>	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
<b>Control set 2</b>	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)		
<b>Control set 1</b>	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
<b>Control set 2</b>	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.*