Morbidity and medicine prescriptions in a nationwide Danish population of patients diagnosed with polycystic ovary syndrome

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Abstract

Objective: The prevalence of type 2 diabetes is increased in polycystic ovary syndrome (PCOS), but the prevalence of other diseases is not clarified. We aimed to investigate morbidity and medicine prescriptions in PCOS.

Design: A National Register-based study.

Methods: Patients with PCOS (PCOS Denmark and an embedded cohort; PCOS Odense University Hospital (OUH)) and one control population. Premenopausal women with PCOS underwent clinical and biochemical examination (PCOS OUH, $n = 1217$). PCOS Denmark ($n = 19\,199$) included women with PCOS in the Danish National Patient Register. Three age-matched controls were included per patient ($n = 57\,483$).

Main outcome measures: Diagnosis codes and filled prescriptions.

Results: The mean (range) age of the PCOS Denmark group and controls was 30.6 (12–60) years. Patients in PCOS Denmark had higher Charlson index, higher prevalence of diabetes, dyslipidemia, and hypertension than controls. PCOS was associated with a two times increased risk of stroke and thrombosis, whereas the risk of other cardiovascular diseases was not increased. Thyroid disease, asthma, migraine, and depression were more prevalent in PCOS Denmark vs controls, whereas fractures were rarer. Infertility was increased in patients compared with controls, but the mean number of births was higher in PCOS. Medicine prescriptions within all diagnosis areas were significantly higher in PCOS patients than in controls. In PCOS OUH, polycystic ovaries (PCO) and irregular menses were associated with a more adverse metabolic risk profile, but individual Rotterdam criteria were not associated with cardiometabolic diagnoses.

Conclusion: Cardiometabolic and psychiatric morbidity were significantly increased in a Danish population with PCOS. Medical diseases are frequent also in young patients with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine condition, which is nowadays most often defined according to the Rotterdam criteria (1, 2). Importantly, PCOS is a diagnosis of exclusion and the Rotterdam criteria include irregular ovulation, biochemical/clinical hyperandrogenism, and/or polycystic ovaries (PCO) (1). In women with hirsutism, the prevalence of PCOS is more

than 75% (3, 4). PCOS is characterized by subclinical inflammation and insulin resistance, which along with obesity may be associated with increased morbidity (3). Hyperandrogenism and hyperandrogenemia in PCOS may further increase the metabolic risk (5, 6). Nearly 50% of patients with PCOS fulfill the criteria of the metabolic syndrome and PCOS is associated with a five to ten times

increased risk of diabetes and thus increased number of cardiovascular risk factors (7, 8, 9). Retrospective studies reported significantly higher frequency of hypertension and cardiovascular disease in PCOS, especially in women with irregular cycles (10, 11, 12, 13). Recommendations for the diagnosis and follow-up of patients with PCOS include screening for the metabolic syndrome and other cardiovascular risk factors with regular intervals (3, 14). These recommendations are based on clinical studies, whereas no register-based studies evaluated the prevalence of diabetes and cardiovascular disease in patients diagnosed with PCOS.

Hyper-inflammation in PCOS could affect the auto-immune function (15) and in small clinical studies the prevalence of autoimmune thyroiditis was increased (16). Furthermore, respiratory function in patients with asthma was associated with menstrual pattern (17) and PCOS could therefore be associated with changed respiratory health (17). These hypotheses could be further tested by studying the prevalence of thyroid and asthma diagnoses in populations with PCOS along with the medicine prescription pattern of thyroid hormones, anti-thyroid medicine, and asthma medicine.

Quality of life is impaired in patients with PCOS and the risk of depression is approximately eight times increased compared with controls (18, 19). PCOS could therefore be associated with increased use of antidepressants, analgesics, and neuropsychiatric medicine, but few studies evaluated this hypothesis. We recently reported that 20% of reproductive-aged patients with PCOS from our uptake area had prescriptions of antidepressants during follow-up compared with 15% healthy controls (20). However, to our knowledge, no population-based study investigated the prevalence of psychiatric and neurological diagnoses in patients with PCOS.

The aim of the present register-based study was to investigate possible associations between the diagnosis of PCOS and morbidity evaluated by diagnosis codes in the Danish National Patient Register (NPR) and medical prescriptions from the National Prescriptions Registry. Possible associations between individual Rotterdam criteria and cardiometabolic health were investigated in a well-described subgroup of patients with hyperandrogenism and/or PCOS.

Patients and methods

The study was designed as a register-based study including two patient populations with PCOS and a control population.

Population 1, PCOS Odense University Hospital

This embedded cohort included premenopausal women referred to the outpatient clinic at the Department of Endocrinology and Metabolism, Odense University Hospital (OUH) during 1997–2012 with the diagnoses of hirsutism (L680) and/or PCOS (E282).

Inclusion criteria

Women were included if they fulfilled the Rotterdam criteria for PCOS or had clinical and/or biochemical hyperandrogenism (21, 22, 23).

Exclusion criteria

Women younger than 15 years were referred to the Department of Pediatrics at Odense University Hospital and patients with a primary complaint of infertility were referred to the local Fertility Clinic. Patients with serious endocrine diseases were excluded as previously described (8). Patients not attending for the measurement of hormonal or metabolic parameters were excluded.

Three patients diagnosed with PCOS before the age of 15 were included in the study as they underwent full evaluation at our department after the age of 15 years. Patients paused oral contraceptives for at least 3 months before evaluation.

Methods

Routine evaluation included medical history, clinical examination, transvaginal ultrasound, and fasting blood samples (8). Patients with regular periods and cycle length of 27–35 days were classified as having regular menses. The remaining patients were classified as anovulatory. Hirsutism was assessed by the Ferriman Gallwey score (FG-score) (24). Waist circumference was measured to the nearest centimeter in a standing position midway between the lower costal margin and the iliac crest.

Fasting blood samples were drawn in follicular phase (cycle days 2–8) in patients with a cycle length shorter than 3 months, while patients with cycle length >3 months had the blood samples drawn on a random cycle day. Blood tests included androgens (total testosterone, free-testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate, 17-hydroxyprogesterone), LH, FSH, prolactin, HbA1c, lipid profile insulin, and blood glucose.

Assays

Serum total testosterone and SHBG were analyzed using a specific RIA after extraction as previously described (25). The method has a close correlation with the determination of testosterone levels by mass spectrometry. The intra-assay coefficient of variation (CV) for total testosterone was 8.2 and 5.2% for SHBG. The inter-assay CV for total testosterone was 13.8 and 7.5% for SHBG. Free testosterone levels were calculated from measurements of total testosterone and SHBG. Insulin was analyzed by a time-resolved fluoroimmunoassay using a commercial kit (AutoDelfia, Wallac Oy, Turku, Finland) with an intra-assay variation 2.1–3.7% and inter-assay variation 3.4–4.0%. Reference intervals for the individual hormones were as follows: total testosterone 0.55–1.8 nmol/l, free testosterone 0.006–0.034 nmol/l, SHBG 41–170 nmol/l, and insulin 18–173 pmol/l.

Plasma total cholesterol, HDL cholesterol, and triglycerides (TG) were analyzed by enzymatic colorimetric reactions (Modular P, Roche), while LDL cholesterol was calculated using the Friedewald equation. Blood glucose was measured on capillary ear blood using Hemo Cue. We calculated HOMA-R = fasting insulin $\times$ fasting blood glucose/22.5 (26), reference ≤ 15 pmol mmol l⁻².

Population 2, PCOS Denmark

Population 2 included patients diagnosed with hirsutism or PCOS according to the International Classification of Diseases (ICD) 10 (L680 and E282) in the Danish NPR from 1995 to 2012 over the age of 12 years. The Danish NPR contains discharge diagnosis codes according to ICD8 during 1977–1993 and ICD10 from 1994 and onwards. From 1977 to 1994 only inpatient contacts were registered, while from 1994 both in- and outpatient contacts are registered (27). The current sub-classification of diabetes mellitus types was not used until 1994, as the ICD8 coding classified diabetes mellitus patients as having insulin-dependent diabetes mellitus (ICD8 code 249) or non-insulin-dependent diabetes mellitus (ICD8 code 250). Hence, the GDM diagnosis did not exist in the ICD8 coding and a decision was made to include data from 1994 and onwards in this study. PCOS can only be diagnosed after menarche (28) and therefore only patients aged 12 years or more were included in the PCOS Denmark study population (29). The index year was defined as the first time a patient received the diagnosis L680 or E282. The PCOS OUH population was a subset of the PCOS Denmark population.

Controls

For each patient in the PCOS Denmark population three controls were randomly drawn from the NPR. The controls were born in the same year as PCOS cases and had to be alive on the index date of their respective PCOS case. Controls were assigned the index date of their matched PCOS cases.

Exclusion diagnoses

The PCOS diagnosis requires exclusion of diagnoses that may cause symptoms similar to the condition (1). We excluded subjects in both study arms with a history of the following conditions: E221 (hyperprolactinemia), E220 (acromegaly), E24 (Cushing's disease), E25 (adrenogenital syndrome), and Q96 (Turner syndrome).

The Danish Health Registries

All individuals in Denmark are assigned with a unique personal identification number and data from all public registers can be linked at an individual level. All ICD10 hospital diagnoses were extracted from the NPR on the total study population. Information on all prescriptions issued by prescribers, general practitioners, or specialists in Denmark from 1995 to 2012 were retrieved from the National Prescriptions Registry. The National Prescriptions Registry database contains a complete record of Anatomic Therapeutic Chemical code, date drug dispensed, number of drug packets, and number of tablets per packet for all prescriptions filled at Danish pharmacies. The National Cause of Death Register contains information on all deaths. It includes death certificate diagnoses and date of death.

The core study was an open register-based cohort study. The present paper is a description of baseline characteristics preceding the first diagnosis of PCOS (the index date). Specifically, for comorbid conditions, we included hospital contacts since 1995. The Charlson Comorbidity Index is based on 19 comorbid conditions (30) and was calculated from the ICD10 operationalization by Quan *et al.* (31). For prescriptions, we made a distinction between recent use (at least one prescription of the drug in question in the last 12 months before the index date) and ever use (at least one prescription since establishment of the register in 1995 to the index date). The study did not need approval from the local Ethics committee or Institutional Review Board by Danish law. Transfer of patient data from the PCOS OUH cohort to Statistics Denmark (project no 704175) for merging with national datasets was approved by the Data Protection Agency.

Figure 1
Flowchart of included subjects.

Statistical analyses

The statistical approach addressed two main questions: i) did the patients in PCOS OUH differ from patients in PCOS Denmark on key characteristics and ii) did the patients in PCOS Denmark differ from random population controls. Descriptive analyses for categorical variables (e.g., diabetes, thyroid disease) were presented as frequencies and evaluated by χ^2 tests. Continuous variables (e.g., number of births) were tabulated as medians (with quartiles) or means (with s.d.) depending on their distribution. Mann–Whitney U tests were used to test for differences between the groups for these variables. P values below 0.05 were considered to be statistically significant. All analyses were conducted using STATA 13 through a remote VPN access to Statistics Denmark and the analysts were blinded to the personal identities of the study subjects.

Results

The flow chart of included women is summarized in Fig. 1.

PCOS OUH ($n = 1217$): clinical, biochemical data, and individual Rotterdam criteria

Clinical and biochemical data from the PCOS OUH cohort are presented in Table 1. Patients with PCO ($n = 1085$) were younger and had higher BMI, waist, T-testosterone, fasting BG, fasting insulin, and HOMA-R levels compared with patients with normal US, whereas FG-score was lower (Table 2).

The majority of patients had biochemical and/or clinical hyperandrogenism ($1124/1211 = 92.8\%$, Table 2). Measures of body composition and metabolic risk profile were comparable in patients with and without hyperandrogenism.

Patients with irregular menses were younger and had higher BMI, waist, total- and free testosterone, TG, fasting BG, fasting insulin, and HOMA-R levels compared with patients with regular menses, whereas FG-score, SHBG, and HDL were lower (Table 2).

Characteristics and diagnoses in patients with PCOS and controls ($n = 76\,682$)

PCOS Denmark ($n = 19\,199$) vs controls ($n = 57\,483$) ► The mean age of the PCOS Denmark group and controls were 30.6 years. The Charlson Index was higher in patients with PCOS compared with controls. The PCOS Denmark group had higher prevalence of the diagnoses obesity, all types of diabetes, dyslipidemia, hypertension, stroke, and thrombosis compared with controls, whereas the risk of cardiovascular disease, myocardial infarction, and transitory cerebral ischemia was not increased in PCOS. Furthermore, patients with PCOS had increased prevalence of all types of thyroid disease, asthma, depression, migraine, cholecystitis, and malignant diseases compared with controls, whereas fractures were found in fewer patients. The prevalence of infertility was higher in PCOS compared with controls, but the mean number of births was higher in PCOS and the distribution of number of births differed significantly between patients and controls.

Table 1 Clinical and biochemical data from the PCOS OUH patient cohort ($n = 1217$). Data presented as median (quartiles).

	<i>n</i>	Median (quartiles)
Age (years)	1217	29 (23–35)
BMI (kg/m ²)	1130	27.3 (23.0–32.7)
Waist (cm)	766	89 (78–104)
FG total	1069	11 (5–15)
T-testosterone (nmol/l)	866	1.74 (1.24–2.38)
SHBG (nmol/l)	1126	44 (31–66)
Free testosterone (nmol/l)	852	0.033 (0.021–0.050)
Cholesterol (mmol/l)	906	4.6 (4.1–5.3)
TG (mmol/l)	894	1.0 (0.7–1.5)
HDL (mmol/l)	895	1.4 (1.1–1.6)
LDL (mmol/l)	892	2.7 (2.2–3.3)
Fasting blood glucose (mmol/l)	550	4.6 (4.3–5.0)
Fasting insulin (pmol/l)	588	56 (38–91)
HOMA-R (pmol mmol l ^{−2})	557	12.2 (8.1–20.1)

Table 2 The PCOS OUH patient cohort ($n=1217$) and presence of individual Rotterdam criteria. Data presented as median (quartiles) or n (%). In some patients data on ultrasound, hyperandrogenism, or menstrual history were not available.

n (%)	Ultrasound ($n=1085$)		Hyperandrogenism ($n=1211$)		Menses ($n=1193$)	
	PCO	Normal	Yes	No	Irregular	Regular
Age (years)	27 [†] (23–32)	32 (23–38)	29 (23–35)	30 (23–35)	27 [†] (22–33)	32 (24–38)
BMI (kg/m ²)	28.4 [†] (23.7–34.1)	26.2 (22.7–30.8)	27.3 (23.1–32.6)	28.8 (22.8–34.5)	28.4 [†] (23.7–34.5)	25.7 (22.4–30.5)
Waist (cm)	93 [†] (80–106)	86 (77–99)	89 (78–103)	94 (78–108)	92 [†] (79–106)	84 (76–97)
FG total	10 [†] (4–15)	12 (7–16)	11 [†] (6–16)	0	10 [†] (4–15)	13 (8–17)
T-testosterone (nmol/l)	1.96 [†] (1.38–2.61)	1.48 (1.1–2.1)	1.81 [†] (1.26–2.42)	1.22 (0.83–1.53)	1.91 [†] (1.32–2.56)	1.53 (1.14–2.06)
SHBG (nmol/l)	42 [†] (29–61)	48 (32–69)	44 (30–66)	45 (33–72)	40 [†] (27–58)	52 (37–72)
F-testosterone (nmol/l)	0.038 [†] (0.024–0.056)	0.028 (0.018–0.040)	0.034 [†] (0.022–0.051)	0.017 (0.014–0.025)	0.038 [†] (0.025–0.055)	0.025 (0.017–0.038)
Cholesterol (mmol/l)	4.6 (4.1–5.2)	4.7 (4.1–5.4)	4.6 (4.1–5.3)	4.8 (4.2–5.3)	4.7 (4.2–5.3)	4.6 (4.0–5.3)
HDL (mmol/l)	1.3 (1.1–1.6)	1.4 (1.1–1.7)	1.4 (1.1–1.6)	1.4 (1.0–1.7)	1.3 [*] (1.1–1.6)	1.4 (1.2–1.7)
LDL (mmol/l)	2.7 (2.2–3.3)	2.7 (2.2–3.4)	2.7 (2.2–3.3)	2.7 (2.1–3.4)	2.7 (2.3–3.3)	2.7 (2.1–3.3)
TG (mmol/l)	1.1 (0.7–1.6)	1.0 (0.7–1.4)	1.0 (0.7–1.5)	1.1 (0.7–1.7)	1.1 [†] (0.8–1.6)	0.9 (0.7–1.3)
Fasting blood glucose (mmol/l)	4.7 [*] (4.3–5.2)	4.6 (4.3–4.9)	4.6 (4.3–5.0)	4.7 (4.2–5.3)	4.7 [*] (4.3–5.1)	4.5 (4.2–4.9)
Fasting insulin (pmol/l)	58 [*] (41–103)	52 (35–85)	55 (38–91)	58 (49–100)	59 [†] (40–107)	51 (35–81)
HOMA-R (pmol mmol l ⁻²)	12.5 [*] (8.8–21.4)	11.5 (7.2–18.8)	12.2 (8.0–20.0)	13.0 (9.5–21.0)	13.0 [†] (9.2–21.8)	11.0 (7.0–16.9)

PCO, polycystic ovaries; US, ultrasound. * $P<0.05$ and $^{\dagger}P<0.001$ vs patients not fulfilling the individual Rotterdam criterion, Mann-Whitney U test.

PCOS OUH ($n=1217$) vs PCOS Denmark ($n=1919$) ► The PCOS OUH group had lower mean age (29.3 years) than patients in PCOS Denmark (Table 3). Patients in the PCOS OUH group had lower prevalence of migraine, malignant disease and infertility compared with the PCOS Denmark group. Otherwise, the prevalence of diagnoses was comparable. Patients in PCOS OUH had lower mean number of births compared with PCOS Denmark and the distribution of number of births differed between the two patient groups.

Medical treatment in patients with PCOS and controls ($n=76682$) ► Table 4 gives all time use of medical treatment in the study population.

PCOS Denmark ($n=1919$) vs controls ($n=57483$) ► Patients with PCOS had higher use of all types of anti-diabetic treatment, anti-lipids, antihypertensives, allergy medicine, asthma medicine, antidepressants, neuroleptics, anxiety medicine, analgesics, thyroid, anti-thyroid treatment, antibiotic treatment, all types of oral contraceptives, gestagen, intrauterine devices, anti-androgen treatment, and fertility treatment compared with controls.

PCOS OUH ($n=1217$) vs PCOS Denmark ($n=1919$) ► The prescription of metformin, drospirenone/ethinylestradiol, and fertility treatment was lower in PCOS OUH vs PCOS Denmark, whereas prescriptions of antibiotic treatment and cyproterone acetate/ethinylestradiol were higher.

Table 5 gives use of medical treatment 1 year before the diagnosis of PCOS.

PCOS Denmark ($n=1919$) vs controls ($n=57483$) ► Patients with PCOS had higher use of metformin, insulin, other anti-diabetics, anti-lipids, antihypertensives, allergy medicine, asthma medicine, antidepressants, neuroleptics, anxiety medicine, analgesics, thyroid and anti-thyroid treatment, antibiotic treatment, oral contraceptives, 3rd generation oral contraceptives, drospirenone/ethinylestradiol, cyproterone acetate/ethinylestradiol, gestagen, intrauterine devices, spironolactone, vaniqa, and fertility treatment compared with controls. Prescriptions of smoke stop, 2nd generation oral contraceptives, and finasteride were comparable between patients and controls.

PCOS OUH ($n=1217$) vs PCOS Denmark ($n=1919$) ► Prescriptions for metformin, other anti-diabetics,

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Table 3 Characteristics of PCOS patients and controls. Data presented as *n* (%) or mean (s.d.) or min–max.

		PCOS OUH (<i>n</i> = 1217)			PCOS Denmark (<i>n</i> = 19 199)			Controls (<i>n</i> = 57 483)		
		<i>n</i>	%	<i>P</i> ^a	<i>n</i>	%		<i>n</i>	%	<i>P</i> ^b
Age (years) at first diagnosis, mean (s.d.) and min–max		29.3 (8.5)		<0.001	30.6 (9.6)			30.6 (9.6)		0.96
Charlson index, mean (s.d.)		0.119 (0.447)		0.062	0.155 (0.537)			0.096 (0.435)		<0.001
Cardio-metabolic diseases	ICD10 codes									
Obesity	E66	167	13.7	0.07	2306	12.0		791	1.4	<0.001
Diabetes	E10, E11, E13, E14	29	2.4	0.70	429	2.2		423	0.7	<0.001
Type 1 diabetes	E10	7	0.6	0.29	166	0.9		307	0.5	<0.001
Type 2 diabetes	E11	23	1.8	0.42	306	1.6		175	0.3	<0.001
Gestational diabetes	O24, P70	18	1.5	0.94	289	1.5		217	0.4	<0.001
Dyslipidemia	E78	5	0.4	0.50	107	0.6		108	0.2	<0.001
Hypertension	I109	14	1.2	0.10	343	1.8		365	0.6	<0.001
Cardiovascular disease	I20, I50	2	0.2	0.24	72	0.3		177	0.3	0.16
Mocardial infarction	I21, I22, I23, I24, I25	2	0.2	0.76	39	0.2		121	0.2	0.85
Transitory cerebral ischemia	G45	2	0.2	0.75	25	0.1		52	0.1	0.13
Stroke	I63, I64	2	0.2	0.54	49	0.3		82	0.1	0.001
Thrombosis, lung embolism	I26, O082, I80, I81, I82	6	0.5	0.19	127	0.7		183	0.3	<0.001
Other diseases										
Thyroid disease	E04, E05, E03	35	2.9	0.49	476	2.5		379	0.7	<0.001
Atoxic goitre	E04	15	1.2	0.15	161	0.8		146	0.3	<0.001
Hyperthyroidism	E05	9	0.7	0.87	150	0.8		159	0.3	<0.001
Hypothyroidism	E03	15	1.2	0.69	213	1.1		106	0.2	<0.001
Asthma	J44, J45	39	3.2	0.76	586	3.0		1270	2.2	<0.001
Depression	F3	13	1.1	0.36	266	1.4		284	0.5	<0.001
Migraine/headache	G43, G44	12	1.0	0.008	398	2.1		539	0.9	<0.001
Fractures	S02–S92	138	11.3	0.11	2481	12.9		9280	16.1	<0.001
Cholecystitis	K8	40	3.3	0.97	628	3.3		613	1.1	<0.001
Malignant diseases	C00–D48	57	4.7	0.001	1368	7.1		2117	3.7	<0.001
Fertility										
Infertility	N97, Z35	207	17.0	<0.001	4431	23.1		2337	4.1	<0.001
Number of births, mean (s.d.)		0.21 (0.57)		0.001	0.28 (0.62)			0.20 (0.55)		<0.001
Number of births	0	936	76.9	0.018	15 447	80.5		49 946	86.9	<0.001
	1	179	14.7		2446	12.7		4403	7.7	
	2	87	7.2		1077	5.6		2561	4.5	
	≥3	15	1.2		229	1.2		573	1.0	

P^a Between PCOS OUH and PCOS Denmark, *P*^b Between PCOS Denmark and controls, χ^2 test (for prevalences) and Mann–Whitney *U* tests (for continuous variables).

antihypertensives, gestagen, and fertility treatment were lower in PCOS OUH than in PCOS Denmark, whereas prescriptions of intrauterine devices were higher.

Rotterdam criteria in the PCOS OUH population and cardiometabolic diagnoses

The presence of PCO, hyperandrogenism, or irregular menses was associated with obesity (Table 6). Six women in the study population had a diagnosis of thrombosis. The prevalence of thrombosis was significantly lower in patients with hyperandrogenism (4/1124 = 0.4%) compared with patients without hyperandrogenism (2/87 = 2.3%). Five of six patients diagnosed with thrombosis had been treated with oral contraceptives (3rd generation *n* = 4, drospirenone/ethinylestradiol *n* = 1).

Discussion

To our knowledge, this is the first nationwide, population-based study that reports increased morbidity in patients with PCOS compared with healthy age-matched controls. We evaluated morbidity by diagnosis codes and medicine prescriptions before the PCOS diagnosis. The Charlson Index was significantly higher in patients with PCOS than in controls, which support an overall increased morbidity in PCOS. Increased morbidity in PCOS included cardio-metabolic as well as autoimmune and psychiatric diagnoses. The mean age of the included study population was 30 years and our data support that medical diseases are prevalent also in young individuals diagnosed with PCOS. In a representative subgroup of patients with PCOS from our outpatient clinic, the presence of individual

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Table 4 Medical treatment in PCOS patients and controls (ever use). Data presented as *n* (%).

Characteristic	WHO ATC	PCOS OUH (<i>n</i> = 1217)		<i>P</i> ^a	PCOS Denmark (<i>n</i> = 19 199)		Controls (<i>n</i> = 57 483)		<i>P</i> ^b
		<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	
Cardiometabolic									
Metformin	A10BA02	92	7.5	<0.001	2262	11.8	211	0.4	<0.001
Glitazone	A10BG03, A10BD09	0	0	0.72	2	0.01	1	0.00	0.021
Insulin	A10A	9	0.7	0.39	190	1.0	349	0.6	<0.001
Other anti-diabetics	A10B	93	7.6	<0.001	2301	12.0	275	0.5	<0.001
Anti-lipids	C10AA, C10AB, C10AC, C10AD, C10AX, C10BA02	17	1.4	0.83	283	1.5	419	0.7	<0.001
Anti-hypertensives	C03, C08, C09, C07A	158	13.0	0.16	2774	14.5	3891	6.7	<0.001
Thyroid, respiratory, CNS, inflammatory									
Thyroid hormones, anti-thyroid treatment	H03A, H03B	32	2.6	0.87	520	2.7	508	0.9	<0.001
Allergy medicine, steroid	R06A H02AB	343	28.1	0.08	5876	30.6	13 336	23.2	<0.001
Asthma medicine	R03AC, R03BB, R03DA, R03BA, R03DC, R03AK	237	19.5	0.85	3697	19.2	8101	14.1	<0.001
Antidepressants	N06AA, N06AB, N06AX, N06A	206	16.9	0.56	3128	16.3	5067	8.8	<0.001
Neuroleptics	N05A	51	4.2	0.18	969	5.0	1613	2.8	<0.001
Anxiety medicine	N06A, N05BA, N05BE, N03AX16	270	22.2	0.97	4270	22.2	7277	12.6	<0.001
Analgesic and migraine	N02	292	24.0	0.26	4885	25.4	8802	15.3	0.001
Antibiotic treatment	J01	1036	85.1	0.002	15 695	81.7	41141	73.3	<0.001
Smoke stop	N07BA03, N07BA01 N06AX12	11	0.9	0.80	188	1.0	486	0.9	0.086
Birth control, anti-androgens, and fertility									
Oral contraceptives	G03AA, G03AB,	607	49.8	0.28	9885	51.5	17 057	29.7	<0.001
2nd generation OCP	G03AA07, G03AA11, G03AB03	181	14.8	0.26	3092	16.1	5414	9.4	<0.001
3rd generation OCP	G03AA09, G03AA10, G03AB06, G03AB05, G02BB01	490	40.2	0.69	7841	40.8	13 527	23.5	<0.001
Drospirenone/ethinylestradiol	G03AA12	135	11.0	0.028	2549	13.2	2626	4.5	<0.001
Cyproterone acetate/ ethinylestradiol	G03HB01	219	18.0	0.012	2943	15.3	1381	2.4	<0.001
Gestagen	G03AC01, G03AC09, G03AC08	53	4.3	0.92	825	4.3	1488	2.6	<0.001
IUD	G02BA, G02BA03	28	2.3	0.70	410	2.1	665	1.2	<0.001
Spirolactone	C03DA01	10	0.8	0.07	279	1.5	70	0.1	<0.001
Finasteride	G04CB	0	0	0.80	1	0.0	45	0.1	<0.001
Vaniqa	D11AX16	0	0	0.47	8	0.0	0	0	<0.001
Fertility treatment	G03GA G03GB, N04BC	163	13.3	<0.001	3318	17.3	1221	2.1	<0.001

OCP, oral contraceptive pills; IUD, intrauterine device. *P*^a Between PCOS OUH and PCOS Denmark, *P*^b Between PCOS Denmark and controls, χ^2 test.

Rotterdam criteria was associated with obesity, but otherwise we found no association between the presence of individual Rotterdam criteria and cardiometabolic diagnoses.

Many different medical conditions have been associated with the diagnosis of PCOS (32). The risk of type 2 diabetes is currently estimated to be five to ten times increased in PCOS, whereas the risk of cardiovascular disease is debated (3, 9, 13, 33, 34). The risk of cardiometabolic disease may be highly influenced by BMI, ethnicity, and the presence of different Rotterdam criteria, especially hyperandrogenism (5, 35), whereas high SHBG was a protective factor (34). In our cohort,

1.5% patients were diagnosed with type 2 diabetes compared with 0.4% controls, which confirmed a five times increased risk of type 2 diabetes in PCOS. Given the register-based design, BMI data were not available in the PCOS Denmark group. The median BMI in PCOS OUH was 27.3 kg/m² and the relative risk of diabetes may be even higher in more obese study populations. Our findings of three times increased risk of dyslipidemia and hypertension in the PCOS Denmark cohort vs controls support clustering of cardiovascular risk factors in PCOS. Furthermore, the prescription of anti-lipids and antihypertensives was two times higher in patients with PCOS vs controls. Antidiabetic medicine including metformin is used to

Table 5 Medical treatment in PCOS patients and controls (last year).

Characteristic	WHO ATC	PCOS OUH (n=1217)		P ^a	PCOS Denmark (n=19 199)		Controls (n=57 483)		P ^b
		n	%		n	%	n	%	
Cardiometabolic									
Metformin	A10BA02	59	4.8	<0.001	1795	9.4	146	0.3	<0.001
Glitazone	A10BG03, A10BD09	0	0	N/A	0	0	1	0.0	0.084
Insulin	A10A	8	0.6	0.46	165	0.9	321	0.6	<0.001
Other anti-diabetics	A10B	59	4.9	<0.001	1826	9.5	193	0.3	<0.001
Anti-lipids	C10AA, C10AB, C10AC, C10AD, C10AX, C10BA02	13	1.0	0.70	229	1.2	335	0.6	<0.001
Anti-hypertensives	C03, C08, C09, C07A	65	5.3	0.006	1431	7.5	1756	3.1	<0.001
Thyroid, respiratory, CNS, inflammatory									
Thyroid hormones, anti-thyroid treatment	H03A, H03B	26	2.1	0.97	413	2.2	358	0.6	<0.001
Allergy medicine, steroid	R06A H02AB	108	8.9	0.78	1752	9.1	3601	6.3	<0.001
Asthma medicine	R03AC, R03BB, R03DA, R03BA, R03DC, R03AK	78	6.4	0.87	1253	6.5	2677	4.7	<0.001
Anti-depressants	N06AA, N06AB, N06AX, N06A	113	9.3	0.49	1672	8.7	2517	4.4	<0.001
Neuroleptics	N05A	24	2.0	0.36	458	2.4	738	1.3	<0.001
Anxiety medicine	N06A, N05BA, N05BE, N03AX16	137	11.3	0.85	2127	11.1	3382	5.9	<0.001
Analgesic and migraine	N02	110	9.0	0.27	1922	10.0	2939	5.1	<0.001
Antibiotic treatment	J01	505	41.5	0.29	7671	40.0	16 110	28.0	<0.001
Smoke stop	N07BA03, N07BA01 N06AX12	2	0.2	0.31	64	0.3	151	0.3	0.10
Birth control, anti-androgens, and fertility									
Oral contraceptives	G03AA, G03AB, G03AA07, G03AA11, G03AB03	227	18.7	0.55	3716	19.4	10 031	17.5	<0.001
2nd generation OCP		38	3.1	0.40	692	3.6	2081	3.6	0.9
3rd generation OCP	G03AA09, G03AA10, G03AB06, G03AB05, G02BB01	138	11.3	0.63	2266	11.8	7207	12.5	0.006
Drospirenone/ethinylestradiol	G03AA12	65	5.3	0.81	996	5.2	1126	2.0	<0.001
Cyproterone acetate/ethinylestradiol	G03HB01	100	8.2	0.11	1347	7.0	533	0.9	<0.001
Gestagen	G03AC01, G03AC09, G03AC08	13	1.0	<0.001	825	4.3	457	0.8	0.01
IUD	G02BA, G02BA03	12	1.0	0.04	101	0.5	198	0.3	<0.001
Spironolactone	C03DA01	7	0.6	0.11	201	1.1	36	0.2	<0.001
Finasteride	G04CB	0	0	0.80	1	0.01	10	0.02	0.22
Vaniqa	D11AX16	0	0	0.48	8	0.04	0	0	<0.001
Fertility treatment	G03GA G03GB, N04BC	36	3.0	<0.001	1674	8.7	292	0.5	<0.001

OCP, oral contraceptive pills; IUD, intrauterine device. P^a Between PCOS OUH and PCOS Denmark, P^b Between PCOS Denmark and controls, χ^2 test.

treat irregular menses, the metabolic syndrome, and infertility in PCOS, which could explain that the use of antidiabetics was up to 30 times increased in PCOS compared with controls. PCOS was associated with a two times increased risk of stroke and thrombosis, whereas the risk of other cardiac diseases was not increased. The presence of individual Rotterdam criteria was not associated with cardiometabolic outcome despite a more adverse metabolic risk profile in patients with PCO and irregular menses. It is possible that the inclusion of a young, relatively lean study population affected our results and further prospective studies are needed to determine

whether the long-term metabolic risk is affected by PCOS phenotype. The number of cases diagnosed with thrombosis in PCOS OUH was limited and more data are needed on risk factors for thrombosis in patients with PCOS. Oral contraceptives are often used to treat hyperandrogenism and irregular menses in PCOS and five of six patients with thrombosis had been treated with oral contraceptives. Accordingly, the risk of venous thromboembolism was reported to be 1.5-fold increased among women with PCOS not taking oral contraceptives and twofold increased among women with PCOS who were taking combined oral contraceptives (36). Furthermore, the risk

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Table 6 Rotterdam criteria in PCOS OUH population ($n=1217$) and cardiometabolic diagnoses. Data presented as n (%).

	Ultrasound ($n=1085$)		Hyperandrogenism ($n=1211$)		Menses ($n=1193$)	
	PCO ($n=580$)	Normal ($n=505$)	Yes ($n=1124$)	No ($n=87$)	Irregular ($n=728$)	Regular ($n=465$)
Obesity	97 (16.7)*	56 (11.1)	149 (13.3)*	18 (20.7)	122 (16.7) [†]	43 (9.3)
Diabetes	13 (2.2)	11 (2.2)	27 (2.4)	2 (2.3)	19 (2.6)	10 (2.2)
Type 1 diabetes	3 (0.5)	3 (0.6)	6 (0.5)	1 (1.2)	6 (0.8)	1 (0.2)
Type 2 diabetes	9 (1.6)	10 (2.0)	21 (1.9)	2 (2.3)	14 (1.9)	9 (1.9)
Gestational diabetes	10 (1.7)	5 (1.0)	15 (1.3)	3 (3.5)	13 (1.8)	5 (1.1)
Dyslipidemia	2 (0.3)	3 (0.6)	3 (0.3)	2 (2.3)	4 (0.6)	1 (0.2)
Hypertension	6 (1.0)	6 (1.2)	12 (1.1)	2 (2.3)	9 (1.2)	5 (1.1)
Cardiovascular disease	1 (0.2)	0	2 (0.2)	0	28 (0.3)	0
Myocardial infarction	1 (0.2)	1 (0.2)	2 (0.2)	0	1 (0.1)	1 (0.2)
Transitory cerebral ischemia	1 (0.2)	1 (0.2)	1 (0.1)	1 (1.1)	2 (0.3)	0
Stroke	1 (0.2)	1 (0.2)	1 (0.1)	1 (1.1)	2 (0.3)	0
Thrombosis, lung embolism	2 (0.3)	3 (0.6)	4 (0.4)*	2 (2.3)	5 (0.7)	1 (0.2)

* $P<0.05$ and [†] $P<0.001$ vs patients not fulfilling the individual Rotterdam criterion, χ^2 -test.

of thrombosis may be affected, which generation of oral contraceptive was used as 4th generation oral contraceptives containing drospirinone had the highest thromboembolic risk (37).

The overall presence of thyroid diseases was 3.6 times increased in PCOS vs controls. Correspondingly, prescriptions of thyroid medicine were three times increased in PCOS. These data are in agreement with clinical studies reporting that thyroid autoantibodies and autoimmune thyroiditis were more prevalent in patients with PCOS compared with controls (16, 38). These findings lead to a hypothesis of altered immune function in PCOS, which could be mediated by increased inflammatory status, unbalanced estrogen/progesterone secretion, or still unknown mechanisms (16). Similar mechanisms were suggested to affect respiratory health and to increase the risk of asthma in women with irregular menses (17). Our findings of significantly increased risk of asthma, however modest, underline the need for studies in patients with PCOS. Furthermore, the levels of various auto-antibodies were higher in PCOS vs controls (15) and the risk of rheumatologic or other autoimmune diseases may also be increased in PCOS (15).

Depression was 2.8 times more common in patients with PCOS vs controls and 1.9 times more patients than controls had prescriptions of antidepressants. The discrepancy between 1.4% patients diagnosed with depression and 16.3% patients treated with antidepressants could be explained by the fact that many patients are treated for depression by their own general practitioner and only hospital diagnoses are included in NPR. The present data support a moderately increased risk of depression in PCOS and are in agreement with recent studies (2, 20, 39). In contrast, some studies reported an up

to eightfold increased risk of depression in PCOS (18), but treatment with antidepressants is only indicated in moderate or severe and psychotherapy should be used in patients with milder symptoms. Based on the present data, we cannot conclude whether patients with PCOS are medically undertreated or have milder depression symptoms without need for medical treatment.

We found that the use of anxiety medicine was higher in patients with PCOS compared with controls. These results are supported by a recent register-based Taiwanese study reporting a hazard ratio of 1.4 for anxiety disorders in PCOS (39). Anxiety could be associated with depression and low quality of life in PCOS, but more studies are needed to test this hypothesis.

A novel finding of the present study was a two times higher risk of migraine/headache in PCOS vs controls and correspondingly a 1.7 times higher prescription rate of analgesic and migraine medicine. We are not aware of similar findings in previous studies and these results need to be reproduced in other cohorts of patients with PCOS. Testosterone treatment improved symptoms of migraine in pre- and postmenopausal women (40), whereas decreased dihydrotestosterone levels during treatment with finasteride improved migraine symptoms (41). Furthermore, increased use of analgesic medicine could be associated with the use of oral contraceptives, decreased quality of life in PCOS, or the presence of somatic diseases. The evaluation of the use of analgesic medicine is complicated by the fact that paracetamol and low dose NSAID can be bought over the counter in Denmark.

The prevalence of prior fractures was significantly lower in PCOS vs controls and support previous findings of normal or higher bone mineral density in PCOS and hirsute patients compared with controls (42). We did not

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evaluate the prevalence of osteoporosis in this study as the maximum age of included subjects was 60 years. Hyperandrogenemia (43), obesity (44), and hyperinsulinemia (45) may be bone protecting in PCOS. In contrast, vitamin D levels were lower in patients with PCOS and hirsutism vs controls (46) and the prevalence of vitamin D levels <50 nmol/l in PCOS was 31–85% (47). To our knowledge, only one previous study evaluated the fracture risk in women with PCOS (48). The fracture risk was unchanged in 25 postmenopausal women previously diagnosed with PCOS (48). Future prospective studies are therefore needed to determine fracture risk and possible predictors of fractures in pre- and postmenopausal women with PCOS.

Oral contraceptive treatment is the most widely applied treatment modality in PCOS (49). Oral contraceptives regulate menstrual cycles and SHBG levels increase, leading to decreased levels of free testosterone and decreased hirsutism scores (49). A nearly double prescription rate of oral contraceptives in PCOS was therefore not surprising. Furthermore, increased use of cycle regulating medicine, IUD, and antiandrogen treatment was expected in patients with PCOS. Fertility and pregnancy outcome was not the primary outcome of this study. Our data supported that the number of births was not reduced in patients with PCOS despite a significantly higher rate of diagnosed infertility and increased prescription of fertility treatment in PCOS. The inclusion of a relatively lean study population could explain some of our results as the number of births were reduced in obese study populations with PCOS (50). The observed fewer diagnoses of infertility and different distribution of number of births in PCOS OUH compared with PCOS Denmark may be explained by the exclusion of women with fertility plans from PCOS OUH.

The strength of this study is the inclusion of a large and well-characterized group of patients with PCOS, the ability to embed a clinical cohort into a national register-based study, and the access to well validated register-based data with a long record of past drug exposures. Some limitations may however apply to this study design. No data were available on patients not attending the outpatient clinic. Patients not attending the clinic could differ from included patients. Many patients with PCOS are not seen at the hospital, but are treated by their general practitioner or a private gynecologist. Therefore, some women in the control group will have undiagnosed PCOS, which will lead to underestimation of morbidity and medicine use in PCOS. This study was not a cross sectional study on the prevalence of PCOS, but included patients diagnosed over a number of years. Therefore, there may be

an influence of temporal trends in obesity and in the diagnostic effort and treatment patterns for other conditions, both in the PCOS patients and in control subjects. Patients with isolated hirsutism were included in both PCOS populations as the majority of patients with clinical and/or biochemical hyperandrogenism are diagnosed with PCOS and hyperandrogenism may be closely linked to metabolic disturbances in PCOS (21, 22, 23). Patients were included from 1994 and onwards, whereas the Rotterdam criteria were introduced in 2003 (1). Especially, the criteria for PCO varied before 2003 and different criteria for PCOS may have been used by endocrinologists and gynecologists (1, 51). Furthermore, the definition of PCOS in adolescents is debated (52). The register-based design did not allow us to test the hypothesis that different definitions of PCOS affected study outcomes. We excluded patients and controls with a history of relevant endocrine conditions (1); however, the findings of the present study need to be confirmed in other study populations. Our cohort (PCOS OUH) differed from PCOS Denmark in terms of age, comorbidity, and prescription history. However, these differences were small and therefore unlikely to be a major source of bias in our findings. It is important to be aware that national registers, from which the PCOS Denmark cohort was drawn, do not contain information on BMI or on serum biochemistry. Hence, we are unable to determine if the higher prevalence of cardiometabolic disorders found in the PCOS cohort can be attributed to higher BMI alone or not. This does not detract from the finding that PCOS patients should be carefully screened for these diseases. Further, we were able to demonstrate that the PCOS Denmark cohort, though selected by ICD10 diagnosis codes alone, is reassuringly similar on key characteristics to our carefully clinically and biochemically evaluated PCOS OUH cohort. This is an important step forward as the validity of ICD10 coding for hirsutism in Denmark was previously not known.

In conclusion, morbidity and medicine use was significantly increased in a Danish population with PCOS. Our data confirm that medical diseases are often occurring also in young patients with PCOS. In this study, we found no association between the presence of individual Rotterdam criteria and cardiometabolic diagnoses in a well characterized group of patients with PCOS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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