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Original Research

Polycystic ovary syndrome presents as a multimorbid condition by age 50: birth cohort linkage to national register data

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Abstract

Objective: This population-based follow-up study investigated register-based disease diagnoses and medication use up till age of 50 years among women with polycystic ovary syndrome (PCOS) that were identified from a population-based birth cohort.

Design: Population-based longitudinal cohort study.

Patients: Women reporting oligo/amenorrhea and hirsutism at age 31 and/or who were diagnosed with PCOS by a physician by age 46 ($n = 244$) and women without PCOS symptoms or diagnosis ($n = 1556$) in the Northern Finland Birth Cohort 1966.

Main Outcome Measures: National register data on diagnosed diseases (International Statistical Classification of Diseases [ICD]-8-10) and medication use (Anatomical Therapeutic Chemical) until the age of 50.

Results: Women with PCOS had a 26% higher risk for any registered diagnosis (risk ratio [RR]: 1.26 [1.09-1.46]) and a 24% higher risk for medication use (RR: 1.24 [1.05-1.46]) compared with non-PCOS women, even after adjusting for several confounders. Several main ICD categories were more prevalent among women with PCOS versus non-PCOS controls, eg, endocrine, metabolic, nervous system, musculoskeletal, and genitourinary diseases in addition with different symptoms and injuries. Surprisingly, even though the overall morbidity was only increased in women with PCOS with a body mass index (BMI) ≥ 25 kg/m^2, there were several ICD main categories that showed higher comorbidity risk especially in women with PCOS with a BMI < 25 kg/m^2. Several medications were prescribed more often to women with PCOS versus non-PCOS controls, eg, medications related to the alimentary tract and metabolism, the cardiovascular system, genitourinary system drugs and sex hormones, dermatologic and hormonal preparations, and medications to treat the musculoskeletal, nervous, and respiratory systems.

Conclusion: Women with PCOS are burdened with multimorbidity and higher medication use, independent of BMI and other confounders. Accordingly, preventive strategies are needed to alleviate the disease burden and improve the health outcomes of women with PCOS.

Keywords: PCOS, comorbidity, medication use, longitudinal cohort study

Significance

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women, with a broad effect on the health of the affected women. In this general population-based study, we report register-based disease diagnoses and medication use up to the age of 50 years among women with PCOS and controls. Women with PCOS had a 26% higher risk for any registered diagnosis and a 24% higher risk for medication use compared with non-PCOS controls. Several disease and medication categories were more prevalent among women with PCOS. Surprisingly, also lean women with PCOS had a higher risk for several disease categories. Acknowledging PCOS-related multimorbidity, preventive strategies are needed to alleviate the disease burden and to improve the health outcomes of women with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, presenting with a broad health impact.[1] Initially, PCOS was considered merely a reproductive condition, one causing irregular cycles and anovulatory infertility. Today, it is known that this complex syndrome affects almost all organ systems and translates to a wide range of comorbidities.[2-5] Obesity is a core feature of PCOS, as most women with PCOS are overweight or obese,[6,7] and the weight starts to accumulate already at childhood.[8] Moreover, women with PCOS are at risk of insulin resistance, type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), nonalcoholic fatty liver disease, and cardiovascular diseases.[6,9-13] In addition, affected women are at increased risk of various psychiatric conditions, such as depression, anxiety, psychosis, and eating disorders.[14-17] Furthermore, a range of other comorbidities have been reported among these women, including asthma, migraine, thyroid diseases, and endometrial cancer.[4,5,18-21] This health burden translates to poor self-rated health, impaired quality of life, and decreased work ability among the affected women.[5,22]

Only a few prior studies have systematically screened for overall comorbidity and medication use among women with PCOS, especially in a population-based study setting. Moreover, one inclusive review indicated that studies of morbidity in women with PCOS at over 40 years of age are lacking, as most of these studies focused on the assessment of fertile-aged women.[23] For this reason, the present study focused on assessing overall comorbidity and medication use among women with PCOS and non-PCOS controls until the age of 50 years. The study population is part of the unique population-based Northern Finland Birth Cohort 1966 (NFBC1966) with data linkage to national registers. In our previous work, we studied selected self-reported comorbidities and symptoms of the same female population,[5] showing a high comorbidity rate in PCOS. Here, we extend our previous work and knowledge on comorbidities by focusing on all hospital-based registered diagnosis (International Statistical Classification of Diseases [ICD-10]) codes and medication purchase registers[24,25] among women with PCOS and non-PCOS controls. Given the unique nature of this birth cohort, we were also able to control for several confounding factors.

Materials and methods

Study population

The study population originated from the longitudinal NFBC1966, including all pregnancies with a predicted birth during 1966 in the 2 northernmost provinces of Finland ($n = 12\,058$, 5889 females, 96.3% of all births).[26] The data collection process and the identification of the PCOS group in the NFBC1966 have been previously described.[6,8,15,24,25] A flow chart of the data collection process and study population is presented in Figure S1. In brief, women with PCOS were identified from the cohort population using questionnaires at ages 31 and 46. For women aged 31, questions were asked about PCOS-related symptoms: oligo/amenorrhea (OA) and hirsutism (HA). Both symptoms were reported by 125 women (6.8%, National Institutes of Health criteria) who were considered as PCOS cases. Women aged 46 were asked whether they had ever been diagnosed with polycystic ovaries (PCOM) and/or PCOS, with 181 of these women answering yes (10.0% of the population). The final PCOS population (*N*: 244, 13.4% of the population) consisted of women who reported both HA and OA at age 31 and/or PCOM/PCOS at age 46. The non-PCOS control population included all remaining women who did not report PCOS symptoms at age 31 nor a PCOS diagnosis by age 46 ($n = 1573$). Due to possible bias toward OA, women who were pregnant or using hormonal contraceptives at age 31 ($n = 1488$) were excluded from all analyses. Moreover, women who did not consent to register linkage were also excluded (PCOS $n = 36$; controls $n = 17$). The validity of identifying women with PCOS in the NFBC1966 data has been confirmed in previous publications.[6,8,27] The ethical committee of the Northern Ostrobothnia Hospital District approved the study (EETTMK 94/2011). All participants from the NFBC1966 gave informed consent to the use of their collected data for scientific purposes. The NFBC1966 study was conducted in accordance with the Helsinki Declaration.

Confounding factors

All confounding variables were evaluated for their potential role in morbidity (Table 1). The detailed description of the measurement of body mass index (BMI) has been previously described.[6] Body mass index was categorized into 3 groups: <25, 25-30, and ≥30 kg/m^2. Physical activity was calculated as the metabolic equivalent of task (MET) scores in hours per week from the frequency and duration of leisure time activities (3 METs = light and 5 METs = brisk physical activity).[28] Alcohol consumption was categorized into 3 groups: abstainer, low-risk drinker (≤20 g/day), or high-risk drinker (>20 g/day).[29,30] Smoking was categorized as nonsmoker, former/occasional smoker, or active smoker. Marital status was categorized into 2 groups: single or in a relationship (cohabitation without a registered relationship was included in this group). Socioeconomic status was classified into three categories based on education level: basic, secondary, and tertiary. Serum testosterone (T) and sex hormone-binding globulin (SHBG) were assayed at age 46, as previously described.[15] Testosterone levels were assayed using Agilent triple quadrupole 6410 LC/MS equipment with an electrospray ionization source operating in positive-ion mode (Agilent Technologies). At age 46, SHBG was assayed using fluoroimmunoassay (Wallac, Inc. Ltd., Turku, Finland). Free androgen index (FAI) was calculated as follows: 100 × T (nmol/L)/SHBG (nmol/L).

Comorbidity assessment using diagnosis code data linkage

The Finnish Care Register for Health Care (CRHC, established in 1967) covers all public hospital discharges in Finland and systematically accumulates data on all patient encounters. In this register, 1 main diagnosis and 2 other diagnoses are recorded for each patient according to ICD codes determined by the physician responsible for discharging the patient from the hospital. These codes are chosen based on their clinical relevance to the hospital visit. Consequently, diagnoses are considered to be accurate and trustworthy and, moreover, are part of the national registers, which are widely used to guide both national healthcare policies and research.[31]

The NFBC1966 cohort population was linked to the national CRHC register with personal identification codes (unique to each Finnish citizen) if the participants were granted permission to do so. Furthermore, data from 1968 to 2016 were collected. The ICD codes were divided into main classes and subclasses according to the WHO classification. Certain subsets of ICD codes were selected for further analysis based on

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Table 1. Population characteristics.

Character	Controls ($n = 1308$-1569)	PCOS ($n = 205$-280)	*P*-value
BMI[a] (kg/m^2)			<.001[b]
Normal weight (<25) *n* (%)	775 (50.2%)	92 (38.7%)	
Overweight (25-30) *n* (%)	470 (30.4%)	74 (31.1%)	
Obese (≥30) *n* (%)	299 (19.4%)	72 (30.3%)	
Testosterone (nmol/L)	0.83 [0.63; 1.05]	0.89 [0.68; 1.11]	.017[c]
SHBG[d] (nmol/L)	53.30 [37.68; 73.65]	49.15 [34.10; 66.00]	.003[c]
FAI[e]	1.53 [1.07; 2.17]	1.82 [1.38; 2.60]	<.001[c]
Physical activity	1565	241	.405[b]
Low	337 (21.5%)	55 (22.8%)	
Moderate	645 (41.2%)	107 (44.4%)	
High	583 (37.3%)	79 (32.8%)	
Alcohol consumption			0.397[b]
Abstinence *n* (%)	192 (12.3%)	37 (15.4%)	
Low-risk drinking *n* (%)	1248 (79.8%)	184 (76.3%)	
High-risk drinking *n* (%)	124 (7.9%)	20 (8.3%)	
Smoking			.524[b]
No smoking *n* (%)	886 (56.9%)	130 (55.1%)	
Former/occasional smoking *n* (%)	346 (22.2%)	49 (20.8%)	
Current smoking *n* (%)	325 (20.9%)	57 (24.2%)	
Marital status			.027[b]
In a relationship *n* (%)	1215 (77.7%)	234 (83.6%)	
Single *n* (%)	351 (22.3%)	46 (16.4%)	
Education			.189[b]
Basic	86 (5.5%)	19 (7.9%)	
Secondary	998 (63.5%)	157 (65.1%)	
Tertiary	489 (31.1%)	65 (27.0%)	

Clinical features in women with PCOS, and the controls at age 46. Data presented as medians [quartiles] and percentages. The number of women varies between the analyses; some of the women who completed the questionnaire did not attend the clinical examination.
Abbreviations: BMI, body mass index; FAI, free androgen index; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin.
[a]Body mass index.
[b]Pearson's χ^2 test.
[c]Mann–Whitney *U* test.
[d]Sex hormone-binding globulin.
[e]Free androgen index.

the literature and the results of the main class analysis. The ICD-8 and ICD-9 codes were converted into corresponding ICD-10 codes and included in the analysis. The analyzed ICD codes are shown in Table 2.

Medication use assessment using pharmacological data linkage

Medication use was assessed by linking the cohort data with the Finnish Prescription register and with personal identification codes if granted permission by the participants. The Finnish Prescription register is held by the Social Insurance Institution of Finland. The collected data consisted of all drug purchases from 1998 to 2016 prescribed by physicians. Drugs were identified according to the Anatomical Therapeutic Chemical (ATC) classification system, which classifies drugs where drugs according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. Anatomical Therapeutic Chemical codes were divided into main classes and subclasses according to the ATC classification system. Certain subsets of ATC codes were selected for further analysis based on the literature and the results of the main class analysis. The analyzed ATC medication classes are shown in Table 3.

Risk for diseases and medication use

The risk for diseases and medication use was calculated based on the sum score of the ICD diagnosis and main medication categories.

Statistical methods

Statistical analyses were performed with IBM-SPSS Statistics version 24 and R version 4.0.3 for Windows software. Figures were created using GraphPad Prism (version 7.03) software. A value of $P < .05$ was considered statistically significant. Differences in the categorical variables among the study groups (PCOS and controls) were analyzed using the Pearson's χ^2 test. The continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. The independent samples *t*-test or the Mann–Whitney *U* test was utilized to analyze the differences in continuous variables between the study groups. The data were described as frequencies and medians with 25% and 75% quartiles. The association between PCOS and overall morbidity as well as the use of medication has been calculated with Poisson regression models. The association between ICD diagnosis codes and medication use among women with PCOS versus controls was analyzed with binary logistic regression models. The adjusted logistic regression models were generated by including the following variables into the models: BMI, FAI, physical activity, alcohol consumption, smoking, marital status, and education. Benjamini–Hochberg correction has calculated for *P*-values to check if the results might be due to chance.

Results

Study population

Characteristics of the study population are presented in Table 1.

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Table 2. International Statistical Classification of Diseases diagnoses among women with PCOS and among controls.

Diagnose		Controls $n = 1556$ (%)	PCOS $n = 244$ (%)	OR (95% CI)	aOR (95% CI)
A00-B99	Certain infectious and parasitic diseases	287 (18.6%)	45 (18.4%)	0.99 (0.70-1.41)	0.89 (0.59-1.34)
C00-D48	Neoplasms	446 (28.8%)	84 (34.4%)	1.30 (0.97-1.73)	1.28 (0.93-1.77)
D10-D36	Benign neoplasms	348 (22.4%)	68 (27.9%)	1.34 (0.99-1.82)	1.28 (0.91-1.79)
D21	Other benign neoplasms of connective and other soft tissue	13 (0.8%)	6 (2.5%)	**2.99 (1.13-7.95)**	**4.03 (1.47-11.03)***
D27	Benign neoplasm of ovary	23 (1.5%)	9 (3.7%)	**2.55 (1.17-5.58)**	**2.49 (1.08-5.77)**
D35	Benign neoplasm of other and unspecified endocrine glands	7 (0.4%)	4 (1.6%)	**3.69 (1.07-12.69)**	**3.66 (1.03-12.96)**
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	123 (8.0%)	17 (7.0%)	0.87 (0.51-1.47)	0.86 (0.47-1.57)
E00-E90	Endocrine, nutritional, and metabolic diseases	154 (10.0%)	67 (27.5%)	**3.42 (2.47-4.75)***	**3.16 (2.15-4.63)***
E00-F07	Disorders of thyroid gland	69 (4.4%)	23 (9.4%)	**2.24 (1.37-3.67)***	**2.18 (1.26-3.78)***
E03	Other hypothyroidism	20 (1.3%)	9 (3.7%)	**2.94 (1.32-6.54)***	2.34 (0.90-6.08)
E04	Other nontoxic goiter	28 (1.8%)	12 (4.9%)	**2.82 (1.42-5.63)***	**3.01 (1.44-6.31)***
E10-E14	Diabetes mellitus	17 (1.1%)	8 (3.3%)	**3.07 (1.31-7.19)***	1.80 (0.55-5.92)
E10	Type 1 diabetes mellitus	6 (0.4%)	2 (0.8%)	2.14 (0.43-10.64)	1.16 (0.12-10.82)
E11	Type 2 diabetes mellitus	12 (0.8%)	7 (2.9%)	**3.80 (1.48-9.75)***	1.96 (0.50-7.71)
E20-E35	Disorders of other endocrine glands	21 (1.3%)	34 (13.9%)	**11.83 (6.74-20.78)***	**9.92 (5.11-19.27)***
E28	Ovarian dysfunction	6 (0.4%)	27 (11.1%)	**32.14 (13.12-78.74)***	**22.84 (8.20-63.63)***
E28.2	Polycystic ovarian syndrome	3 (0.2%)	25 (10.2%)	**59.09 (17.69-197.36)***	**36.18 (10.28-127.37)***
E65-E68	Obesity and other hyperalimentation	28 (1.8%)	12 (4.9%)	**2.82 (1.42-5.63)***	1.86 (0.77-4.48)
E66	Obesity	27 (1.7%)	12 (4.9%)	**2.93 (1.46-5.86)***	**2.34 (1.01-5.40)**
F00-F99	Mental and behavioral disorders	186 (12.0%)	38 (15.6%)	1.35 (0.93-1.97)	1.30 (0.84-2.02)
G00-G99	Diseases of the nervous system	368 (23.7%)	82 (33.6%)	**1.63 (1.22-2.18)***	**1.71 (1.23-2.36)***
G40-G47	Episodic and paroxysmal disorders	196 (12.6%)	45 (18.4%)	**1.57 (1.10-2.24)***	**1.67 (1.13-2.48)***
G40	Epilepsy	35 (2.2%)	7 (2.9%)	1.28 (0.56-2.92)	1.21 (0.47-3.12)
G43	Migraine	79 (5.1%)	19 (7.8%)	1.58 (0.94-2.66)	1.68 (0.95-2.96)
G44	Other headache syndromes	66 (4.2%)	16 (6.6%)	1.58 (0.90-2.78)	1.66 (0.91-3.03)
G45	Transient cerebral ischemic attacks and related syndromes	19 (1.2%)	8 (3.3%)	**2.74 (1.19-6.34)***	**3.78 (1.50-9.57)***
G50-G59	Nerve, nerve root, and plexus disorders	166 (10.7%)	42 (17.2%)	**1.74 (1.20-2.52)***	**1.66 (1.08-2.53)**
G60-G64	Polyneuropathies and other disorders of the peripheral nervous system	2 (0.1%)	3 (1.2%)	**9.67 (1.61-58.18)***	**8.44 (1.38-52.18)**
G90-G99	Other disorders of the nervous system	26 (1.7%)	9 (3.7%)	**2.25 (1.04-4.87)**	**3.14 (1.32-7.47)***
H00-H59	Diseases of the eye	250 (16.1%)	47 (19.3%)	1.25 (0.88-1.76)	1.35 (0.93-1.98)
H60-H95	Diseases of the ear	162 (10.4%)	27 (11.1%)	1.07 (0.70-1.65)	1.11 (0.69-1.79)
I00-I99	Diseases of the circulatory system	392 (25.3%)	75 (30.7%)	1.31 (0.97-1.76)	1.30 (0.93-1.81)
I10-I15	Hypertensive diseases	79 (5.1%)	20 (8.2%)	1.67 (1.00-2.78)	1.28 (0.69-2.36)
I10	Essential (primary) hypertension	75 (4.8%)	19 (7.8%)	1.67 (0.99-2.81)	1.41 (0.81-2.46)
I20-I25	Ischemic heart diseases	13 (0.8%)	6 (2.5%)	**2.99 (1.13-7.95)**	2.87 (0.94-8.78)
I80	Phlebitis and thrombophlebitis	26 (1.7%)	9 (3.7%)	**2.25 (1.04-4.87)**	2.04 (0.85-4.86)
J00-J99	Diseases of the respiratory system	610 (39.4%)	108 (44.3%)	1.22 (0.93-1.60)	1.19 (0.87-1.61)
J20-J22	Other acute lower respiratory infections	26 (1.7%)	9 (3.7%)	**2.25 (1.04-4.87)**	2.19 (0.89-5.35)
J20	Acute bronchitis	23 (1.5%)	9 (3.7%)	**2.55 (1.17-5.58)**	**2.39 (1.03-5.51)**
J40-J47	Chronic lower respiratory diseases	118 (7.6%)	24 (9.8%)	1.33 (0.84-2.11)	1.14 (0.67-1.95)
J45	Asthma	107 (6.9%)	21 (8.6%)	1.28 (0.78-2.08)	1.19 (0.72-1.97)
J46	Status asthmaticus	3 (0.2%)	3 (1.2%)	**6.44 (1.29-32.11)**	**6.60 (1.26-34.65)**
K00-K93	Diseases of the digestive system	594 (38.4%)	115 (47.1%)	**1.43 (1.09-1.88)***	1.32 (0.97-1.79)
K40-K46	Hernia	85 (5.5%)	20 (8.2%)	1.55 (0.93-2.57)	1.41 (0.80-2.50)
K42	Umbilical hernia	11 (0.7%)	6 (2.5%)	**3.54 (1.30-9.66)***	2.78 (0.94-8.23)
K44	Diaphragmatic hernia	24 (1.5%)	9 (3.7%)	**2.45 (1.12-5.32)**	2.38 (0.98-5.76)
K55-K64	Other diseases of intestines	146 (9.4%)	28 (11.5%)	1.25 (0.82-1.92)	1.39 (0.86-2.23)
K58	Irritable bowel syndrome	36 (2.3%)	5 (2.0%)	0.88 (0.34-2.27)	1.27 (0.48-3.38)
K60	Fissure and fistula of anal and rectal regions	24 (1.5%)	9 (3.7%)	**2.45 (1.12-5.32)**	2.31 (1.00-5.34)
K80-K87	Disorders of gallbladder, biliary tract and pancreas	110 (7.1%)	28 (11.5%)	**1.70 (1.10-2.64)***	1.55 (0.95-2.54)
K80	Cholelithiasis	102 (6.6%)	26 (10.7%)	**1.70 (1.08-2.68)***	1.48 (0.92-2.39)
L00-L99	Diseases of the skin and subcutaneous tissue	270 (17.5%)	56 (23.0%)	**1.41 (1.02-1.95)**	**1.47 (1.02-2.12)**
L10-L14	Bullous disorders	1 (0.1%)	3 (1.2%)	**19.35 (2.01-186.85)***	**23.69 (2.41-233.11)***
L60-L75	Disorders of skin appendages	37 (2.4%)	22 (9.0%)	**4.07 (2.36-7.02)***	**4.34 (2.34-8.07)***
L68	Hypertrichosis	2 (0.1%)	8 (3.3%)	**26.34 (5.56-124.78)***	**28.96 (3.13-268.14)***
L68.0	Hirsutism	2 (0.1%)	9 (3.7%)	**29.76 (6.39-138.57)***	**35.40 (4.02-311.47)***
M00-M99	Diseases of the musculoskeletal system and connective tissue	664 (42.9%)	128 (52.5%)	**1.47 (1.12-1.92)***	**1.51 (1.11-2.05)***
M00-M25	Arthropathies	339 (21.8%)	75 (30.7%)	**1.59 (1.18-2.15)***	**1.50 (1.08-2.09)***
M15	Polyarthrosis	4 (0.3%)	3 (1.2%)	**4.83 (1.07-21.71)**	4.08 (0.88-19.06)

(*continued*)

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Table 2. Continued

Diagnose		Controls $n = 1556$ (%)	PCOS $n = 244$ (%)	OR (95% CI)	aOR (95% CI)
M17	Gonarthrosis [arthrosis of knee]	53 (3.4%)	13 (5.3%)	1.60 (0.86-2.97)	1.43 (0.74-2.76)
M22	Disorders of patella	26 (1.7%)	10 (4.1%)	**2.52 (1.20-5.28)***	**2.92 (1.29-6.62)***
M23	Internal derangement of knee	73 (4.7%)	20 (8.2%)	**1.81 (1.09-3.03)***	1.57 (0.87-2.83)
M25	Other joint disorders, not elsewhere classified	97 (6.2%)	29 (11.9%)	**2.03 (1.31-3.15)***	**2.06 (1.25-3.38)***
M40-M54	Dorsopathies	311 (20.0%)	63 (25.8%)	**1.39 (1.02-1.90)**	**1.56 (1.11-2.20)***
M54	Dorsalgia	155 (10.0%)	38 (15.6%)	**1.67 (1.14-2.45)***	**1.86 (1.22-2.83)***
M60-M79	Soft tissue disorders	266 (17.1%)	63 (25.4%)	**1.65 (1.20-2.27)***	**1.49 (1.04-2.14)**
M72	Fibroblastic disorders	10 (0.6%)	6 (2.5%)	**3.90 (1.40-10.82)***	**3.91 (1.27-12.05)***
M75	Shoulder lesions	77 (4.9%)	24 (9.8%)	**2.10 (1.30-3.39)***	**1.98 (1.15-3.42)***
M79	Other soft tissue disorders, not elsewhere classified	98 (6.3%)	28 (11.5%)	**1.93 (1.24-3.01)***	**1.86 (1.12-3.09)***
M79.0	Rheumatism, unspecified	14 (0.9%)	9 (3.7%)	**4.22 (1.81-9.86)***	**5.14 (2.03-12.98)***
M79.6	Pain in limb	52 (3.3%)	16 (6.6%)	**2.03 (1.14-3.62)***	1.93 (0.99-3.76)
M95-M99	Other disorders of the musculoskeletal system and connective tissue	33 (2.1%)	10 (4.1%)	1.97 (0.96-4.06)	**2.40 (1.10-5.24)**
N00-N99	Diseases of the genitourinary system	813 (51.7%)	179 (63.9%)	**1.66 (1.27-2.16)***	**2.26 (1.62-3.15)***
N30-N39	Other diseases of urinary system	116 (7.5%)	28 (11.5%)	**1.61 (1.04-2.49)***	**1.73 (1.08-2.78)***
N32	Other disorders of bladder	9 (0.6%)	5 (2.0%)	**3.60 (1.20-10.82)***	**4.23 (1.28-12.90)***
N35	Urethral stricture	7 (0.4%)	5 (2.0%)	**4.63 (1.46-14.70)***	**7.37 (1.88-28.89)***
N60-N64	Disorders of breast	105 (6.7%)	26 (10.7%)	**1.65 (1.05-2.59)***	**1.77 (1.08-2.89)***
N62	Hypertrophy of breast	33 (2.1%)	11 (4.5%)	**2.18 (1.09-4.37)***	**2.48 (1.19-5.14)***
N80-N98	Noninflammatory disorders of female genital tract	625 (40.2%)	143 (58.6%)	**2.11 (1.60-2.77)***	**2.22 (1.63-3.03)***
N80.0	Endometriosis of uterus (adenomyosis)	22 (1.4%)	9 (3.7%)	**2.67 (1.22-5.87)***	**3.85 (1.57-9.46)***
N83	Noninflammatory disorders of ovary, fallopian tube, and broad ligament	154 (9.9%)	45 (18.4%)	**2.06 (1.43-2.96)***	**2.17 (1.46-3.23)***
N92.0	Excessive and frequent menstruation with regular cycle	144 (9.3%)	38 (15.6%)	**1.81 (1.23-2.66)***	**1.91 (1.25-1.87)***
N97.0	Female infertility associated with anovulation	12 (0.8%)	20 (8.2%)	**11.49 (5.54-23.82)***	**10.89 (4.82-24.62)***
O00-O99	Pregnancy, childbirth, and the puerperium	1389 (88.3%)	235 (83.9%)	0.69 (0.47-0.99)	1.56 (0.88-2.77)
P00-P96	Certain conditions originating in the perinatal period	65 (4.1%)	16 (5.7%)	1.41 (0.80-2.47)	1.67 (0.88-3.15)
Q00-Q99	Congenital malformations, deformations, and chromosomal abnormalities	133 (8.5%)	23 (8.2%)	0.97 (0.61-1.54)	1.15 (0.68-1.95)
R00-R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	804 (52.0%)	152 (62.3%)	**1.53 (1.16-2.02)***	**1.60 (1.17-2.20)***
R00-R09	Symptoms and signs involving the circulatory and respiratory systems	276 (17.7%)	62 (25.4%)	**1.58 (1.15-2.17)***	**1.52 (1.07-2.17)***
R07	Pain in throat and chest	57 (3.7%)	19 (7.8%)	**2.22 (1.30-3.80)***	**2.09 (1.13-3.87)**
R10-R19	Symptoms and signs involving the digestive system and abdomen	369 (23.7%)	84 (34.4%)	**1.69 (1.27-2.25)***	**1.85 (1.34-2.55)***
R10	Abdominal and pelvic pain	342 (22.0%)	77 (31.6%)	**1.64 (1.22-2.20)***	**1.74 (1.25-2.42)***
R13	Dysphagia	15 (1.0%)	7 (2.9%)	**3.03 (1.22-7.52)***	**3.77 (1.46-9.73)***
S00-T98	Injury, poisoning, and certain other consequence of external causes	586 (37.9%)	113 (46.3%)	**1.42 (1.08-1.86)***	**1.56 (1.14-2.12)***
S20-S29	Injuries to the thorax	11 (0.7%)	6 (2.5%)	**3.54 (1.30-9.66)***	**5.92 (1.77-19.86)***
S90-S99	Injuries to the ankle and foot	64 (4.1%)	17 (7.0%)	**1.75 (1.01-3.03)**	1.36 (0.67-2.77)
T80-T88	Complications of surgical and medical care, not elsewhere classified	111 (7.1%)	30 (12.3%)	**1.83 (1.19-2.80)***	1.62 (0.98-2.66)

Confounding factors: BMI, alcohol, smoking, physical activity, marital status, education, FAI. The results are reported as unadjusted ORs and aORs (BMI, FAI, physical activity, alcohol consumption, smoking, marital status, and education) with 95% CIs. The values in **bold** were statistically significant after adjustments and with * after Benjamini–Hochberg correction.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; FAI, free androgen index; OR, odds ratio; PCOS, polycystic ovary syndrome.

Risk for diseases

Only 10% of the PCOS cases had ICD code for PCOS in their register. Women with PCOS had a 26% higher risk of having any ICD diagnosis (risk ratio [RR]: 1.26 [1.09-1.46]) compared with non-PCOS controls, even after adjusting for confounding factors (RR: 1.27 [1.07-1.50]) (Figure 1A).

The ICD main classes

The ICD main classes were analyzed among the PCOS population and the controls at two different levels: first, the differences between the PCOS and control populations (Figure 1B); second, by BMI group—BMI < 25 and ≥25 (Table S1).

The following ICD-10 main classes were more prevalent among women with PCOS versus controls: "endocrine, nutritional, and metabolic diseases"; "diseases of the nervous system"; "diseases of the digestive system"; "diseases of the musculoskeletal system and connective tissue"; "diseases of the genitourinary system"; "symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified"; and "injury, poisoning, and certain other consequences of external causes." After adjusting for confounding factors (BMI, FAI, physical activity, alcohol consumption, smoking, marital status, and education), the main class "diseases of the digestive system" (due to FAI adjustment) was no longer significant, but the association with the rest of the main classes remained significant (Table 2).

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Table 3. Medication use (ATC classes) among women with PCOS and among controls.

Medication		Controls $n = 1\,556$ (%)	PCOS $n = 244$ (%)	OR (95% CI)	aOR (95% CI)
A	Alimentary tract and metabolism	929 (59.7%)	182 (74.6%)	**1.98 (1.46-2.69)***	**1.81 (1.28-2.54)***
A02	Drugs for acid related disorders	799 (51.3%)	148 (60.7%)	**1.46 (1.11-1.92)***	**1.45 (1.06-1.98)***
A03	Drugs for functional gastrointestinal disorders	134 (8.6%)	37 (15.2%)	**1.90 (1.28-2.81)***	**1.85 (1.19-2.89)***
A03F	Propulsives	117 (7.5%)	34 (13.9%)	**1.99 (1.32-3.00)***	**1.92 (1.20-3.06)***
A10	Drugs used in diabetes	53 (3.4%)	40 (16.4%)	**5.56 (3.60-8.60)***	**4.10 (2.34-7.20)***
A10A	Insulins and analogs	16 (1.0%)	8 (3.3%)	**3.26 (1.38-7.71)***	1.17 (0.32-4.21)
A10B	Blood glucose lowering drugs, excluding insulins	43 (2.8%)	38 (15.6%)	**6.49 (4.10-10.28)***	**4.79 (2.61-8.77)***
B	Blood and blood forming organs	352 (22.6%)	64 (26.2%)	1.22 (0.89-1.66)	1.22 (0.87-1.73)
C	Cardiovascular system	671 (43.1%)	145 (59.4%)	**1.93 (1.47-2.54)***	**1.95 (1.42-2.68)***
C01	Cardiac therapy	50 (3.2%)	16 (6.6%)	**2.11 (1.18-3.78)***	1.90 (0.97-3.71)
C01D	Vasodilators used in cardiac diseases	22 (1.4%)	10 (4.1%)	**2.98 (1.39-6.37)***	1.97 (0.77-5.06)
C03	Diuretic drugs	122 (7.8%)	42 (17.2%)	**2.44 (1.67-3.58)***	**2.34 (1.49-3.70)***
C05	Vasoprotective drugs	129 (8.3%)	31 (12.7%)	**1.61 (1.06-2.45)***	**1.62 (1.03-2.56)**
C07	Beta-blocking agents	354 (22.8%)	77 (31.6%)	**1.57 (1.17-2.10)***	**1.62 (1.16-2.26)***
C09	Agents acting on the renin–angiotensin system	293 (18.8%)	69 (28.3%)	**1.70 (1.25-2.31)***	**1.57 (1.09-2.27)***
C10	Lipid-modifying agents	129 (8.3%)	31 (12.7%)	**1.61 (1.06-2.45)***	1.24 (0.74-2.08)
D	Dermatologicals	845 (54.3%)	156 (63.9%)	**1.49 (1.13-1.97)***	**1.52 (1.10-2.08)***
D10	Acne drugs	82 (5.3%)	22 (9.0%)	**1.78 (1.09-2.91)***	**1.98 (1.15-3.44)***
G	Genito urinary system and sex hormones	969 (62.3%)	190 (77.9%)	**2.13 (1.55-2.93)***	**1.94 (1.36-2.77)***
G03	Sex hormones and modulators of the genital system	744 (47.8%)	160 (65.6%)	**2.08 (1.57-2.76)***	**2.17 (1.58-2.99)***
G03D	Progestogens	315 (20.2%)	93 (38.1%)	**2.43 (1.82-3.23)***	**2.31 (1.67-3.19)***
G03G	Gonadotropins and other ovulation stimulants	91 (5.8%)	28 (11.5%)	**2.09 (1.34-3.26)***	**2.22 (1.34-3.68)***
G03H	Antiandrogens	53 (3.4%)	26 (10.7%)	**3.38 (2.07-5.52)***	**3.86 (2.18-6.84)***
H	Systemic hormonal preparations, excluding sex hormones and insulins	509 (32.7%)	100 (41.0%)	**1.43 (1.08-1.88)***	**1.51 (1.11-2.06)***
H03	Thyroid therapy	168 (10.8%)	37 (15.2%)	**1.48 (1.01-2.17)**	1.38 (0.90-2.12)
J	Anti-infective for systemic use	1519 (97.6%)	242 (99.2%)	2.95 (0.71-12.31)	2.60 (0.62-10.99)
J02	Antimycotic drugs	605 (38.9%)	119 (48.8%)	**1.50 (1.14-1.96)***	**1.48 (1.09-2.01)***
J02A	Antimycotics for systemic use	605 (38.9%)	119 (48.8%)	**1.50 (1.14-1.96)***	**1.48 (1.09-2.01)***
J02AC	Triazole derivatives	600 (38.6%)	118 (48.4%)	**1.49 (1.14-1.96)***	**1.50 (1.11-2.03)***
L	Antineoplastic and immunomodulating agents	131 (8.4%)	31 (12.7%)	**1.58 (1.04-2.40)**	**1.70 (1.07-2.70)**
L02	Endocrine therapy	75 (4.8%)	25 (10.2%)	**2.25 (1.40-3.62)***	**2.22 (1.30-3.79)***
L02A	Hormones and related agents	53 (3.4%)	20 (8.2%)	**2.53 (1.49-4.32)***	**2.11 (1.14-3.87)***
L02AE	Gonadotropin-releasing hormone analogs	49 (3.1%)	19 (7.8%)	**2.60 (1.50-4.49)***	**2.20 (1.17-4.14)***
M:	MUSCULOSKELETAL SYSTEM	1429 (91.8%)	237 (97.1%)	**3.01 (1.39-6.52)***	**4.24 (1.54-11.73)***
M01	Anti-inflammatory and antirheumatic drugs	1408 (90.5%)	234 (95.9%)	**2.46 (1.28-4.74)***	**3.27 (1.41-7.58)***
M01A	Anti-inflammatory and antirheumatic products, nonsteroids	1408 (90.5%)	234 (95.9%)	**2.46 (1.28-4.74)***	**3.27 (1.41-7.58)***
M02	Topical products for joint and muscular pain	285 (18.3%)	71 (29.1%)	**1.83 (1.35-2.48)***	**2.04 (1.45-2.85)***
M03	Muscle relaxants	886 (56.9%)	155 (63.5%)	1.32 (1.00-1.74)	**1.43 (1.04-1.97)**
N	Nervous system	1205 (77.4%)	213 (87.3%)	**2.00 (1.35-2.97)***	**1.99 (1.27-3.11)***
N02	Analgesic drugs	1040 (66.8%)	191 (78.3%)	**1.79 (1.30-2.47)***	**1.74 (1.21-2.51)***
N02A	Opioid drugs list	640 (41.1%)	122 (50.0%)	**1.43 (1.09-1.88)***	**1.53 (1.13-2.08)***
N02B	Other analgesics and antipyretics	765 (49.2%)	159 (65.2%)	**1.93 (1.46-2.56)***	**1.91 (1.38-2.64)***
N02C	Migraine medication	204 (13.1%)	46 (18.9%)	**1.54 (1.08-2.19)***	**1.56 (1.05-2.33)**
N03A	Antiepileptic drugs	223 (14.3%)	54 (22.1%)	**1.70 (1.22-2.37)***	**1.93 (1.33-2.80)***
N03AX	Other antiepileptics	184 (11.8%)	47 (19.3%)	**1.78 (1.25-2.53)***	**1.95 (1.31-2.90)***
N06	Psychoanaleptics	488 (31.4%)	99 (40.6%)	**1.49 (1.13-1.97)***	**1.52 (1.11-2.08)***
N06A	Antidepressant drugs	480 (30.8%)	99 (40.6%)	**1.53 (1.16-2.02)***	**1.56 (1.14-2.14)***
N06C	Psycholeptics and psychoanaleptics in combination	34 (2.2%)	13 (5.3%)	**2.52 (1.31-4.85)***	1.79 (0.71-4.50)
P	Antiparasitic products, insectisides, and repellents	35 (2.2%)	6 (2.5%)	1.10 (0.46-2.63)	1.43 (0.58-3.52)
R	Respiratory system	1182 (76.0%)	207 (84.8%)	**1.77 (1.22-2.56)***	**1.81 (1.20-2.73)***
R01	Nasal preparations	855 (54.9%)	159 (65.2%)	**1.53 (1.16-2.03)***	**1.52 (1.10-2.08)***
R03	Drugs for obstructive airway diseases	614 (39.5%)	121 (49.6%)	**1.51 (1.15-1.98)***	**1.41 (1.04-1.91)**
R05	Cough and cold drugs	457 (29.4%)	89 (36.5%)	**1.38 (1.04-1.83)***	**1.47 (1.06-2.02)***
S	Sensory organs	482 (31.0%)	85 (34.8%)	1.19 (0.90-1.58)	1.31 (0.95-1.80)

Confounding factors: BMI, alcohol, smoking, physical activity, marital status, education, and FAI. The results are reported as unadjusted ORs and aORs (BMI, FAI, physical activity, alcohol consumption, smoking, marital status, and education) with 95% CIs. The values in **bold** were statistically significant after adjustments and with * after Benjamini–Hochberg correction.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; FAI, free androgen index; OR, odds ratio; PCOS, polycystic ovary syndrome.

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Disease subclasses

Endocrine, nutritional, and metabolic diseases

Thyroid gland disorders were more prevalent among women with PCOS than in controls, especially hypothyroidism and other nontoxic goiter. As expected, T2DM and obesity were more common in women with PCOS. Notably, although the number of hospital-based PCOS diagnoses (E28.2) was greater among PCOS cases (odds ratio: 59.09 [17.69-197.36]), 3 PCOS diagnoses occurred among the control population. After adjusting for BMI, the odds for hypothyroidism and T2DM became nonsignificant (Table 2).

Diseases of the nervous system

Regarding diseases of the nervous system, episodic and paroxysmal disorders, such as transient cerebral ischemic attacks and related syndromes, and other diseases of the nervous system were more prevalent in women with PCOS also in the adjusted model (Table 2).

Diseases of the digestive system

The umbilical hernia was more common among women with PCOS. Moreover, disorders of the gall bladder, biliary tract, and pancreas, such as cholelithiasis, were more prevalent among the affected women. After adjusting for all confounding factors (the factor causing loss of significance is given in parentheses), the significance regarding umbilical hernia (BMI), disorders of the gallbladder, biliary tract, and pancreas (smoking), and cholelithiasis (smoking) disappeared (Table 2).

Skin diseases

Skin diseases affecting subcutaneous tissue, bullous disorders, and HA were more common in women with PCOS even after adjustments (Table 2).

Diseases of the musculoskeletal system and connective tissue

Women with PCOS presented with arthropathies more often compared with non-PCOS controls. Knee and other joint disorders were also more prevalent. Furthermore, PCOS was also associated with dorsalgia (back pain) as well as soft tissue disorders, such as fibroblastic disorders, shoulder lesions, and other soft tissue disorders, including rheumatism, and limb pain. After adjusting for the confounding factors, significance regarding internal derangements of the knee (FAI) and limb pain (FAI) was eliminated (Table 2).

Diseases of the genitourinary system

Women with PCOS had more often a diagnosis of other diseases of the urinary system, such as other disorders of the bladder and urethral stricture, than the controls. Furthermore, disorders of the breast, such as hypertrophy of the breast, were also more prevalent. Gynecological conditions, including adenomyosis, ovarian disorders, excessive menstruation, and anovulatory infertility, were all more common among women with PCOS than in controls, also after adjustments (Table 2).

Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified

Women with PCOS more often had a diagnosis of symptoms and signs involving the circulatory, respiratory, and digestive systems, such as abdominal and pelvic pain and dysphagia (difficulty in swallowing). The adjustments did not influence the significance of these findings (Table 2).

Injury, poisoning, and certain other consequences of external causes

Women with PCOS had more often a diagnosis of injuries to the thorax and complications due to surgical and medical care than the controls, although the latter was not significant after adjustments (smoking) (Table 2).

Overall morbidity and ICD categories after BMI stratification

After BMI-based division into women with a BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2, the overall risk for any diseases or medication use was significant only in the overweight/obese women with PCOS (BMI < 25 kg/m^2: RR: 1.11 [0.91-1.36]; BMI ≥ 25 kg/m^2: RR: 1.42 [1.21-1.66] (Figure 1C).

The ICD main categories that showed higher comorbidity in women with PCOS with BMI ≥ 25 kg/m^2 were "endocrine, nutritional, and metabolic diseases" and "diseases of the genitourinary system." There were surprisingly many ICD categories that were more prevalent among women with PCOS with a BMI < 25 kg/m^2 compared with controls with the same BMI: "neoplasms"; "endocrine, nutritional, and metabolic diseases"; "mental and behavioral disorders"; "diseases of the nervous system"; "diseases of the genitourinary system"; "pregnancy, childbirth, and puerperium"; "symptoms, signs, and abnormal clinical and laboratory findings"; and "injury, poisoning, and certain other consequences of external causes." After adjusting for multiple testing, the categories of "neoplasms"; "endocrine, nutrition, and metabolic diseases"; "diseases of the nervous system"; "diseases of the genitourinary system"; and "injury, poisoning, and certain other consequences of external causes" remained significant (Table S1).

Risk for medication use

In line with the higher disease risk in women with PCOS, the risk for medication use was 24% higher among affected women (RR: 1.24 [1.05-1.46]), and this risk remained as high after adjustments (RR: 1.22 [1.03-1.44]; Figure 1A). In BMI stratified analysis, the overall medication use risk was only observed in women with PCOS with BMI ≥ 25 kg/m^2 (BMI < 25 kg/m^2: RR: 0.96 [0.72-1.27]; BMI ≥ 25 kg/m^2: RR: 1.39 [1.13-1.73] (Figure 1C).

ATC main classes for medication use

The following ATC main medication classes were more often used among women with PCOS: "alimentary tract and metabolism"; "cardiovascular system"; "dermatologicals"; "genitourinary system and sex hormones"; "systemic hormonal preparations, excluding sex hormones, and insulins"; "musculoskeletal system"; "nervous system"; and "respiratory system" (Table 3).

ATC subclasses

Alimentary tract and metabolism

Medications categorized in the alimentary tract and metabolism main class were more often used among women with PCOS—ie, drugs used for acid-related disorders and drugs for functional gastrointestinal disorders, such as propulsives. Furthermore, drugs used in diabetes, such as insulins and

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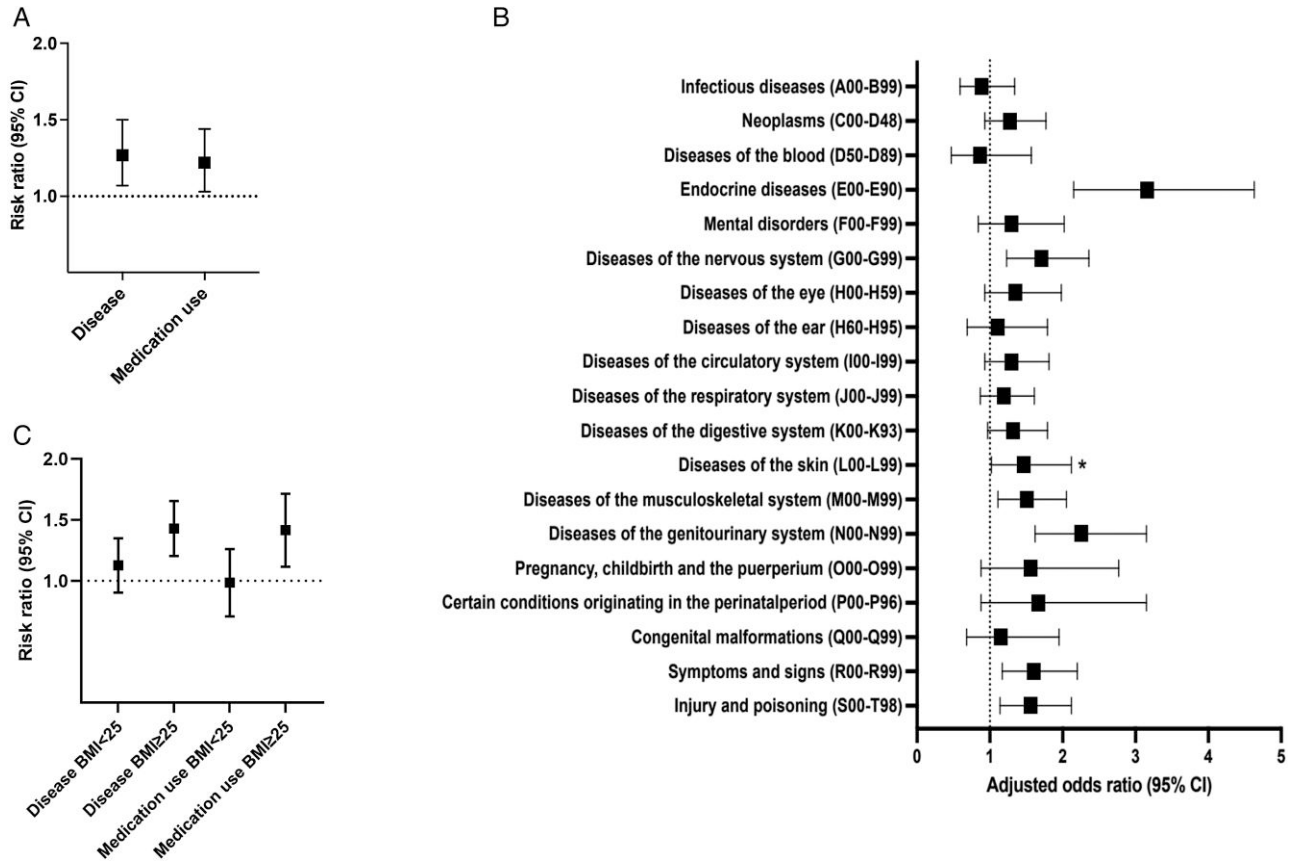


Figure 1. Morbidity and medication use related to PCOS. (A) Association between PCOS and overall morbidity and use of medication. (B) Association between PCOS and ICD codes from the Care Register for Health Care. The results are reported as adjusted (BMI, FAI, physical activity, alcohol consumption, smoking, marital status, and education) RRs and ORs with 95% CIs. All *P*-values were also corrected for multiple testing error with Benjamini–Hochberg. *The significance was lost after Benjamini–Hochberg correction. (C) Association between PCOS and overall morbidity and use of medication in BMI < 25 and ≥25 classes. BMI, body mass index; CI, confidence interval; FAI, free androgen index; HA, hirsutism; ICD, International Statistical Classification of Diseases; OA, oligo/amenorrhea; OR, odds ratio; PCOS, polycystic ovary syndrome; RR, risk ratio.

analogs and blood glucose-lowering drugs, excluding insulins, were more prevalent in women with PCOS compared with controls. Adjustments did not influence the significance of these findings, except for insulin use (BMI) (Table 3).

Cardiovascular system

Medications for cardiac therapy, such as vasodilators, diuretic drugs, vasoprotective drugs, beta-blocking agents, agents acting on the renin–angiotensin system, and lipid-modifying agents, were more commonly used in the PCOS group compared with the control group. After adjusting for BMI, vasodilators and lipid-modifying agents were no longer significant (Table 3).

Genitourinary system and sex hormones

Sex hormones and medications related to the reproductive system, such as progestogens, gonadotropins and other ovulation stimulants, and antiandrogens, were more often used among women with PCOS than in controls as were endocrine therapy drugs, such as hormones and related agents, and gonadotropin-releasing hormone analogs were more commonly used among women with PCOS. The adjustments did not influence the significance of these results (Table 3).

Musculoskeletal system

Anti-inflammatory and antirheumatic products, nonsteroids, and topical products for joint and muscular pain were more commonly used in the PCOS group than in the control group, also after adjustments (Table 3).

Nervous system

Analgesics, such as opioid drugs, other analgesics and antipyretics, migraine medications, antiepileptic drugs, psychoanaleptics, antidepressant drugs, psycholeptics, and psychoanaleptics in combination were more often used among women with PCOS than among the controls. The significance of these results remained after adjustments for all these medications except for migraine medications and psycholeptics and psychoanaleptics in combination (Table 3).

Other drugs

Medications for acne were more often used among women with PCOS than among the controls, as were antimycotic drugs, such as triazole derivatives. Moreover, the use of nasal preparations and cough and cold drugs was more common among women with PCOS. The adjustments did not influence the significance of these findings (Table 3).

Discussion

This is the first population-based data on morbidity and medication use in PCOS linking to national registers. Based on the present study and the extant literature, it can be concluded that PCOS is a multimorbid condition.[2,4-6,15] In line with this

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conclusion, we noted a 26% higher risk for any registered diagnosis and a 24% higher risk for the use of any medication main class in the PCOS population, which supports our previous results on self-reported diseases and symptoms.[5] We found a variety of comorbidities, many of them reported here for the first time, to be more prevalent among women with PCOS compared with control women. The strongest association was between PCOS and endocrine and musculoskeletal diseases, with the latter conditions not generally considered to be linked with PCOS, as few previous studies have indicated this association.[32,33] Overall medication use among women with PCOS has been assessed in only a few studies: in our recent study, using self-reported diagnoses and symptoms[5] and in a register-based study.[4] Many of our findings confirmed the previous findings, such as increased use of hypertensive medications, antidiabetic drugs, antidepressants, and analgesics.

Interestingly, after dividing the study population into normal-weight and overweight women, normal-weight women with PCOS did not have an increased risk for overall comorbidity, in contrast to overweight/obese PCOS cases. Nevertheless, they still had an increased risk for several ICD-10 main classes compared with control women of the same weight group, in line with our self-reported comorbidity work.[5] This indicates that higher BMI is not a sole cause of comorbidities in PCOS and that we should also pay attention to other mediators when treating these women.

In the Finnish healthcare system, many common diseases, such as hypertension, diabetes, depression, obstructive sleep apnea, and asthma, are often diagnosed and treated in outpatient care, with only the most severe forms diagnosed and treated in hospitals. Since the CRHC diagnoses are hospital based, it is understandable that many milder comorbidities commonly diagnosed in outpatient care are not found in these data. However, drug purchases for drugs prescribed in outpatient care are also recorded, thus supporting the observation of an increased risk of various diseases in PCOS women. For example, diuretic drugs, beta-blocking agents, agents acting on the renin–angiotensin system, diabetic drugs and antidepressants, and drugs for obstructive airway diseases are more often used among women with PCOS. The higher use of diabetic drugs in women with PCOS can be partially accounted by metformin, as it is one of the key medications for the treatment of PCOS. Nevertheless, these findings indicate that hypertension, T2DM, depression, and asthma are more common in PCOS, in line with previous findings.[6,14-16,34-36]

For diagnosed conditions, musculoskeletal diseases, such as arthropathies, dorsalgia, rheumatism, and joint disorders, were 50% more prevalent among women with PCOS even after adjusting for BMI and other confounding factors. There is some evidence supporting this finding,[32,33] including our self-report data from the same cohort.[5] Whether this relates to altered bone formation, chronic inflammation, and altered hormonal and metabolic environment, despite obesity, remains to be investigated.[37-39] Concerning medications, topical products for joint and muscular pain were used more often among women with PCOS, in line with the ICD code data. Moreover, the use of analgesic and anti-inflammatory drugs was notably higher in the PCOS group, which is a relevant finding considering that musculoskeletal symptoms are known to be one of the main reasons for their use.[40] The data here also relate to our recent finding of increased early retirement in PCOS that was shown to be partly due to musculoskeletal symptoms.[41]

Breast disorders (eg, hypertrophy) as well as noninflammatory disorders of the ovary, fallopian tube, and broad ligament were diagnosed more often in the PCOS population. To our knowledge, these conditions are reported for the first time and may also link to more extensive fertility-related care among the affected women. It is possible that breast hypertrophy relates to PCOS-related higher adiposity, prolonged estrogen exposure due to long menstrual cycles or progesterone resistance, although serum estrogen levels are usually comparable to controls.[42] Interestingly, the study by Vanky et al.[43] noted that hyperandrogenism was not associated with breast size or success to breastfeed. Nevertheless, more studies, with mechanistic approach, are warranted. As expected, we found an increased risk of anovulatory infertility in PCOS, also well reported in the literature.[44,45] Interestingly, excessive and frequent menstruation with a regular cycle was also more common in PCOS, despite oligomenorrhea usually being considered a typical feature of the syndrome.[46] Few previous studies have linked endometriosis to PCOS,[2,47] including our self-report study,[5] confirmed by the finding of an increased risk for adenomyosis and higher use of drugs used in endometriosis among women with PCOS in this study. This finding may, however, be related to the increased likelihood of ultrasound assessments in PCOS given the anovulation, menstrual irregularities, and infertility aspects related to the syndrome.

Additionally, triazole derivatives, which are commonly used for candidiasis, were more often prescribed for women with PCOS, whereas differences in diagnoses of candidiasis were not found, likely since they are often diagnosed in outpatient care. Whether this finding could be due to disturbed glucose metabolism related to PCOS[12,48] or to differences in the vaginal microbiome of women with PCOS[49,50] needs further investigation.

Our previous finding of an increased risk for recurrent infections and common colds was strengthened in this study, as cough and cold drugs were used almost twice more often by women with PCOS.[5] Whether this lower resistance to mild diseases among women with PCOS is associated with the systemic low-grade inflammation often detected in this population,[38] the altered microbiome of women with PCOS,[51] or something else, cannot be concluded here.

According to the CRHC data, women with PCOS are more often diagnosed for the following pain-related diseases: dorsalgia, limb pain, and abdominal and pelvic pain. Moreover, as previously noted, analgesics are more commonly used among women with PCOS, thereby strengthening our findings. Additionally, a recent review revealed pain perception to be more prevalent among women with PCOS,[52] although further research is warranted to investigate the etiology linking pain and PCOS. Notably, in the clinical experience of the authors, many patients with PCOS often express abdominal pain. Whether this is associated with large-size ovaries or with some yet unknown factors remains unclear. It is noteworthy that irritable bowel syndrome has also been linked to PCOS[53] and is often associated with abdominal pain,[54] although, in our data, prevalence was not increased among women with PCOS. However, drugs for functional gastrointestinal disorders were used nearly twice as often among women with PCOS. All in all, the etiology behind the association between pain and PCOS requires further research.

Of interest are the differences in diagnoses between the different BMI classes. The shared ICD main categories in both BMI groups in women with PCOS were endocrine disease and genitourinary system-related diseases explained by PCOS diagnosis, ovarian dysfunction, anovulatory infertility, diseases of breast,

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endometriosis, and some urinary system diseases. Diseases of the nervous system were also increased in lean women with PCOS as well as neoplasm risk, both being >2-fold increase in PCOS. The diseases of the nervous system are difficult to explain, whereas neoplasm risk may relate to insulin resistance and hyperandrogenism and low-grade inflammation also affecting normal-weight women with PCOS. However, in subclass analysis, any specific subclass was not significant after adjustments and multiple testing (data not shown), and therefore, more studies are warranted. Women with PCOS with a BMI < 25 kg/m^2 had several categories that were not significant after multiple testing most likely due to reduced statistical power but still supported the previous findings in the literature. For example, mental disorders are commonly known to relate with PCOS, and here, mental disorders were almost twice as common in normal-weight women with PCOS. However, to support this finding, the use of antidepressants was 50% higher in the whole PCOS population, regardless of adjustment with BMI. Moreover, pregnancy complications and overall unspecific symptoms have also been previously linked with PCOS. The fact that these seemed to be more prevalent in lean women with PCOS most likely underlines the role of obesity in comorbidity risk also in non-PCOS population.[5,55]

This study has many strengths, such as the potential to apply trustworthy national register data together with unique birth cohort data. Moreover, multiple confounding factors were utilized, which was possible only due to the nature of the data set. The collection of birth cohort data focused on comprehensive health and work ability—not PCOS per se—and therefore, self-awareness bias was low. Whereas many previously published studies on PCOS were derived from infertility clinics and focused on PCOS patients, our data included a study population from the same general community, with low variation regarding education or ethnicity. Additionally, in Finland, access to healthcare is equal, as the healthcare system is public and accessible to everyone regardless of residence area or socioeconomic status. Self-reported PCOS diagnosis can be considered a limitation, but, nowadays, the validity of this diagnostic approach has been well justified in many studies.[15,27,56] To support this, PCOS diagnosis was 60 times more common in the PCOS group than in the controls, supporting the validity of the self-reported diagnosis. Our population was partly identified based on self-reported diagnosis for PCOM/PCOS; nevertheless, the population used here, also including the PCOM/PCOS cases, has been previously shown to have a PCOS-like phenotype although most likely diluted for the difference between cases and controls.[12] In our subanalysis (data not shown), the women identified based on the OA + HA questions alone had an almost identical risk for overall morbidity as our full population, including also women reporting PCOM/PCOS. Another possible bias toward diluting the PCOS population/phenotype was the removal of women who were on hormonal contraceptives. In addition, as a limitation, the differences in metabolic and hormonal profiles between PCOS cases and controls were quite small, indicating that the cases do not represent the most severe PCOS phenotypes. The small differences are also understandable as this is a population-based study and not a clinical cohort. Moreover, the differences in hormonal and metabolic parameters tend to diminish during aging between PCOS and control women. Despite this limitation, our study demonstrates the high health burden related to PCOS, which nevertheless often remains underdiagnosed among healthcare professionals. In this data set, only 10% of the cases had a hospital-based ICD diagnosis for PCOS.

We conclude that PCOS is a multimorbid condition and requires more attention, targeted treatment plans, research funding, and support for the affected women themselves.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Linda Kujanpää (Conceptualization [equal], Data curation [equal], Formal analysis [lead], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Visualization [equal], Writing—original draft [lead], Writing—review & editing [equal]), Riikka Arffman (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Project administration [equal], Resources [equal], Supervision [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Paula Pesonen (Formal analysis [equal], Software [equal], Writing—review & editing [equal]), Elisa Korhonen (Data curation [equal], Formal analysis [equal], Software [equal], Visualization [equal]), Marjo-Riitta Jarvelin (Writing—review & editing [equal]), Stephen Franks (Writing—review & editing [equal]), Juha Tapanainen (Writing—review & editing [equal]), Laure Morin-Papunen (Writing—review & editing [equal]), and Terhi Piltonen (Conceptualization [equal], Data curation [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—review & editing [equal])

Data availability

NFBC data are available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be applied for research purposes via an electronic material request portal. In the use of data, we follow the EU general data protection regulation (679/2016) and the Finnish Data Protection Act. The use of personal data is based on cohort participant's written informed consent at his/her latest follow-up study, which may cause limitations to its use. Please contact the NFBC project center (NFBCprojectcenter@oulu.fi) and visit the cohort website (www.oulu.fi/nfbc) for more information.

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