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Original Article

Increased Prevalence of Adverse Health Outcomes Across the Lifespan in Those Affected by Polycystic Ovary Syndrome: A Canadian Population Cohort

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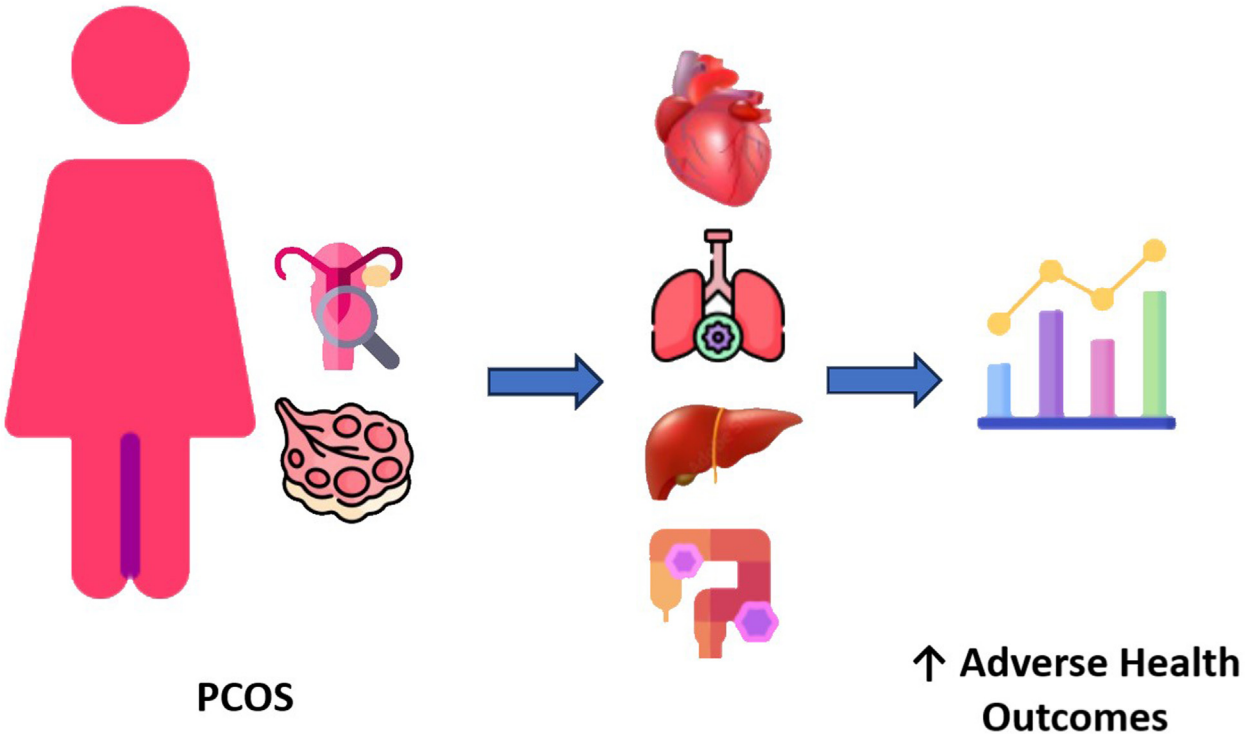

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common metabolic-endocrine disorder impacting the health and quality of life of women over the lifespan. Evidence-based data on the scope of adverse health outcomes in those affected by PCOS is critical to improve healthcare and quality of life in this population. The aim of this study was to determine the prevalence of adverse health outcomes in those with PCOS compared to age-matched controls.

Methods: We conducted a retrospective observational case-control study in those diagnosed with PCOS and age-matched controls using

RÉSUMÉ

Contexte : Le syndrome des ovaires polykystiques (SOPK) est le trouble métabolique et endocrinien le plus courant à toucher la santé et la qualité de vie des femmes de tout âge. Il est essentiel de disposer de données probantes sur l'ampleur des effets néfastes sur la santé des personnes qui en sont atteintes afin d'améliorer les soins de santé offerts à cette population et sa qualité de vie. Le but de la présente étude était de déterminer la prévalence des effets néfastes sur la santé des personnes atteintes du SOPK et de les comparer aux effets chez des témoins appariés selon l'âge.

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the Alberta Health Services Health Analytics database and the International Classification of Diseases, for the period from 2002-2018 in Alberta, Canada.

Results: The cohort consisted of n = 16,531 exposed PCOS cases and n = 49,335 age-matched un-exposed controls. The prevalences of hypertension, renal disease, gastrointestinal disease, eating disorders, mental illness, depression-anxiety, rheumatoid arthritis, respiratory infections, and all malignancies were 20%-40% ($P < 0.0001$) higher in those with PCOS, compared to controls. The prevalence of obesity, dyslipidemia, nonalcoholic fatty liver disease, and type 2 diabetes was 2-3 fold higher in those with PCOS ($P < 0.001$). Cardiovascular, cerebrovascular, and peripheral vascular disease were 30%-50% higher, and they occurred 3-4 years earlier in those with PCOS ($P < 0.0001$); a 2-fold higher prevalence of dementia occurred in those with PCOS, compared to controls.

Conclusion: These findings provide evidence that PCOS is associated with a higher prevalence of morbidities over the lifespan, and the potential scope of the healthcare burden in women affected by PCOS.

Méthodologie : Nous avons mené une étude cas-témoin observationnelle rétrospective chez des personnes diagnostiquées avec un SOPK et des témoins appariés selon l'âge en utilisant la base des données analytiques de santé de l'Alberta Health Services et la classification internationale des maladies pour l'Alberta (Canada) de 2002 à 2018.

Résultats : La cohorte à l'étude était composée de cas de SOPK (n = 16 531) et de témoins appariés selon l'âge qui n'y étaient pas exposés (n = 49 335). L'hypertension, les maladies rénales, les maladies gastro-intestinales, les troubles alimentaires, les troubles de santé mentale, la dépression et l'anxiété, la polyarthrite rhumatoïde, les infections respiratoires, et les cancers de tout type étaient de 20 % à 40 % plus fréquents ($p < 0{,}0001$) chez les personnes atteintes de SOPK que chez les témoins. La prévalence de l'obésité, de la dyslipidémie, de la stéatose hépatique non alcoolique et du diabète de type 2 était 2 à 3 fois plus élevée chez les personnes atteintes de SOPK ($p < 0{,}001$). L'incidence des maladies cardiovasculaires, vasculaires cérébrales et vasculaires périphériques était 30 % à 50 % plus élevée et ces maladies survenaient 3 à 4 ans plus tôt chez les personnes atteintes de SOPK ($p < 0{,}0001$), et la prévalence de démence était 2 fois plus élevée chez les personnes atteintes de SOPK que chez les témoins.

Conclusions : Ces résultats démontrent que le SOPK est associé à une prévalence plus élevée de morbidité tout au long de la vie et démontrent l'ampleur possible du fardeau en soins de santé chez les femmes touchées par le SOPK.

Lay Summary

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder that increases the male hormone testosterone to affect menstrual cycles and fertility. PCOS also impacts the health and well-being of women throughout their lifetimes. Using healthcare data from Alberta, adverse health outcomes were compared in women with vs without PCOS. Women with PCOS had 2- to 4-fold more adverse health outcomes than did women without PCOS, including anxiety, depression, diabetes, and kidney, digestive tract, and heart diseases.

Polycystic ovary syndrome (PCOS) is the most common metabolic-endocrine disorder impacting the health and quality of life of 10%-15% women across the lifespan.[1-5] PCOS is a complex heterogenous disorder that has emerged as not only a reproductive-endocrine disease associated with infertility but also a disorder with a range of morbidities that impact patients' health and well-being.[6-11] PCOS is diagnosed following criteria inclusive of menstrual and ovulatory dysfunction, clinical or biochemical hyperandrogenemia and/or polycystic ovaries.[1] Menstrual and ovary dysfunction, and associated infertility, have been associated with increased mortality and morbidity in women.[12-16] Women with PCOS experience increased cardiometabolic risk—including the metabolic syndrome, hypertension, insulin resistance, obesity and dyslipidemia—predisposing them to increased risk for diabetes and cardiovascular disease (CVD).[2,10,17-20] PCOS is associated with a higher incidence of fertility assistance and complications of pregnancy, including gestational hypertension and diabetes.[12,17,18,21-24] These pregnancy complications are coupled with an increased risk of diabetes and CVD, and with an economic healthcare burden.[19,21,22,25-27] In addition, women with PCOS have an increased prevalence of mental health disorders, and an increased psychosocial and economic burden attributable to anxiety, depression, and eating disorders.[2,7,28-30]

Few population studies have been conducted on the range of morbidities that are experienced in women with PCOS, as compared to age-matched controls across the lifespan—adolescence, reproductive age, the menopausal period, and the elderly years.[2,31-33] Chronic diseases, including diabetes, cancer, and CVD, often do not present with a clinical diagnostic event until perimenopause, postmenopause, or in the elderly years; as a result, whether those with PCOS have both an increased prevalence of chronic disease and an earlier age of onset of morbidities has been unclear.[2,27,32,34]

PCOS has been recognized recently as a lifelong disease affecting individuals into the postmenopausal years.[35-39] The increased risk of developing adverse health outcomes in PCOS has not been investigated fully and often is underrecognized, overlooked, or not prioritized in the healthcare of those affected by PCOS.[2,31] Clinicians and those affected by PCOS remain unfamiliar with the adverse health risks of PCOS across the lifespan.[6,40-44] PCOS has received significantly less research funding compared to other diseases that have a lower prevalence, economic healthcare burden, morbidity level, and impact on quality of life.[27,45] This situation has led to a lack of

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See page 322 for disclosure information.

evidence-based data to guide healthcare system practices in managing lifelong healthcare in PCOS in different populations. An understanding of what the health risks are is important, as a means to raise awareness, improve surveillance, and implement effective risk reduction and management of healthcare at each stage of life in those affected by PCOS.[1] Currently, we are likely to be underestimating the health risks, morbidities, and associated healthcare costs in PCOS in Canada. Therefore, determining health outcomes across the lifespan in those with PCOS is essential to raise awareness from a clinical and patient healthcare perspective, to inform public health and research funding initiatives and aid in the planning of healthcare resource allocation.

The aim of this study was to determine the prevalence of adverse health outcomes across the lifespan in those with PCOS, compared to age-matched controls. We hypothesised that women with PCOS would have an increased prevalence of adverse health outcomes across the lifespan.

Methods

In this retrospective cohort study, the administrative data from the regional health authority, Alberta Health Services, were used to identify both a qualifying cohort with PCOS and controls (defined below) who had heath system encounters in Alberta, Canada from April 1, 2002 to March 31, 2018. Alberta has a single-payer government-funded healthcare system that provides universal access to essential services to all residents. Each individual patient is assigned a personal healthcare number that acts as a unique lifetime identifier (ULI) that is captured in all health system encounters. Activities across the healthcare system are collected in different databases and are linked using this ULI. These databases include data for approximately 4.3 million people (3.1 million adults) across Alberta. These databases have been used in various studies and have been proven to be representative of a Canadian province, and have been validated for multiple morbidities. [46-48] The study protocol was approved by the Human Research Ethics Board of the University of Alberta (Pro00094712).

Data sources

Administrative database. Four databases used in this project include the Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System (NACRS) database, and the Physician Claims and Alberta Health Care Insurance Plan (AHCIP) registry.[49,50] The Discharge Abstract Database captures admissions to acute care hospitals with an event date and includes up to 25 International Classification of Diseases (ICD), 10th revision (-10) Canadian (CA) diagnosis codes and up to 20 procedures (Canadian Classification of Health Interventions codes). The National Ambulatory Care Reporting System database includes visits to hospital-based ambulatory care centres, including emergency departments, in Alberta. Each record contains the date of visit, up to 10 ICD-10-CA diagnosis codes, and up to 10 procedure codes (Canadian Classification of Health Interventions codes). Physician billing claims data capture information on fee-for-service claims by physicians and include relevant dates, up to 3 ICD, 9th revision (-9) diagnosis codes, and a procedure or billing code. The AHCIP provides basic medical and hospital insurance coverage for Albertans under the Canada Health Act, and it is used to represent the Alberta population. This database was used to select the matching controls for the PCOS cohort.

Health outcomes. Patient diagnosis and health outcomes were identified using ICD-9 and ICD-10 codes (see Supplemental Table S1) in any hospitalization or ambulatory encounter during the observation period.[47,51,52] The date of a health outcome diagnosis, including PCOS and morbidities, was determined using the earliest date of the first hospital encounter with a PCOS diagnosis, or the second time a PCOS diagnosis was recorded in a community physician or specialist encounter. The Charlson Comorbidity Index using 19 validated comorbid conditions was used, along with the associated ICD-9 and ICD-10 codes for operationalization of the administrative data.[51,53,54]

Study design and population

We conducted a retrospective observational cohort study in adolescents and women aged $\geq$ 12 years who were diagnosed with PCOS in the period from 2002 to 2018, using the Alberta Health Services administrative health database, and in a ratio of 1:3 with an age-matched control non-PCOS population. PCOS is a disease that affects exclusively the female sex, and the role of gender in the diagnosis and prevalence of PCOS was not explored in this study, as this variable is not available in the administrative database.

Exposure. We identified all patients aged $\geq$ 12 years with a PCOS diagnosis, using the ICD-9 code (256.4) or the ICD-10 code (E28.2) for PCOS, excluding endocrine or other disorders that present like PCOS.[55-58] The date of the first diagnosis of PCOS was considered to be the index date. Patients with an index date during the study period (2002-2018) were included. Patients with an index date before the start of the study period (preexisting condition) were excluded from the exposure cohort as well as the control cohort.

Unexposed. The unexposed or controls in this study were drawn randomly from the AHCIP registry using the 1:3 case-to-control ratio. Controls were identified by their ULI and were linked to other databases for demographics and health outcomes.

Matching. The unexposed or controls in this study were drawn randomly from the AHCIP registry using the 1:3 case-to-control ratio. Controls were identified by their ULI and were linked to other databases for demographics and health outcomes. The greedy matching algorithm was used, and for each patient with PCOS, 3 controls born within 3 years before or after the start of a PCOS case were matched.[59,60] Each patient was matched only once. Each control was assigned a pseudo-index date, which is the date of the first PCOS diagnosis for their matched PCOS case.

Outcomes. The primary outcome was the prevalence of morbidities in PCOS and non-PCOS controls from 2002-2018. The secondary outcome was the age of diagnosis of select morbidities.

Statistical analyses

The proportion of individuals with each morbidity was expressed as a percentage. X^2 tests were applied to examine the statistical significance of the difference between PCOS-exposed and PCOS-unexposed groups. Significance was set at $P < 0.05$. Statistical analyses used STATA 13.0 (StataCorp, College Station, TX).

Results

Prevalence of PCOS and age of first diagnosis

We found that 16,531 cases of PCOS were diagnosed in Alberta in the period 2002-2018, with the median age of first diagnosis being 28 years. The PCOS-exposed cases were matched with 49,335 non-exposed controls without PCOS (Table 1). The diagnosis of PCOS increased 8-fold, from 359 cases in 2002, to 2861 cases in 2016 (Fig. 1). This change is likely attributable to both the increased awareness of PCOS over this period and the development and implementation of international diagnostic criteria in adolescents and adults.[1,61-64]

Health outcomes in PCOS patients compared to non-PCOS controls

Circulatory. The prevalence of hypertension and CVD was 30% higher in those with PCOS, compared to the non-PCOS control population (Table 1). Peripheral vascular disease and cerebrovascular disease had a 50% and 40% higher prevalence in those with PCOS, compared to non-PCOS controls, and these diseases occurred on average 3 years earlier in those with PCOS, compared to non-PCOS controls (at ages 35 vs 37 years, respectively, for peripheral vascular disease, and at ages 38 vs 40 years, respectively, for cerebrovascular disease). The prevalence of myocardial infarction was 40% higher in those with PCOS, with a median age of diagnosis at age 43 years in PCOS patients, compared to age 47 years in non-PCOS

Table 1. Prevalence of adverse health outcomes in patients with polycystic ovary syndrome (PCOS) and non-PCOS controls across the lifespan

Health outcomes	Non-PCOS controls, n (%)	PCOS patients, n (%)	*P*
N	49,335	16,531	
Gynecological-endocrine			
Infertility	2879 (5.83)	4474 (27.06)	< 0.0001
Menstrual dysfunction	17,731 (35.94)	12,259 (74.16)	< 0.0001
Hyperandrogenism	8784 (17.80)	15,308 (92.60)	< 0.0001
Polycystic ovaries	1699 (3.44)	14,980 (90.62)	< 0.0001
Endometriosis	4114 (8.34)	3747 (22.67)	< 0.0001
Circulatory			
Hypertension	18,216 (36.92)	8846 (53.51)	< 0.0001
Cardiovascular disease	1235 (2.50)	614 (3.71)	< 0.0001
Myocardial infarction	226 (0.31)	134 (0.55)	< 0.0001
Congestive heart failure	325 (0.47)	233 (0.95)	< 0.0001
Cerebrovascular disease	4094 (8.29)	2332 (14.11)	< 0.0001
Peripheral vascular disease	189 (0.36)	261 (0.76)	< 0.0001
Endocrine-metabolic			
Dyslipidemia	1721 (3.48)	1264 (7.64)	< 0.0001
Obesity	3287 (6.66)	4203 (25.42)	< 0.0001
Metabolic syndrome	2065 (4.18)	643 (3.89)	< 0.097
Non-alcoholic fatty liver disease	611(1.12)	443 (2.68)	< 0.0001
Type 1 diabetes	1414 (2.87)	1442 (8.72)	< 0.0001
Type 2 diabetes	1504 (3.05)	1649 (9.98)	< 0.0001
Renal disease	330 (0.67)	213 (1.29)	< 0.0001
Respiratory	43,167 (57.86)	20,208 (79.97)	< 0.0001
Bronchitis	27,824 (56.40)	12,223 (73.93)	< 0.0001
Influenza-pneumonia	4674 (9.47)	2396 (14.49)	< 0.0001
CPD	1212 (14.99)	826 (27.67)	< 0.0001
Cancer			
Any malignancy	1519 (3.08)	998 (6.04)	< 0.0001
Metastatic solid tumour	296 (0.60)	176 (1.08)	< 0.0001
Mental health			
Mental illness	14,196 (28.77)	7193 (43.51)	< 0.0001
Depression-anxiety	18,887 (38.28)	9222 (55.78)	< 0.0001
Eating disorders	1573 (3.19)	937 (5.67)	< 0.0001
Dementia (unspecified)	132 (0.22)	106 (0.48)	< 0.0001
Gastrointestinal disease			
Peptic ulcer	799 (1.62)	540 (3.27)	< 0.0001
Nonalcoholic fatty liver disease	611(1.12)	443 (2.68)	< 0.0001
Muscoloskeletal			
Rheumatoid disease	617 (1.30)	330 (2.00)	< 0.0001
Communicable diseases			
AIDS/HIV	889 (1.80)	371 (2.20)	0.0003
STD	3066 (1.30)	1291 (7.80)	< 0.0001
Tuberculosis	49 (0.10)	16 (0.10)	0.9285

See Supplemental Table S1 for health outcomes using International Classification of Diseases codes.
AIDS/HIV, acquired immune deficieny syndrome/human immunodeficiency virus; CPD, chronic pulmonary disease; STD, sexually transmitted disease.

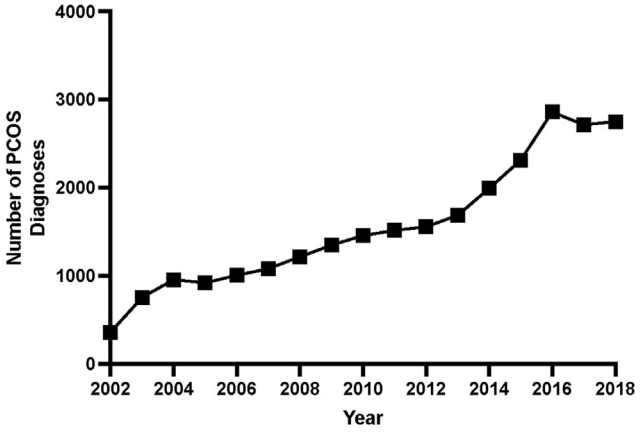

Figure 1. The prevalence of diagnosis of polycystic ovary syndrome (PCOS) in the cohort from 2002-2018. The cohort was determined using the Alberta Health Services Provincial Research Data Service, which links administrative datasets including the Discharge Abstract Database (inpatient), the National Ambulatory Care Reporting System, Physician Claims, and a province-wide laboratory repository for all residents of Alberta.[53,54] PCOS diagnosis was defined using the International Classification of Diseases, 9th and 10th revision codes.

controls. Congestive heart failure had a 50% higher prevalence in those with PCOS, with a median age of diagnosis of 43 years, compared to age 42 years in non-PCOS controls.

Endocrine-metabolic. Obesity had a 3.8-fold higher prevalence in those with PCOS, occurring in 25.4% of the cohort, compared to 6.7% of non-PCOS controls (Table 1). The prevalence of the metabolic syndrome was not different between the PCOS patients and the non-PCOS controls, occurring in approximately 4.0% of the population. Type 2 diabetes had a 3-fold higher prevalence in those with PCOS (10%), compared to non-PCOS controls (3%), and no difference was present in the age of onset, at 32 years for both. Dyslipidemia had a 2-fold higher prevalence in PCOS patients (7.6%), compared to non-PCOS controls (3.5%), and the diagnosis of dyslipidemia occurred 3 years earlier in PCOS patients, at age 35 years, vs age 38 years in non-PCOS controls. Type 1 diabetes was 3-fold more prevalent in PCOS patients (8.7%), compared to the non-PCOS controls (2.9%).

Renal disease. Renal disease was 30% higher in those with PCOS, yet it occurred 3 years earlier in non-PCOS controls, at age 35 years, compared to age 37 years in those with PCOS (Table 1).

Gastrointestinal disorders. All types of gastrointestinal disorders, including inflammatory bowel disorders, ulcerative colitis, crohn's disease, and celiac disease, had a more than 3.5-fold higher prevalence in PCOS patients (94.1%) than in non-PCOS controls (24.9%) (Table 1). Non-alcoholic fatty liver disease (NAFLD) had a 2-fold higher prevalence in PCOS patients (2.7%), compared to non-PCOS controls (1.2%).

Respiratory. All respiratory disease had a 30% higher prevalence in those with PCOS (79%) compared to non-PCOS controls (57%). Bronchitis had a 20% higher prevalence in those with PCOS (73.9%), compared to non-PCOS controls (56.4%). The prevalences of influenza and pneumonia were 1.5-fold higher in those with PCOS, compared to non-PCOS controls. Chronic pulmonary disease (CPD), which includes all conditions related to breathing or respiratory symptoms (asthma, bronchitis, emphysema) and is commonly coded in physician claims, had a 1.8-fold higher prevalence in those with PCOS (27.6%), compared to non-PCOS controls (14.9%) (Table 1).

Cancer. All malignant cancers had a 50% higher prevalence in those with PCOS (6.0%), compared to non-PCOS controls (3.1%) (Table 1).

Mental illness, dementia and eating disorders. All types of mental disorders, including bipolar disorder, psychosis, and schizophrenia, had a 1.5-fold higher prevalence in those with PCOS (43.5%), compared to non-PCOS controls in the cohort (28.8%), with a median age of diagnosis at age 27 years and 28 years, respectively. Depression-anxiety disorders had a 1.4-fold higher prevalence in those with PCOS (55.8%), compared to non-PCOS controls (38.3%) (Table 1). Eating disorders are classified as psychiatric disorders, and the prevalence was 40% higher in those with PCOS (5.7%), compared to non-PCOS controls (3.2%). Dementia, which may include coding for several related symptoms in primary care, and for symptoms associated with other neurological diseases such as Parkinson's disease and unspecified dementia, occurred 19 years earlier in those with PCOS, at a median age of 43 years, compared to age 62 years in non-PCOS controls, and the prevalence was 2-fold higher in those with PCOS (0.48%), compared to non-PCOS controls (0.22%).

Musculoskeletal disorders. Rheumatoid disease had a 30% higher prevalence in those with PCOS (1.3%) vs non-PCOS controls (2.0%) (Table 1).

Communicable disease. Only very limited reports have been published on acquired immune deficiency syndrome/human immunodeficiency virus (AIDS/HIV) and sexually transmitted diseases in those with PCOS, and thus, this area requires further investigation. We found that AIDS/HIV had a 20% higher prevalence in those with PCOS, compared to non-PCOS controls, with prevalences of 2.2% and 1.8%, respectively (Table 1). Sexually transmitted diseases occurred at a 6-fold higher rate in those with PCOS, compared to non-PCOS controls.

Discussion

Our results have shown for the first time in a Canadian cohort that women with PCOS have an increased prevalence of adverse health outcomes across the lifespan, compared to non-PCOS controls. These findings are consistent with those of other retrospective cohort studies demonstrating a predisposition in those with PCOS to the development of morbidities with potentially, shared pathophysiological pathways.[2,6,17,18,31,32] The likelihood of onset of non-communicable diseases increases with age, and in those with PCOS, the onset of circulatory disease occurred strikingly earlier, by 3-4 years, including end-stage myocardial

infarction, and peripheral and cerebrovascular disease. Mental health disorders were 30%-40% more prevalent in those with PCOS across the lifespan, including depression, and anxiety and eating disorders. The most striking finding was the 2-fold higher prevalence of dementia and related symptoms in those with PCOS, and the finding that a diagnosis occurred, on average, 19 years earlier in those with PCOS.

Cardiometabolic risk factors

A well established finding is that women with PCOS have increased cardiometabolic risk, and this was affirmed in our Canadian cohort.[1] In our cohort, the prevalence of obesity in those with PCOS was 25.4%, compared to 6.7% in non-PCOS controls, which is comparable to other population cohort studies of PCOS. In an Australian cohort, those with PCOS had an obesity prevalence of 16.0%, compared to 3.7% in non-PCOS controls.[6] In a US cohort, 39.5% of those with PCOS had obesity, compared to 10.1% of non-PCOS controls.[31] In other case-control and epidemiologic studies, the prevalence of overweight and obesity in those with PCOS is estimated at 50%, and it ranges from 33% to 88%.[65,66] Obesity is associated with a more adverse PCOS phenotype, particularly type A (classic PCOS), which includes hyperandrogenism, menstrual-ovulatory dysfunction, and polycystic ovary morphology.[65-67] In gene-wide association studies, cross-trait analysis has shown that obesity-related traits and body mass index share a genetic basis with PCOS.[68] However, genetic predisposition to PCOS may not predict obesity-related traits, and PCOS has been shown to be independent of obesity and to be dependent on ethnicity, nationality, socioeconomic status, and demographics.[65,66,68] Our data showed no difference in the prevalence of the metabolic syndrome between those with PCOS and controls, despite the higher prevalence of obesity and diabetes in those with PCOS. The metabolic syndrome had a low prevalence (4%) compared to that identified in other Canadian studies that have found prevalences in adult women of 16.5% (age $\geq$18 years), 31.5% (age $\geq$18 years), and 13.4% (age 40-79 years).[48,69,70] PCOS is diagnosed in young women of reproductive age (18-35 years), and the metabolic syndrome may not be coded simultaneously at the time of PCOS diagnosis or at follow-up encounters recorded in physician claims and the acute care administrative databases. Furthermore, studies use different methods for defining the metabolic syndrome, including the documentation of a specific ICD code, documentation of a cluster of ICD codes, and/or individual laboratory results.[48,70-72] These factors may explain the apparent lower prevalence of the metabolic syndrome in this cohort.

Dyslipidemia is common in PCOS and is estimated to occur in 70% of those with PCOS.[73-76] We and others have reported that those with PCOS have a more adverse fasting lipid profile, and this is positively associated with hyperandrogenemia, independent of obesity.[73-75,77-79] Atherogenic dyslipidemia in the fasted and non-fasted state has been described in those with PCOS and commonly includes elevated plasma triglycerides, apoB-lipoproteins, remnant cholesterol and lowered high-density lipoprotein cholesterol, and impairments in postprandial clearance of triglycerides and apoB48-lipoproteins.[73,76-78,80-83] Atherogenic dyslipidemia, in particular elevated triglycerides and apoB-associated remnant cholesterol, is a causative factor in atherosclerotic CVD and is associated with end-stage cardiovascular ischemic events.[84,85] Young women and adolescents with PCOS have been shown to have early atherosclerotic CVD, including increased carotid intimal medial thickness and carotid plaque.[86-89] Our studies have shown that these atherosclerotic vascular indices are positively correlated with apoB-lipoproteins and remnant cholesterol in young women aged 18-45 years.[90] We have found the prevalence of dyslipidemia in this cohort to be 2-fold higher (7.60%) in those with PCOS, compared to non-PCOS controls (3.5%). A higher prevalence of dyslipidemia predisposes those with PCOS to having an increased risk of atherosclerotic CVD, and in those with PCOS, dyslipidemia was diagnosed earlier, at age 35 years, compared to age 38 years in non-PCOS controls. In a US population cohort of young women aged 15-45 years, dyslipidemia had a prevalence of 20.7%, compared to 6.8% in those with PCOS and in non-PCOS controls, respectively.[31] In a Danish cohort study, the prevalence of dyslipidemia, defined as hypercholesterolemia only, using ICD-9 (code E78) was double that in those with PCOS, with a prevalence of 2%, compared to 1% in non-PCOS controls.[18] We and others have shown that dyslipidemia, particularly hypertriglyceridemia and apoB-lipoproteinemia,[73,75,79] occurs in youth and young adults with PCOS and obesity.[77,78,83] Currently, PCOS is not listed as a cardiovascular risk factor in Canadian Cardiovascular Society dyslipidemia guidelines.[91] However, dyslipidemia and atherosclerosis in PCOS are very early subclinical indicators of CVD risk and highlight the need for early screening and intervention in the prevention of long-term CVD in this population.

Gastrointestinal disease

The prevalence of gastrointestinal disorders, inclusive of gastric, intestinal, splenic, pancreatic, and hepatic dysfunction, was very high in PCOS patients, compared to controls, indicating that increased symptom presentation of these disorders occurs in primary, acute, and ambulatory care settings.[47] The higher prevalence of gastrointestinal disorders in PCOS may be associated with several factors, including the following: a higher prevalence of inflammatory bowel disorders in Canada and Alberta[92], and globally[93-95]; a higher prevalence of gut dysbiosis in those with PCOS[96,97]]; a high prevalence of metformin use in those with PCOS, which causes gastrointestinal side effects[58,83,98]; a higher prevalence of NAFLD and bariatric surgery in those with PCOS, which may be associated withgastrointestinal symptoms.[99-102]

The prevalence of NAFLD has been reported to be either not different or higher in prevalence in adolescent and adult individuals with PCOS, and it has been associated with higher rates of obesity, insulin-resistance, hypertriglyceridemia, and hyperandrogenemia indices.[103-107] NAFLD also is associated with an increased transition and incidence of type 2 diabetes in the general population and in those with PCOS.[108] The 4.27% prevalence of NAFLD in those with PCOS in our results is very low compared to findings in other population cohort studies, which show a 40%-50% prevalence in those with PCOS.[100,103] This difference may be reflective of the low level of screening for NAFLD in Canada. Early screening for NAFLD has been recommended to prevent progression to

nonalcoholic steatohepatitis (NASH) and advanced liver disease in those with PCOS.[100,103]

Diabetes

Our data showed that type 2 diabetes had a 3-fold higher prevalence in those with PCOS in Canada (10% vs 3% in controls), consistent with other epidemiologic studies.[6,17,27,31,109] In our cohort, the median age of diagnosis of type 2 diabetes was 32 years, in both those with PCOS and non-PCOS controls. This finding is in contrast to results in a Danish cohort of women aged 12-60 years, who showed an earlier median age of diagnosis of 33 years in those with PCOS, compared to 38 years in non-PCOS controls.[17] Similar to our findings, in those that developed type 2 diabetes, a higher rate of risk factors, including body mass index, and levels of fasting blood HbA1c, glucose, insulin, and triglycerides at baseline, was shown in the Danish cohort.[17] At present, we do not know the economic burden of diabetes or gestational diabetes in PCOS in Canada. In the US, the excess economic burden in those with PCOS and type 2 diabetes is estimated at $1.5 billion, and this figure is based on an odds ratio of 2.4 and a prevalence of 0.5% to 21.4% in those with PCOS, compared to the control population, across the lifespan.[27]

Type 1 diabetes has been observed to have a higher prevalence (7%-25%) in those with PCOS, and in those with menstrual and reproductive dysfunction, and this has been associated with hyperandrogenemia.[110-114] Our results are consistent with these findings and support the concept that type 1 diabetes may predispose individuals to the development of PCOS. The predisposing risk factors and mechanisms remain unclear, but studies suggest that insulin therapy may increase ovarian androgen synthesis ensuing the PCOS phenotype.[113,115]

Circulatory disease

Our results show that the incidence of a diagnosis of hypertension and CVD was 1.5-fold higher in those with PCOS, compared to non-PCOS controls, and ischemic CVD events occurred in young women, consistent with findings in other population studies.[6,11,13,18,27,31,32,116,117] Of note, our results showed that diagnosis of myocardial infarction, and peripheral and cerebrovascular disease occurred in young premenopausal women, and 3-4 years earlier in those with PCOS. In another Canadian cohort, 5.6% and 8.4% of women with a median age of 51.7 years were reported to have had a previous myocardial infarction and spontaneous coronary artery dissection, respectively.[118] In a Danish cohort, CVD incidence, including hypertension, occurred at a median age of 35 and 36 years in those with PCOS and in non-PCOS controls, respectively, and $>$ 95% of those diagnosed with CVD were aged $<$ 50 years.[18] In an Australian cohort, the prevalence of coronary heart disease was 0.0% and 0.8% in controls and those with PCOS, respectively, for whom the median age was 35.8 years.[6] The reproductive and premenopausal years represent periods of increased cardiovascular risk in those with PCOS, and this may be associated with a higher prevalence of obesity and diabetes.[11] The increased incidence of obesity and type 2 diabetes in those with PCOS may contribute to the higher prevalence and earlier age of diagnosis of cardiovascular events. In a Danish cohort with PCOS, diabetes and obesity predicted a 4.9 and a 2.7 higher hazard ratio for CVD ischemic events, respectively.[18] To our knowledge, our study is the first Canadian study to show an increased CVD risk in young premenopausal women with PCOS, and it highlights the need for early screening of cardiac dysfunction and atherosclerotic CVD in this population.

Respiratory disease

An increased prevalence of menstrual dysfunction, infertility, obesity, and insulin resistance has been reported in women with asthma.[119-121] The link between asthma and PCOS is proposed to occur via inflammatory pathways that are shared in obesity and insulin resistance.[119-121] Those with PCOS appear to have a higher risk of developing asthma, and the level of use of asthma medication prescriptions is reported to be higher in those with PCOS.[32,122] In a Danish cohort, asthma had a prevalence of 25% in those with PCOS who were aged 12-60 years.[32] In an Australian study, a hazard ratio of 2.5 was reported for asthma-related hospitalizations in those with PCOS, as compared to non-PCOS controls.[6] The same study showed a higher rate of hospitalization in those with PCOS associated with respiratory disease, with a hazard ratio of 1.7 in those with PCOS.[6] Consistently, our data show that the incidence of respiratory disease is 25%-35% higher in those with PCOS, including bronchitis and influenza-pneumonia.

Cancer

The prevalence of malignant cancer has been reported to be 2-fold greater or not different in those with PCOS.[6,32] The prevalence of endometrial cancer has been reported to be increased 3-5 fold in those with PCOS in the postmenopause years, and an increased risk for ovarian cancer has been reported in younger women with PCOS in the premenopause years.[6,123-125] In our cohort, we have shown that all malignancy was increased by 30% in those with PCOS, suggesting that increased awareness and screening may be warranted.

Mental health disorders

Our data showed that mental health and psychiatric disorders had a 30% higher prevalence in those with PCOS, consistent with findings of previous population cohort studies.[6,29,31,32,126,127] In particular, the prevalence of depression and anxiety in those with PCOS has been reported to be markedly elevated, with a 30%-50% prevalence and an odds ratio of 1.4 to $>$ 2.5 in those with PCOS.[7,29,32,127,128] Eating disorders can be a product of depression and anxiety in the PCOS patient, and we have shown that eating disorders have a 5.7% prevalence in those with PCOS, and a 40% higher prevalence, as compared to non-PCOS controls. This prevalence of eating disorders is relatively high compared to that found in other population studies that report a 0.3%-2.45% prevalence in those with PCOS.[31,126,129,130] However, in meta-analyses, a prevalence ratio of 1.2 and an odds ratio of 3.8 have been reported for eating disorders in those with PCOS, compared to controls,[29,131] and in case control studies, the prevalence of an eating disorder has been reported to range from 11% to 62%.[132-136] We have reported that the eating disorders seen in those with PCOS are most commonly

bulimia nervosa and binge eating disorder.[137] The healthcare costs associated with anxiety, depression, and eating disorders in the US were estimated to be $4.26 billion per year in 2021.[29] Our data show that dementia-related symptomology coded in the administrative database was increased 2-fold in those with PCOS and that it occurs 19 years earlier in those with PCOS, compared to the age in controls. This finding requires further investigation into the symptoms vs the early onset of cognitive decline specific to dementia or Alzheimer's disease. Studies of PCOS and risk of cognitive decline, dementia, and Alzheimer's disease are lacking, but the postulation has been made that increased risk may be associated with chronic inflammation, obesity, insulin resistance, and androgenic-mediated effects on the central nervous system that affect cognitive function.[138]

Strengths and limitations of the study

We have established the first Canadian cohort of those with PCOS, using a provincial administrative health database. A strength of the study is the large size of the cohort and that prevalence of disease was determined for a long time period. We had the ability to match PCOS cases to non-PCOS controls using administrative databases that are linked together, which provided a comprehensive ability to capture cases of or those exposed to PCOS, and to match them with non-PCOS controls, using the ULI. We used validated ICD coding for diseases using the Charlson Comorbidity Index and specific ICD codes for disease. For example, we used separate coding for hypertension, myocardial infarction, and CVD, whereas in other epidemiologic studies, these are often combined within one definition of CVD.[18,51-53,139] The diagnosis of PCOS included the ICD-9 and ICD-10 codes, and these have been validated and used in previous epidemiologic studies.[6,10,17,27,32,55-57]

The limitations of the study are that the administrative database does not contain information on quality-of-life indices, gender, socioeconomic status, lifestyle, or dietary habits, all of which can significantly impact health outcomes in different populations and across the lifespan. Individual patient laboratory data used as biomarker risk factors were not accessed to investigate their potential mechanisms and association with disease outcomes, to determine potential causality in this study. We used validated ICD codes for disease prevalence, based on the ICD code first inputted into the administrative database, but this coding can be based on symptomology at the primary-care or acute-care level, which may cause overestimation of prevalence rates. In future studies, a secondary or tertiary inputting of the ICD code to confirm a diagnosis of a disease, such as a malignant cancer or dementia, rather than related symptomology, is recommended. In addition, primary-care claims may have codes that were inputted for the purposes of billing, based on symptomology, and this may impact assessment of prevalence rates, particularly for gastrointestinal and respiratory complaints. Health system—encounter activity may also impact prevalence rates for all conditions, owing to the greater frequency of code input, and in future studies, we will address the matching of cases and controls for this activity. The diagnosis of PCOS included the ICD-9 and ICD-10 codes, but it did not include codes for symptomology of PCOS, including hyperandrogenism (hirsutism) and menstrual dysfunction, which may be coded separately and are criteria that are used to diagnose PCOS.[58] Not including these symptoms in the PCOS exposure definition may underestimate the number of cases in epidemiologic studies, but it may also prevent inclusion of nonconfirmed PCOS and non-PCOS cases that do not present with 2 out of 3 symptoms of the diagnostic criteria.[18,55] Different phenotypes of PCOS have been linked to severity of symptoms and risk for adverse health outcomes.[55] We have not explored the phenotypes of PCOS in this study, as this information is not directly available in the databases and requires validation on a case-by-case basis using patient chart review, which was beyond the scope of this cohort study.[55] Individual symptoms were not used to define different conditions, such as the metabolic syndrome; therefore, the prevalence of this syndrome may have been underestimated in the population cohort we examined. We have not explored the prevalence of comorbidities in those with PCOS compared to non-PCOS controls or to those with one of the entire ICD of diseases, but rather, we have provided an epidemiologic snapshot into common diseases over the lifespan. In this study, we have not investigated medication use and its relationship to disease outcomes, or economic health costs, but these research questions can be explored in future studies using this population cohort.

Conclusion

The results of this study have shown in this Canadian cohort for the first time that those with PCOS have an increased prevalence of morbidities that impact them across their lifespan. The prevalences of cardiometabolic risk factors, mental illness, diabetes, and CVD were significantly increased in those with PCOS. These findings provide evidence-based data on the potential economic and healthcare burden of those affected by PCOS, and highlight the need for the development of early screening, monitoring, and prevention of morbidities and long-term chronic disease in this high-risk population. Our data also highlight the imminent need for increased research funding and resource allocation to target the healthcare burden for those affected by PCOS in Canada.

Ethics Statement

The study protocol was approved by the Human Research Ethics Board of the University of Alberta (Pro00094712).

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective cohort study using de-identified data; therefore, the IRB did not require individual patient consent.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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