Title: Endometriosis as a risk factor for premature cardiovascular disease: a population-based cohort study

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Funding: This study was funded by the Canadian Institutes of Health Research, Institute of Gender and Health (IGH), operating grant: women's health clinical mentorship grant, grant number WHC - 394408. The funder had no role in the study design, in the collection, analysis and interpretation of data, reporting, writing, or in the decision to submit the article for publication.

Data Sharing: The data set from this study is held securely in coded form at ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset, creation plan and underlying analytic code are available from the authors upon request, with the understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Acknowledgements: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and information compiled and provided by MOHLTC, the Canadian Institute of Hospital Information (CIHI), the Ontario Health Insurance Program (OHIP), and Immigration, Refugees and Citizenship Canada permanent resident (IRCC-PR) databases. The analyses, conclusions, opinions, and statements, expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended nor should be inferred.

Competing interests: None to declare

Abstract word count: 250

Text word count: 2660

Abstract

INTRODUCTION: Cardiovascular disease (CVD) remains the leading cause of premature death in females worldwide however, screening, diagnosis and treatment strategies were developed based on the male clinical experience. Endometriosis, a prevalent condition in reproductive age females, may increase risk of CVD through chronic inflammation and early menopause. The OBJECTIVE of this study was to estimate the association between endometriosis and subsequent risk of CVD.

METHODS: A population-based cohort study was conducted using universal access administrative health data for Ontario residents from 1993 to 2015. The incidence of CVD and cardiovascular health outcomes was compared between females with endometriosis (exposed) and two age-matched females without endometriosis (unexposed). The primary outcome was composite hospitalizations due to CVD. Secondary outcomes were composite CVD events. Cox-proportional hazards models were used to estimate adjusted hazard ratios (aHR) between exposure and CVD events.

RESULTS: We identified 500,559 eligible patients. Females with endometriosis had a higher incidence of hospitalization for CVD (195.04/100,000 person-years; 95% CI 189.51, 200.72) compared to unexposed females (162.98/100,000 person-years; 95% CI 159.35, 166.69). Similarly, the incidence of secondary CVD events was slightly higher in the exposed group (292.46/100,000 person-years; 95% CI 285.65, 299.43) compared to unexposed (223.93/100,000 person-years; 95% CI 219.66, 228.27). Females with endometriosis had an increased risk of hospitalization (aHR 1.14; 95% CI 1.10-1.19) and secondary CVD events (aHR 1.26; 95% CI 1.23-1.30).

CONCLUSION: In this large population-based study, endometriosis was associated with a small increased risk of CVD events. Females with endometriosis may be candidates for early targeted CVD screening.

INTRODUCTION:

Cardiovascular disease (CVD) is the leading cause of premature death for females in Canada (1). There is a recognized need to decrease CVD incidence, which may be achieved through effective primary prevention. Such efforts necessitate identification of risk factors in younger populations, including those unique to females, given the difficulty in diagnosis and management in this population (2). An emerging CVD risk factor is endometriosis: a chronic, multisystemic inflammatory condition which affects approximately 10% of the female population (3). Endometriosis typically manifests as pelvic pain and infertility, and can have a significant negative impact on quality of life (4, 5). Some studies also indicate that patients with endometriosis also have an altered lipid profile, with higher levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL) in their serum (6). In addition to inherent risk factors associated with endometriosis, medical and surgical endometriosis treatments also place patients at risk of CVD.

To date, three studies have evaluated the association between endometriosis and cardiovascular risk. The US Nurses' Health Study II prospectively examined patients with laparoscopically-confirmed endometriosis, and identified that these females had a higher risk of myocardial infarction, angiographically-confirmed angina, and coronary heart disease, as compared to females without endometriosis (7). The population in this study was fairly sociodemographically homogeneous, and well educated with a greater access to medical care than the general population, thus questioning the generalizability of the results. More recently, two population-based cohort studies in the United Kingdom and in Taiwan have also demonstrated an increased risk of CVD in patients with endometriosis (8, 9).

We sought to contribute to the growing body of evidence of an association between endometriosis and CVD using a population-based cohort study linking health administrative datasets from the diverse population in Ontario, Canada.

METHODS:

Data sources and study population

We conducted a population-based matched cohort study using universal coverage administrative health data for Ontario residents available at ICES (www.ices.on.ca). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze deidentified health care and demographic data for

health system evaluation and improvement. A description of all data sources used can be found in **Appendix A1**.

Definition of Exposure, Covariates, and Outcomes

Patients aged 18-50 with a diagnosis of endometriosis (exposed) between 1993 and 2015 were identified based on hospital or outpatient records. These individuals were matched to two age (birth year) and geographically-matched females with no diagnosis of endometriosis (unexposed). Geographic matching was by census subdivision. Individuals were considered to have endometriosis if they had ≥ 2 medical diagnostic codes within one year (ICD9-617 OHIP outpatient diagnosis and hospital codes ICD9-617, ICD10-N80) or one hospital admission for endometriosis. They were considered to have had a surgical confirmation of disease if they had qualified for a medical diagnosis and had a qualifying surgical procedure at any time during the study period (**Appendix A2** for eligible surgeries).

Females were eligible for inclusion if they were registered with OHIP for at least 2 years before cohort entry to ensure an appropriate lookback window for exclusion criteria. Exclusion criteria included CVD parameters prior to index diagnosis, endometriosis diagnosis prior to the study window, and missing census subdivision data. Cohort creation is presented in **Figure 1.** Females were classified as living in urban or rural areas according to the 2002 Agriculture and Rural Working Paper Series, Statistics Canada (10). Females were classified as immigrant or Canadian born with information from the IRCC-PR dataset. Income quintile was assigned using the Postal Code Conversion File (PCCF)/census dataset. The first date of diagnosis of endometriosis served as the index date. Unexposed patients were assigned the same index date as their matched exposed endometriosis patient.

Patient demographic information, including age, obesity, hypertension, diabetes, previous childbirth, and gynecologic conditions (pelvic pain, fibroids, premature ovarian insufficiency) was obtained from administrative data records of healthcare encounters and hospitalizations. Basic demographic information for age, date of birth, and date of death, as well as health insurance eligibility was obtained from the Registered Persons Database (RPDB). Hypertension and diabetes diagnoses were determined through validated ICES cohorts; the Ontario Hypertension cohort (HYPER) and Ontario Diabetes Dataset (ODD), respectively. Previous childbirth was determined through the MOMBABY dataset, which is a validated database of linked maternal and infant health

records for all live births and stillbirths delivered at Ontario hospitals (11). Medical visits were obtained from several databases: inpatient visits from the hospital discharge abstracts database (DAD; mandatory submission from hospitals to the Canadian Institute for Health Information), outpatient from the Ontario Health Insurance Plan database (OHIP; the physician fee-for-service claims file), emergent visits from the CIHI National Ambulatory Care Reporting System database (NACRS; mandatory submissions from hospitals for emergency department visits), and same day surgeries from the Same Day Surgery Database (SDS) **Appendix A2-A4**.

The primary outcome was composite hospitalizations due to CVD events (acute myocardial infarction, stroke, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft surgery, ischemic heart disease, and cerebrovascular disease). Secondary outcomes included secondary CVD hospital events of interest (cardiac catheterization, unstable angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, atrial fibrillation, abdominal aortic aneurysm, peripheral artery disease, and cardiac stent) and emergency department visits for CVD (hypertension, diabetes, and cardiovascular disease). Outcomes were based on previously validated composite measures from the CANHEART study (12), and included information from DAD, NACRS, SDS, and OHIP based on International Classification of Disease (ICD) 9 and 10 codes (**Appendix A5**). Data on emergency department visits is reported on a separate cohort of patients as NACRS outcomes were only available starting July 2000.

Statistical analysis

Participant characteristics at baseline were reported using means (± standard deviation) and proportions. Due to the large study size, characteristics were statistically compared by exposure using standard differences; those with a standardized difference greater than 0.10 were considered statistically significant (13). For each outcome, crude incidence rates of primary and secondary outcomes by exposure were calculated. The Kaplan-Meier estimator was used to estimate outcome free survival by exposure status and was assessed using the Log-Rank test. Univariate and multivariate Cox-proportional hazards models were used to estimate crude and adjusted hazard ratios (HR) by endometriosis status. In the multivariate models, adjustments were made for age, parity, hypertension, diabetes, obesity, and immigration status. Proportional hazard assumptions were assessed using log of negative log versus log time curves and time interactions in models

where appropriate. Statistical significance was set at $p < 0.05$. All analyses were completed using SAS software v9.4 (SAS Institute Inc. Cary, NC, USA).

Ethics approval

Study ethics approval was obtained from the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board. File number 6029490 9OBGY – 374 – 20.

RESULTS:

A total of 500,559 females were included in the study cohort (166,853 with a diagnosis of endometriosis and 333,706 without endometriosis). Baseline study population characteristics are presented in **Table 1**. The average age at index date (for those with endometriosis, with matched date for those without endometriosis) was 36.4 years. Baseline sociodemographic characteristics (rurality, immigration status, income quintile) were similar by exposure. A higher proportion of patients with endometriosis were nulliparous (65.3%) than those without endometriosis (59.6%). The proportion with obesity, diabetes and hypertension at baseline was similar by exposure.

A higher proportion of patients in the endometriosis group were diagnosed with pelvic pain and fibroids both prior to index diagnosis, and during study follow-up. Patients with endometriosis were more likely to undergo bilateral oophorectomy or hysterectomy, or receive a diagnosis of premature ovarian insufficiency (menopause diagnosis <40 years old) as compared to the unexposed group during the study period (**Table 2**). The mean age at menopause was lower in the endometriosis group as compared to the unexposed group (43 years vs 46 years).

During the study period, females with endometriosis had a higher incidence of hospitalization for CVD (195.04 cases / 100,000 person-years; 95% CI 189.51, 200.72) as compared to females without endometriosis (162.98 cases / 100,000 person-years; 95% CI 159.35, 166.69). The incidence of secondary CVD events was also higher in the exposed group (292.46 cases / 100,000 person-years; 95% CI 285.65, 299.43) as compared to unexposed (223.93 cases / 100,000 person-years; 95% CI 219.66, 228.27). Similarly, the incidence of CVD-related emergency department visits (composite ED visits for CVD) was higher in the exposed (569.04 cases / 100,000 person-years; 95% CI 554.28, 584.19) as compared to the unexposed population (427.32 / 100,000 person-years; 95% CI 418.16, 436.69) (**Table 3**).

In the models adjusted for parity, age, immigration status, and hypertension, diabetes and obesity at baseline, females with endometriosis had an increased risk of hospitalization for a major CVD event (aHR 1.14; 95% CI 1.10-1.19), secondary CVD event (aHR 1.26; 95% CI 1.23-1.30), and ED visits (aHR 1.28; 95% CI 1.23-1.32) compared to females without endometriosis (**Figure 2 & 3**).

Adjusted models suggested an interaction between age of exposure and primary study outcomes with the risk of any major outcome decreasing with increasing age (**Figure 4**).

INTERPRETATION:

This is the first North American population-based cohort study to examine the association between endometriosis and CVD. Our study results suggest an association between endometriosis and future risk of developing CVD, as has been observed by others (7, 9, 14). Endometriosis was associated with a higher risk of hospitalization due to CVD, CVD-related emergency department visits, and our secondary CVD outcomes. These risks remained elevated when adjusting for potential confounders, including hypertension and diabetes at the time of endometriosis diagnosis. Risks of these adverse CVD outcomes appeared to be higher with younger age of endometriosis diagnosis.

Our findings agree with results from the Nurses' Health Study II, a prospective cohort study from the United States, which demonstrated that the risk of combined CVD endpoints was higher in a population with laparoscopically confirmed endometriosis as compared to those without endometriosis (RR 1.62, 95% CI 1.39-1.89) (7). Similarly, two recent population based studies in Taiwan and the United Kingdom, also indicated higher risks of CVD for young women with endometriosis (HR 1.17, 95% CI 1.05-1.29 and 1.24, 95% CI 1.13-1.37, respectively) (8, 9). As with our cohort, both the Nurses' Health Study II and the UK population-based study demonstrated a difference in risk when the population was stratified by age. In each study, the highest risk was demonstrated in women diagnosed at a younger age (<40 years). The average age of enrollment in our study was 36.4 years for both groups. This is similar to all three prior studies (38 years in the Taiwanese study, 36.7 years in the UK study, and 36 years for the endometriosis group vs. 34.7 years for the control group in the Nurses' Health Study II). Thus, the age of females enrolled in the Nurses' Health Study is unlikely to explain the increased relative risk in that

population. This may, however, be explained by the entirety of the exposed population in that study requiring a surgical diagnosis – which is a possible indicator of more severe disease.

There are several strengths of our study. Our cohort is the largest population studied to date, and followed for the longest duration: 500,559 participants with 22 years of coded analysis. Our cohort is likely ethnically diverse, given that Canada has the highest proportion of foreign-born populations among the G8 countries (20.6%) (15). Furthermore, our cohort consists of a socioeconomically diverse population in the context of a universal health care system. Confounding from socioeconomic status for health care access is less likely in a system with universal coverage for health care given improved health care accessibility (16, 17). We used administrative health datasets to define endometriosis based on diagnosis codes. The use of administrative health datasets to define endometriosis has been previously validated by comparing ICD codes with medical records in Sweden, a country that has a health system similar to Canada (18). The reported positive predictive value for endometriosis in this study was 97.8%.

There is likely under-diagnosis of endometriosis in those who remain asymptomatic or do not receive an accurate diagnosis (19); however, these individuals would be expected to be included in the unexposed group; if they had similar rates of outcomes as those with diagnosed endometriosis the expected direction of bias is towards the null. Further, unlike the Nurses' Health Study II, our study included females diagnosed with endometriosis based not only on laparoscopic findings but also clinically diagnostic terms. This is prudent given that there is growing acceptance that a clinical diagnosis of symptomatic endometriosis is sufficient and perhaps even more reliable than previously recognized (20, 21). Clinical diagnoses were also used in the UK and Taiwanese studies. This is particularly important given the recognized delay in diagnosis prior to treatment. Many clinically diagnosed patients who may be fortunate to have a diagnosis earlier in their disease course may receive treatment without requiring surgery. These patients may, however, still be susceptible to the same endometriosis related risk factors for CVD.

The findings of our study must be interpreted in the context of possible limitations. Our study does not detail personal history for each patient enrolled, including presence of modifiable lifestyle risk factors for CVD such as smoking and diet. We also did not include information on stage of endometriosis or treatments used by many females with endometriosis which may affect the risk of CVD, including NSAIDS, opioids, or hormonal treatment measures such as GnRH agonist suppression, which may induce medical menopause (22-24). This is a limitation of

administrative health datasets to study endometriosis (25); unmeasured confounding from these factors may be present.

We demonstrate that endometriosis is associated with a higher risk of CVD outcomes suggesting a possible underlying causal mechanism with features of endometriosis disease. Our study does not address the potential mechanism of risk association: whether inherent risks associated with dysregulated immune system are associated with both CVD and endometriosis, or endometriosis itself worsens CVD is yet to be determined. Associations could include dysregulated inflammation, increased reactive oxygen species, and an unfavourable lipid profile (6, 26). Additional factors may include treatment modalities used to manage endometriosis, including regular NSAID and opioid use, hysterectomy, and oophorectomy (3, 22, 24, 27).

Further studies will need to elucidate the potential mechanism, including the mediating role of surgical menopause, which is associated with a higher Framingham risk score than natural menopause (28). Given the role for surgical management in endometriosis, it was not surprising that in our population more women with endometriosis had hysterectomies, oophorectomies, and premature menopause than women in the unexposed group. As previously demonstrated in the Women's Health Initiative cohort, women who eventually undergo a hysterectomy have been shown to have a worse cardiovascular risk profile and higher incidence of CVD (29). This is in concordance with findings of Mu *et al.*, suggesting that hysterectomy/oophorectomy at a younger age in women with endometriosis may increase risk of coronary heart disease (7). A future mediation analysis will determine the risks associated with these endometriosis related treatments in our population.

Although we suggest that women with endometriosis have higher risk of CVD morbidity, risk of mortality due to CVD likely remains in the older age bracket (30), which is outside the follow-up period of this study. Although CVD mortality may present later in life, CVD morbidity can remain substantial, even at younger ages (31). Studies with a longer follow-up duration are required to elucidate the risk of CVD related mortality in the long term in this population.

Conclusions

Endometriosis is a multisystemic disease of chronic inflammation. Our findings indicate that this disease is associated with a significant increased risk for earlier onset of CVD. Endometriosis is not currently included on the list of factors associated with CVD warranting early

screening in females in Canada (32). The findings from this study highlight patients with endometriosis as a population of high risk individuals who may be candidates for early targeted CVD screening and possible intervention to mitigate risk at a younger age. These types of early targeted screening and treatment strategies may reduce the healthcare burden of CVD disease in women in Canada.

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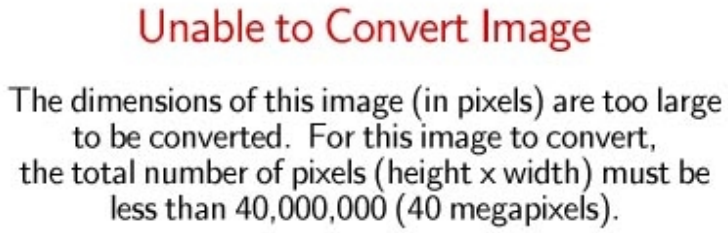

Figure 1. Inclusion and exclusion criteria for creation of cohort.

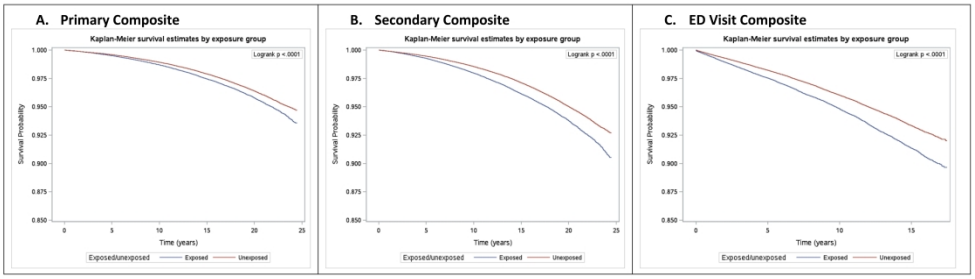

Figure 2. Kaplan-Meier curves for survival without CVD related endpoints among women with endometriosis (exposed) and those without endometriosis (unexposed). Curves are for probability of A) hospitalizations for major CVD (composite primary outcome), B) secondary CVD outcomes of interest, and C) emergency department visits for CVD related disease. P < 0.001 in A, B, and C.

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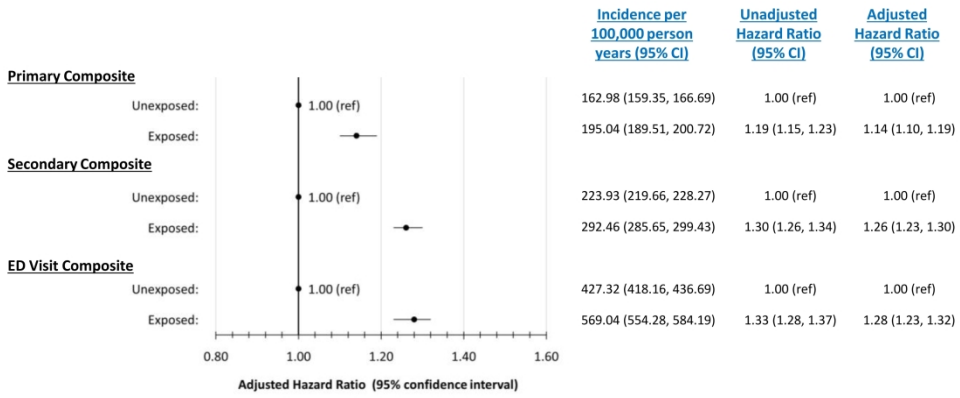

Figure 3. Incidence per 100,000 person-years and hazard ratios for primary, secondary, and emergency department visit composite endpoints among women with endometriosis (exposed) and those without endometriosis (unexposed).

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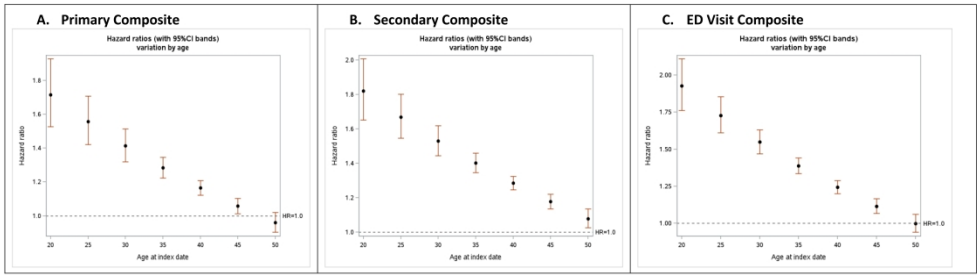

Figure 4. Hazard ratios comparing women with endometriosis (exposed) and those without endometriosis (unexposed) for A) the primary composite (hospitalizations for major CVD), B) secondary composite (secondary CVD outcomes of interest) and C) ED composites by age at index.

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Patient Characteristics	Exposed N=166,853	Unexposed N=333,706	Standardized Difference
Mean ± SD Age, years	36.4 ± 8.0	36.4 ± 8.0	0
Income quintile (Q)			
1 (lowest)	31,904 (19.1)	64,631 (19.4)	0.006
2	33,899 (20.3)	65,962 (19.8)	0.014
3	34,446 (20.6)	67,767 (20.3)	0.008
4	35,030 (21.0)	68,629 (20.6)	0.011
5 (highest)	31,153 (18.7)	65,824 (19.7)	0.027
Rural residence	21,282 (12.8)	42,559 (12.8)	0
Immigrant	22,898 (13.7)	48,478 (14.5)	0.023
Nulliparity	108,964 (65.3)	198,877 (59.6)	0.118
Comorbidities at Index			
Obesity	16,124 (9.7)	27,780 (8.3)	0.047
Diabetes	4,576 (2.7)	7,803 (2.3)	0.026
Hypertension	12,937 (7.8)	18,799 (5.6)	0.085
Pelvic Pain	66,102 (39.6)	52,519 (15.7)	0.554
Fibroids	32,950 (19.7)	11,388 (3.4)	0.528
Infertility	40,766 (24.4)	28,881 (8.7)	0.435
Premature Menopause	18,298 (11.0)	17,171 (5.1)	0.215
Surgical History at Index			
Bilateral Oophorectomy	15,978 (9.6)	1,549 (0.5)	0.427
Hysterectomy	46,710 (28.0)	7,660 (2.3)	0.768
Exposure Characteristics			
Index Year			
1993-1999	64,628 (38.7)	129,256 (38.7)	0
2000-2007	58,818 (35.3)	117,636 (35.3)	0
2008-2015	43,407 (26.0)	86,814 (26.0)	0
Method of Diagnosis			
Medical Only	27,695 (16.6)	N/A	N/A
Surgical at Any Time	139,158 (83.4)	N/A	N/A

Mortality	Exposed N=166,853	Unexposed N=333,706	Standardized Difference
Death before study end	4,131 (2.5)	8,258 (2.5)	0
Comorbidities			
Diabetes diagnosis at any time	19,900 (11.9)	32,956 (9.9)	0.066
Hypertension diagnosis at any time	45,152 (27.1)	74,802 (22.4)	0.108
Pelvic pain at any time	93,149 (55.8)	88,832 (26.6)	0.621
Pelvic pain in follow-up	55,487 (33.3)	48,686 (14.6)	0.448
Fibroids at anytime	48,642 (29.2)	34,587 (10.4)	0.486
Fibroids in follow-up	26,833 (16.1)	26,428 (7.9)	0.253
Surgical History			
Hysterectomy at any time	77,831 (46.6)	25,213 (7.6)	0.979
Bilateral oophorectomy at any time	32,504 (19.5)	9,084 (2.7)	0.554
Menopause History			
Menopause diagnosis at any time	72,086 (43.2)	99,161(29.7)	0.283
Premature menopause diagnosis at any time	40,903 (24.5)	32,698 (9.8)	0.398
Mean ± SD Age at menopause diagnosis, years	42.97 ± 7.62	46.18 ± 7.75	0.418
Menopause diagnosis or bilateral oophorectomy at any time	81,544 (48.9)	102,324 (30.7)	0.379

Any time includes diagnoses and surgeries before index and during follow up

	Exposed N=166,853	Unexposed N=333,706	Standardized Difference
Primary Composite - Hospitalization for CVD	**4,653 (2.8)**	**7,587 (2.3)**	**0.033**
Acute MI	1,370 (0.8)	2,366 (0.7)	0.013
Stroke	970 (0.6)	1,706 (0.5)	0.01
Congestive Heart Failure	636 (0.4)	1,141 (0.3)	0.007
Percutaneous coronary intervention	1,186 (0.7)	2,034 (0.6)	0.013
Coronary artery bypass graft	324 (0.2)	585 (0.2)	0.004
Ischemic heart disease	3,150 (1.9)	5,005 (1.5)	0.03
Cerebrovascular disease	1,318 (0.8)	2,216 (0.7)	0.015
Secondary Composite for CVD	**6,930 (4.2)**	**10,382 (3.1)**	**0.056**
Cardiac catheterization	5,293 (3.2)	7,575 (2.3)	0.055
Unstable angina	850 (0.5)	1,198 (0.4)	0.023
Ischemic stroke	680 (0.4)	1,119 (0.3)	0.012
Hemorrhagic stroke	331 (0.2)	650 (0.2)	0.001
Transient ischemic attack	218 (0.1)	332 (0.1)	0.009
Atrial fibrillation	787 (0.5)	1,323 (0.4)	0.011
Abdominal aortic aneurysm	21 (0.0)	32 (0.0)	0.003
Peripheral artery disease	175 (0.1)	370 (0.1)	0.002
Stent	74 (0.0)	151 (0.0)	0
Emergency Department Composite	**5,563 (5.7)**	**8,172 (4.2)**	**0.07**
Hypertension ED visit	1,406 (1.4)	2,189 (1.1)	0.028
Diabetes ED visit	713 (0.7)	1,196 (0.6)	0.014
CVD ED visit	4,998 (5.1)	7,235 (3.7)	0.069

Table A1. Data sources accessed at ICES

Dataset	Description
Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD)	The DAD is compiled by the Canadian Institute for Health Information and contains administrative, clinical (diagnoses and procedures/interventions), demographic, and administrative information for all admissions to acute care hospitals, rehab, chronic, and day surgery institutions in Ontario. At ICES, consecutive DAD records are linked together to form 'episodes of care' among the hospitals to which patients have been transferred after their initial admission.
National Ambulatory Care Reporting System (NARCS)	The NACRS is compiled by the Canadian Institute for Health Information and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centres (emergency departments, day surgery units, hemodialysis units, and cancer care clinics). At ICES, NACRS records are linked with other data sources (DAD, OMHRS) to identify transitions to other care settings, such as inpatient acute care or psychiatric care.
Ontario Health Insurance Plan Claims Database (OHIP)	The OHIP claims database contains information on inpatient and outpatient services provided to Ontario residents eligible for the province's publicly funded health insurance system by fee-for-service health care practitioners (primarily physicians) and "shadow billings" for those paid through non-fee-for-service payment plans. The main data elements include patient and physician identifiers (encrypted), code for service provided, date of service, associated diagnosis, and fee paid.
Same-Day Surgery (CIHI SDS)	The SDS is compiled by the Canadian Institute for Health Information and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to day surgery institutions in Ontario. The main data elements include patient demographics, clinical data (diagnoses, procedures, physician), administrative data (institution/hospital number etc.), financial data, service-specific data elements for day surgery and emergency.

Population and Demographics	
Registered Persons Database (RPDB)	The RPDB provides basic demographic information (age, sex, location of residence, date of birth, and date of death for deceased individuals) for those issued an Ontario health insurance number. The RPDB also indicates the time periods for which an individual was eligible to receive publicly funded health insurance benefits and the best known postal code for each registrant on July 1st of each year.
Vital Statistics – Office of the Registrar General – Deaths (ORGD)	The ORGD Vital Statistics Database contains information on all deaths registered in Ontario starting on January 1, 1990. Information on the causes of death (immediate, antecedent, and underlying) recorded on the death certificate are captured. At ICES, a single cause of death variable is derived based on the underlying cause of death if available and, otherwise, the immediate cause of death using the ICD-9 coding system.
Postal Code Conversion File (PCCF)	The PCCF database will link to postal codes within a given cohort and determine other census geographic identifiers such as, dissemination/enumeration area, census division, longitute/latitude, urban/rural flag and neighbourhood income quintile.
Immigration, Refugees and Citizenship Canada Dataset (IRCC)	The Ontario portion of the IRCC Permanent Resident Database includes immigration application records for people who initially applied to land in Ontario since 1985. The dataset contains permanent residents' demographic information such as country of citizenship, level of education, mother tongue, and landing date. New immigrants who are currently residing in Ontario but originally landed in another province are not captured in this dataset.
ICES-Derived Cohorts	
Ontario Hypertension Dataset (HYPER)	The Ontario Hypertension Database is an ICES-derived cohort and created using a definition of ≥2 physician billing claims with a diagnosis of hypertension (OHIP diagnosis codes: 401-405) and/or ≥1 inpatient hospitalization or same day surgery record with a diagnosis of hypertension (ICD-9 diagnosis codes: 401-405; ICD-10 diagnosis codes: I10-I13, I15; in any diagnostic code space) in a two-year period applied to hospitalization (DAD), same day surgery (SDS), and physician billing claims (OHIP) data to determine the

	diagnosis date for incident cases of hypertension in Ontario. Physician claims and hospitalizations with a diagnosis of hypertension occurring within 120 prior to and 180 days after a gestational hospitalization record are excluded.
Linked Delivering Mothers and Newborns (MOMBABY)	The ICES MOMBABY Database is an ICES-derived cohort that links the DAD inpatient admission records of delivering mothers and their newborns. From 2002 onward, this linkage is performed deterministically using a maternal-newborn chart matching number. Prior to 2002, mothers were linked to their children by matching on the institutions they were admitted, their postal codes, and their admission/discharge dates.
Ontario Diabetes Dataset (ODD)	The Ontario Diabetes Database is an ICES-derived cohort and is created using algorithms applied to inpatient hospitalization (DAD) records, same day surgery (SDS) records, and physician billing claims (OHIP) data to determine the diagnosis date for incident cases of diabetes in Ontario. For adults aged 19 years and greater, the definition for diabetes is 2 physician billing claims with a diagnosis for diabetes (OHIP diagnosis code: 250) or 1 inpatient hospitalization or same day surgery record with a diagnosis for diabetes (ICD-9 diagnosis code: 250; ICD-10 diagnosis codes: E10, E11, E13, E14; in any diagnostic code space), or 1 Ontario Drug Benefit (ODB) claim for diabetes. Physician claims and hospitalizations with a diagnosis of diabetes occurring within 120 prior to and 180 days after a gestational hospitalization record were excluded.

Table A2. Codes and descriptions for group classifications

Group	Specific Code	Database
Endometriosis medical	617	OHIP
	(ICD-9) 617	CIHI (DAD/SDS)
	(ICD-10) N80	CIHI (DAD/SDS)
Endometriosis surgical	(ICD-9) 617 and one of: Hysterectomy: 8020, 8030, 8040, 8050, 8060,	CCP CIHI (DAD/SDS)

	Major surgery: 5741, 5742, 5743, 5451, 5752, 5753, 5754, 5755, 5756, 5759, 6611, 6619, 682, 6831, 6832, 6833, 6841, 6842, 6871, 6872, 6873, 6879, 6881, 6882, 6883, 6884, 6885, 6886, 6889, 6911, 6912, 6913, 6914, 6915, 6921, 6929, 6931, 6939, 694, 6951, 6959, 696, 7101, 7103, 7109, 7111, 7119, 802, 807, Intermediate surgery: 660, 662, 663, 664, 6681, 6682, 6683, 6684, 6981, 6982, 6983, 6989, 770, 7711, 7712, 7719, 772, 773, 774, 7741, 7742, 775, 7751, 7752, 777, 781, 7821, 7822, 8011, 8019, 8129, 8132, Minor surgery: 6683, 7781, 7782, 7789, 780, 787, 7881, 7889, 8081, 8083, 8109, 814, 8169, 8192, 8222, 8223	
	(ICD-10) N80 and one of: Hysterectomy: 1RM91AA, 1RM91DA, 1RM91CA, 1RM91LA, 1RM89AA, 1RM89DA, 1RM89CA, 1RM89LA, 1RM87DAGX with extent attribute SU, 1RM87LAGX with extent attribute SU Major surgery: 1RB59, 1RF59, 1RF50, 1RB52, 1RD52, 1RF52, 1RB87, 1RF87, 1RB89, 1RD89, 1RF89, 1RB57, 1RB74, 1RF74, 1RB58, 1RD72, 1RF72, 1RB56, 1RF56, 1RB80, 1RF80, 1RB83, 1RF83, 1RB85, 1RF51, 1RM52, 1RM57, 1RM74, 1RM73, 1RM72, 1RM80 Minor surgery: 1OT72DA, 2OT70DA, 2OT71DA, 2RM70, 2RM71, 2NM70, 1RM59DAAG, 1RM59DAGX Oophorectomy: 1RD89, 1RB89	CCI CIHI (DAD/SDS)

Table A3. Variables used to define covariates

Group	Specific code	Descriptor	Database
Immigration status		1) Immigrant, Refugee or Other 2) Canadian born	IRCC
Parity		1) Parous – any birth (live or stillbirth) prior to the index date 2) Nulliparous – no evidence of live or stillbirth prior to index date *birth date of baby is used; if this is missing, mother's admission date is used	MOMBABY
Obesity	278		OHIP
Hypertension		ICES derived hypertension cohort (see Table A1)	
Diabetes		ICES derived diabetes cohort (see Table A1)	

Table A4. Other group classifications

Group	Specific Code	Database
Pelvic pain	625	OHIP
	(ICD-9) 6250, 6253	CIHI (DAD/SDS)
	(ICD-10) N941, N944, N945, N946, R102, R103	CIHI (DAD/SDS)
Fibroids	628	OHIP
	(ICD-9) 2180, 2181, 2182, 2189	CIHI (DAD/SDS)
	(ICD-10) D250, D251, D252, D259	CIHI (DAD/SDS)
Premature ovarian insufficiency	627, diagnosed at age <45 yo	OHIP
Infertility	628	OHIP

Table A5. Outcome Classifications

Group	Specific Code	Database
PRIMARY OUTCOME: HOSPITALIZATION DUE TO MAJOR CVD EVENT		
Acute MI	(ICD-9) 410	CIHI (DAD/SDS)
	(ICD-10) I21, I22	CIHI (DAD/SDS)
Stroke	(ICD-9) 430, 431, 434, 436, 3623	CIHI (DAD/SDS)
	(ICD-10) I60, I61, I630, I631, I632, I633, I634, I635, I637, I638, I639, I64, H341	CIHI (DAD/SDS)
Congestive Heart Failure	(ICD-9) 428	CIHI (DAD/SDS)
	(ICD-10) I50	CIHI (DAD/SDS)
Ischemic Heart Disease	(ICD-9) 410, 411, 412, 413, 414	CIHI (DAD/SDS)
	(ICD-10) I20, I21, I22, I23, I24, I25	CIHI (DAD/SDS)
Cerebrovascular Disease	(ICD-9) 430, 431, 432, 433, 434, 435, 436, 437, 438	CIHI (DAD/SDS)
	(ICD-10) I60, I61, I62, I63, I64, I65, I66, I67, I68, I69	CIHI (DAD/SDS)

Percutaneous coronary intervention	4802, 4803, 4809	CCP CIHI (DAD/SDS)
	1IJ50, 1IJ57GQ	CCI CIHI (DAD/SDS)
Coronary artery bypass graft surgery	481	CCP CIHI (DAD/SDS)
	1IJ76	CCI CIHI (DAD/SDS)
SECONDARY OUTCOME: SECONDARY CVD EVENTS OF INTEREST		
Cardiac catheterization	Z442 G297	OHIP feecode
	4892, 4893, 4894, 4895, 4896, 4897, 4898, 4995, 4996, 4997	CCP CIHI (DAD/SDS)
	3IP10	CCI CIHI (DAD/SDS)
Unstable Angina	(ICD-9) 411, 413	CIHI (DAD/SDS)
	(ICD-10) I20	CIHI (DAD/SDS)
Ischemic stroke	(ICD-9) 434, 436, 3623	CIHI (DAD/SDS)
	(ICD-10) I630, I631, I632, I633, I634, I635, I637, I638, I639, I64, H341	CIHI (DAD/SDS)
Hemorrhagic stroke	(ICD-9) 430, 431	CIHI (DAD/SDS)
	(ICD-10) I60, I61	CIHI (DAD/SDS)
Transient ischemic attack	(ICD-9) 435	CIHI (DAD/SDS)
	(ICD-10) G450, G451, G452, G453, G455, G456, G457, G458, G459, H340	CIHI (DAD/SDS)
Atrial fibrillation	(ICD-9) 4273	CIHI (DAD/SDS)
	(ICD-10) I48	CIHI (DAD/SDS)
Peripheral vascular disease	Abdominal Aortic Aneurysm: (ICD-9) 4413, 4414 Peripheral Artery Disease: (ICD-9) 4402, 4439, 4442 Carotid Endarterectomy/Stent CCP code: 5012	CIHI (DAD/SDS) & CCP CIHI (DAD/SDS)
	Abdominal Aortic Aneurysm: (ICD-10) I713, I714 Peripheral Artery Disease: (ICD-10) I702, I739, I743, I744	CIHI (DAD/SDS) &

	Carotid Endarterectomy/Stent CCI codes: 1JE57, 1JE50, 1JE87	CCI CIHI (DAD/SDS)
SECONDARY OUTCOME: EMERGENCY DEPARTMET VISITS FOR CVD:		
Hypertension	(ICD-9) 401, 402, 403, 404, 405	CIHI (NARCS)
	(ICD-10) I10, I11, I12, I13, I15	CIHI (NARCS)
Diabetes Mellitus	(ICD-9) 250	CIHI (NARCS)
	Type 1: (ICD-10) E10 Type 2: (ICD-10) E11, E13, E14	CIHI (NARCS)
Cardiovascular Disease	(ICD-9) 4100 – 4599 excluding: 4161, 4170, 420, 4210, 4211, 4219, 422, 4231, 4249, 4252, 4253, 4255, 4256, 4258, 4268, 4290, 4417, 443, 4460, 4461, 4462, 4463, 4464, 4467, 4470, 4474, 4475, 4477, 4480, 4481, 455, 4560, 4561, 4562, 4563, 4564, 4565, 4566, 4567, 4568, 4570, 4572, 459	CIHI (NARCS)
	(ICD-10) I00 – I99 excluding: I01, I02, I05, I06, I07, I08, I09, I271, I301, I320, I321, I328, I330, I39, I400, I410, I411, I412, I418, I426, I427, I430, I681, I84, I85, I891, I972, I980, I981, I982, I983	CIHI (NARCS)