ERECTILE DYSFUNCTION MEDICATIONS:

A GATEWAY DRUG FOR MEN

by

SEAN CHRISTOPHER TOSHIAKI SKELDON

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Abstract

Background – Erectile dysfunction (ED) has been described as providing a 'window of curability' for men at risk of future cardiovascular disease, however there is little evidence on the relationship between erectile dysfunction and modifiable cardiometabolic risk factors. The primary objectives of this thesis were to: 1) determine whether men with ED have a higher risk of having an undiagnosed cardiometabolic risk factor (hypertension, hypercholesterolemia and diabetes), and 2) determine whether the prescription of a phosphodiesterase type 5 inhibitor (PDE5i) for ED leads to an increase in the diagnosis and treatment of these risk factors.

Methods – This thesis comprised of two original studies. The first, a cross-sectional analysis using a nationally representative survey from the United States. The second, a population-based empirical study of changes in drug utilization for cardiometabolic risk factors following PDE5i prescription in British Columbia. An individual-level time series analysis with switching replications was utilized for this analysis.

Results – Men with ED were found to have double the odds of having undiagnosed diabetes compared to those without ED. This was most significant among middle-aged men (ages 40-59 years), as the predicted probability of having undiagnosed diabetes increased from 1 in 50 in men without ED to 1 in 10 in men with ED. Among men aged 40 to 59 years old in British Columbia, we found a sudden increase in prescriptions for antihypertensives (28 per 1,000), statins (15 per 1,000), and antidiabetics (18 per 1,000) in the 90 days following a new prescription for a PDE5i. For both hypercholesterolemia and diabetes, relevant screening tests performed in the 30 days following PDE5i prescription were responsible for this change. This increase was followed by a significant declining trend in prescriptions for all three drugs.

Conclusions – Men with ED have an increased risk for undiagnosed cardiometabolic risk factors. PDE5is can act as a 'gateway drug' for men to be newly treated for these risk factors provided physicians perform the requisite screening investigations. Increased education and awareness of this relationship among both patients and physicians is critical for exploiting the potential for preventing future cardiovascular disease.

Preface

The work presented in this thesis was conducted and written by Sean Skeldon (SS). SS developed the research objectives, study design and analytical approach with the assistance of the thesis committee (Drs. Michael Law, Steven Morgan, Allan Detsky and Larry Goldenberg).

The study from Chapter 2 used publicly available data from the National Health and Nutrition Examination Survey. SS designed the study, abstracted all data, performed all data analyses and drafted all material related to the study.

The study using data from Population Data BC and PharmaNet (Chapter 3) is a contribution to a broader research project managed by Steven Morgan entitled "Sex, gender and equity in prescription drug access, appropriateness, and affordability". The study was approved by the Behavioural Research Ethics Board at the University of British Columbia (certificate number: H11-02273). With the assistance of Michael Law and Steven Morgan, SS completed the documentation for data access requests and data extractions from Population Data BC related to this project. Lixiang Yan, a programmer at CHSPR, extracted the data according to SS requests and removed all personal identifiers prior to providing the dataset for analysis, as per confidentiality data agreements. SS designed the empirical approach, study design, methodology, compiled results and drafted all material related to the study. Lucy Cheng, an analyst at CHSPR, conducted the data analyses for this study.

The thesis committee provided guidance at various steps in the research process and offered critical feedback on earlier drafts prior to submission of this thesis to the UBC Faculty of Graduate Studies.

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List of Abbreviations

BC   British Columbia

BMI   body mass index

CI   confidence interval

CMRF   cardiometabolic risk factor

CVD   cardiovascular disease

ED   erectile dysfunction

MEC   Mobile Examination Center

NHANES   National Health and Nutrition Examination Survey

OR   odds ratio

PDE5i   phosphodiesterase type 5 inhibitor

PPI   proton pump inhibitor

WC   waist circumference

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Sincere thanks to Dr. Larry Goldenberg for his endless encouragement and support in my career and research pursuits. His passion for men's health and willingness to take me under his wing is the reason I came to Vancouver to complete my thesis. Throughout my time in Vancouver he always found time to meet despite how busy his schedule was, and always provided great insight and support for my work. Thanks to Dr. Allan Detsky for his amazing support, guidance, and counselling for both my research and career goals. I would also like to thank Dr. Steve Morgan for allowing me access to his grant and for his insightful feedback and suggestions.

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1 Introduction

1.1 Background and rationale

1.1.1 The dilemma: men and cardiovascular disease

In Canada, heart disease and stroke comprise two of the top three leading causes of death.[1] There exists a discrepancy in deaths from cardiovascular disease (CVD) between men and women, with men having a higher age-standardized mortality rate of 177.2 per 100,000 population for major CVD compared to 109.5 for women.[2] In comparing ischemic heart disease, the difference is two-fold with men having a rate of 103.2 versus 51.1 for women. One reason for this difference is that men are dying of cardiovascular disease at a younger age than women, with 61.4% of all CVD deaths in men occurring between 45 to 64 years of age, compared to only 36.7% in women.[3] As such, men are candidates for early screening and preventive care to reduce the burden of death from CVD. This is evident in the Canadian Cardiovascular Society (CCS) screening guidelines, as screening for lipid disorders is recommended in men starting at 40 years of age but not until 50 years of age in women.[4]

1.1.2 The obstacle: men and health-seeking behaviour

Unfortunately, men are less likely to utilize the healthcare system and ultimately be screened. This was evident in the 2005 Canadian Community Health Survey (CCHS), as women aged 18 to 64 were much more likely to have consulted with a general practitioner in the previous 12 months compared to men (OR 1.77, 95%CI 1.68-1.86).[5] This is not a problem unique to Canadians either, as The Commonwealth Fund survey conducted in the United States found that men were three times more likely to have not seen a physician in the previous 12 months (24% vs 8%).[6] Furthermore, 41% of men had not received any preventive services in the past year, compared to only 16% of women. To compound the matter, men are more likely to ignore health symptoms and to not seek health services for them.[7,8] Expecting men to visit a healthcare practitioner for asymptomatic cardiometabolic risk factors (CMRF) such as hypertension,

hypercholesterolemia, and diabetes becomes even more challenging. Without an impetus for men in this age range to see a doctor, they will remain an elusive target for screening and preventive care.

1.1.3 The canary in the coal mine: erectile dysfunction

Erectile dysfunction is defined as "an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function".[9] It is a highly prevalent disease in Canada, with one cross-sectional study finding a 49.4% prevalence in Canadian men aged 40 to 88 years old seen by primary care physicians.[10] What makes erectile dysfunction relevant to the discussion of CVD in men is that both diseases share common risk factors including diabetes mellitus, current smoking, metabolic syndrome, and hypertension.[11] In fact, over the past decade research has suggested that erectile dysfunction could in fact be a marker or precursor to CVD. Thompson et al. first demonstrated this in 2005 using data from the Prostate Cancer Prevention Trial, which prospectively evaluated men over 55 years of age for CVD and erectile dysfunction every 3 months between 1994 and 2003.[12] They found that incident erectile dysfunction was associated with a hazard ratio of 1.27 (95%CI 1.05-1.55) for subsequent cardiovascular events. The predictive strength of erectile dysfunction was stronger than body mass index (BMI) and similar to age and having a family history of myocardial infarction. Recently, a meta-analysis of prospective cohort studies found an overall relative risk of 1.48 (95%CI 1.25 to 1.74) for CVD and 1.19 (95%CI 1.05 to 1.34) for all-cause mortality.[13] The proposed explanation for this relationship is the 'artery size hypothesis', which posits that the smaller luminal diameter of the penile arteries will obstruct and become symptomatic faster than the coronary arteries.[14]

1.1.4 The link: phosphodiesterase type 5 inhibitors (PDE5i)

With the advent and widespread availability of PDE5is, beginning with sildenafil in 1999, men with erectile dysfunction have had an accessible and effective treatment at their disposal. In light of this, erectile dysfunction has been suggested as a motivator for men to access the healthcare system.[15,16] As well, these men are already at risk of CVD and are the optimal screening targets.

Data from the BC Rx Atlas and Statistics Canada was obtained to depict the age-related increase in

PDE5i prescriptions in BC and deaths from ischemic heart disease in Canada.[17,18] As shown in Figure 1.1,

there is a rapid rise in PDE5i prescriptions in BC beginning in men in their thirties and peaking in their

sixties. This is paralleled in death from ischemic heart disease in Canada, however with a 10-year lag in

ages. This 10-year delay is the ideal period for men with erectile dysfunction to undergo CVD screening

and preventive therapy.

Figure 1.1   Erectile dysfunction medication use (red) in British Columbia and death from
ischemic heart disease (blue) among men in Canada
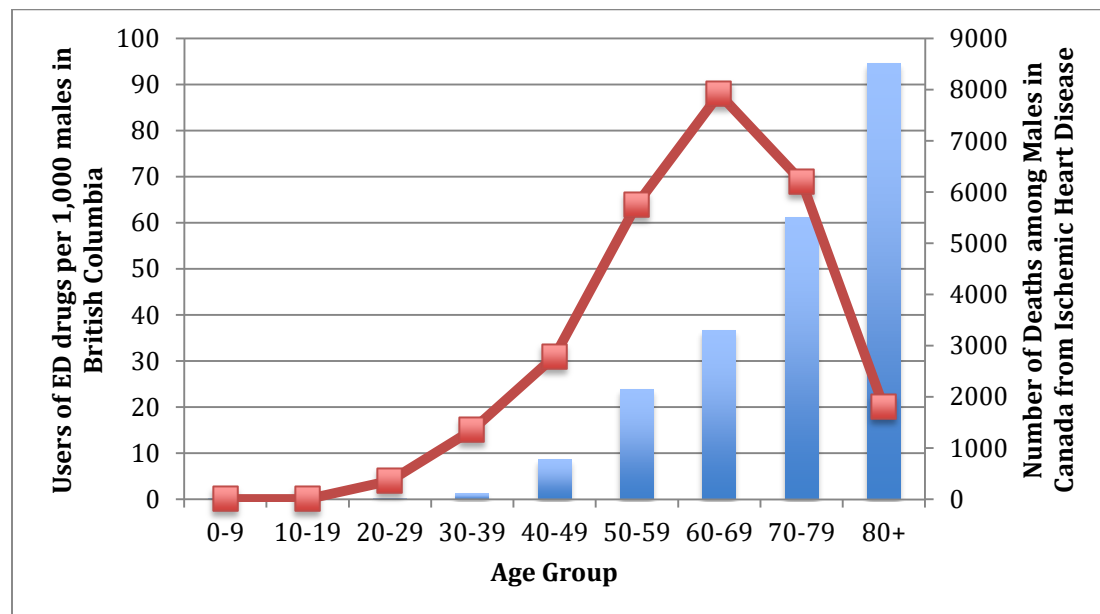
The Princeton III Consensus Recommendations for the management of erectile dysfunction and CVD

outline specific risk assessments (Table 1.1).[19] With these guidelines, the hope is that men seeking care

for erectile dysfunction will undergo screening for cardiometabolic risk factors, leading to early

recognition and prevention of CVD.

Table 1.1   Princeton III consensus recommendations for men with erectile dysfunction and no previous history of cardiovascular disease[19]

Patient history, including age, presence or absence of comorbid conditions (e.g. abdominal obesity, hypertension, dyslipidemia, prediabetes, and symptoms suggestive of obstructive sleep apnea), family history of premature atherothrombotic CVD (father aged <55 years or mother aged <65 years; ACCF/AHA class I, LOE B), and lifestyle factors (e.g. diet, excessive use of alcohol, limited physical activity, and smoking)
Physical examination noting BP, waist circumference (WC), body mass index (BMI), fundal arterial changes, cardiac auscultation, carotid bruits, and palpation of femoral and pedal pulses
ED severity (International Index of Erectile Function score or Sexual Health Inventory of Men) and duration
Resting electrocardiogram (ACCF/AHA class IIa, LOE C in asymptomatic adults with hypertension or diabetes and ACCF/AHA class IIb, LOE C in asymptomatic adults without hypertension or diabetes)
Fasting plasma glucose level
Serum creatinine level (estimated GFR) and albumin to creatinine ratio
Total testosterone (TT) level (before 11 AM)
Plasma lipid levels (total, low-density lipoprotein and HDL cholesterol and triglyceride values

1.2   Research objectives

While there is ample evidence supporting erectile dysfunction as a marker for future cardiovascular disease,[13] what remains unclear is the potential benefits that can be gained from exploiting this association. Men with erectile dysfunction have been shown to have a higher prevalence of cardiometabolic risk factors such as hypertension and diabetes,[11] but whether these men also have a higher rate of undiagnosed cardiometabolic risk factors is unknown. While several studies have attempted to investigate this question,[20–23] they have all drawn their samples from non-representative sources such as outpatient clinics.

Furthermore, whether PDE5is can in fact act as a 'gateway drug' for men to be newly treated for these CMRFs is not clear. Whether men seeking treatment for erectile dysfunction leads to an increase in appropriate cardiovascular screening strategies and preventive therapies is unknown. Only one study by Kirby et al. attempted to assess whether the prescription of PDE5is for ED lead to an increase in new diagnoses.[24] This study used medical records registered in The Health Improvement Network (THIN) database in the UK, which is a primary-care administrative database containing the electronic medical

records of 5% of the UK population. They found that compared with an age-matched control population, the additional detection rate of an unknown underlying disease at index PDE5i prescription was 45 for hypertension, 61 for hypercholesterolemia, 38 for diabetes and 5 for hypogonadism per 10,000 men. The study only included men with a continuous medical history of 5 years or more, thereby necessitating that all men in their study were regularly using the healthcare system prior to PDE5i prescription. As well, the authors were unable to determine how many men had screening bloodwork done following prescription of the PDE5i. This thesis will attempt to address these questions and investigate the relationship between erectile dysfunction and cardiovascular prevention.

The objectives of this thesis are:

1) To determine whether men with erectile dysfunction have a higher risk of having an undiagnosed cardiometabolic risk factor (hypertension, hypercholesterolemia and diabetes).

2) To determine whether the prescription of a PDE5i leads to an increase in the diagnosis and treatment of cardiometabolic risk factors (hypertension, hypercholesterolemia and diabetes).

1.3   Thesis outline

This thesis is presented in four chapters. Research chapters two and three contain a complete description of the rationale, methods, results, interpretation, and conclusions of the two original studies conducted: 1) a study examining the presence of undiagnosed cardiometabolic risk factors in men with erectile dysfunction using a nationally representative survey from the United States, and 2) a population-based study of changes in drug utilization for cardiometabolic risk factors following PDE5i prescription in British Columbia. Drawing on the findings of both research chapters, chapter four provides a summary of overall findings, strengths and limitations of the thesis research, and recommendations for future research and initiatives.

2 Erectile dysfunction and the presence of undiagnosed type 2 diabetes, hypertension and hypercholesterolemia

2.1 Introduction

One of every three deaths in the United States (U.S.) is attributable to cardiovascular disease (CVD).[25] The importance of hypertension, hypercholesterolemia, and diabetes as risk factors for cardiovascular disease is well-recognized.[26] With 45% of U.S. adults having one of these cardiometabolic risk factors (CMRF), early diagnosis and effective management can significantly reduce the impact of CVD.[27] Unfortunately, in over 15% of U.S. adults, one or more of these three CMRFs is undiagnosed.[27] Approximately 8% of adults have undiagnosed hypertension, 8% have undiagnosed hypercholesterolemia and 3% have undiagnosed diabetes. From a public health perspective this is concerning, as the potential benefits of early recognition and risk reduction are limited. This is particularly true for men, owing to their greater reluctance for preventive care and significantly higher prevalence of CVD compared to women.[28,29] Identifying easily observable risk factors associated with undiagnosed CMRFs, particularly in men, may improve early diagnosis and subsequent treatment.

Over the past decade, evidence has suggested that erectile dysfunction (ED) is an early indicator for cardiovascular disease. Thompson et al. first demonstrated this in 2005, finding that incident erectile dysfunction was associated with a hazard ratio of 1.27 (95% confidence interval [CI] 1.05-1.55) for subsequent cardiovascular events.[30] In fact, the predictive strength of erectile dysfunction for adverse cardiovascular events was stronger than body mass index (BMI) and similar to age and a family history of myocardial infarction. Recently, a meta-analysis of prospective cohort studies found erectile dysfunction was associated with an overall relative risk of 1.48 (95%CI 1.25 to 1.74) for CVD.[13] Further studies have suggested that the prognostic value of ED for future CVD is strongest in middle-aged men under the age of 60.[31–33] In light of this, ED has been described as providing a "window of curability" for men at risk of future CVD.[16]

As a marker of endothelial dysfunction, ED shares many of the same risk factors as CVD, including hypertension, hypercholesterolemia and diabetes.[34] Although numerous studies have shown that men with these CMRFs are at higher risk of having ED, there is a lack of empirical evidence for the inverse relationship.[20,21] Specifically, it is not known whether ED is a risk factor for having underlying hypertension, hypercholesterolemia or diabetes. Although several studies have suggested at a possible relationship,[20–23] they have all drawn their samples from non-representative sources such as outpatient clinics. The largest such study was by Grover et al.,[10] who surveyed a cross-sectional sample of 3,921 Canadian men attending primary care clinics. After only adjusting for age, they found that ED was positively associated with undiagnosed hyperglycemia (odds ratio 1.46, 95%CI 1.02-2.10). Such studies suffer from potential detection bias, however, as patients visiting their physicians are more likely to have already been screened for CMRFs due to increased health-seeking behaviour. Therefore, we studied the association between erectile dysfunction and undiagnosed cardiometabolic risk factors (hypertension, hypercholesterolemia, and diabetes mellitus) using a nationally representative sample of men.

2.2 Methods

2.2.1 Data source

Our study used the National Health and Nutrition Examination Survey (NHANES) conducted by the U.S. National Center for Health Statistics for the Centers for Disease Control and Prevention. The NHANES is a nationally representative survey of the resident civilian, non-institutionalized U.S. population conducted in 2-year cycles. A complex, 4-stage probability sampling design is used to provide a representative sample of residents and has been described previously.[35] NHANES consists of questionnaires administered in the home and a standardized physical examination conducted in specially equipped mobile examination centers (MECs). Additional questionnaires covering more sensitive topics are administered in private rooms in the MECs. The standardized physical examination consists of medical, dental, physiological and laboratory assessments. A 50% subsample of participants completing the MEC

component of NHANES had fasting blood work completed. We pooled the 2001-2002 and 2003-2004 cycles of NHANES, as these survey waves were the most recent that asked questions regarding erectile dysfunction.

2.2.2 Erectile dysfunction

Erectile dysfunction was assessed in NHANES with the question: "*Many men experience problems with sexual intercourse. How would you describe your ability to get and keep an erection adequate for satisfactory intercourse?*" This question was asked through an audio computer-assisted self-interview in a private room in the MEC. This single, self-reported question has previously been validated for clinical erectile dysfunction.[36] We classified erectile dysfunction similar to previous studies,[34,37,38] and considered men responding "*never able*" or "*sometimes able*" to have erectile dysfunction and considered those responding "*usually able*" or "*always or almost always able*" to have normal erectile function.

2.2.3 Study definitions

We determined the presence of previously diagnosed CMRFs using a similar approach to prior studies.[39–43] We classified men responding "*Yes*" to the question "*Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure*" or those reporting use of antihypertensive medications as having known or diagnosed hypertension. Antihypertensive medications included angiotensin-converting enzyme inhibitors, angiotensin II receptors blockers, beta-blockers, calcium channel blockers, diuretics, centrally acting alpha-blockers, and renin inhibitors. We identified men responding "*Yes*" to similarly worded questions for "*... your blood cholesterol level was high*" or "*... you have diabetes or sugar diabetes*" and those taking antihyperlipidemic agents or antidiabetic agents (including insulin) as having previously diagnosed hypercholesterolemia or diabetes, respectively.

2.2.4 Other variables

In our statistical models, we also included potential confounding variables based on those used in earlier studies.[34,37,44] These included age (20-39, 40-59, ≥60 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), current smoking status, and alcohol use. Relevant medical

history included a previous history of cardiovascular disease (included angina, heart attack, coronary heart disease, congestive heart failure or stroke) and a family history of diabetes, hypertension or stroke before the age of 50, and heart attack or angina before the age of 50. We considered men responding "*more active*" to the question "*Compared with most men your age, would you say that you are ...*" to be physically active.[41] Otherwise, those responding "*less active*" or "*about the same*" were considered not physically active. We also used the World Health Organization classification of obesity using BMI and waist circumference (WC) to categorize men as obese (BMI ≥30 kg/m^2 or WC ≥102 cm), overweight (BMI ≥25 kg/m^2 but <30 kg/m^2 or WC ≥94 cm but <102 cm) or not overweight or obese (BMI <25 kg/m^2 or WC <94 cm).[45]

2.2.5   Outcomes

Our study used physical examination and laboratory measures to identify undiagnosed CMRFs. For each CMRF, we only assessed undiagnosed disease in men without a previous diagnosis, as described above. We used the same diagnostic criteria as the National Center for Health Statistics in their estimates of national rates of undiagnosed CMRFs in the U.S.[27,46] In NHANES, blood pressure measurements were performed by trained health professionals using a mercury sphygmomanometer and up to three blood pressure determinations were taken. We considered men with an average systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg to have undiagnosed hypertension. We classified men as having undiagnosed hypercholesterolemia if they had a total cholesterol measurement of ≥6.21 mmol/L (≥240 mg/dL). Finally, we classified men as having undiagnosed diabetes if they presented with a fasting plasma glucose level ≥7.0 mmol/L (≥126 mg/dL).

2.2.6   Study design

From the 21,161 respondents to NHANES for 2001 to 2004, we studied the 4,519 men aged ≥20 years who had completed both the interview and MEC components (Figure 2.1). We also excluded men with a reported history of prostate cancer (142, 3.0%) due to their increased risk of erectile dysfunction from

cancer treatment. We also excluded 523 (11.6%) of the 4,519 men who had missing responses to the question on erectile function, and 526 (13.2%) men with missing values on the other covariates.

The remaining 3,470 men were then used to create two study subsamples, one for examining undiagnosed hypertension (Blood Pressure sample) and one for undiagnosed hypercholesterolemia (Cholesterol sample). After removing men without a systolic or diastolic blood pressure measurement and those with a previous diagnosis of hypertension, our final Blood Pressure analytic sample consisted of 2,224 men. After similar exclusions specific to hypercholesterolemia, our final analytic sample for Cholesterol consisted of 2,287 men.

From the 4,159 men, a Fasting Glucose subsample was derived based on those that had undergone fasting bloodwork. This Fasting Glucose subsample included 1,950 men. A total of 161 (8.3%) men had missing responses to the question on erectile function and were excluded. A further 220 (12.3%) men with missing values for the other covariates were excluded. After we excluded men with missing fasting glucose levels and previous diabetes diagnoses, our final Fasting Glucose analytic sample consisted of 1,417 men.

Figure 2.1 Flowchart depicting creation of three analytic subsamples (Blood Pressure, Cholesterol, Fasting Glucose) from NHANES 2001-2004 for undiagnosed hypertension, hypercholesterolemia and diabetes
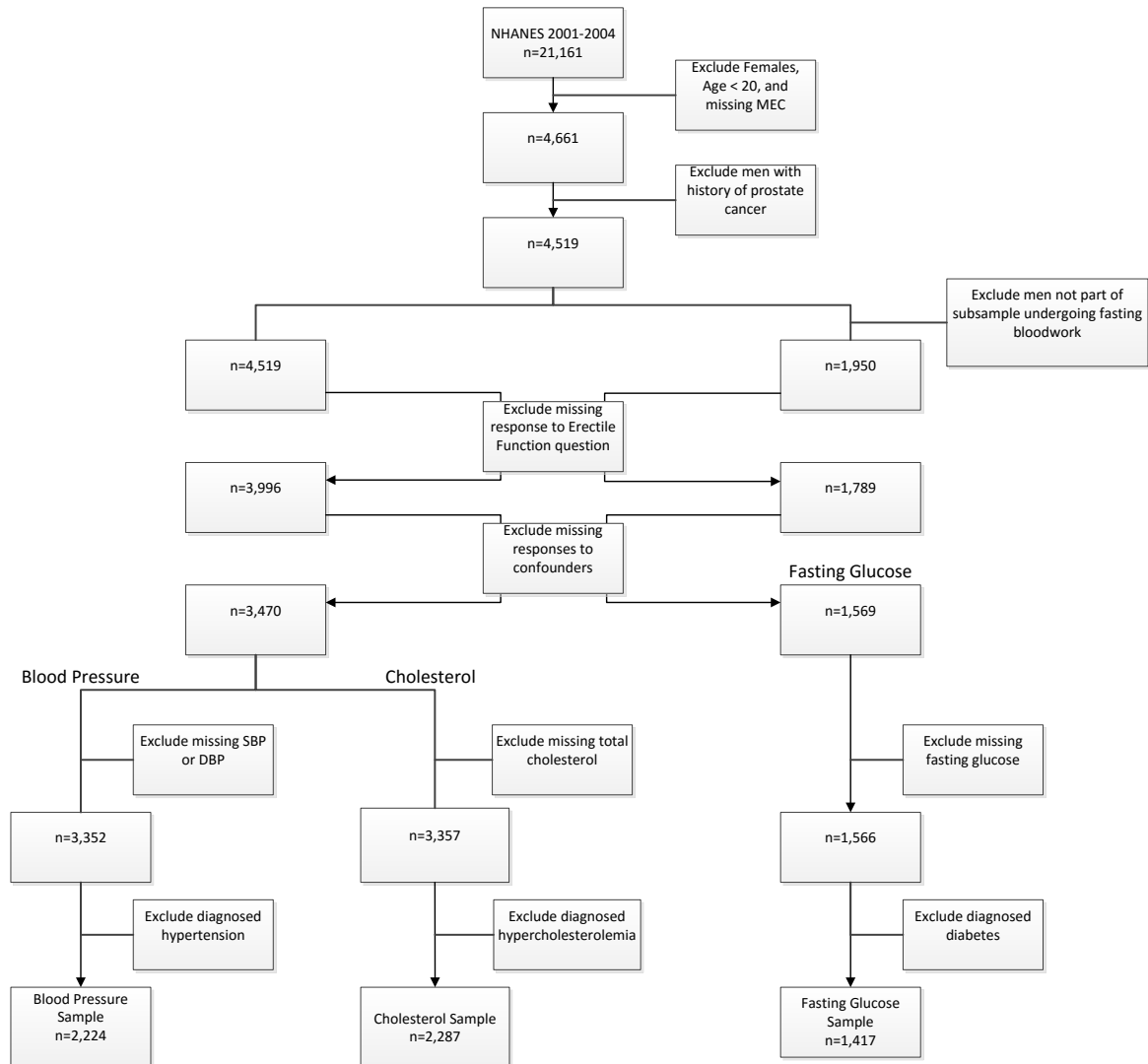
2.2.7 Statistical analysis

We used logistic regression analysis to investigate the relationship between erectile dysfunction with undiagnosed hypertension, undiagnosed hypercholesterolemia, and undiagnosed diabetes in each of the corresponding analytic samples (Blood Pressure, Cholesterol, Fasting Glucose). Probability sampling weights based on the 2000 U.S. census were assigned to each individual in the sample to account for the complex sampling design of the survey. Subsample fasting sampling weights were utilized for analysis of the Fasting Glucose sample. Standard errors for all estimates were obtained using the Taylor series

(linearization) method.[35] Adjusted odds ratios (OR) and their 95% confidence intervals were then estimated using multivariable logistic regression analysis. We performed an additional post-hoc analysis to test for interactions between ED and age as well as a stratified analysis in men without a previous history of cardiovascular disease. The predicted probability of each outcome in the average man was then determined using the regression coefficients from each model.

Due to missing data for erectile dysfunction in both the Blood Pressure and Cholesterol samples (11.6%) and the Fasting Glucose sample (8.3%), the demographics of individuals with missing data were examined. Individuals with missing data were found to be significantly different in race/ethnicity (p<0.001 for both). Because of this, we adjusted the original sampling weights for nonresponse as described by Lohr[47] and recommended in the NHANES analytic guidelines.[48] Past studies using NHANES data have also utilized this approach.[49,50] We used SAS (version 9.3; SAS Institute, Cary, NC) for all analyses.

2.3   Results

The descriptive characteristics of the three analytic samples were largely similar (Table 2.1). Among those in each cohort, the prevalence of ED was 10.9% in the Blood Pressure sample, 12.7% in the Cholesterol sample and 16.2% in the Fasting Glucose sample, respectively.

Table 2.1 Characteristics of analytic study samples for undiagnosed hypertension, hypercholesterolemia, and diabetes: sample sizes and percentages

CHARACTERISTIC	BLOOD PRESSURE Sample (n=2,224)		CHOLESTEROL Sample (n=2,287)		FASTING GLUCOSE Sample (n=1,417)	
	n	%[a]	n	%	n	%
Erectile Dysfunction						
No	1874	89.1%	1813	87.3%	1090	83.8%
Yes	350	10.9%	474	12.7%	327	16.2%
Age Category						
20-39 years	1029	49.8%	1027	51.5%	539	43.6%
40-59 years	789	40.3%	732	37.1%	487	40.5%
60+ years	350	9.9%	528	11.5%	391	15.9%
Ethnicity						
White	1142	71.4%	1158	70.4%	788	72.6%
Black	391	9.1%	441	10.2%	242	9.8%
Mexican American	539	10.2%	542	10.1%	297	8.5%
Other	152	9.3%	146	9.3%	90	9.1%
Physically Active						
No	1267	58.1%	1329	59.4%	834	61.2%
Yes	957	41.9%	958	40.6%	583	38.8%
Alcohol Use						
Never	159	7.1%	164	7.3%	97	6.8%
Former	195	8.2%	209	8.8%	130	9.1%
Current	1870	84.6%	1914	83.8%	1190	84.1%
Current Smoker						
No	1559	69.8%	1596	68.6%	1043	72.5%
Yes	665	30.2%	691	31.4%	374	27.5%
History of Hypertension						
No	2224	100.0%	1799	82.4%	1042	75.6%
Yes	0	0.0%	488	17.6%	375	24.4%
History of High Cholesterol						
No	1779	79.5%	2287	100.0%	1025	72.2%
Yes	445	20.5%	0	0.0%	392	27.8%
History of Diabetes						
No	2130	96.9%	2159	96.8%	1417	100.0%
Yes	94	3.1%	128	3.2%	0	0.0%
History of Cardiovascular Disease						
No	2154	97.7%	2160	96.8%	1282	93.4%
Yes	70	2.3%	127	3.2%	135	6.6%
Family History of Hypertension/Stroke						
No	1668	72.8%	1669	70.5%	1028	69.6%
Yes	556	27.2%	618	29.5%	389	30.4%
Family History of Angina/Heart Attack						
No	1985	87.0%	2043	87.0%	1263	86.6%
Yes	239	13.0%	244	13.0%	154	13.4%
Family History of Diabetes						
No	1217	54.3%	1262	55.3%	779	54.8%
Yes	1007	45.7%	1025	44.7%	638	45.2%
Obesity[b]						
Not overweight or obese	681	30.8%	689	30.8%	364	25.4%
Overweight	760	33.6%	727	31.3%	476	33.2%
Obese	783	35.7%	871	37.9%	577	41.5%

CHARACTERISTIC	BLOOD PRESSURE Sample (n=2,224)		CHOLESTEROL Sample (n=2,287)		FASTING GLUCOSE Sample (n=1,417)	
	n	%[a]	n	%	n	%
Undiagnosed Disease						
No	1933	89.3%	2017	87.9%	1352	95.8%
Yes	291	10.4%	270	12.1%	65	4.2%

[a] All percentages are probability weighted to account for the NHANES sampling design.
[b] Obesity classified as: obese (BMI $\geq$30 kg/m^2 or WC $\geq$102 cm), overweight (BMI $\geq$25 kg/m^2 but <30 kg/m^2 or WC $\geq$94 cm but <102 cm) or not overweight or obese (BMI <25 kg/m^2 or WC <94 cm)

2.3.1   Erectile dysfunction and undiagnosed hypertension

In the Blood Pressure analytic sample, we found the overall prevalence of undiagnosed hypertension was

10.4% or 1,040 cases per 10,000 men 20 years of age and older. Among men with ED, 19.4% of men had

undiagnosed hypertension compared to 9.3% of men without ED (Table 2.2). Prior to statistical

adjustment (Table 2.3), the odds of having undiagnosed hypertension was higher among men with erectile

dysfunction (OR 2.35 95%CI 1.78-3.11) compared to those without erectile dysfunction. However, after

we adjusted for potential confounders, the association between erectile dysfunction and undiagnosed

hypertension was attenuated and was no longer statistically significant (OR 1.27 95%CI 0.87-1.85).

Table 2.2 Prevalence of undiagnosed hypertension, hypercholesterolemia and diabetes in men with and without erectile dysfunction stratified by age

Age Category	%[a] UNDIAGNOSED HYPERTENSION (N=2224)		% UNDIAGNOSED HYPERCHOLESTEROLEMIA (N = 2287)		% UNDIAGNOSED DIABETES (N=1417)	
	ED	No ED	ED	No ED	ED	No ED
All Ages	19.4%	9.3%	9.4%	12.4%	11.5%	2.8%
20-39 years	7.7%	5.2%	13.1%	9.2%	0.0%	0.8%
40-59 years	15.4%	11.7%	7.5%	17.4%	19.1%	3.3%
60+ years	29.3%	28.6%	9.4%	11.5%	8.5%	11.1%

[a] All percentages are probability weighted to account for the NHANES sampling design.

Table 2.3   Unadjusted and adjusted odds ratios (95%CI) for undiagnosed hypertension, hypercholesterolemia and diabetes among men ≥20 years of age in NHANES 2001-2004

CHARACTERISTIC	UNDIAGNOSED HYPERTENSION (N=2224)		UNDIAGNOSED HYPERCHOLESTEROLEMIA (N = 2287)		UNDIAGNOSED DIABETES (N=1417)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Erectile Dysfunction	2.35 (1.78-3.11)	1.27 (0.87-1.85)	0.73 (0.47-1.15)	0.67 (0.42-1.07)	4.58 (2.54-8.24)	2.20 (1.10-4.37)
Age Category						
20-39 years	REF	REF	REF	REF	REF	REF
40-59 years	2.47 (1.69-3.61)	2.38 (1.55-3.66)	1.88 (1.25-2.84)	1.84 (1.24-2.75)	8.24 (2.49-27.19)	5.56 (1.78-17.35)
60+ years	7.29 (4.90-10.84)	7.41 (4.43-12.37)	1.12 (0.76-1.65)	1.45 (0.87-2.43)	14.83 (5.19-42.34)	8.70 (2.91-26.03)
Ethnicity						
Non-Hispanic White	REF	REF	REF	REF	REF	REF
Non-Hispanic Black	1.47 (1.07-2.02)	1.99 (1.34-2.97)	0.76 (0.47-1.23)	0.87 (0.54-1.40)	0.78 (0.39-1.56)	1.25 (0.57-2.71)
Mexican American	0.64 (0.41-0.98)	0.90 (0.60-1.35)	0.92 (0.64-1.31)	0.97 (0.65-1.46)	0.25 (0.11-0.58)	0.53 (0.21-1.33)
Other	0.66 (0.34-1.30)	0.92 (0.46-1.85)	1.13 (0.64-1.99)	1.37 (0.77-2.44)	1.21 (0.46-3.15)	2.39 (0.87-6.55)
Physically Active	0.99 (0.77-1.28)	0.84 (0.62-1.13)	0.82 (0.59-1.14)	0.84 (0.60-1.18)	0.70 (0.33-1.47)	0.73 (0.35-1.55)
Alcohol Use						
Never	REF	REF	REF	REF	REF	REF
Former	1.57 (0.78-3.17)	1.31 (0.53-3.25)	1.28 (0.54-3.04)	0.90 (0.36-2.26)	1.73 (0.56-5.36)	1.42 (0.47-4.30)
Current	0.85 (0.47-1.51)	0.95 (0.44-2.06)	3.12 (1.57-6.21)	2.48 (1.20-5.10)	0.62 (0.23-1.68)	0.67 (0.29-1.55)
Current Smoker	0.65 (0.43-0.98)	0.82 (0.50-1.32)	1.59 (1.16-2.18)	1.65 (1.17-2.32)	0.57 (0.25-1.34)	1.00 (0.41-2.41)
History of Hypertension	Men with previous history excluded		1.10 (0.72-1.68)	0.95 (0.56-1.61)	3.88 (2.16-6.96)	1.83 (0.92-3.65)
History of High Cholesterol	1.21 (0.87-1.68)	0.71 (0.48-1.05)	Men with previous history excluded		2.89 (1.68-4.98)	1.55 (0.81-2.99)
History of Diabetes	0.96 (0.46-1.98)	0.56 (0.28-1.14)	0.54 (0.27-1.08)	0.45 (0.21-0.97)	Men with previous history excluded	
History of Cardiovascular Disease	1.11 (0.45-2.74)	0.59 (0.20-1.76)	1.20 (0.62-2.33)	1.24 (0.60-2.59)	1.48 (0.71-3.07)	0.46 (0.18-1.17)
Family History of Hypertension/Stroke	0.90 (0.60-1.35)	1.22 (0.76-1.95)	0.75 (0.53-1.06)	0.68 (0.47-0.99)	0.93 (0.54-1.62)	0.96 (0.54-1.72)

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CHARACTERISTIC	UNDIAGNOSED HYPERTENSION (N=2224)		UNDIAGNOSED HYPERCHOLESTEROLEMIA (N = 2287)		UNDIAGNOSED DIABETES (N=1417)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Family History of Angina/Heart Attack	0.59 (0.38-0.92)	0.68 (0.41-1.13)	1.12 (0.71-1.78)	1.18 (0.74-1.90)	1.36 (0.65-2.86)	1.26 (0.50-3.14)
Family History of Diabetes	0.93 (0.74-1.18)	1.02 (0.78-1.32)	1.33 (0.95-1.87)	1.30 (0.92-1.84)	2.24 (1.40-3.59)	2.35 (1.50-3.68)
Obesity						
Not overweight or obese	REF	REF	REF	REF	REF	REF
Overweight	2.10 (1.45-3.04)	1.75 (1.15-2.67)	2.23 (1.51-3.30)	2.17 (1.46-3.23)	2.83 (0.74-10.81)	2.28 (0.74-6.99)
Obese	3.11 (2.18-4.46)	2.37 (1.64-3.43)	2.79 (1.70-4.58)	2.74 (1.68-4.47)	5.98 (1.69-21.10)	3.60 (1.30-9.93)

2.3.2   Erectile dysfunction and undiagnosed hypercholesterolemia

In the Cholesterol analytic sample, we found the prevalence of undiagnosed hypercholesterolemia was 12.1% or 1,210 cases per 10,000 men. There was a lower proportion of men with ED that had undiagnosed hypercholesterolemia (9.4%) compared to those without ED (12.4%) (Table 2.2). We found no statistically significant association between erectile dysfunction and undiagnosed hypercholesterolemia in either the unadjusted or adjusted analysis (Table 2.3).

2.3.3   Erectile dysfunction and undiagnosed diabetes

In the Fasting Glucose analytic sample, we found the prevalence of undiagnosed diabetes to be 4.2% or 420 cases per 10,000 men 20 years of age and older. The prevalence of undiagnosed diabetes in men with ED was 11.5% compared to 2.8% in men without ED (Table 2.2). The most noticeable difference occurred in middle-aged men (40-59 years), in whom the prevalence of undiagnosed diabetes was 19.1% among men with ED compared to 3.3% in men without ED (Table 2.2). We found that ED was strongly associated with undiagnosed diabetes in both the unadjusted (OR 4.58 95%CI 2.54-8.24) and adjusted analyses. In our adjusted analyses, men with ED had 2.2 (95%CI 1.10-4.37) times higher odds than men without ED of having undiagnosed diabetes (Table 2.3).

2.3.4   Interaction analysis

Our post-hoc analysis found a significant interaction between ED and age in the Fasting Glucose sample ($p<0.0001$), but not in the Blood Pressure or Cholesterol samples. In short, this interaction suggested that the relationship between ED and undiagnosed diabetes was strongest in the 40-59 age group. For the average man between the age of 40 to 59, the predicted probability of having undiagnosed diabetes increased from 1 in 50 (2.04% of men) without ED to 1 in 10 (10.4%) with ED. Conversely, for the average man 60 years of age or older, the predicted probability of having undiagnosed diabetes decreased from 1 in 12 (8.24%) without ED to 1 in 18 (5.56%) with ED.

2.3.5   Men without a history of cardiovascular disease

In stratified analysis of men without a history of cardiovascular disease, erectile dysfunction was still strongly associated with the odds of having undiagnosed diabetes in multivariable analysis (OR 2.73, 95%CI 1.31-5.69). No significant association was seen for undiagnosed hypertension or hypercholesterolemia.

2.4   Discussion

In a nationally representative sample of U.S. adult men, we investigated the association between erectile dysfunction and undiagnosed hypertension, hypercholesterolemia and diabetes. We found that men who reported erectile dysfunction based on a single, self-reported question had 2-fold and 4-fold higher odds of undiagnosed hypertension and diabetes, respectively. Even after adjusting for many cardiovascular confounders, these associations were diminished but ED was still associated with a statistically significant 2-fold higher odds of undiagnosed diabetes. Finally, we observed a significant interaction between ED status and age for undiagnosed diabetes in middle-aged men. This supports previous studies suggesting that the prognostic value of ED is strongest in middle-aged men below the age of 60.[31–33]

Our results provide further evidence of the importance of erectile dysfunction as a marker of undiagnosed diabetes, particularly in middle-aged men. ED can act as an important tool to trigger both patients and physicians to screen for diabetes mellitus. Several studies have identified other risk factors for undiagnosed diabetes such as older age, family history, obesity, physical activity and a history of hypertension.[39–41] These have been incorporated into diabetes risk calculators and promoted by the American Diabetes Association.[51] Both gestational diabetes and macrosomia have been identified as female-specific risk factors for undiagnosed diabetes, but thus far no male-specific risk factors have been evaluated.[52] Although we observed significant associations between undiagnosed diabetes and more traditional cardiovascular risk factors, ED is unique due to its common symptomatology and available treatment options. As such, ED can act as a useful incentive for men to access the healthcare system and be readily screened. Future research is needed to investigate the utility of including erectile dysfunction as a component of these widely disseminated diabetes risk tools.

In our study a significant association between ED and undiagnosed hypertension or hypercholesterolemia was not found after adjusting for potential confounders. It is possible that the association between ED and undiagnosed hypertension (OR 1.27 95%CI 0.87-1.85, p=0.22) may have become statistically significant with a larger sample size. Conversely, the association between ED and undiagnosed hypercholesterolemia was trending towards a protective effect. Both a family history of diabetes and a family history of hypertension or stroke before the age of 50 were associated with significantly lower odds of undiagnosed hypercholesterolemia, which was contrary to the expected result. This suggests a possible detection bias in our sample, as men with these risk factors may already have been screened for high cholesterol and therefore would have a lower chance of it being undiagnosed. When the sample was limited to men that reported that they had never had their blood cholesterol checked, these two family history variables were no longer statistically significant.

2.4.1 Limitations

There are a number of limitations to this study that should be addressed. First, although the question on ED was asked in a private room through computer-assisted self-interview, due to the sensitive nature of the condition it is possible that ED was underreported. This misclassification would have diluted the reported effect size. As a result, the estimates reported may in fact underestimate the association between ED and undiagnosed CMRFs. Second, increased recognition of the relationship between ED and cardiovascular disease may have altered screening practices of physicians. As such, the prevalence of undiagnosed CMRFs may in fact be lower now. Finally, as this study is cross-sectional, it is not possible to determine the temporal relationship between ED and the undiagnosed CMRFs. This does not, however, affect the importance of ED as a marker of undiagnosed cardiovascular risk factors for early intervention.

2.5 Conclusions

In conclusion, we found that reporting erectile dysfunction based on a single question was found to be associated with undiagnosed diabetes. This suggests that ED can be a useful marker for potential underlying disease in men for early diagnosis and treatment. Men with erectile dysfunction, particularly those middle-aged, should be made

aware of their potential for having underlying diabetes and be encouraged to obtain screening. In the same vein, physicians should be vigilant in performing sexual histories in middle-aged men and screening those with erectile dysfunction for diabetes.

3 Erectile dysfunction medications and treatment for cardiometabolic risk factors: a pharmacoepidemiologic study

3.1 Introduction

Heart disease is the second leading cause of death among men in Canada[1] and the leading cause in the United States and United Kingdom.[53,54] Detection and treatment of cardiometabolic risk factors (CMRFs) such as hypertension, hypercholesterolemia and diabetes has been shown to be effective in preventing future heart disease.[25,55,56] Unfortunately, as these CMRFs are typically asymptomatic, many affected individuals are undiagnosed.[27] This is particularly true for men,[42] who utilize the healthcare system less than women and subsequently miss opportunities for screening and preventive care.[6,7,57–59]

While men are generally reluctant to seek out medical care, they are more inclined to do so when it concerns their sexual function.[60] Erectile dysfunction (ED) is a common condition affecting men, with almost half of men over the age of 40 reporting some degree of it.[10] ED has been shown to be an independent risk marker for cardiovascular disease,[12,13] particularly in men under the age of 60.[31,32] This is perceived to be due to a shared pathophysiology including endothelial and smooth muscle dysfunction.[14,61] Similarly, ED is also associated with modifiable CMRFs such as hypertension, hypercholesterolemia and diabetes.[62,63] As a readily available, effective treatment for ED exists in the form of phosphodiesterase type 5 inhibitors (PDE5i),[64] it has been suggested that ED can provide a 'window of curability' for men to receive targeted cardiometabolic risk assessment.[16,19] Whether the prescription of PDE5is for ED leads to the detection and treatment of previously undiagnosed CMRFs remains unclear.

In order to address these concerns, we performed an individual-level time series analysis with switching replications using population-based health data. This self-matching design controls for within-person confounding such as genetics, socioeconomic status and lifestyle factors while the use of switching replications allows for the

comparison of men with similar risk profiles. Therefore we investigated whether men seeking treatment for ED are screened and treated for newly diagnosed CMRFs.

3.2   Methods

3.2.1   Setting

We conducted a retrospective, population-based cohort study of residents of British Columbia (BC), Canada using linked health care databases inclusive of January 1, 2004 and December 31, 2011. BC is the most ethnically diverse province in Canada, with a population of more than 4.4 million persons. All residents of BC have universal coverage to hospital and physician services through the BC Medical Services Plan. The University of British Columbia Behavioural Research Ethics Board approved this study (Appendix A).

3.2.2   Data sources

This study was conducted using individual-level, de-identified, longitudinal data from three population-based linked health care databases: Population Data BC, PharmaNet and the College of Physicians and Surgeons of BC. Population Data BC includes information on demographics, hospitalizations and physician services (both inpatient and outpatient) for all residents of BC excluding those with federal coverage of health care services such as Status Indians, veterans, federal inmates and members of the Royal Canadian Mounted Police. PharmaNet records all prescriptions, regardless of payer, dispensed from community pharmacies or hospital outpatient pharmacies in the province of BC. Demographic and specialty data for all physicians licensed to practice in BC was obtained from the College of Physicians and Surgeons of BC. These databases have been shown to be of high quality and valid at the population level and have been used extensively in pharmacoepidemiology research.[65–67]

3.2.3   Cohort design

We first identified a cohort of patients aged 40 to 59 years newly prescribed a PDE5i (sildenafil, tadalafil, or vardenafil) between January 1, 2007 and December 31, 2010 (Figure 3.1). We analyzed men 40-59 years old as studies have suggested that the prognostic value of ED for future cardiovascular disease is strongest in middle-aged men under the age of 60.[31–33] To identify the date in which the PDE5i was actually prescribed, the unique

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practitioner (physician) number was used to link the prescription to the closest outpatient visit within 60 days

prior to the date the prescription was dispensed. This date was considered the index date or time zero, for each

patient. To ensure that each patient was newly prescribed a PDE5i, we excluded all patients not registered with

the Medical Services Plan of BC (required of all BC residents) in the full 3 years prior to their index date. Patients

with a history of prostate cancer or primary pulmonary hypertension were also excluded due to their having a

predisposing iatrogenic risk for erectile dysfunction or a different indication for receiving a PDE5i, respectively.[68]

Figure 3.1   Matching protocol used for time series analysis. Matched pairs were formed from men in the ED cohort and the controls cohort based on age and calendar month and year of the index date. In the example below, a patient that received their PDE5i prescription at age 53 on March, 2009 (ED cohort in blue) would be matched with a patient that received their PDE5i prescription at age 54 on March, 2010, with a corresponding pseudo-intervention date on March, 2009 (control cohort in red). Therefore both patients would be the same age and have an index date within the same calendar month and year.
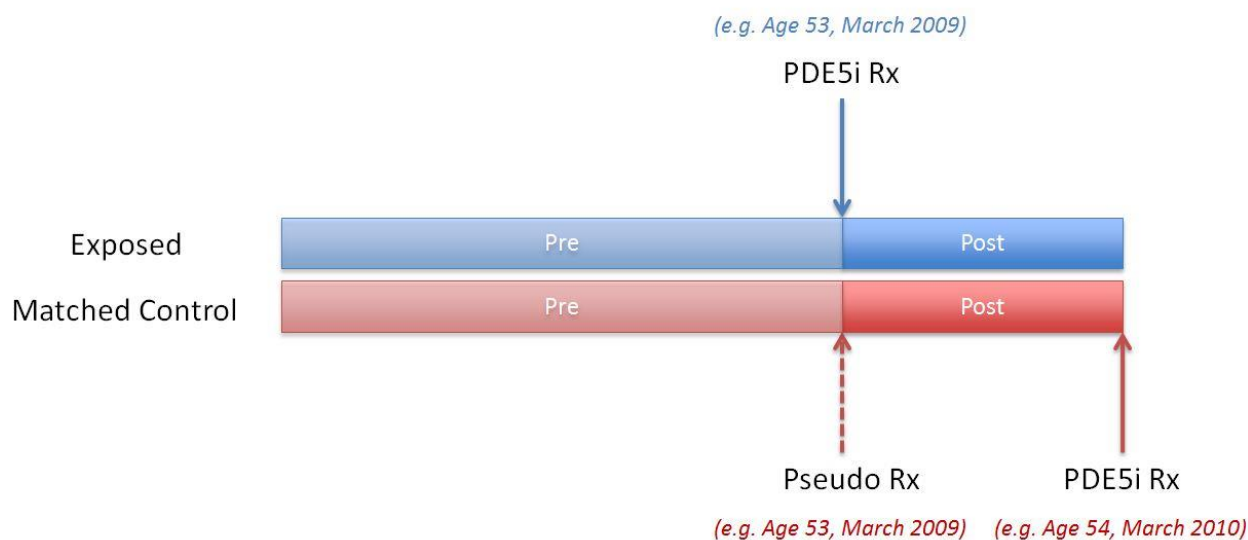
3.2.4   Control group

With ED sharing similar pathophysiology[14] and risk factors as cardiovascular disease,[10,62] using an age-matched

control group, as done in previous studies,[24] would lead to an obvious selection bias. To avoid this, an innovative

approach was implemented by utilizing switching replications for the time series analysis (Figure 3.1).[69,70] A

control cohort was derived from the initial ED cohort. For each patient in the ED cohort, a control patient was

created with an index date or pseudo-intervention date exactly one year prior to their actual index date (Figure

3.1). This interval was chosen to control for seasonality between groups. Therefore prior to matching, each patient would be in both the ED and control cohorts, with follow-up time 24 months pre- and 12 months post-index date. This was done in an attempt to reduce potential age and selection bias based on cardiovascular risk.

From each cohort, men were then excluded if they had a history of cardiovascular disease (ischemic heart disease, cerebrovascular disease, or congestive heart failure) or had received cardiac procedures (coronary artery bypass graft or percutaneous coronary intervention) in the 2 years prior to their index date. As these men would already have established cardiovascular disease, they would be managed with secondary prevention therapies (Figure 3.1).

3.2.5 Matching

A matching algorithm was then applied to select matched pairs from the ED and control cohorts. First, a patient in the ED cohort was randomly selected. All potential matches from the control cohort were then identified based on having the same age and calendar month and year of index date (Figure 3.1). This was done in an attempt to control for history and maturation biases, important threats to internal validity. One patient was then randomly selected from the group of potential matches and the matched pair was then included in the analytic dataset. If there were no potential matches identified for the randomly selected patient from the ED cohort, he was then excluded.

3.2.6 Outcomes

The objective of this study was to assess whether prescriptions for ED medications led to men receiving an increase in appropriate cardiovascular screening strategies and preventive therapies for undiagnosed cardiometabolic risk factors. The primary outcomes for this study were changes in prescriptions for antihypertensives (includes antiadrenergic agents, diuretics, beta blocking agents, calcium channel blockers and agents acting on the renin-angiotensin system), statins (HMG-CoA reductase inhibitors), and oral antidiabetic drugs (non-insulins). These were identified through anatomical therapeutic chemical (ATC) classification codes.[71] Changes in prescriptions for statins and oral antidiabetic drugs were also stratified on whether men had a corresponding screening test as a result of their visit, considered to be within 30 days after their index date. These

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included laboratory tests for plasma cholesterol (including total cholesterol, HDL cholesterol and triglycerides) and glucose (including oral glucose tolerance test and hemoglobin A1C) as determined by Medical Services Plan fee codes. The prescription of proton pump inhibitors, considered not related to ED, was used as a tracer outcome to examine the effect of the physician visit on prescriptions.

3.2.7   Statistical analysis

Descriptive analyses were used to compare baseline characteristics of the matched patients from the ED and control cohorts. We used interrupted time series analysis, one of the strongest quasi-experimental designs,[70,72] to study the impact of an index PDE5i prescription on longitudinal changes in treatment for cardiometabolic risk factors.

The observation window for each patient was divided into 12 time periods consisting of 90 days per period, with the index date indicating the start of time period 0. Therefore, each patient was assessed approximately 24 months pre- and 12 months post-index date. Our models used the following form to model each outcome measure:

$$Outcome = \beta_0 + \beta_1 \cdot time + \beta_2 \cdot time \cdot postscript + \beta_3 \cdot PDE5i + \beta_4 \cdot PDE5i \cdot time + \beta_5 \cdot PDE5i \cdot time \cdot postscript + e_t$$

in which time = 90-day period in study time (-8, -7, -6, …, 2, 3, 4); postscript = indicator for time following index date; PDE5i = indicator for men receiving PDE5i prescription at index date.

Time series models were fitted to assess for changes in the level (step) and trend (slope) in the study outcomes following PDE5i prescription per 1,000 men, with differences compared between those in the ED and control cohorts. This method controls for existing trends in treatment rates prior to the PDE5i prescription. A generalized least squares model was used and included autoregressive terms to control for correlation over time. Statistical estimates were also confirmed using longitudinal models employing generalized estimating equations (results not shown).

All tests were two-tailed, and p<0.05 was considered statistically significant. Analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, North Carolina).

3.2.8 Role of the funding source

This study was funded by a grant from the Canadian Institutes of Health Research. The funding source had no involvement in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

3.3 Results

We identified 59,856 men between the ages of 40-59 years that were newly prescribed a PDE5i (sildenafil, tadalafil, or vardenafil) between January 1, 2007 and December 31, 2010. After applying exclusion criteria and following matching, 6,702 men aged 40-59 were included in both the ED and control cohorts (Table 3.1).

Table 3.1 Baseline characteristics of patients in the matched ED cohort used for time series analysis.

Characteristic	ED Cohort (n)	(SD or %)
Mean age, y	50.5337	5.5252
Rural location, n (%)	468	6.98
Income quintile, n (%)		
1	1111	16.58
2	1229	18.34
3	1317	19.65
4	1480	22.08
5	1484	22.14
Unknown	81	1.21
Mean unique prescription drugs in prior year, n	4.5974	3.5725
Mean outpatient physician visits in prior year, n	3.0791	4.9991
Mean hospitalizations in prior 2 years, n	0.2905	0.7486
Medications used in 2 years prior to index date, n		
Antihypertensives	1654	24.68
Statins	982	14.65
Antidiabetics	573	8.55
Screening tests performed in prior year, n		
Cholesterol	3072	45.84
Glucose	3407	50.84

Of the men in the ED cohort, 25% of men were already being treated with an antihypertensive, 15% with a statin, and 9% with a non-insulin anti-diabetic medication. 46% of men had completed a cholesterol laboratory test and 51% of men had completed a glucose laboratory test in the year prior to their PDE5i prescription. Men in the ED cohort were significantly different from those in the control cohort in number of prescriptions, physician visits, hospitalizations, screening tests in the prior year, and use of antihypertensives and antidiabetics.

3.3.1 Prescriptions

Among men 40-59 years old, there was a sudden increase in prescriptions for antihypertensives (28 per 1,000, p=0.03), statins (15 per 1,000, p<0.001), and antidiabetics (18 per 1,000, p=0.002) in the 90 days following a new prescription for a PDE5i in the ED cohort (Figure 3.3). No significant level change was observed in the control

cohort for any of the three outcomes. In the ED cohort, this increase was followed by a significant declining trend in prescriptions for each drug. The increase in prescriptions observed for each drug following the PDE5i prescription would be expected to be nullified after 24 months for antihypertensives, 30 months for statins, and 18 months for antidiabetics (Figure 3.2). There was a significant increase in trend in the control group for all three outcomes. For the tracer outcome (proton pump inhibitors), there was no significant difference observed between the ED and control cohorts following the index date in both level (p=0.51) or trend (p=0.86).

Figure 3.2 Trend in prescriptions per 1,000 men aged 40-59 years for antihypertensives (blue), statins (orange), and antidiabetics (green). The shaded grey area indicates the period from the start of the index date (first prescription for a PDE5i). The solid lines represent the fitted analysis, and the dashed lines represent the expected number of prescriptions based on the trend prior to the PDE5i prescription. The analysis indicated that there was a statistically significant change in level for antihypertensives (28 per 1,000, p=0.03), statins (15 per 1,000, p<0.001), and antidiabetics (18 per 1,000, p=0.002) in the 90 days following the initial PDE5i prescription.
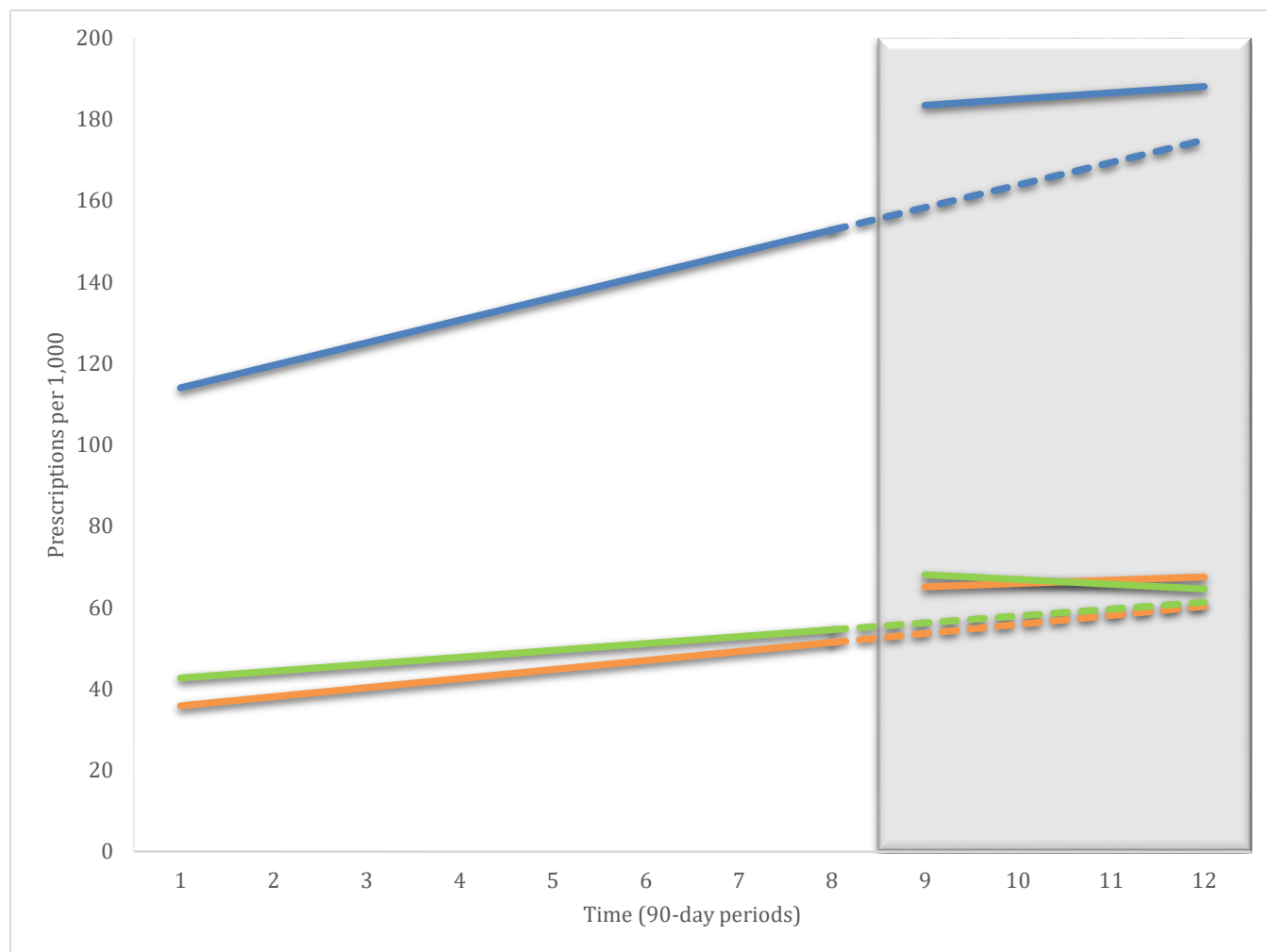
3.3.2 Screening test analysis

Subgroup analysis was performed on men based on whether they had a screening test or not in the 30 days following their index date. This found that having a cholesterol or glucose test during this period was responsible for the change in level and trend of statins and antidiabetics, respectively (Figure 3.3). For men aged 40-59, there was a sudden increase in prescriptions for statins among men that had their cholesterol tested (67 per 1,000, $p < 0.001$) compared to those that did not ($p = 0.95$). Similarly, men that had their glucose tested in the 30 days following their index date had a significant increase in antidiabetic prescriptions (133 per 1,000, $p < 0.001$) compared to those that did not ($p = 0.11$). No significant level change was observed in both control groups.

Figure 3.3   Trend in prescriptions per 1,000 men aged 40-59 years for statins (orange) and antidiabetics (green). The darker orange represents men that had a cholesterol level performed in the 30 days following the index date and the light orange represents those that did not. Similarly, the dark green represents men that had a glucose level performed in the 30 days following the index date and the light green represents those that did not. The shaded grey area indicates the period from the start of the index date (first prescription for a PDE5i). The solid lines represent the fitted analysis, and the dashed lines represent the expected number of prescriptions based on the trend prior to the PDE5i prescription. The analysis indicated that there was a statistically significant change in level for statins (67 per 1,000, p<0.001) and antidiabetics (133 per 1,000, p=0.002) in the 90 days following the initial PDE5i prescription only in those that had a corresponding laboratory test in the 30-day window.
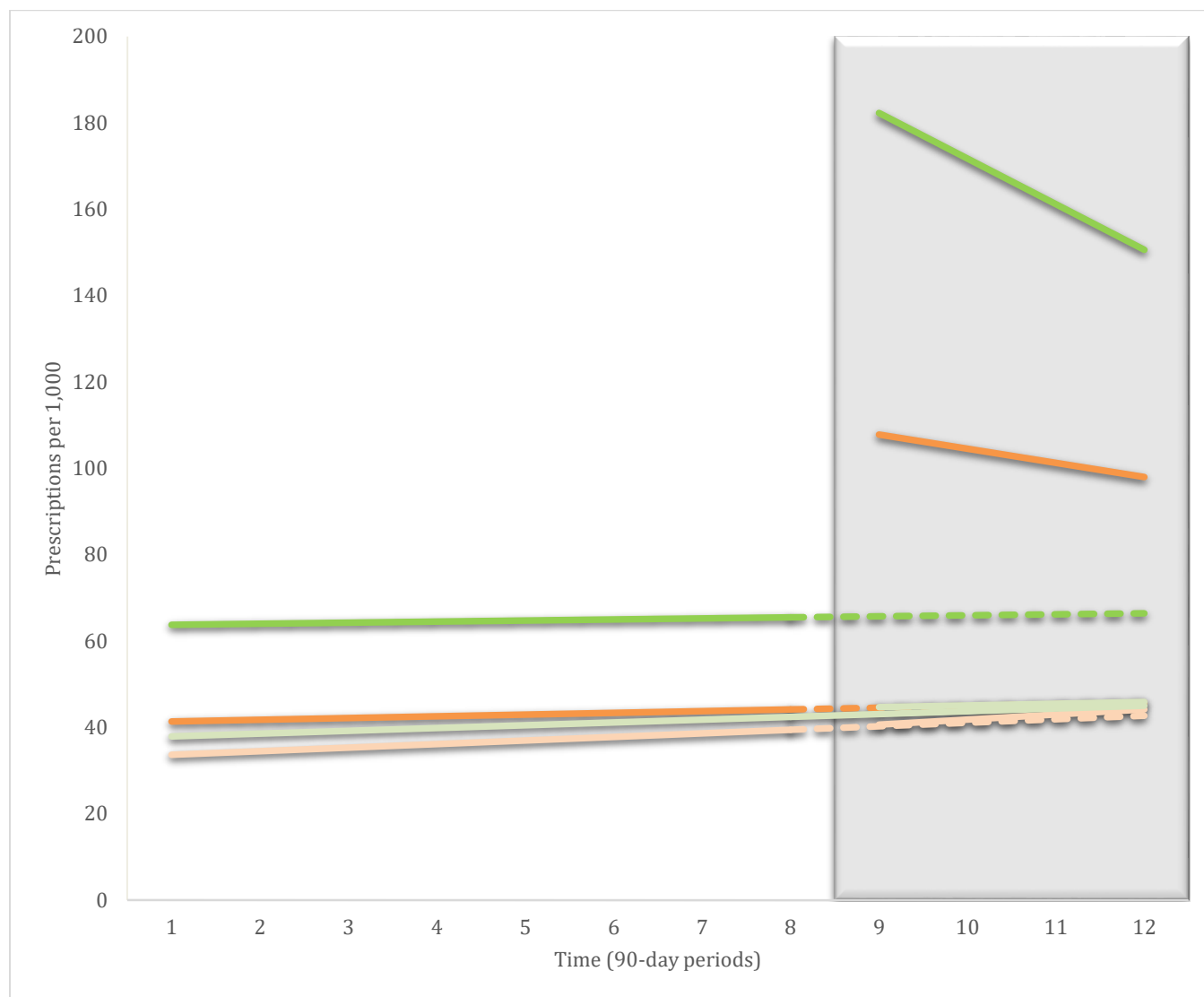
Among men not previously being treated with a statin prior to their index date and without a cholesterol test in the previous year (n=3432), 388 (11%) had a cholesterol laboratory test within 30 days of their index date. 9.5% of these men were subsequently started on a statin within 90 days of their index date. Of the 3255 men not previously on an antidiabetic and without a glucose test in the previous year, 430 (13%) had their glucose level assessed within 30 days of their index date and 1.4% of these men were started on an antidiabetic.

3.4   Discussion

The early identification and treatment of cardiometabolic risk factors is essential for reducing the burden of cardiovascular disease.[25,56] Our results showed that men newly treated for erectile dysfunction had a sudden increase in prescriptions for antihypertensives, hypercholesterolemia and diabetes. In stratified analysis, we observed that this increase in prescriptions for statins and antidiabetic medications was exclusive to men that had a corresponding laboratory test ordered as a result of their visit. Our study demonstrates the importance of screening for CMRFs in men newly treated for ED. With studies suggesting that sexual health may be one of the few motivating factors for men to see a physician,[60] PDE5is may provide a portal or gateway for these men to receive preventive care. Furthermore, only 11-13 percent of men that did not have a screening test for cholesterol or glucose in the year prior to their visit went on to have one in the following month. This suggests that physicians need to be more cognizant of the inherent risk for cardiovascular disease in men with ED and follow current guidelines.[4,19]

While several small case series have reported on the prevalence of undiagnosed CMRFs in men presenting with ED,[20–23] we are aware of only one other study that investigated this among a large cohort of men newly prescribed a PDE5i.[24] Using a large primary-care database from the UK, a previous study reported that compared to an age-matched control population, new PDE5i prescriptions led to an additional detection rate of 45 for hypertension, 61 for hypercholesterolemia and 38 for diabetes per 10,000 men. Comparatively, we observed a higher rate of new diagnoses for hypertension, hypercholesterolemia and diabetes. This apparent discrepancy is most likely due to differences in the cohorts, as Kirby et al. used a primary care database from the UK with electronic medical

records for men with ≥60 months of continuous medical history. This necessitated that all men were regularly using the healthcare system prior to PDE5i prescription, which would also explain the higher prevalence of preexisting comorbidities observed in their cohort. There are other limitations to the aforementioned study, first, the authors were unable to determine how many men had screening blood work done as a result of their prescription. Second, as men with ED would be expected to have an underlying vascular pathology, using age-matched controls would lead to a clear selection bias.

Despite observing a sudden increase in prescriptions for antihypertensives, antidiabetic agents and statins following treatment for ED, this was followed by a declining trend in prescriptions that eliminated this increase after 15 to 30 months. This would imply that nonadherence, an important and recognized impediment to primary preventive therapy,[73,74] was evident in our cohort. This emphasizes the importance of physicians educating men newly treated for ED of their increased risk for future cardiovascular disease and motivating them to engage and commit to preventive measures.[75]

3.4.1 Limitations

Our study has several limitations. First, we could not determine the nature of the physician visit or degree of ED for each patient. Therefore we cannot exclude the possibility that the chain of causal events may not follow as we expected and that the index PDE5i prescription may serve only as a marker but not mechanism for the observed changes. However, based on current guidelines regarding ED and screening for CMRFs,[19,76] the possibility that the diagnosis of one of the CMRFs would lead to the inquiry and treatment of ED would appear unlikely. As well, we observed no changes in prescriptions for our tracer outcome, proton pump inhibitors, following treatment for ED, suggesting that our results are not due to a change in healthcare use. Second, we had no information on other potential confounders such as body mass index, smoking status, or family history, however the self-controlled design of the analysis should have accounted for this. Third, we could not differentiate between men newly diagnosed with one of the CMRFs versus those that were previously diagnosed and discontinued taking the medication. Fourth, although we did employ a time series analysis we only analyzed 12 time periods, which may

limit the generalizability of our results. Finally, due to the nature of administrative data, we had no information on men who were ordered a laboratory test or written a prescription but chose not to complete or fill it, respectively. We also could not determine the number of men given free PDE5i samples or those bypassing the healthcare system through online prescriptions.[77]

3.5   Conclusions

Erectile dysfunction can be a sentinel marker for future cardiovascular disease in men. Our study suggests that treatment for ED can act as a trigger for the early detection and treatment of cardiometabolic risk factors. We also observed a lack of adherence following these treatments, suggesting that physicians need to educate men with ED about their increased risk for cardiovascular disease and the importance of continuing on primary preventive therapies. Physicians should be encouraged to follow recommended screening guidelines[19] in all men newly prescribed ED medication.

4   Conclusions

4.1   Summary of findings

This thesis had two primary aims: to determine whether men with erectile dysfunction have a higher risk of

having an undiagnosed cardiometabolic risk factor, and to determine whether the prescription of a PDE5i for

erectile dysfunction leads to an increase in the diagnosis and treatment of cardiometabolic risk factors. These aims

were pursued through two distinct studies: 1) a study examining the presence of undiagnosed cardiometabolic risk

factors in men with erectile dysfunction using a nationally representative survey from the United States, and 2) a

population-based study of changes in drug utilization for cardiometabolic risk factors following PDE5i

prescription in British Columbia.

In the first study, we examined a representative sample of men aged ≥20 years in the United States from 2001

through 2004. We found that men with ED had a higher risk of having undiagnosed diabetes but not hypertension

or hypercholesterolemia. Men with erectile dysfunction had double the odds of having undiagnosed diabetes

compared to men without. We also found that there was a significant interaction between ED and age. For the

average middle-aged man (40-59 years old), the predicted probability of having undiagnosed diabetes increased

from 1 in 50 for men without ED compared to 1 in 10 for men with ED. The relationship we observed for middle-

aged men is particularly important, as men in this age are the optimal group that could benefit from preventive

therapies. It also supports previous studies that have suggested that the prognostic value of ED is strongest in

middle-aged men below the age of 60.

We did not find any significant relationship between ED and undiagnosed hypertension or hypercholesterolemia

in this study, which was unexpected. This may in part be due to our sample size, as we did observe a significant

relationship between ED and undiagnosed hypertension in our unadjusted analysis. We provided some

suggestions as to why we did not observe a relationship between ED and undiagnosed hypercholesterolemia. It

may be that by excluding men with a previous diagnosis of high cholesterol, we excluded too broad a group of

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men. Men with a history of high triglyceride levels, low HDL levels, or high total cholesterol levels may all have responded in the affirmative to this question, thereby excluding higher risk men more likely to demonstrate a significant relationship. In light of this we feel that assuming there is no relationship between ED and undiagnosed hypertension or hypercholesterolemia should be done with caution.

In the second study, we analyzed changes in drug utilization for cardiometabolic risk factors following PDE5i prescription in British Columbia among men 40-59 years old. Men were newly prescribed a PDE5i between January 1, 2007 and December 31, 2010. For middle-aged men 40 to 59 years old, we observed a sudden increase in prescriptions for antihypertensives (28 per 1,000), statins (15 per 1,000), and antidiabetics (18 per 1,000) in the 90 days following a new prescription for a PDE5i. That we did not observe any significant difference with our tracer outcome (proton pump inhibitor prescriptions) was reassuring of a true effect. Compared to Kirby et al,[24] we observed an almost 10-fold greater effect, which is not unexpected given the highly selective population examined in their study.

Among men newly prescribed a PDE5i, 33% were already being treated with one or more of an antihypertensive, statin, or antidiabetic. Approximately half of men had had a cholesterol (46%) or glucose (51%) laboratory test in the year prior to receiving their PDE5i prescription, suggesting that this population of men are good candidates for screening interventions. However, only a similarly small proportion of these men completed a cholesterol (11%) or glucose (13%) laboratory test within 30 days of receiving a PDE5i prescription. This implies that there is significant room for improvement in educating physicians about the cardiovascular implications of erectile dysfunction. We found that having a screening test done during this 30-day window was responsible for the changes in prescriptions observed for both statins and antidiabetic medications.

In both age groups we observed a declining trend in prescription utilization for all three outcomes following the initial 90-period after the PDE5i prescription. Although this was not unexpected given the poor compliance

observed with these medications,[73,74] it does imply that continued education and reinforcement is needed in this population to achieve the expected benefits of early screening.

We also observed an increasing trend in prescription utilization in our control arm for men aged 40 to 59 years old. This population of men were newly prescribed a PDE5i exactly one year after this rate change. Men visiting their family physician on yearly intervals may have been seen one year prior to their PDE5i prescription and as such would be more likely to receive screening tests in the intervening year.

4.2 Strengths and limitations

4.2.1 NHANES study

The first study reported in this thesis, which used the National Health and Nutrition Examination Survey, to our knowledge, is the first to examine the relationship between erectile dysfunction and undiagnosed cardiometabolic risk factors using a nationally representative population. As already mentioned, previous studies have all used non-representative samples, typically from outpatient clinics, which introduces a detection bias and likely underestimates the true relationship. Men regularly seeing a physician or attending health clinics have typically already undergone screening tests and are likely more health conscious as well. Our study also used a single, self-reported and validated question on erectile dysfunction, which we believe has more utility than more common questionnaires used in research settings such as the International Index of Erectile Function (IIEF).[78] The direct clinical application of this study is to create awareness among men with ED that they may be harboring an undiagnosed CMRF such as diabetes. Similarly, physicians seeing men for the first time with ED should be encouraged to screen for potential undiagnosed CMRFs. While questionnaires such as the IIEF, which is a 15-item questionnaire, may be useful from an academic perspective, a single question has much more practical application.

This study is not without limitations. We were limited in our study by the years in which the question on erectile dysfunction was included in NHANES. As the question was removed in the 2005 survey, we only had data from 2001-2004. This dramatically limited our sample size, as the four most recent iterations of the survey could not be used. This may have impacted on our ability to find a significant result between ED and undiagnosed hypertension or hypercholesterolemia. This highlights the importance of maintaining standardized questions through future iterations of surveys such as NHANES. Furthermore, the generalizability of our findings to the present day are unclear, as the recognition that ED is a marker for future cardiovascular disease has likely increased. Screening practices have also evolved over the past decade. For instance, screening tests for type 2 diabetes mellitus now include glycated hemoglobin (A1C) and an oral glucose tolerance test in addition to fasting plasma glucose, which was the gold standard test at the time of our study. The inclusion of these two tests would increase the pool of men with undiagnosed diabetes, and may increase the strength of the relationship observed with ED. Similarly, we only examined the relationship between ED and hypercholesterolemia, and did not look at other cholesterol tests such as triglyceride or HDL levels.

The applicability of our findings to the Canadian population is also not clear. Owing to different funding models, our findings from NHANES may not directly translate to the Canadian population. Unfortunately, the Canadian equivalent to NHANES, the Canadian Health Measures Survey, has never asked questions about erectile function and so our study could not be replicated with Canadian data. Studies conducted using the Canadian Health Measures Survey have estimated that among Canadian adults, 17% with hypertension, 20% with type 2 diabetes, and 10% with high cholesterol are undiagnosed.[79–81] Men in particular are at a higher risk of having undiagnosed hypertension (OR 1.6, 95%CI 1.1-2.2).[82] There may also be a greater recognition of ED and cardiovascular disease in Canada. For example, the 2009 Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia recommend screening all men having erectile dysfunction, regardless of age, with a plasma lipid profile.[83] Despite this, previous studies have suggested a congruence between Canada and the United States in terms of hypertension and diabetes prevalence.[84,85]

4.2.2. Population-based study

The second study of this thesis explored the real-world application of the relationship between ED and unrecognized cardiometabolic risk factors. We implemented a strong quasi-experimental research design to assess for changes in healthcare screening and diagnosis in men prescribed PDE5is, the first such study conducted in Canada. Our approach had several strengths. In this study, all prescription drugs dispensed in British Columbia, regardless of reimbursement, were captured. Using the PharmaNet database overcomes the potential threats to external validity common in single or small-centre studies or those based on enrolment in specific health insurance plans. It also avoids the potential for reporting bias seen in many retrospective studies. The fact that we only measured dispensed prescriptions also increases the likelihood that these medications were actually used, compared to studies examining the point of care that measure only if a prescription was given to the patient and not necessarily filled. Using actual prescriptions for PDE5is overcomes potential concerns that may be found if we had instead focused solely on visits that had sexual dysfunction as the diagnostic billing code. Patients often present with multiple complaints, and in the case of erectile dysfunction, may not be completely forthcoming about the true motivation for their visit initially. Jackson has labeled this phenomenon as the 'doorknob syndrome.'[86] Using this method would mean that a significant number of physician encounters for erectile dysfunction would be excluded from analysis.

Our analytic approach used an innovative design to create our control groups using switching replications. This was done to minimize potential selection bias. While this technique has been used before to match specific populations in a quasi-experimental design,[70] we believe this is the first study to implement it by matching individuals in a population-based study. In our study there was a significant difference between our ED and control groups, as those men in the ED group had higher measures of comorbidity and health care use. This would however bias results towards the null, which emphasizes the significance of the changes that we observed. The self-controlled nature of our study also controls for the effect of potential demographic and lifestyle confounders. The breadth of our dataset also allowed us to qualify new PDE5i prescriptions with a three year look-back period, enabling our results to more accurately reflect men newly diagnosed or treated for erectile dysfunction.

This study also has limitations that should be considered when interpreting the results. As with any study using administrative data, our results may not completely reflect the actual patient-physician interaction. For example, although our results were based on actual prescriptions dispensed at pharmacies, we cannot determine whether patients actually took the medication once they obtained it. Similarly, the number of patients prescribed either a PDE5i or medication for a cardiometabolic risk factor that did not fill their prescription is impossible to know. There may also be some level of coding error which is inherent to all administrative data.

We used a 90-day window after the date of the PDE5i prescription in our study to assess for significant changes in our three outcome measures. This may however not reflect all men newly diagnosed with one of the cardiometabolic risk factors. For example, men found to have impaired glucose tolerance suggestive of diabetes may have been started on lifestyle recommendations initially (such as diet and exercise) or alternatively may have simply refused to start an antidiabetic medication. Although non-insulin antidiabetic medications and statins are typically first-line medications to initiate for their respective diseases, it is possible some patients were started on other alternatives instead. We classified all antihypertensives into one category as there is no clear first-line drug for hypertension and the selection of which medication to start can be based on both patient characteristics as well as physician discretion and comfort. While this approach helps accommodate for the heterogeneity observed in hypertension treatment, it meant that we could not discriminate between men newly treated for hypertension or those being started on additional antihypertensives.

We observed a declining trend in prescription utilization for antihypertensives, antidiabetic medications and statins following the initial 90-day window after PDE5i prescription. There was insufficient follow-up time in our study however to assess whether prescription levels in fact returned to the level expected based on the baseline trend. In designing our study we elected to analyze more recent PDE5i prescriptions so as to more accurately reflect current practices and also to optimize our look-back period. The obvious implication of this is that it

limited our follow-up time. Determining the long-term utilization of treatments for these cardiometabolic risk factors is critical to understanding the clinical importance of erectile dysfunction in preventive health.

4.3   Recommendations for future research and initiatives

Erectile dysfunction has been demonstrated to be a marker for future cardiovascular disease. It is unique in that it is symptomatic, meaning men recognize when they have the disease and, even more importantly, are inclined to seek treatment for it. We have demonstrated evidence that men with erectile dysfunction are at high risk of having unrecognized cardiometabolic risk factors and men being treated for it are being screened for, diagnosed and ultimately treated for these risk factors. However, there are a number of opportunities that we have identified which can help to fully take advantage of this important relationship. Below, we provide recommendations for future research and considerations for initiatives to improve the health of these men.

4.3.1   Diabetes risk tools

We found evidence that erectile dysfunction is a marker of undiagnosed diabetes, particularly in middle-aged men. Our study used similar methodology to previous ones that have identified other important risk factors for undiagnosed diabetes and have subsequently been incorporated into diabetes risk calculators. Both the American Diabetes Association and the Canadian Diabetes Association offer online risk assessment tools on their websites to inform patients whether they are at increased risk for diabetes. The Canadian Diabetes Association website has the Canadian Diabetes Risk Questionnaire, or CANRISK, which provides both a numerical risk score for diabetes and recommendations for seeking treatment or improving one's health. Neither risk assessment tool however includes erectile dysfunction as part of their questionnaire. Validation studies to assess the utility of including erectile dysfunction in these tools are needed as it has the potential to significantly improve both the accuracy and impact of them.

4.3.2   Raising awareness

A significant impediment to men with erectile dysfunction getting screened for cardiometabolic risk factors is the stigma associated with it and the lack of knowledge of its importance. National organizations such as the Canadian Diabetes Association and Heart and Stroke Foundation should raise awareness among the general public about the importance of erectile dysfunction by promoting it on their respective websites and including it in educational material. The more men and women understand the potential significance of erectile dysfunction the less stigma and uncertainty there will be surrounding it. Encouraging men to see their doctors for their erectile dysfunction will increase the potential for men to adequately be screened and treated. The majority of coverage of erectile dysfunction in the mainstream media involve direct-to-consumer advertisements from pharmaceutical companies, which produce both a biased view of the disease and may also create the notion of disease mongering. The more non-biased, educational material that is available on erectile dysfunction, such as from the Canadian Men's Health Foundation, the higher the chance that men will have a balanced understanding about its significance to their health.

4.3.3   Physician education

In this study, we found that screening rates for patients presenting for erectile dysfunction were extremely low for both hypercholesterolemia and diabetes. This suggests that either physicians ordered screening bloodwork for patients which were not completed, or more concerning, that physicians did not order it to begin with. For PDE5is to act as a potential gateway drug for men to receive increased screening and preventive care, not only do men need to access the healthcare system for their disease, but physicians must be cognizant of the associated risk factors for ED as well. Although we could not determine which scenario was more likely from our study, educating physicians to assess cardiovascular risk in patients presenting with new diagnoses of erectile dysfunction is critical. The chain of events requires men to recognize they have erectile dysfunction and seek treatment, their physicians to recognize the cardiovascular implications and subsequently screen and treat men at risk, and finally for patients to follow through on the recommendations of their physician. Strengthening each

component in the chain is needed to maximize the potential for prevention. This could also lead to potential cost savings, as one study has estimated that screening and treating men presenting with ED could prevent 1.1 million cardiovascular events and save 21.3 billion dollars in the U.S. over 20 years.[87] As mentioned previously, men may not present with erectile dysfunction as their primary complaint, and so physicians may not prioritize the appropriate investigations for it during the patient encounter. Including erectile dysfunction in screening guidelines can help improve physician awareness of the issue, with both the Canadian Cardiovascular Society's dyslipidemia guidelines and the Princeton III Consensus Recommendations providing current examples.[4,19]

There may also be other obstacles to physician screening that take place outside of the patient encounter. For instance, the ability to obtain prescriptions for PDE5is from other providers or sources such as pharmacists or the internet essentially bypass the opportunity for screening investigations. Recent proposals to make PDE5is available over-the-counter would also exclude the physician from providing the appropriate investigations for erectile dysfunction.[88] Health policy makers need to be cognizant of the potential implications of any decision to take the prescribing of PDE5is away from the hands of physicians.

4.3.4 Long-term impact

Our study found that there was a declining trend in prescriptions for antihypertensives, antidiabetics and statins following the initial 90-day window after PDE5i prescription. Studies examining the long-term adherence of men to these medications following their diagnosis of erectile dysfunction are important to fully understand the potential benefit of this interaction. It has been reported that half of patients started on lipid therapy will discontinue it within one year and only one-quarter will continue on it after two years.[4] Not being convinced of the need for treatment is also one of the most common reasons for discontinuation, emphasizing the importance of this in these men.[4] Longitudinal studies are therefore necessary to understand the motivations of men who discontinue using these preventive therapies and opportunities to increase compliance. Continued education and

instruction may be required on the part of the physician to ensure men with erectile dysfunction receive the optimum care.

There is also a lack of evidence investigating the effect of long-term preventive therapies on the degree of erectile dysfunction. Continued treatment with statins, for example, may help slow the progression of the disease or improve erectile function.[89] Randomized-controlled trials or post-hoc analysis of previously conducted trials are needed to help address these questions. Evidence supporting a therapeutic benefit for these medications may provide an important incentive for men to be adherent on their preventive therapies.

Ultimately, the relationship between erectile dysfunction and these cardiometabolic risk factors will prove beneficial if it leads to the prevention of cardiovascular disease. Understanding the components in the chain of events involved in this process and optimizing each of them must be a priority to improve the health of these men.

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