The influence of physicians on medication adherence

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Abstract

Background:

Medication adherence is defined as the extent to which patients take medications according to agreed recommendations from a health care provider. Correspondingly, medication non-adherence is the failure to take medications according to a prescribed medication regimen. Considered one of the greatest challenges to the successful management of people with chronic conditions in the community setting, patients who are non-adherent to medications have higher risks for hospitalization and even death compared to patients who take medications as prescribed. According to a report in 2008, the costs due to non-adherence in the United States (US) was estimated to be between US$100 billion to US$310 billion per year; however, these numbers are based on general assumptions and rigorous estimates are not available in the US or Canada. Despite years of research, major gaps remain in our understanding of the causes of non-adherence. Studies often focus on patient characteristics and patient behaviour. Although some of these factors are influential, they typically only explain a small fraction of the variance in models predicting non-adherence. Prescribing physicians have been identified as having a strong influence on their patient's adherence to medications; however, their impact has never been comprehensively incorporated into population-based models to help explain the residual variance.

Purpose and research approach:

The purpose of this research was to examine the impact of physicians on population-based models of medication adherence. Three retrospective cohort studies were conducted using population-based, administrative databases from Saskatchewan,

Canada. The study population consisted of new statin users (no statin claims in the previous five year) between 2012 and 2017. Statin medication was the focus in these studies because they are prescribed for chronic treatment only, they had no therapeutic equivalent during the period of study, they are prescribed to a large percentage of the population, and they are associated with reduced morbidity and mortality from atherosclerotic cardiovascular disease. Each study focused on different aspects of the physician's potential impact on the outcome of optimal medication adherence to statins defined as proportion of days covered (PDC) of at least 80%. Study 1 measured the impact of continuity of care (COC) provided by physician prescribers on optimal adherence; study 2 focused on the impact of demographic characteristics of physicians on optimal adherence; and study 3 measured the overall effect of physicians on the outcome of optimal adherence.

Study 1 – The impact of physician continuity of care on medication adherence

The first study investigated continuity of care (COC), a factor related to physician practice that is associated with medication adherence and is commonly used as a baseline explanatory variable in population-based studies. COC is typically represented by the usual provider continuity index (UPCI), which is calculated exclusively from the number of outpatient physician visits. However, the number of outpatient visits only represents one aspect of COC. Our aim was to improve the measurement of COC by integrating information on physician services and pharmacy claims (i.e., medication dispensing) data. Our new "integrated COC" definition required patients to have one physician who satisfied all three criteria: a) the most frequently visited general practitioner physician (i.e., usual care provider); b) the statin prescriber; and c) provider of a complete medical

examination within the past year. Logistic regression models were constructed with each measure of COC (high UPCI index or integrated COC) on the outcome of optimal statin adherence (PDC ⩾80%). Predictive performance of the two models was compared using the DeLong test. In a cohort of 55,144 new statin users, the integrated COC measure had a stronger association with optimal adherence [adjusted odds ratio (aOR) =1.56, 95% confidence interval (CI) 1.50 to 1.63] than UPCI (aOR = 1.23, 95% CI 1.19 to 1.28), and produced greater prediction accuracy of the multivariable model (DeLong test, $p<0.0001$). The results suggest that physician service and pharmacy claim data should be adopted in COC measures for population-based adherence models because of greater predictive performance in models predicting optimal adherence to statin.

Study 2 – Physician demographic factors and medication adherence

The second study examined the impact of age or sex concordance (i.e., same age range or same sex) between physicians and patients on optimal adherence to statin medications. We hypothesized that age or sex concordance between physicians and patients would result in higher medication adherence through improved communication and trust compared to non-concordant pairs. Multivariable logistic regression models by generalized estimating equations were applied to examine odds of optimal adherence associated with age and/or sex concordance. Among 51,874 pairs of new statin users and 1,562 prescribers, no influence of age concordance on the odds of optimal adherence could be detected (aOR = 1.02, 95%CI 0.97 to 1.07). The association between sex concordance and optimal statin adherence was stronger but failed to reach statistical significance by a very small margin (aOR=1.05, 95%CI 1.00 to 1.11). It suggested that

the potential for an important influence of sex concordance remains and should be investigated in other health care settings.

Study 3 – The overall impact of physicians on medication non-adherence

The third study aimed to quantify the overall impact of physicians on optimal statin adherence. We identified the prescriber for each new statin user and measured each patient's adherence one-year after the initial dispensation. The overall physician impact on optimal medication adherence (i.e., PDC >= 80%) was estimated from the intraclass correlation coefficient (ICC) derived from a random intercept model controlled by numerous patient-level variables (e.g., sex, residence, income, etc.). We also examined the impact of unmeasured physician factors or latent effects based on the ICC of a random intercept model controlled by both patient variables and physician-level factors (e.g., country of medical training, remuneration type, statin patient count, etc.). Finally, we estimated the impact of specific physician-level factors [sex, country of medical training, years in practice, remuneration type, number of patients, and number of patients taking a statin (statin patient count)]. Unadjusted odds ratios (uOR) for each factor were generated from logistic regression models; adjusted odds ratios (aORs) were obtained from non-linear mixed-effects logistic regression models adjusted by patient-level variables. Our results were derived from 51,874 new statin users. Addition of the physician effect to a model consisting of multiple patient-level factors only explained an additional 6.4% of the observed variance in adherence between patients, of which physician-level factors had a minimal contribution. The vast majority of the overall physician impact (5.2% out of a possible 6.4%) was attributed to a "latent effect" of the

prescriber. The results suggest that the overall impact of prescribers on optimal statin adherence appears to be very limited.

Future research

Research on the influence of physicians should continue with different types of medications and conditions. Also, specific factors such as COC, type of physician remuneration, sex concordance, and country of medical education require further study to help understand the complex role of physicians and potential new targets for improving medication adherence.

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Without the support from my family, none of this would be possible. I want to thank my wife Jin, and my lovely kids, for being so understanding and supporting during my study. Thanks mom, for everything.

I recalled a scene from the short story that I read in the first English literature class of my undergraduate study. The scene, which is still vivid to me till today, can best describe my delightfulness on completing this project:

"*Calmed by the liquid autumn gold that flowed through the streets, he walked out Whitney Avenue toward the butte-like hill of East Rock. He observed the caress of the light upon the scarped rock, heard the delicate music of leaves, breathed in air pregnant*

with tales of old New England. He exulted: 'Could write poetry now if I yust - if I yust could write poetry!'"

- Young man Axelbrod by Harry Sinclair Lewis

And finally, this little piece of work is for you high up there, my old man. Nothing is happier than seeing your boy do well in school, isn't it?

Declaration

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List of Acronyms

Acronym	Description
ATC	Anatomical Therapeutic Chemical
AUROC	Area Under The Receiver Operating Characteristic Curve
CCDSS	Canadian Chronic Disease Surveillance System
CI	Confidence Interval
CME	Complete Medical Examination
CMEP	Complete Medical Examination Provider
COC	Continuity of Care
COVID	Coronavirus Disease
DIN	Health Canada Drug Identification Number
FFS	Fee-For-Service
GDP	Gross Domestic Product
GEE	Generalized Estimating Equations
GP	General Practitioner
HBM	Health Belief Model
HIV	Human Immunodeficiency Virus
HMG CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme
ICC	Intraclass Correlation Coefficient
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9th Revision
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada
IQR	Interquartile Range

LDL	Low-Density Lipoproteins
LRT	Likelihood Ratio Test
NFFS	Non-Fee-For-Service
NPV	Negative Predictive Value
OR	Odds Ratio
PCMH	Patient-Centered Medical Home
PDC	Proportion of Days Covered
PKI	Protein Kinase Inhibitors
PPV	Positive Predictive Value
QAIC	Quasi-Akaike Information Criterion
SES	Socioeconomic Status
SK	Saskatchewan
TNF	Tumor Necrosis Factor
UPCI	Usual Provider Continuity Index
USP	Usual Statin Prescriber
VIF	Variance Inflation Factor

Chapter 1 Introduction

1.1 Medication use in Canada

Prescription medications are used very frequently in Canada. In 2019, total health care spending in Canada was 11.5% of gross domestic product (GDP), or $265.5 billion, of which medications were the second highest contributor ($40.4 billion, 15.2%) after hospital services ($70.1 billion, 26.4%).[1] Almost half of all spending on medications in Canada comes directly from provincial/territorial governments (approximately $15.0 billion) who are struggling to contain health care costs to ensure sustainability in the future.[2]

Although medications contribute substantial costs to Canada's health care system, their use can be associated with substantial downstream savings. Medications that treat chronic diseases can lower morbidity, mortality, and improve quality of life.[3] Among patients with cardiovascular diseases, blood-pressure-lowering regimens and blood-cholesterol-lowering agents can reduce risk for coronary events by 16% to 20%, stroke by 17% to 42%, total cardiovascular events by 11% to 30%, and death by 11% to 17%.[4-6] Among patients with type II diabetes, metformin has been associated with a reduction in the risk of myocardial infarction by 33%, and death by 24% to 33%.[7, 8] Among patients diagnosed with depressive disorders, anti-depressants can prevent recurrence of symptoms for 0.5 to 5 years.[9, 10] Anti-depressant agents are also effective in mitigating the impact of mental health on employment.[11] Ultimately, appropriate medication use in the community can reduce the demand for expensive hospital care and costs due to loss

of productivity. Thus, managing chronic diseases in the community is a key strategy for sustainable health care in the future.

1.2 Medication adherence

Overview

Medication adherence is defined as the extent to which patients take medications according to agreed recommendations from a health care provider.[3, 12] Several terms have been used to describe this concept over the years including "concordance" and "compliance".[13, 14] The term "compliance" was criticized by some scholars because it ignores the importance of patient engagement.[15] A more recent term that has been proposed is "medication concordance". The term was thought to better reflect the patient's participation in their own care.[15] At present, the term "medication adherence" has been widely adopted because it represents the collective effort by both patients and prescribers.[15, 16]

Conversely, medication non-adherence is the failure to take medications according to a prescribed medication regimen. It is generally classified into three types: primary non-adherence, poor execution, and non-persistence.[17] Primary non-adherence refers to a situation where patients fail to initiate a prescribed medication.[17] Poor execution is the failure to follow the recommended timing, dosage, and/or frequency of medication (e.g., skipping doses).[17] Non-persistence refers to the premature discontinuation of a required medication.[17] These patterns of non-adherence may represent distinct situations and likely have some unique causes. For example, an individual exhibiting non-persistence (i.e., quitting a medication altogether) is likely

influenced by unique factors compared to another individual exhibiting poor execution (i.e., skipping doses/taking irregularly).[17] As a result, non-adherence has been associated with multiple possible determinants but no single factor has been shown to play a strong role.[3]

The prevalence of medication non-adherence in Canada is concerning. In a study of Saskatchewan's senior population (aged 65+), non-adherence was found in 40% of the patients receiving anti-depressant agents, 39% of those receiving oral blood-glucose-lowering agents, 33% of those receiving blood-cholesterol-lowering agents, and 24% of those receiving blood-pressure-lowering agents.[18] Patients exhibiting non-adherence have poor outcomes compared to those who take medications regularly. For example, patients exhibiting non-adherence to antihypertensive medications are half as likely to achieve target blood pressure levels.[19] Similarly, low adherence to cholesterol-lowering medications is associated with a 25 to 27% increase low-density lipoproteins (LDL) levels and 26% higher risk of developing cerebrovascular events.[20] Among diabetic patients, those exhibiting non-adherence to oral blood-glucose-lowering medications are 58% more likely to be hospitalized, and 81% more likely to die.[21] Medication non-adherence is also associated with higher health care costs, primarily resulting from the occurrence of avoidable hospitalizations.[12] A study in 2008 reported that, in the United States (US), the costs due to non-adherence are assumed to be between US$100 billion to US$310 billion per year; however, these numbers are based on general assumptions and rigorous estimates are not available in the US or Canada.[22]

The staggering estimates regarding the cost of non-adherence has drawn significant attention over the years. The problem appears so great that some have

suggested solutions to non-adherence may be more important than the discovery of new therapeutic agents.[23, 24] As a result, research about medication adherence is a main focus of pharmacoepidemiology because of its impact at the population level. It is important to identify drivers behind medication non-adherence at the population level to help guide strategies to mitigate its health and economic consequences.

Measures of medication adherence

Research into medication adherence has many challenges depending on the setting and patient population. One of the challenges facing all studies about adherence is accurate measurement. Medication adherence can be measured in various ways.[12, 14] It is possible to directly measure adherence through biochemical testing of drug levels. However, this approach is costly and would be difficult to carry out routinely and in large populations.[12, 14] Indirect methods of adherence measurement include subjective ratings/surveys and objective records of medication administration.[3, 23]

Subjective records include patient diaries or self-reported surveys.[23] Self-report adherence measures are disadvantaged by imprecision and susceptibility to bias.[25] In a review by Conn and colleagues, studies using self-report measures exhibited significantly higher heterogeneity as opposed to studies not using self-report measures, with a heterogeneity statistic of 4.208 ($p = 0.04$). The authors argued that such heterogeneity indicated the presence of bias.[26] Similar findings were reported by other researchers; subjective records were associated with recall bias or social stigma.[16, 24]

Objective measures include pill counting, electronic pill bottles, and algorithms to calculate adherence levels (e.g., proportion of days covered, which will be articulated in

the following section) based on electronic pharmacy data (i.e., medication dispensations).[3, 12, 14] Pill counting records the number of pills returned by patients to estimate the number of non-adherent days. Pill counting measures have also been criticized for the risk of inaccurate estimation of adherence. [27, 28] Studies suggest that pill counting overestimates adherence.[27, 28] Electronic pill bottles typically involve sensors that record every time the medication container is opened. Thus, every record represents a "pill-taking event". These devices appear to be very precise in measuring adherence. [29] However, they are costly and difficult to implement in large populations.[29] Also, they are prone to Hawthorne effects (i.e., patients tend to behave adherent to medication as they know that they are being watched), and the adherence level can be overestimated.[30]

Among all available methods, analyses of electronic pharmacy data have multiple advantages.[31, 32] First, electronic pharmacy data are usually population-based.[33] Population-based data can provide high statistical power to detect even small effects due to the large number of observations.[33] It contains data going back decades, enabling longitudinal research of trend and temporal relationships, and improves generalizability of results.[33] Electronic pharmacy data is often managed by government or private insurance companies, thus, quality of data is typically high due to standardization and regular validation.[32] These data contain information on the medications dispensed (e.g., date, strength, and quantities) and also capture a large number of variables including prescriber, social-demographic information, and cost. [32, 33] Another major advantage of electronic pharmacy data is the collection of medication use in real-world settings. As such, they are not prone to recall bias or Hawthorne effects.[32, 33]Finally, electronic pharmacy data can be linked to other health administrative databases such as physician

services, hospitalization records, or vital statistics to increase the availability of covariates (e.g., patient and physician characteristics) that can be used to characterize variation in adherence outcomes.[31-35] As such, electronic pharmacy data are considered as one of the best sources for measuring medication adherence.[32]

Saskatchewan is home to world-renowned administrative databases that have been used frequently to study medication adherence.[32] The databases include a population registry, electronic pharmacy claims (for dispensations of prescription medications), hospital services, emergency services, physician claims, physician registry, and more.[32] The data is complete by covering all segments of the population in the province. The annual turnover of the registered population is lower than 5%, which provides a stable population for follow up.[32] The major databases in Saskatchewan can be traced back for decades.[32, 36] The pharmacy prescription claims file and the hospital claims file follow the same structures used by other jurisdictions in Canada allowing consolidation of data on national level.[32, 37]

The common methods of measuring medication adherence from electronic pharmacy data include medication possession ratio (MPR),[38, 39] continuous measure of medication acquisition (CMA),[39] and proportion of days covered (PDC).[40, 41 42] MPR estimates proportion of days' supplied within a specified observation period.[38] The advantage of MPR is its ease of calculation.[43] However, the algorithm of MPR is not standardized. Hess and colleagues reported that there were at least four different published measures under the term "MPR", which may cause confusion when comparing adherence across studies.[38, 43] Use of days supply can be a problem as overlapping periods are not adjusted.[41] As a result, MPR values can exceed 100% and the average

MPR across a population can be overestimated.[43] If MPR is not truncated at 100%, the report on average MPR across patients can be overestimated.[43] Also, when the denominator is measured between the first and last dispensations, it may bring multiple problems: 1) MPR cannot be calculated for those who had one dispensation; 2) The estimation on adherence can be imprecise if data is not available to trace back to the very first dispensation; 3) The ratios cannot be directly compared across patients as the length of observation is different; 4) Discontinuation of medications is not captured since observation ceases on the last dispensation.[43] CMA is identical in measure of adherence,[38] and shares the same problems as MPR has.[39]

PDC measures the proportion of days covered by medication.[40, 41, 42] PDC requires the number of days supply to be determined for every medication claim (or dispensation from the pharmacy). The days supply allows an estimate of when the next medication refill will be needed. For example, a medication claim of 60 tablets corresponds to 30 days supplied for medications taken twice daily (i.e., two tablets per day). The PDC uses the total number of days supply divided by the number of days observed producing a percentage that is equated to an individual's adherence during that time. For example, a patient who received 50 days supplied of medication during 100 days of observation is considered to have an adherence level of 50% (i.e., PDC = 50%).

PDC is considered a precise algorithm to evaluate medication availability.[40-43] However, several modifications are often applied. First, accumulated supplies from previous dispensations, and days in hospital should be considered in the measurement of PDC.[40] Second, although a common practice to define optimal adherence at PDC >=80%, sensitivity analyses should be performed taking cut-off values ranged from 50% to

95%.[42] Third, prevalent users should be analyzed separately from incident users for the following reasons: 1) for prevalent users, the date of first fill cannot be identified, which undermines the precision of adherence calculation; 2) studies often showed high occurrence of discontinuation during the first year of therapy, suggesting that a mixed population of prevalent and incident users may confound the results.[40] Finally, PDC does not detect medication discontinuations. Thus, low PDC values should be investigated for evidence of poor execution (i.e., skipping doses or late refills) versus non-persistence (i.e., complete medication discontinuation).

Determinants of adherence

Using a clinically-oriented framework, determinants of adherence can be classified into five categories: patient-related factors; socio-economic environmental factors; disease related factors; treatment related factors; and health care provider/system related factors.[22, 44, 45] However, certain factors may fall into multiple categories, and have interactions with each other. For example, lack of education can be considered as a patient-related factor and a social-economic related factor. In addition, factors such as age, low income, and high treatment cost are often correlated, making it difficult to quantify their independent effects.

A vast number of possible determinants of medication adherence have been examined in the literature. However, these factors virtually always have weak predictability in multivariable models.[46-48] For example, in a study involving 444,418 diabetic subjects, a prediction model was built with many patient-level factors that are typically available in administrative databases, such as demographic characteristics (e.g.,

age, sex, and marital status), comorbidities (e.g., vascular disease, mental illness, and chronic lung or renal disorders), and regimen complexity. The study also included clinical factors such as disease severity, and laboratory test results. Despite the access to a wide array of clinical and administrative information, multivariate models only explained 2.9% of the adherence variation observed in the study population.[47]

It is unknown why such models have failed to predict non-adherence. In general, prediction models contain numerous variables representing widely accepted theoretical frameworks (including patient-level, disease, drug factors, etc.). A few factors have been consistently associated with adherence in multiple studies.[49] For example, ethnic minority status, higher regimen complexity, higher co-payment, and higher medication cost are related to poorer adherence.[49] In contrast, employment and income are related to better adherence.[49] However, many well-recognized factors have failed to exhibit consistent effects on adherence. For example, studies often show heterogeneous associations between adherence and both sex and age.[49] One possible reason for the variation is due to the use of different measures or different analytic methods.[49] Mathes and colleagues reviewed seven systematic reviews on adherence of medications for a range of diseases, including chronic cancer pain, cancer, Parkinson's disease, heart failure, rheumatoid arthritis.[49] The authors found that adherence was higher in the middle age groups when measured as a categorical variable. [49] However, when measured as a continuous variable, the effect of age was insignificant or heterogeneious.[49] Inconsistent results for a given factor can be due to differences in measurement or analytic approaches. Socioeconomic status (SES) is linked to education, economic status, and social support; therefore lower SES is commonly expected to have negative effect on medication adherence.[50] However,

in a systematic review of 56 studies, Alsabbagh and colleagues observed very high heterogeneity in the reported associations between SES and non-adherence to blood-pressure-lowering medications.[50] The authors argued that a major source of the heterogeneity was different measures on SES.[50] For example, seventeen studies used drug coverage or medication co-payment as proxies of SES, four used income-level,[50] and three studies measured SES by social assistance benefits or income security benefits.[50] These measures reflected different aspects of SES, and could have different impact to medication adherence.[50] Only seven of the reviewed studies tested more than one measure of SES.[50] Indeed, measurement of adherence determinants is another possible contributor to the weak predictive performance of adherence models at the population level. One of the studies in this dissertation evaluated alternative measures for a commonly used covariate in adherence research, continuity of care.

Behavioural theories and models related to medication adherence

Since medication adherence has been strongly linked to knowledge, attitudes, and beliefs of patients, research in health behaviours has been commonly applied to the context of medication taking. The most widely studied theory of health behaviour is the health belief model (HBM).[51] The term HBM is widely used, but indeed it refers to a behavioural theory. [51] Other commonly examined theories include the protection motivation theory, the theory of reasoned action, the theory of planned behaviour, and the social-cognitive theory and self-efficacy.[52] The core of these theories is that human beings can change their behaviour through a dynamic social learning process.[52] For example, HBM identifies three elements: a) perception of the health issue (e.g., susceptibility to a disease, severity of disease, and high risk towards an unfavorable

outcome); b) belief in treatment (e.g., perceived benefits of treatment, or perceived barriers of treatment); and c) a stimulus to facilitate participation in treatment (e.g., cues of action such as education and tools to help patients overcome barriers).[51] These elements can determine patients' self-efficacy (e.g., confidence in ability of coping with a particular disease), which leads to the expected outcomes.[52]

Research on behaviour change could potentially guide interventions that are meant to increase an individual's adherence to medications. Behaviour change has been commonly explained by the self-efficacy/social-cognitive theory, the relapse prevention model, and the transtheoretical or stages-of-change model.[52] These theories focus on three factors in behaviour change, namely the person, the behaviour, and the environment.[52] These factors dynamically interact with each other.[52] Each theory however focuses on different aspects of the process. For instance, the self-efficacy/social-cognitive theory focus on building efficacy beliefs.[52] According to these theories, patients will achieve medication adherence if they believe that they have sufficient efficacy (e.g., skills and knowledge about treatment).[52] Barclay and colleagues conducted a cross-sectional study on the effect of self-efficacy to adherence behaviour among 185 human immunodeficiency virus infected (HIV-infected) patients. [53] Each unit increase of self-efficacy score was associated with 30% increase of odds of good adherence measured by electronic pill bottle cap devices (OR=1.33, 95%CI 1.06-1.67).[53]

Despite the numerous associations identified, behavioural theories and models have not necessarily translated into effective adherence interventions.[52] Jones and colleagues reviewed 18 interventional studies based on HBM theories.[54] Interventions of 16 studies targeted beliefs on benefits of adherence, fifteen targeting beliefs about

susceptibility of disease, fourteen targeting perceived barriers of adherence, and eleven targeting perceived disease severity.[54] The authors were not convinced that successful interventions on adherence were due to HBM elements in these studies.[54] The authors also noted that measures of HBM elements were heterogeneous, making it difficult to compare results from different studies. [54] With respect to the models focusing on behavioural change and medication adherence interventions, evidence also tends to be weak.[52] Although these models and theories help to understand potential factors required to improve medication adherence, further study is required to clarify the complexity of predicting or influencing medication taking behaviour.

1.3 The influence of physicians on medication adherence

Physicians may influence medication adherence in numerous ways. There are studies on choice of regimen complexity, professional training/specialty, cultural/language experience, and workload.[55, 56] Frequent reminders from physicians have been associated with improved adherence to antihypertensives[57] and patients recently started on statin medications were more likely to be adherent if the physician monitored their adherence status.[58] Moreover, studies have shown that the number of visits to physicians is associated with higher medication adherence.[59, 60]

The strongest evidence for the impact of physicians on medication adherence can be observed in studies asking patients about the interpersonal relationship with their physician.[61] Many studies that use survey methods to collect information about relationships have found that trust levels are positively related to adherence.[62-67] Similarly, ratings of physician communication are mostly positive with respect to adherence.[68, 69 9,

[64, 70, 71] In theory, physicians possessing good communication skills (usually measured by patient satisfaction ratings) can forge trust with patients and strengthen the patient-physician relationship.[72, 73] Evidence for this association was supported by results of a meta-analysis that included studies examining physician communication as rated by a patient, health professional, or researcher. When communication was rated as poor, the risk of medication non-adherence increased by 19%.[73] In addition, it was reported that training physicians in communication skills was linked to improved patient adherence (OR=1.62) comparing with physician receiving no training.[73] One limitation is that most of these studies used self-report measures of adherence, which correlate poorly with objective measures such as refill records.[64, 74-78] Perhaps there exists unidentified factors that are associated with stronger relationships and thus better adherence. Identification and analysis of such factors could help provider deeper understanding of the role of communication and trust. For example, physicians and patients of the same sex and/or age may relate more effectively but we do not know if this is associated with improved adherence.

Evidence for the importance of the physician-patient relationship has also been suggested in other types of studies. An ongoing relationship between one family physician has been associated with improved satisfaction, trust, and effective communication in primary care.[79] Also, having a single family physician can maximize the coordination of disease management and ensures the completeness of patient's health records.[80] The ongoing relationship between physicians and patients is often measured by continuity of care (COC).[81] Indeed, studies suggest that COC is associated with improved medication adherence, [82-85] and these observations align with the observed associations

between trust, communication, and medication adherence.[67, 69] However, upon close examination, the measures used to support the relationship between COC and adherence in most population-based studies are based on methods that only identify the most commonly visited physician. Frequency of visits to a physician is undoubtedly part of the concept; however, COC also involves the delivery or coordination of multiple different services or dimensions of care for a given patient.[85] Although various approaches to the measurement of COC have been examined,[82-85] none have attempted to address the over-reliance on physician visit claims to represent this complex concept. Another study in this PhD dissertation will examine a potential strategy to improve the validity of the traditional measure of COC and determine if a new approach can improve the performance of the measure.

Despite the positive associations observed in multiple studies examining the importance of physician characteristics, skills, or their practice patterns, these studies often focused on a single factor, relied solely on self-reported adherence measures, or lacked adherence measurements of any kind. It is generally recognized that medication non-adherence is a multi-factorial problem that requires multi-faceted solutions.[30, 86] As such, it would be contrary to conventional thinking to assume that activities delivered by a single physician would have an overwhelming effect on medication adherence.

1.4 Review of study designs in adherence research

Medication adherence has been studied with many different research designs. Basically, adherence studies have been conducted using two major approaches: Experimental or observational. Experimental designs include randomized control trials

(RCT). Observational designs include cross-section studies, case-control studies, and cohort studies.

RCTs are considered the gold standard design for clinical research studies.[87-90] In a RCT design, study individuals are randomly assigned to the exposed and unexposed groups. The randomization process minimizes bias, and minimizes the impact of both measured and unmeasured confounding.[91, 92] Among all designs, the RCT design offers the strongest inference of causality.[91, 92] However, heterogeneity is common across published RCTs because of different populations, diseases, medications, interventions, and adherence outcomes.[30] These differences make it virtually impossible to compare or pool results crossing disease areas and therapeutic classes, even within the same disease area.[30] In addition, RCTs in adherence research have been often limited by small sample sizes and short follow-up periods.[25, 26, 93-95] Also, an RCT design is difficult to implement if multiple factors are to be examined in the same study.

Cross-sectional studies are commonly used in adherence research, in particular for developing hypotheses and assessing prevalence of non-adherence at a certain point in time. In a cross-sectional study, participants are analyzed at one particular time, i.e., both exposures and outcomes are measured at the same time.[87-89] As such, it offers a "snap-shot" of disease prevalence and coexisting factors, and thereby provides an economical way to explore the association between an outcome of interest and potential predictors.[87-89] However, the associations found in these studies cannot be interpreted as causal relationship due to limitations of the research design.[89] In addition, selection bias, and reliability of data collection are of concern.[89]

In case-control studies, participants are initially grouped by outcome of interest.[87, 89] Participants who developed the outcome are assigned to the case group. Those who did not develop the outcome are assigned to the control group.[87, 89] The case and control groups are then compared for the proportion of participants who were exposed to one or multiple interested explanatory factor(s).[87, 89] To establish a temporal relationship, the exposure has to occur before the outcome. Controls are matched to cases on important variables such as date of entry, or length of follow-up, and thus are assigned the matching index date.[87, 89] Case-control studies can be used to evaluate associations when other study designs are not feasible, or not ethical. In addition, these studies are often used when the outcome of interest is rare.[87-89] The case-control study design offers efficiency in developing hypotheses and examining multiple predictors with small sample size.[89] However, its primary limitation with respect to medication adherence studies relates to the short time period (usually several months) used to assess exposure.[89] Medication adherence is measured over an extended period of time, often one year, so the short exposure window in case-control studies limits opportunity for measurement.[89]

Among observational study designs, cohort studies are commonly used in medication adherence research.[96, 97] Cohort studies are similar to RCTs in that the study individuals are free of the outcome on entry, and comparator groups are stratified by exposure (i.e., exposed vs unexposed).[87, 89] Cohort studies can be classified into prospective cohort studies, and retrospective cohort studies.[87-89] A prospective cohort study begins when none of the participants have developed the outcome of interest. Prospective design guarantees the temporal relationship, collects pre-specified data (both

clinical and demographic), and strengthens the argument of causality. However, prospective studies are often plagued by high drop-out rates during follow-up.

A retrospective cohort is performed after study outcomes have already occurred. Retrospective cohort studies are extremely popular designs in adherence research.[98] Well-designed retrospective cohort studies have advantages over prospective cohort studies in some situations, in particular when data is collected from administrative databases. First, data on medication dispensations is pre-collected so researchers do not have to wait for the duration of follow-up as in prospective studies. Second, retrospective studies frequently enable larger sample size. For example, in Czarny's review the median size of the retrospective studies was 5,263 [216 to 9,256, interquartile range (IQR) =716], as opposed to the median size of 1,981 (12 to 15,157, IQR=6,418) among prospective studies.[98] Third, retrospective studies are more flexible in extending the length of data collection as long as historical data is available. In Czarny's review, the median length of data collection period was 1,187 days (821 to 2,253, IQR=838) among retrospective cohort studies, as opposed to the median length of 701 days (90 to 2284, IQR=548) among prospective studies.[98] With the lengthier data collection, researchers can more easily conduct long-term evaluations of medication adherence and its impact on clinical outcomes.

In cohort studies (and all other observational designs), study individuals are not randomly assigned to the exposure group or the control. As a result, most well-designed cohort studies attempt to adjust for multiple confounding factors. Regardless, selection of patients into the exposure group can be due to factors not observed by researchers. LaFleur and colleagues illustrated how unmeasured confounding likely caused an

overestimation of the benefit of medication adherence.[99] For example, patients who exhibit high adherence to antihypertensive medications have lower risks for adverse outcomes (i.e., hospitalization, myocardial infarction, and mortality).[100] However, this relationship is likely confounded by an unmeasured "healthy user" effect.[99] Adherent patients likely adopted healthier behaviours such as exercise, diet, or quitting smoking). In this retrospective cohort study, the authors found that the association between optimal adherence and adverse outcomes did not change after controlling for blood pressure measures during follow-up.[99] As such, the reduced risk to adverse outcomes may be largely due to an unmeasured "healthy user" effect rather than from reduced blood pressure due to regular use of medications.[99]

Researchers have devised various methods to deal with the healthy user effect in adherence research. One strategy is to adjust unmeasured confounding by the instrumental variable method.[92, 101] An instrumental variable is a factor related to exposure but not outcome.[92, 101, 102] Potential instrumental variables can be calendar time, physician preference, geographic distance, or insurance plan.[103]

1.5 Aims and objectives

The aim of this PhD program was to evaluate physician influence on medication adherence and determine if their influence addresses the substantial gap in performance of population-based prediction models.

Research objectives

1) To investigate a practice related factor, continuity of care.

1a) to determine if high Usual Provider Continuity Index (UPCI) values predict physicians who deliver different clinical services;

1b) to compare UPCI with an integrated COC measure in a multivariable model of patients receiving statin medications.

2) To examine demographic factors with the focus on age and/or sex concordance (same age range and/or same sex) between physicians and patients.

3) To explore the extent to which 'physician effects' may help explain variance in patient adherence to statin medications.

3a) to examine physician effect unexplained by patient and physician characteristics;

3b) to examine specific association between physician characteristics and statin adherence.

Studies

Three studies were conducted from different perspectives in this PhD dissertation. The first (Chapter Two) investigated a practice related factor, continuity of care. The second (Chapter Three) examined demographic factors with the focus on age and sex concordance between physicians and patients. The third (Chapter Four) examined overall physician influence adjusted by physician characteristics.

Publications

Chapter Two and Three are two manuscripts that have been submitted to journals, and are currently under review. Chapter Four contains research from which multiple

manuscripts are under development. These chapters are corresponding to the research objectives of my PhD research projects. Contribution in detail (of Shenzhen Yao and the co-authors) is listed in the beginning of each chapter.

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Chapter 2 The Impact of Continuity of Care on Medication Adherence: a Population Based Study

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Rationale to include the manuscript in the thesis:

The aim of the manuscript is to investigate a practice related factor, continuity of care, which is corresponding to objective one of my PhD thesis research projects.

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Contribution to this manuscript by Shenzhen Yao and the coauthors:

Contributor Role	Role Definition	SY*	LL	GT	CE	DB
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.	Y	Y	Y	Y	Y
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.	Y				
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	Y	Y			Y
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.					Y
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	Y				Y
Methodology	Development or design of methodology; creation of models	Y	Y	Y	Y	Y
Project Administration	Management and coordination responsibility for the research activity planning and execution.	Y				Y
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.	Y				Y
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.	Y				
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.		Y	Y	Y	Y
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.	Y	Y	Y	Y	Y
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.	Y				Y
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).	Y				Y
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.	Y	Y	Y	Y	Y

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2.1 Abstract

Objectives:

Continuity of care (COC) is considered an important determinant of medication adherence based on measures such as the usual provider continuity index (UPCI) that are derived exclusively from physician visit claims. This study aimed to: a) determine if high UPCI values predict physicians who deliver different clinical services; and b) compare UPCI with an integrated COC measure in a multivariable model of patients receiving statin medications.

Methods:

This was a retrospective cohort study of new statin users between 2012 and 2017 in Saskatchewan, Canada. We calculated sensitivity/specificity of a high UPCI value for predicting physicians who were prescribers of statins and/or providers of complete medical examinations. Next, we used logistic regression models to test two measures of COC (high UPCI value or an integrated COC measure) on the outcome of optimal statin adherence (proportion of days covered ≥80%). The DeLong test was used to compare predictive performance of the two models.

Results:

Among 55,144 new statin users, a high UPCI was neither a sensitive or specific marker of physicians who prescribed statins or performed a complete medical examination. The integrated COC measure had a stronger association with optimal adherence [adjusted odds ratio (OR) =1.56, 95% confidence interval (CI) 1.50 to 1.63]

than UPCI (adjusted OR = 1.23, 95% CI 1.19 to 1.28), and improved predictive performance of the adherence model.

Conclusion:

The number of physician visits alone appears to be insufficient to represent COC. An integrated measure improves predictive performance for optimal medication adherence in patients initiating statins.

2.2 Introduction

Studies suggest that individual physicians can improve medication adherence by establishing continuity of care (COC) for their patients.[1-4] The precise nature of this association is unknown but is likely mediated by factors promoting a strong relationship between patients and physicians.[5, 6] Indeed, an ongoing relationship between a physician and a patient is associated with higher satisfaction, improved trust, and more effective communication.[7] Having a single physician also helps ensure the completeness of a patient's health records, and can facilitate the coordination of disease management activities.[8]

COC is a complex concept.[9] Although previous studies have demonstrated a positive correlation with medication adherence, conventional measures of COC have limitations that may be improved upon using a more comprehensive definition that is specific for medication adherence.[1-4] COC is commonly measured by the usual provider continuity index (UPCI) .[9, 10] UPCI is determined by a simple calculation of the percentage of visits to a specific physician relative to all other physician visits in a given time period.[9, 10] As a result, it is highly influenced by total number of visits, and total number of different physicians.[10] For example, a patient with multiple chronic conditions may visit many different physicians in a given year. In this situation, the UPCI for that patient's regular physician may be low because the denominator (i.e., total number of visits with all physicians) is increased compared to a different patient who visits a single physician exclusively. Moreover, since the UPCI is based solely on visit occurrences, the nature of the visits is not accounted for. The UPCI approach does not consider prescribing activities despite evidence suggesting that individuals are more likely to be

adherent if their regular physician is the prescriber of their treatment regimes.[11] Certainly, it seems logical that a continuity of care measure applied to a cohort of medication users should consider the physician's prescribing activities relating to the drug(s) of interest. Further, the UPCI does not represent clinical services such as complete medical examinations (CME), which would be expected from a patient's regular physician. Although this activity has been identified as a measure of COC, few studies have examined the impact of CME providers on medication adherence.[12, 13] Although previous studies have attempted to improve on measures of COC with minimal success, the updated definitions have continued to focus on visit frequency only.[1, 4]

We hypothesized that 1) a high UPCI value will perform poorly in predicting physicians who provide other clinical activities to specific patients (i.e., prescribing, and complete medical examinations); and 2) an integrated COC measure consisting of physician visits, prescribing, and claims for a complete medical examination would result in a stronger association with medication adherence, and improve the predictive ability of medication adherence models. The objectives of this study were: 1) to examine the accuracy of UPCI for predicting other COC-related clinical activities, including prescribing statin medications, and/or performing complete medical examinations; and, 2) to determine if an integrated measure of COC is superior to UPCI in discriminating adherent statin users, and therefore improving the predictive performance of a covariate-adjusted model of adherence to statins.

2.3 Methods

Data sources

Study data were extracted from administrative databases for the province of Saskatchewan, Canada. These databases include the person registration file, the physician service claims file, the hospital discharge abstract database, the emergency service file and the prescription drug claims files.[14] The person registration file captures birth, sex, rural/urban residence, health insurance coverage start/end dates, and median household income quintiles estimated by linking the first three digits of postal code to Statistics Canada Census data. The physician service claims file captures the date of the service, the type of the service (in-hospital or out-patient), the diagnosis of the service using three-digit International Statistical Classification of Diseases and Related Health Problems, 9th Revision codes (ICD-9),[15] the encrypted identification code of the service provider, the specialty of the service provider, the fee code for billing, and the type of payment to the provider. The hospital discharge abstract database captures admission and discharge date, up to 25 diagnoses by ICD-9 or International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) codes,[15, 16] and an indicator on whether the recorded event was for acute care or alternative care (i.e., a patient was occupying a bed in a hospital and did not require the intensity of services as for acute care).[17] The emergency service file captures admission and discharge date of visits to emergency departments. The prescription drug claims files capture dispensations of prescription medications in out-patient settings. Each claim includes a Health Canada drug identification number (DIN), a dispensation date, the quantity dispensed, total cost

(including medication acquisition cost and markup/dispensing fee), and the proportion covered by government insurance.

Study design and population

A retrospective cohort was conducted consisting of individuals who initiated a new 3-hydroxy-3-methylglutaryl-coenzyme (HMG CoA) reductase inhibitor medication (i.e., statin) between January 1, 2012, and December 31, 2017. The new initiation was defined as receiving no dispensations for a statin medication in the five years prior. We chose to study statin medications because they are prescribed for chronic treatment only, they had no therapeutic equivalent during the period of study, they are prescribed to a large percentage of the population, and they are associated with reduced morbidity and mortality from atherosclerotic cardiovascular disease.[18]

The date of the earliest dispensation of a statin medication was the index date, and patients were followed for 365 days. The cohort exclusion criteria were: 1) missing age or sex information in the person registration file; 2) age on the index date less than 18 years; 3) not continuously registered in the provincial health plan during five years prior to the index date, or the one-year follow-up period; 4) admitted to a long term care facility within five years prior to the index date, or 365 day follow-up period; 5) admitted to an out-province hospital during the 365 day follow-up; 6) a claim for pregnancy (ICD-9: 641-676, V27; ICD-10 and ICD-10-CA: O1, O21-95, O98, O99, Z37) in the 365 days prior to the index date or in the 365 days after the index date;[19] or 7) no visits to a general practitioner (GP) during the 365 day follow-up period.

COC measures and physician classifications

For each patient, we defined the following COC measures: a) usual care provider and the UPCI;[9, 10] b) usual statin prescriber (USP); c) complete medical examination provider (CMEP);[12] and d) an integrated COC measure that combined all three measures (i.e., a single GP identified as the usual care provider, USP, and CMEP).

For determination of the usual care provider, we first identified all distinct service claims provided by GP physicians during each patient's follow-up period. Multiple claims by the same GP for the same patient on the same date were treated as one visit.[10] Service claims were not included if: 1) the claim was marked as invalid in the database; 2) if the service was provided to a hospitalized patient; or 3) if the claim originated from an out-of-province provider. For each patient, a usual care provider was identified as the GP with the most frequent visits during the follow-up period. In the case of a tie, multiple GPs could be assigned as usual care providers for a given patient.

Next, a UPCI value was calculated for each patient by the following formula: $UPCI = \frac{\boldsymbol{n_{max}}}{\boldsymbol{N}}$;[10] where n_{max} was the number of visits between the patient and the most frequently visited GP (i.e., the usual care provider) within the follow-up period and N was the total number of visits between the patient and all GP physicians visited within the same period. Based on the calculated UPCI value, each patient was assigned into a high or low UPCI category using the median UPCI value of the study cohort as the cut off. This process has been used previously to measure COC.[10]

The usual statin prescriber (USP) was any type of physician (i.e., not necessarily a GP) of a patient listed on the highest number of statin dispensation claims during the

follow-up period. In cases where a tie was observed, more than one physician was identified as USPs. Complete medical examination providers (CMEP) were identified on at least one claim for a complete medical examination during the follow-up period (i.e., a fee code billed for complete assessment, or chronic disease management).[20] A patient could have multiple CMEPs within the study period,[12] and any type of physician listed in the physician service claims was considered (i.e., not necessarily a GP). Finally, we combined these definitions into an integrated COC measure (yes/no) depending on whether a single GP was identified as: 1) the usual care provider; 2) the USP; and 3) the CMEP.[12]

Outcome measures

The study outcome was optimal adherence to statin medications defined as proportion of days covered (PDC) >=80%.[21, 22] PDC was calculated for the 365-day period from the index date for each patient. As these drugs are typically prescribed once daily, the number of days supplied during this time was estimated from the total quantity of tablets dispensed.[23] Quantities dispensed near the end of the follow-up period were truncated based on the number of days remaining in the follow-up period. Switching between statin medications was allowed. The total number of statin tablets dispensed was divided by 365 days (minus days spent in hospital) to obtain the adherence percentage. Details of the PDC method have been described, and validated previously.[21, 22]

Covariates

We built a multivariable model with covariates previously used to predict medication adherence from administrative databases.[24] These covariates were organized

under a framework with five categories: patient, socioeconomic status, treatment, health care system, and condition factors.[24] The covariates were measured in the period up to 365 days prior to the index date if not otherwise specified. The patient covariates included age, sex, and residence (rural/urban) on the index date. The socioeconomic status covariates included income level, which was based on neighborhood median household income quintiles (lowest=1, highest=5) on the index date.[25, 26] The treatment covariates included number of distinct prescription medications, which were determined from unique drug identification numbers. The health care system covariates included number of out-patient visits (to GPs and to specialists, respectively), and percentage of prescription medication cost paid by government health insurance. The condition covariates included number of hospitalizations for acute care, number of emergency department visits, Charlson comorbidity score, and clinical conditions (yes/no) identified from published models of medication adherence.[27] These clinical conditions included osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer.[19] These clinical conditions were identified using validated case definitions provided by the Canadian Chronic Disease Surveillance System and were based on diagnoses recorded in the service claims file and hospital discharge abstract database, and medications in the prescription drug claims dating back to January 1st, 1996.[19]

Statistical analysis

We described the baseline characteristics of the study cohort using descriptive statistics for all patients as well as subgroups based on COC measured by UPCI and the integrated COC measure. These characteristics included median age, percentages by sex (female/male), residence (rural/urban), and median income quintile (1= lowest, 5=highest). We also described the use of health services, including the percentage of patients with one or more hospitalizations for acute care (0, or >=1), the percentage with one or more visits to emergency department, the median number of visits to GPs, and the median number of visits to specialists.

To determine if a high UPCI value was predictive of patients receiving various clinical activities from a given physician, we calculated its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Kappa statistic [28] for predicting the usual statin prescriber (USP), the CMEP, and the integrated COC measure as the reference standards.

Next, we built logistic regression models to test the effect by two measures of COC on optimal adherence to statins: a high UPCI value (representing traditional measures of COC) versus presence of the integrated COC measure. Both unadjusted and adjusted models were tested separately for each COC measure as the independent variable. The unadjusted models had a single COC measure as the explanatory variable. The adjusted model had the COC measure plus all covariates described above. To maximize the control for confounding, all covariates were included regardless of statistical significance in each of the two adjusted models, except for those exhibiting

collinearity with the independent variable. Multicollinearity between COC and the adherence covariates were examined by the variance inflation factor (VIF) obtained from a regression model. If the VIF value was greater than 2.5, the covariate was removed.[29] Odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported.

We performed the DeLong test to compare predictive performance of the two adjusted models that each contained a COC measure.[30] The model that produced a larger estimate of the area under the receiver operating characteristic curve (AUROC) was considered to have better predictive performance if the difference in the AUROC estimates was statistically significant ($p<0.05$).[30]

To test the consistency of our results, several subgroup and sensitivity analyses were conducted. In subgroup analyses, we assessed the impact of an integrated COC measure (yes/no) among patients with a high UPCI and with a low UPCI separately. We also assessed the impact of UPCI (high/low) among patients with and without integrated COC. We conducted sensitivity analyses for a modified adherence measure, which was recalculated without allowing accumulated supplies between refills, and changed the threshold for "low" UPCI level to the 25^{th} and 75^{th} percentile rather than the median. SAS statistical software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to conduct all analyses.[31]

Ethical considerations

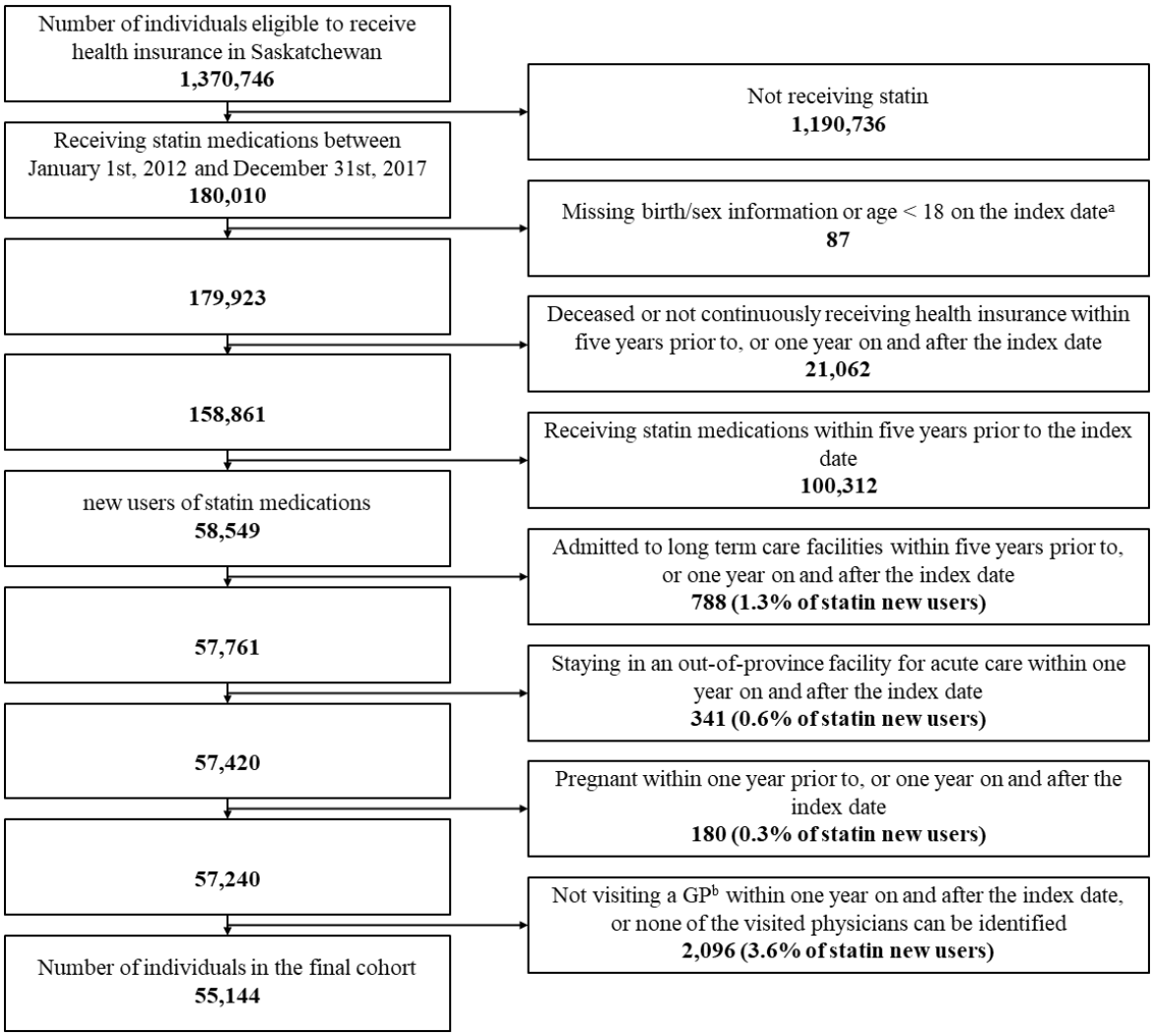
Ethics approval was granted by the University of Saskatchewan Biomedical Research Ethics Board (certificate number: 14-143). Data was accessed at the

Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan.

2.4 Results

Overall 180,010 patients received statin medications between January 1, 2012, and December 31, 2017. Among them, 21,149 (11.8%) were excluded due to missing demographic information, death during the study period, or a lack of continuous beneficiary status (Figure 2.1). The final cohort was comprised of 55,144 (30.6% of 180,010) new users of statin medications. The median age of the final cohort at the index date was 59.0 years [interquartile range (IQR) 51.0 to 67.0], 44.2% (24,385/55,144) were females and 32.3% (17,811/55,144) lived in a rural setting. The median number of GP visits in the 365 day period prior to index date was 6.0 (IQR 3.0 to 9.0, Table 2.1).

Figure 2.1: Study flow chart.



[a]Index date = the earliest date receiving a statin medication between January 1st, 2012 and December 31st, 2017; [b]GP = general practitioner.

Table 2.1: Baseline characteristics of the final cohort.

Baseline characteristics[a]	All	Patients grouped by UPCI[b]		Patients grouped by integrated COC[c]	
		High(>=0.82)	Low(<0.82)	Yes	No
	n=55,144	n=27,859	n=27,285	n=15,579	n=39,565
Median age (IQR[d])	59.0 (51.0, 67.0)	59.0 (52.0, 68.0)	58.0 (50.0, 67.0)	59.0 (51.0, 67.0)	59.0 (51.0, 67.0)
Females (n, %)	24,385 (44.2)	11,635 (41.8)	12,750 (46.7)	6,840 (43.9)	17,545 (44.3)
Patients with one or more hospitalizations for acute care (n, %)	12,528 (22.7)	6,203 (22.3)	6,325 (23.2)	2,626 (16.9)	9,902 (25.0)
Visits to GPs[e], median (IQR)	6.0 (3.0, 9.0)	5.0 (3.0, 9.0)	6.0 (3.0, 10.0)	6.0 (3.0, 9.0)	5.0 (3.0, 9.0)
Visits to specialists, Median (IQR)	2.0 (0.0, 6.0)	2.0 (0.0, 6.0)	2.0 (0.0, 6.0)	2.0 (0.0, 5.0)	2.0 (0.0, 7.0)
Patients with one or more visits to emergency department (n, %)	11,450 (20.8)	5,519 (19.8)	5,931 (21.7)	2,739 (17.6)	8,711 (22.0)
Patients by income level (n, %)					
1 (lowest)	10,339 (18.7)	4,787 (17.2)	5,552 (20.3)	2,675 (17.2)	7,664 (19.4)
2	10,207 (18.5)	5,058 (18.2)	5,149 (18.9)	2,761 (17.7)	7,446 (18.8)
3	10,093 (18.3)	5,182 (18.6)	4,911 (18.0)	2,942 (18.9)	7,151 (18.1)
4	11,289 (20.5)	5,897 (21.2)	5,392 (19.8)	3,251 (20.9)	8,038 (20.3)
5 (highest)	10,268 (18.6)	5,456 (19.6)	4,812 (17.6)	3,052 (19.6)	7,216 (18.2)
missing	2,948 (5.3)	1,479 (5.3)	1,469 (5.4)	898 (5.8)	2,050 (5.2)
Patients by residence location (n, %)					
Rural	17,811 (32.3)	8,666 (31.1)	9,145 (33.5)	4,364 (28.0)	13,447 (34.0)
Urban	37,333 (67.7)	19,193 (68.9)	18,140 (66.5)	11,215 (72.0)	26,118 (66.0)

[a] Median age, number of females, residence (rural/urban), and patient income level were measured on the index date; Number of patients with one or more hospitalizations, median visits to GPs/specialists, patients with one or more visits to emergency departments were measured within one year prior to the index date; [b]UPCI = usual provider continuity index; [c]COC = continuity of care; [d]IQR = interquartile range; [e]GP = general practitioners.

A single usual care provider (i.e., the GP with the highest number of visits) was identified for 92.6% (n=51,071) of the cohort, whereas 7.4% (n=4,073) of patients had two or more GPs tied for the highest number of visits. The median UPCI among the cohort was 0.82 (IQR 0.62 to 1.00), meaning half of all patients visited the same physician for 82% to 100% of their total GP visits during the one-year follow-up period. Similarly, a single usual statin prescriber (USP) could be identified for the vast majority of patients (n=52,693, 95.6%). In contrast, only 22,017 (39.9%) of the patients received complete medical examinations from a GP physician. The rest 33,127 (60.1%) of the patients either had no complete medical examinations during the follow-up period or received the examinations from a specialist. Finally, 15,579 (28.3%) of the patients were classified as receiving integrated COC, defined as having a single GP for their usual care provider, USP, and CMEP.

A high UPCI (i.e., above the median value) was neither a sensitive or specific marker to identify a physician who was also the USP or CMEP [Table 2.2]. The sensitivity ranged from 0.55 (95% CI 0.55 to 0.56, using UPCI to predict usual statin provider) to 0.58 (95% CI 0.58 to 0.59, using UPCI to predict integrated COC). The specificity ranged from 0.52 (95% CI 0.51 to 0.52, using UPCI to predict CMEP) to 0.61 (95% CI 0.60 to 0.62, using UPCI to predict the usual statin provider, Table 2.2).

Table 2.2: Measures of accuracy using UPCI to predict USP, CMEP, and integrated COC status.

	Sensitivity (95%CI[e])	Specificity (95%CI)	PPV[f] (95%CI)	NPV[g] (95%CI)	Kappa (95%CI)
UPCI[a] to predict the USP[b]	0.55 (0.55, 0.56)	0.61 (0.60, 0.62)	0.78 (0.77, 0.78)	0.35 (0.35, 0.36)	0.13 (0.13, 0.14)
UPCI to predict a CMEP[c]	0.55 (0.54, 0.56)	0.52 (0.51, 0.52)	0.39 (0.39, 0.40)	0.67 (0.66, 0.68)	0.06 (0.05, 0.07)
UPCI to predict integrated COC[d]	0.58 (0.58, 0.59)	0.53 (0.52, 0.53)	0.33 (0.32, 0.33)	0.76 (0.76, 0.77)	0.09 (0.08, 0.09)

[a]UPCI = usual provider continuity index; [b]USP=usual statin prescriber; [c]CMEP = complete medical examination provider; [d]COC = continuity of care; [e]CI = confidence interval; [f]PPV=positive predictive value; [g]NPV=negative predictive value.

Both high UPCI and the integrated COC measure showed statistically significant associations with optimal adherence to statin medications. Optimal adherence was observed in 56.0% (15,606/27,859) of patients with a high UPCI versus 49.9% (13,604/27,285) of those with low UPCI (unadjusted OR = 1.28, 95% CI 1.24 to 1.32, adjusted OR =1.23, 95% CI 1.19 to 1.28). In comparison, a stronger association with optimal adherence was observed when UPCI was included in the integrated COC measure (unadjusted OR = 1.45, 95% CI 1.40 to 1.51, adjusted OR=1.56, 95% CI 1.50 to 1.63). Optimal adherence was observed in 59.5% (9,277/15,579) of patients meeting the integrated COC criteria versus (versus 50.4%, 19,933/39,565) of those who did not.

The significant association between the integrated measure of COC and optimal adherence was consistently observed among subgroups with either a high UPCI value (adjusted OR=1.48, 95% CI 1.40 to 1.56) as well as those with a low UPCI value (adjusted OR=1.60, 95% CI 1.51 to 1.70). In contrast, the impact of a high UPCI appeared to have a weaker impact when tested in subgroups based on the presence or

absence of integrated COC (OR= 1.13, 95% CI 1.06 to 1.21; and OR= 1.22, 95% CI 1.17 to 1.27; respectively) [Table 2.3]. Finally, patients receiving integrated COC with a low UPCI score had 31% higher odds of achieving optimal adherence versus those without integrated COC but a high UPCI value (OR = 1.31, 95%CI 1.24 to 1.39). In the Delong test, the adjusted model using the integrated COC term significantly improved the AUROC (+0.006, $\chi 2$ statistic = 38.8, $p < 0.0001$) compared to the model using the UPCI measure of COC.

Table 2.3: Odds ratios (OR) and 95% confidence intervals (95% CI) for the association of measures of COC with optimal adherence (Proportion of days covered >= 80%).

	Unadjusted model OR[a] (95%CI[b])	Adjusted model[f] OR (95%CI)
Integrated COC[c,d]	1.45 (1.40, 1.51)	1.56 (1.50, 1.63)
Among patients with high UPCI[e]		1.48 (1.40, 1.56)
Among patients with low UPCI		1.60 (1.51, 1.70)
UPCI	1.28 (1.24, 1.32)	1.23 (1.19, 1.28)
Patients presenting integrated COC		1.13 (1.06, 1.21)
Patients not presenting integrated COC		1.22 (1.17, 1.27)

[a]OR = odds ratio; [b]CI = confidence interval; [c]COC = continuity of care; [d]Integrated COC = having a single physician identified as the usual care provider, the usual statin prescriber, and the complete medical examination provider; [e]UPCI = usual provider continuity index; [f]Covariates in the adjusted model included 1) age, sex, residence (rural/urban), and income level (i.e., the neighborhood median household income quintile, lowest=1, highest=5) on the index date; 2) the following were measured within 365 days prior to the index date: number of hospitalizations, number of out-patient visits (to GPs and to specialists, respectively), number of emergency department visits, Charlson comorbidity score, number of distinct prescription medications (by drug identification numbers), and percentage of prescription medication cost paid by government health insurance; and 3) a list of chronic conditions identified between January 1st, 1996, and the index date, including osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer.

In sensitivity analyses, the effect of UPCI and integrated COC were similar to the primary analysis when the days supply of statin medications were not allowed to be accumulated between refills. Also, we changed the threshold to define "high UPCI" from the median value to the 25th percentile. In this case the association of the UPCI measure on optimal adherence was stronger (adjusted OR = 1.39, 95% CI 1.34 to 1.45) but weaker when the threshold was changed to the 75th percentile (adjusted OR = 1.09, 95% CI 1.05 to 1.13). Regardless of the threshold changes, the impact of the UPCI alone was still weaker than the effect by the integrated COC measure.

2.5 Discussion

COC is considered to be an important determinant of medication adherence. It aligns with the paradigm of patient-centred care through coordination of services, especially when multiple providers are involved.[10] Quantitative studies appear to have confirmed this association with adherence; however, the most commonly used measure, the UPCI, is derived exclusively from the number of physician visits and fails to account for the coordination of care that is fundamental to the spirit of COC.[1-4] Our results indicate that a high UPCI value did not identify physicians who were providing core services (for example, prescribing statins to a cohort of new statin users or providing complete medical examinations). However, adding these clinical activities to the UPCI definition of COC resulted in a stronger association with medication adherence and significantly improved the predictive power of a medication adherence model. Further, the integrated COC measure added significant discrimination even when patients were stratified by high or low UPCI values. Our findings align with studies of patient-centered

medical homes (PCMH) in which medication adherence appeared to be improved by care coordination.[27, 32]

Despite the vast number of variables linked to medication adherence from published studies, almost all confer weak predictability in multivariable models.[33-35] Wong and colleagues conducted a population-based study with many patient-level factors including demographic characteristics (e.g., age, sex, and marital status), comorbidities (e.g., vascular disease, mental illness, and chronic lung or renal disorders), and regimen complexity.[34] The study also included clinical factors such as disease severity, and laboratory test results. Yet the authors found that all these variables only explained 2.9% of the adherence variation between patients.[34] Indeed, one of the major gaps in medication adherence research is the inability to explain more than a fraction of the variance observed with respect to adherence outcomes. We believe that adherence research needs to improve on the poor predictive ability of population-based models, which will require the identification of new variables as well as improving upon traditional measures such as COC.

Our study was not without limitations. First, the effect of COC on adherence was not adjusted by GP-related characteristics (e.g. age, sex, medical training background, workload, and prescribing habits), although the literature suggests that these characteristics may affect medication adherence.[11-13, 36] Second, GP physicians paid on salary (rather than fee-for service) are not required to submit service claims. As a result, the number of visits may have been underestimated. Alternatively, GPs paid by a fixed salary may perform differently than GPs paid by fee-for-service but that factor could not be assessed.[37] Third, the association between the integrated COC measures and adherence

may not be causal. Having all services from the same GP could be a sign of a successful relationship rather than its cause. Nonetheless, COC measures have been used in many studies on medication adherence with positive findings and have a strong theoretical link to the origins of the problem.[1-4] Finally, including complete medical examination (CME) in the integrated COC measure may have limitations. One potential issue is that CME may confound the adherence outcome. It is possible that sicker patients were more likely to have a complete medical examination, and the literature suggests that sicker patients were more likely to be adherent than healthier patient.[24] Another limitation is the generalizability of applying the integrated COC measure to other Canadian provincial settings. In some jurisdictions, CME is not included as a benefit of health insurance plans, or is included with restrictions on who should receive it. Under these circumstances, it is certainly possible that CME may not be the ideal component of an integrated COC measure despite the positive results from this study. On the other hand, the improvement associated with the CME may not have been due to this specific service per se, rather it may have indicated evidence for patient-physician relationships that include a diverse variety of services (i.e., from prescribing statins to other types of examinations).

Despite these limitations, we improved upon an existing measure of COC that not only produced a robust odds ratio, but also improved the predictive success of an adherence model containing a large number of established covariates. Our findings do not merely identify a new variable for models of medication adherence but they contribute to an important and elusive goal of explaining the phenomenon within a framework that remains highly theoretical.

2.6 Conclusion

The most common approach for measuring COC in adherence models fails to account for a key principle of service coordination. An updated measure that integrates other clinical services with physician visits is more consistent with the concept of COC and the value of patient-centred care. In addition, the use of an integrated measure of COC provided better discrimination of adherent patients and improved predictive performance of a covariate-adjusted adherence model. An integrated measure should be considered as the standard approach for representing COC in population-based adherence models.

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Chapter 3 The Impact of Age and Sex Concordance between Patients and Physicians on Medication Adherence: a Population-based Study

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Rationale to include the manuscript in the thesis:

The aim of the manuscript is to examine demographic factors with the focus on age and/or sex concordance (same age range and/or same sex) between physicians and patients, which is corresponding to objective two of my PhD thesis research projects.

Manuscript publication status:

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Contribution to this manuscript by Shenzhen Yao and the coauthors:

Contributor Role	Role Definition	SY	LL	GT	CE	DB
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.	Y	Y	Y	Y	Y
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.	Y				
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	Y	Y			Y
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.					Y
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	Y				Y
Methodology	Development or design of methodology; creation of models	Y	Y	Y	Y	Y
Project Administration	Management and coordination responsibility for the research activity planning and execution.	Y				Y
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.	Y				Y
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.	Y				
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.		Y	Y	Y	Y
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.	Y	Y	Y	Y	Y
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.	Y				Y
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).	Y				Y
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.	Y	Y	Y	Y	Y

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3.1 Abstract

Objective: To determine the impact of age and sex concordance on optimal adherence to statin medications.

Design: A retrospective cohort study.

Setting: Population-based health administrative data from Saskatchewan, Canada.

Participants: Patients newly initiated on statin medications between January 1, 2012 and December 31, 2017.

Explanatory variables: Sex concordance (i.e., same sex) and age concordance (i.e., age within five years) between patients and prescribers.

Main Outcome Measure(s): Optimal adherence (i.e., proportion of days covered $\geqslant$ 80%) measured at one year after the first statin claim.

Statistical analysis: Multivariable logistic regression models using generalized estimating equations.

Results: Among 51,874 new statin users, 20.6% (n=10,710) were age concordant with prescriber. The vast majority of age concordance occurred in patients younger than 66 years (88.6%, 9,486/10,710). Sex concordance was observed in 62.8% (n=32,551) of patients and age-sex combined concordance in 13.2% (n =6,856). Among patients younger than 66 years (n= 36,641), age concordance did not have a significant impact on optimal adherence [adjusted OR (aOR) = 1.02, 95%CI 0.97 to 1.07]. The association of sex concordance (aOR=1.05, 95%CI 1.00 to 1.11), and age-sex combined concordance

(aOR = 1.05, 95%CI 0.99 to 1.12) within adherence were stronger than age concordance but failed to reach statistical significance by a very small margin.

Conclusions: Age and sex concordance were not statistically significant predictors of optimal statin adherence. However, a weak signal was detected for sex concordance. Future studies should examine this factor in different health care settings.

3.2 Introduction

Over decades of research on medication adherence, the impact of age and sex has been evaluated countless times without a clear and consistent signal.[1] Mathes and colleagues concluded that the effects of patient age on medication adherence were heterogeneous after reviewing 22 systematic reviews published between January 1990 and June 2018.[2, 3] Similarly, a consistent impact of sex on medication adherence has not been demonstrated.[2, 3]

Although age and sex of patients appear to have weak influences on medication adherence, few studies have evaluated the extent to which they may influence medication adherence through interactions with other factors. The existence of interactions between demographic characteristics may be important for medication adherence. For example, Schoenthaler and colleagues found that African-American patients under care of white physicians (i.e., discordance on ethnicity) had lower medication adherence compared to white patients under care of white physicians.[4] Presumably, this 'concordance' of race may have facilitated a more effective or trustful relationship between physicians and patients, improving medication adherence.[4, 5] Indeed, a strong physician-patient relationship has clearly been associated with high medication adherence as multiple studies have identified trust and communication between patients and physicians as important factors.[1, 6-11] Thornton and colleagues' found that patient-physician concordance on age and sex has positive effect on communication and satisfaction of care.[12] However, despite the strong connection between communication and medication adherence, the impact of age and/or sex concordance on medication adherence to prescribed medications has not been examined.

Based on these findings, we hypothesized that age and/or sex concordance may also be associated with medication adherence through the presumed mechanism of facilitating a more effective patient-physician relationship. The aims of this study were: 1) To describe the prevalence of age and/or sex concordance between prescribers and patients initiating statin medications; 2) To determine if age concordance, sex concordance, or age-sex combined concordance is associated with the occurrence of optimal adherence within the first year since initiating statin therapy.

3.3 Methods

Data sources

The study was conducted using administrative databases for Saskatchewan, Canada. These databases, linked by a common encrypted identification number for each patient, include the provincial health insurance registry file, the physician service claims file, the physician registry file, the hospital discharge abstract database, the emergency services file, and the prescription drug claims files.[13] The provincial health insurance registry file contains birth month/year, sex, rural/urban residence, provincial health insurance coverage start and end dates, and dissemination area (smallest standard geographic area for census data defined by Statistics Canada)[14] code of residence. The latter is used to assign area-level median household income based on 2006 census data.[15] The physician service claims file contains the date of the service, setting (in-hospital or out-patient), diagnosis (using three-digit International Classification of Diseases (ICD-9) codes),[16] physician identification number (encrypted), physician specialty, the billing code pertaining to the service provided, and the remuneration type of the provider [fee-

for-service (FFS) /non-fee-for-service type (NFFS)]. Although non-fee-for-service physicians are encouraged to submit "shadow claims", compliance is not enforced, and not all claims are captured. However, the percentage of missing shadow claims is not likely to be large, given previous Canadian research.[17] The physician registration file contains physicians' birth year, sex, and an indicator to distinguish general physicians (GPs) from other specialty physicians. It also provides information on country of medical training of physicians in Saskatchewan. The hospital discharge abstract database contains admission and discharge dates, up to 25 diagnostic codes (ICD-9 (2001 and before) or ICD-10-CA (after 2001),[16, 18] and an indicator about the event type (i.e., whether it was for acute or alternative care, of which a patient occupied a bed but did not require the intensity of services as for acute care).[19] The emergency service file provides admission and discharge date of visits to emergency departments. The prescription drug claims files capture dispensation claims of prescription medications, each containing a Health Canada drug identification number (DIN), a dispensation date, the quantity dispensed, total cost (including medication acquisition cost and markup/dispensing fee), and the proportion covered by government insurance. The drug files only contain claims in outpatient settings.

Study design and population

We conducted a retrospective cohort study of new statin users at least 18 years of age who received their first statin medication between January 1, 2012 and December 31, 2017. New users were defined as receiving no dispensations for a statin medication in the previous five years. The date of the first dispensation of a statin medication was the index date, and the patients were followed for 365 days. For each patient, a single statin

prescriber was identified using the following criteria: a) the physician with a GP specialty, and b) the GP identified on the highest number of statin dispensation claims for a specific patient (compared to all other GPs) during the 365 day follow-up period. In Saskatchewan, GPs provide primary care to the majority of patients with chronic conditions.

Exclusion criteria included: missing age or sex of patients or statin prescribers; unable to determine the remuneration type of statin prescribers; inability to follow patients between 1,825 days before and 365 days after the first statin claim due to loss of beneficiary status (including death), or admission to a long term care facility; patients admitted to an out-of-province hospital in the year after initiating the statin; a diagnosis of pregnancy (ICD-9: 641-676, V27; ICD-10 and ICD-10-CA: O1, O21-95, O98, O99, Z37) within one year before or after the index date; or if none of their statin prescribers was a GP physician.

Patient and public involvement

Patients and/or the public were not involved in the design or conduct of this study.

Outcome measures

The primary outcome was optimal adherence to statin medications defined by the proportion of days covered (PDC) of at least 80%.[20, 21] PDC was measured over the 365 days following the index date using the sum of the number of pills dispensed divided by 365 (assuming once-daily satin dosing), deducting the number of days spent in a hospital for acute care if applicable.[22] Pills dispensed during overlapping/early refills were

counted in the numerator for the primary analysis and removed in sensitivity analyses. Switching between different statin medications was allowed.

Age/sex concordance between patients and their statin prescriber

Age of each patient and their corresponding statin prescriber was determined on each patient's index date. Patients were categorized as age-concordant if their age was within five years above or below the prescriber's age; sex-concordance was assigned if the patient and the prescriber were of the same sex. Age-sex combined concordance was determined if both age and sex concordance were satisfied.

Covariates

Numerous patient and provider-related covariates were identified to minimize confounding based on previous studies.[1] Covariates were measured during the 365 days prior to the index date if not otherwise specified. Patient-related covariates included patient characteristics [age, sex, and residence (rural/urban) on the index date]; socioeconomic status [income level based on census area-level median household income quintiles (lowest=1, highest=5) on the index date];[23, 24] treatment factors [number of distinct prescription medications (by the Anatomical Therapeutic Chemical Classification System)[25]]; health care system factors [percentage of prescription medication cost paid by government health insurance], and patient health/health care utilization factors [number of out-patient visits (to GPs and to specialists, respectively), number of hospitalizations for acute care, number of emergency department visits, Charlson comorbidity score,[26] and presence of patient clinical conditions (yes/no) used in published models of medication adherence].[27] The clinical conditions included osteoporosis, rheumatoid

arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer.[27] Conditions were identified using validated case definitions developed by the Canadian Chronic Disease Surveillance System and were based on diagnoses recorded in the service claims file, hospital discharge abstract database, and medications in the prescription drug claims dating back to January 1st, 1996.[27]

Prescriber-related covariates included the statin prescribers' age and sex on the index date, country of medical graduation, as well as a categorical variable of remuneration type [fee-for-service (FFS) or non-fee-for-service" (NFFS)]. These covariates were adopted in previous studies on quality of care provided by physicians.[28-30] The remuneration type for each prescriber was determined using physician-specific claims to all their patients (i.e., not only limiting to study patients) in the physician-service file between 365 days prior and 365 days on and after the index date. FFS remuneration practitioners were defined by at least 80% of claims coded as the FFS type; NFFS remuneration practitioners were defined by at least 80% of claims coded as the NFFS type. Over 95% of GP physicians could be categorized into one of the groups using this approach.

Finally, we included a variable identifying patients receiving comprehensive continuity of care where the patient's statin prescriber also: 1) claimed at least one comprehensive medical exam on the patient; and 2) had the highest number of service claims to the study patient compared to all other GPs. We found that this measure of

continuity of care is superior to traditional approaches (unpublished). The comprehensive continuity of care was estimated during the 365 days after the index date (inclusive).

Statistical analysis

The prevalence of age and sex concordance was described using percentages, medians and the interquartile range (IQR), as appropriate. Since age concordance was strongly influenced by patient age, we stratified the cohort based on age (> 65 years, or ≤65 years, respectively).

For each of the concordance variables under analysis (age concordance, sex concordance, and age-sex combined concordance), we fit univariate logistic regression models using optimal adherence (PDC ≥80%) as the dependent variable. Generalized estimating equations (GEE) were used to account for the clustering of patients within prescribers in all univariate and multivariable models.[31] GEE models using different types of working covariance matrices were compared and the one with the smallest quasi-Akaike's information criterion (QAIC) statistic was selected as the final model. Odds ratios (ORs) and 95% confidence intervals (95% CI) for the concordance variables were obtained from the robust estimators.

Next, we estimated adjusted effects of the concordance variables using multivariable logistic regression models that included patient and prescriber-related covariates. Multicollinearity between a concordance variable and each covariate was examined using the variance inflation factor (VIF) derived from a regression model. If the VIF value was greater than 2.5, the covariate was removed. Two multivariable

models were constructed; one included both of the age concordance and sex concordance variables, while the second included the age-sex combined concordance variable.

Age concordance with prescribers was uncommon for patients over 65 years of age; therefore, due to the potential bias associated with disproportionately high number of elderly patients in the discordant (vs concordant) age group, all adjusted models were tested in a subgroup of patients age at or below 65 years.

In sensitivity analyses, we changed age concordance to 10 years (i.e., instead of five) and we modified the threshold of optimal adherence to PDC ≥70%, and PDC ≥90%. In addition, we examined the effect of sex concordance within stratified groups based on the statin prescribers' sex. For each prescriber sex group, we reported the proportion of patients achieving optimal adherence. We also repeated the analysis of sex concordance among the entire cohort of statin users (i.e., not just those ≤65).

SAS statistical software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to conduct all analyses.[32]

Ethical considerations

Ethics approval was granted by the University of Saskatchewan Biomedical Research Ethics Board (14-143). Data were accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan.

3.4 Results

Between January 1, 2012, and December 31, 2017, 180,010 patients received statin medications. Among them, 21,149 were excluded for missing demographic information, age < 18 on the index date, or lacking continuous beneficiary status. Of the 58,549 patients who were defined as new statin users, 3,405 (5.8%) were excluded for admission to a long term care facility, staying in an out-of-province hospital, pregnancy/delivery, or having zero service claims by a GP within the follow-up period. Further, 3,270 (5.5%) patients were excluded for having a statin prescriber with missing birth year, sex, or remuneration type. The final cohort was comprised of 51,874 new users of statin medications [Figure 3.1].

Initially 1,789 GPs had been identified as statin prescribers for at least one new statin user. Among them, 227 (12.7%) prescribers were excluded for missing data on year of birth, sex, or undetermined remuneration type. Thus, 1,562 statin prescribers remained in the study, and were linked to at least one of the 51,874 patients [Figure 3.1].

The utility of using statin dispensation claims to identify a single GP prescriber was supported by the underlying data. There were 415,564 claims of statin medications for the cohort patients within the follow-up period. Most of these claims (85.5%, 355,206/415,564) originated from GPs who were identified as statin prescribers, while only 14.5% (60,358/415,564) from other GPs or specialists. The median number of total statin claims per patient during the follow-up period was 9.0 (IQR, 4.0/11.0) and the median number of statin claims from the identified prescriber (i.e., the most frequently listed GP) was 7.0 (IQR, 3.0/10.0). Other prescribers (e.g., other GPs or specialists)

accounted for only 2.0 statin claims per patient (IQR, 1.0/3.0). Moreover, of all patients in the cohort, 31,539/51,874 (60.8%) received all statin prescriptions from a single GP [Table 3.1].

The median age of patients on the index date was 59.0 years (IQR, 51.0/67.0), and 43.9% (22,781/51,874) were females [Table 3.1]. Among the 51,874 patient-prescriber pairs, the median age of physicians on the index date was 50.0 (IQR, 40.0/59.0). There were 36.0% (562/1,562) female statin prescribers and they appeared in 13,532 (26.1%) patient-prescriber pairs [Table 3.1].

The median age of patients was 10 years older than the median age of prescribers (IQR, -3/22 years). Age differences were higher among patients over 65 (median difference = 25 years, IQR: 15/35 years) versus those ≤ 65 years (median difference = 4 years, IQR: -7/14 years) [Table 3.1]. Overall, only 20.6% (n=10,710) of the entire cohort were concordant by age (i.e., within 5 years) with their statin prescriber on the index date. Most of these age concordant patients were 65 years or younger (88.6% or 9,486/10,710). Among those older than 65, only 8.0% (1,224/15,233) were age concordant to their statin prescribers and 90.5% (13,780 /15,233) were more than five years older [Table 3.1]. Sex concordance was observed in 62.8% (32,551/51,874) of patients. Age-sex combined concordance was relatively infrequent, observed in only 13.2% (6,856/51,874) of patients overall and 16.7% (6,133/36,641) of patients ≤ 65 years. Among those older than 65, there were only 4.7% (723/15,233) patients were both age and sex concordant [Table 3.1].

In the multivariate models, the GEE method using the exchangeable working covariance matrix had the smallest QAIC value among the tested structures. Logistic

regression analysis did not detect an impact of age concordance on optimal adherence [unadjusted OR (uOR) = 1.02, 95%CI 0.96 to 1.08; adjusted OR (aOR) = 1.02, 95%CI 0.97 to 1.07, Table 3.2]. The odds ratios of sex concordance on optimal adherence were uOR = 1.05 (95%CI 1.01 to 1.10), and aOR =1.05 (95%CI 1.00 to 1.11), while the impact of age-sex combined concordance was similar to sex concordance only: uOR = 1.06 (95%CI 0.99 to 1.13), aOR = 1.05 (95%CI 0.99 to 1.12) [Table 3.2]. Results were similar when analyses were repeated with age concordance measured by a broader range of years (i.e., age ± 10 years) or when changing the optimal adherence threshold to PDC ≥70%, and PDC ≥90% (data not shown).

In stratified analyses of patients ≤ 65 years of age, sex concordance appeared to have a weak association with optimal adherence for patients with male prescribers (aOR = 1.06, 95%CI 1.00 to 1.11, Table 3.2). Optimal adherence was observed in 50.9% (8,961/17,601) of male patients with male prescribers versus 49.4% (4,529/ 9,173) of female patients with male prescribers [Table 3.3]. When restricting to patients of female prescribers the result was similar (aOR = 1.05, 95%CI 0.95 to 1.16). In this subgroup, optimal adherence was observed in 49.8% (3,011/6,048) of female patients under female prescribers versus 48.3% (1,824/3,779) of male patients under female prescribers [Table 3.3].

Within the subgroup of patients > 65 years, sex concordance with male prescribers was significantly associated with optimal adherence (aOR = 1.10, 95%CI 1.01 to 1.19) [Table 3.2]. Optimal adherence was observed in 63.9% (4,127/6,455) of male patients with male prescribers versus 60.6% (3,098 /5,113) of female patients with male prescribers [Table 3.3]. For patients with a female prescriber, sex concordance was not

associated with optimal adherence (aOR = 0.96, 95 %CI 0.81 to 1.13) [Table 3.2]. In this group, 60.3% (1,476/2,447) of female patients under female prescribers achieved optimal adherence versus 62.5% (761/1,218) of male patients under female prescribers [Table 3.3].

When the analysis of sex concordance was repeated among the entire cohort of statin users (i.e., not just those ≤ 65 years), results were consistent (aOR = 1.05, 95%CI 1.00 to 1.10). Sex concordance among the subgroup of patients with male physician prescribers was significantly associated with the odds of optimal adherence (aOR = 1.06, 95%CI 1.02 to 1.11); however, sex concordance was not significantly associated with optimal adherence among patients with female physicians (aOR = 1.03, 95%CI 0.94 to 1.13) [Table 3.2].

3.5 Discussion

We performed a population-based study of new statin users and their prescribing GPs to test whether age and/or sex concordance influences the odds of optimal adherence. Age concordance was relatively infrequent, owing largely to the high percentage of patients who were over the age of 65 years. Although patients under the age of 65 were much more likely to be of similar age with their prescribing physician, no influence of age concordance on the odds of optimal adherence could be detected. In contrast, sex concordance between patients and physicians was observed more frequently (62.8% in all age groups) and the association with optimal medication adherence was stronger than age-concordance, albeit with a non-significant, small effect size. Although we cannot rule out the possibility that sex concordance with the prescribing physician may influence

adherence of some patients, the impact appears to be small in our cohort. To our knowledge, our study is the first to investigate age and sex concordance on medication adherence, using population based administrative data, and controlled by a wide range of patient- and physician-related covariates.

The literature suggests that patient-physician concordance on certain demographic characteristics may influence medication adherence. It appears that patients exhibiting the same race/ethnicity as their physician may be more likely to exhibit optimal adherence, presumably because of a more effective relationship and/or increased trust. Schoenthaler and colleagues reported that the odds of high adherence among white patients treated by white physicians were 27% (OR: 1.27, 95% CI 1.01 to 1.61) higher compared with patients receiving care from physicians with different ethnicity.[4] Traylor and colleagues found that Spanish speaking patients treated by Spanish speaking physicians were more likely to be adherent to medications compared to Spanish speaking patients treated by Non-Spanish speaking physicians (50.6% vs 44.8%, $p<0.05$).[5]

A possible association between sex concordance and optimal adherence was observed (aOR=1.05, 95% CI 1.00 to 1.11) in the initial analysis of patients ≤ 65 years and a consistent finding was produced using the entire cohort of statin users (aOR 1.05, 95%CI 1.00 to 1.10). Although the absolute impact of sex concordance appeared relatively small and it did not reach statistical significance, it should be noted that these trends occurred in a health care system where patients are free to choose their GP physician. In other words, patients with strong preferences for a same-sex prescriber would have likely been disproportionately represented in the sex-concordant group, especially in areas where multiple physicians were accessible to patients. Saskatchewan

offers a universal health care system where patients are free to choose any general practitioner who is accepting new patients. Thus, the weak signal observed in this analysis occurred despite a clear bias towards the null effect.

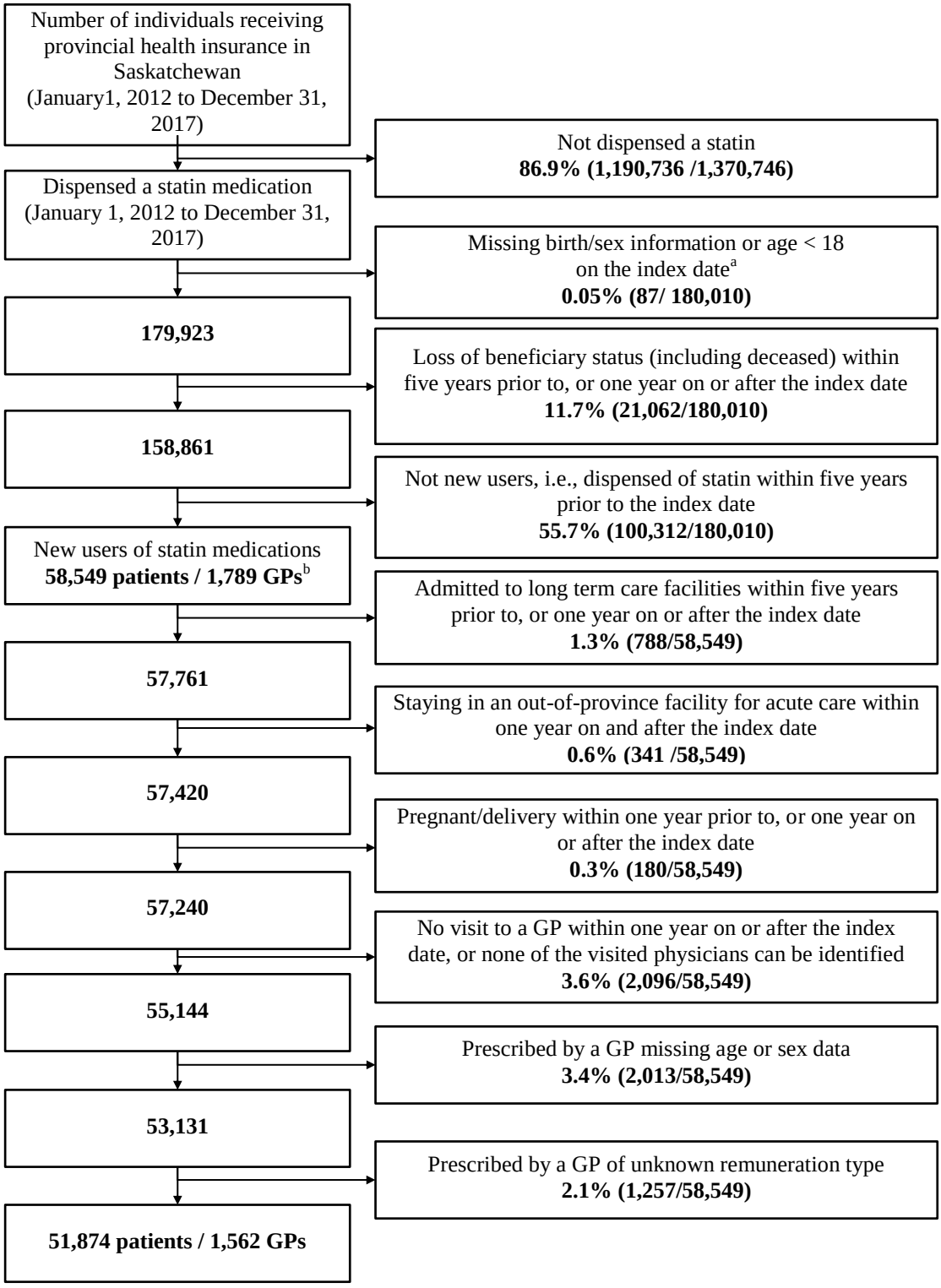
Our study was not without limitations. First, the administrative data used in this study only captures dispensations but not consumption of medications. However, administrative data have been widely used in medication adherence research and have high validity.[33] Second, administrative databases do not capture clinical data such as disease status, treatment effectiveness, or medication tolerability. Although misclassification of non-adherence could occur, it is unlikely to correlate with concordance groupings. Third, lack of randomization increases the chance of unmeasured confounding between concordance groups. Fourth, the income quintile data from the administrative database was old (from the census data of 2006). More recent data should be used when it is available in future studies. Fifth, patients above 65 years of age were excluded from the analyses of age concordance. However, the issue of age-concordance with physicians is not relevant to elderly patients as very few physicians in our cohort practiced during their elderly years (i.e., median age of prescribers was 50 years). Finally, the impact of concordance was examined in a health care system that allows patients to choose their own providers. As discussed above, the direction of the bias is likely towards the null.

3.6 Conclusion

Age concordance between patients and statin prescribers does not appear to impact the odds of optimal adherence. However, a weak signal was detected for a

possible effect of sex concordance. Future studies should re-examine the impact of sex-concordance in areas where provider access is limited or in health systems that limit choice of providers. Sex-concordance may play a more important role in these contexts.

Figure 3.1: Study flow chart.



[a]Index date = the first date receiving a statin medication between January 1, 2012 and December 31, 2017; [b]GP = general practitioner.

Table 3.1: Baseline characteristics of new statin users.

	Total n=51,874	Age≤65 n=36,641	Age > 65 n=15,233
Age of patients, median (IQR[a])	59.0 (51.0, 67.0)	54.0 (48.0, 60.0)	73.0 (69.0, 79.0)
Age of prescribers[b], median (IQR)	50.0 (40.0, 59.0)	50.0 (40.0, 59.0)	49.0 (40.0, 59.0)
Age difference (patient minus prescriber), median (IQR)	10.0 (-3.0, 22.0)	4.0 (-7.0, 14.0)	25.0 (15.0, 35.0)
Age concordance[c], n (%)	10,710 (20.6)	9,486 (25.9)	1,224 (8.0)
Age discordance[d]			
Patients > 5 years younger than prescribers, n (%)	10,804 (20.8)	10,575 (28.9)	229 (1.5)
Patients >5 years older than prescribers, n (%)	30,360 (58.5)	16,580 (45.2)	13,780 (90.5)
Female patients, n (%)	22,781 (43.9)	15,221 (41.5)	7,560 (49.6)
Female prescribers/prescribers of all sex, n (%)	562/1,562 (36.0)	545/1,495 (36.5)	465/1,309 (35.5)
Patients whose statin prescribed by a female GP[e], n (%)	13,532 (26.1)	9,867 (26.9)	3,665 (24.1)
Sex concordance, n (%)	32,551 (62.8)	23,649 (64.5)	8,902 (58.4)
Age-sex combined concordance, n (%)	6,856 (13.2)	6,133 (16.7)	723 (4.7)
Statin claims per patient, median (IQR)	9.0 (4.0, 11.0)	9.0 (4.0, 11.0)	10.0(5.0, 12.0)
Statin prescribers per patient, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Patients with a unique statin prescriber, n (%)	31,539 (60.8)	23,543 (64.3)	7,996 (52.5)
Patients with multiple statin prescribers, n (%)	20,335 (39.2)	13,098 (35.7)	7,237 (47.5)
Statin claims by the paired prescriber, median (IQR)	7.0 (3.0, 10.0)	7.0 (3.0, 10.0)	7.0 (4.0, 11.0)
Statin claims by other prescribers, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)

Table 3.1 Baseline characteristics of new statin users (continued).

	Total n=51,874	age≤65 n=36,641	Age > 65 n=15,233
1+ acute care hospitalizations[f], n (%)	11,493 (22.2)	6,154 (16.8)	5,339 (35.0)
GP visits[f], median (IQR)	6.0 (3.0, 9.0)	5.0 (3.0, 8.0)	7.0 (4.0, 11.0)
Specialist visits[f], median (IQR)	2.0 (0.0, 6.0)	2.0 (0.0, 5.0)	4.0 (1.0, 10.0)
1+ emergency department visits[f], n (%)	10,952 (21.1)	6,789 (18.5)	4,163 (27.3)
Income level[f], n (%)			
1 (lowest)	9,569 (18.4)	6,772 (18.5)	2,797 (18.4)
2	9,500 (18.3)	6,728 (18.4)	2,772 (18.2)
3	9,540 (18.4)	6,718 (18.3)	2,822 (18.5)
4	10,685 (20.6)	7,519 (20.5)	3,166 (20.8)
5 (highest)	9,782 (18.9)	6,857 (18.7)	2,925 (19.2)
missing	2,798 (5.4)	2,047 (5.6)	751 (4.9)
Patients living in a rural area[f], n (%)	15,830 (30.5)	10,729 (29.3)	5,101 (33.5)
Charlson comorbidity score[f] > 0, n (%)	16,988 (32.7)	9,463 (25.8)	7,525 (49.4)

[a]IQR = interquartile range; [b]Age of individual prescribers was re-calculated for each of their patients on the date of the earliest statin dispensation; [c]Age concordance was defined as patient age falling within five years above or below the prescriber's age; [d]Age discordance was defined as patient age falling at least five years above or below the prescriber's age; [e]GP = general practitioners; [f]Characteristics measured within 365 days prior to the date of the earliest statin dispensation.

Table 3.2: Odds Ratios (95% confidence intervals) for age and sex concordance with optimal adherence proportion of days covered >=80%) among new statin users

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio[b] (95% confidence interval)
Patients aged ≤65 years		
Age concordance[a] (yes vs no)	1.02 (0.96, 1.08)	1.02 (0.97, 1.07)
Sex concordance (yes vs no)	**1.05 (1.01, 1.10)[c]**	1.05 (1.00, 1.11)
Patients paired to a male prescriber	1.02(0.97, 1.07)	**1.06 (1.00, 1.11)**
Patients paired to a female prescriber	**1.15(1.05, 1.27)**	1.05 (0.95, 1.16)
Age-sex combined concordance	1.06 (0.99, 1.13)	1.05 (0.99, 1.12)
Patients aged > 65 years		
Sex concordance (yes vs no)	**1.08(1.00, 1.15)**	1.03 (0.94, 1.12)
Patients paired to a male prescriber	**1.12(1.04, 1.21)**	**1.10 (1.01, 1.19)**
Patients paired to a female prescriber	0.93(0.79, 1.09)	0.96 (0.81, 1.13)
Patient age ≤65 and > 65		
Sex concordance (yes vs no)	1.03(0.99, 1.07)	1.05 (1.00, 1.10)
Patients paired to a male prescriber	1.00(0.96,1.05)	**1.06 (1.02, 1.11)**
Patients paired to a female prescriber	**1.12(1.02,1.22)**	1.03 (0.94, 1.13)

[a]Age concordance = prescriber and patient age difference within ±5 years (age measured on the patient's date receiving the first dispensation of a statin medication); [b]Adjusted odds ratios were from models with covariates including: age, sex, residence (rural/urban),income quintile based on census area, number of distinct prescription medications, number of out-patient visits (to GPs and to specialists, respectively), percentage of prescription medication cost paid by government health insurance, number of hospitalizations for acute care, number of emergency department visits, Charlson comorbidity score, clinical conditions (including osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer), status of comprehensive continuity of care, prescribers' age, sex, country of medical graduation, and remuneration type,; [c]Odds ratios are in bold if statistically significant using 95% confidence interval.

Table 3.3: Frequency (%) of adherent patients (having a proportion of days covered by statin ⩾ 80%) by sex concordance status.

	Adherent patients in the sex concordance[b] group % (adherent patients / total in the group)	Adherent patients in the sex discordance[c] group % (adherent patients / total in the group)
Patient age[a] ≤65 years		
paired to a male prescriber	50.9(8,961/17,601)	49.4(4,529/9,173)
paired to a female prescriber	49.8(3,011/6,048)	48.3(1,824/3,779)
Patient age > 65 years		
paired to a male prescriber	63.9(4,127/6,455)	60.6(3,098/5,113)
paired to a female prescriber	60.3(1,476/2,447)	62.5(761/1,218)
Patients of all age groups		
paired to a male prescriber	54.4(13,088/24,056)	53.4(7,627/14,286)
paired to a female prescriber	52.8(4,487/8,495)	51.7(2,585/4,997)

[a]Patient age was measured on the index date (the date receiving the first statin medication);[b]Sex concordance = the patient and the prescriber were of the same sex (e.g., a female patient matching to a female prescriber);[c]Sex discordance = the patient and the prescriber were of the different sex (e.g., a female patient matching to a male prescriber).

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Chapter 4 Physician influence on medication adherence, evidence from a population-based study

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December 9, 2021

Rationale to include the chapter in the thesis:

The aim of the chapter is to explore the extent to which 'physician effects' may help explain variance in patient adherence to statin medications, which is corresponding to objective three of my PhD thesis research projects.

Manuscript publication status:

Unpublished: currently under the process of developing multiple manuscripts regarding research conducted in this chapter.

Contribution to this manuscript by Shenzhen Yao and the coauthors:

Contributor Role	Role Definition	SY	LL	GT	CE	DB
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.	Y	Y	Y	Y	Y
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.	Y				
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	Y	Y			Y
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.					Y
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	Y				Y
Methodology	Development or design of methodology; creation of models	Y	Y	Y	Y	Y
Project Administration	Management and coordination responsibility for the research activity planning and execution.	Y				Y
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.	Y				Y
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.	Y				
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.		Y	Y	Y	Y
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.	Y	Y	Y	Y	Y
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.	Y				Y
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).	Y				Y
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.	Y	Y	Y	Y	Y

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4.1 Abstract

Background: Physician-prescribers may have a strong influence on patient medication adherence but their overall effect has never been quantified.

Objective: We explored the extent to which the influence of physician-prescribers may help explain variance in patient adherence to statin medications. We further examined the association between statin medication adherence and specific components of physician-prescriber effects including: a) a 'latent' effect (i.e., physician effect unexplained by patient and prescriber characteristics); and b) specific prescriber characteristics.

Design: A retrospective cohort study.

Setting: Population-based health administrative data from Saskatchewan, Canada.

Participants: Physician prescribers and their patients receiving a new statin medication between January 1, 2012 and December 31, 2017.

Explanatory Variables: Prescriber variables included sex, country of medical training; years in practice; remuneration type; number of patients; number of patients taking a statin (statin patient count). Patient variables included sex; residence; income; number and cost of medications; number of out-patient visits; number of visits to emergency departments; hospitalizations; comorbidities; and an indicator of continuity of care.

Main Outcome Measure(s): Optimal adherence to statin medications (i.e., proportion of days covered $\geqslant$ 80%) measured at one year after the first statin dispensation.

Statistical analysis: The overall physician impact on optimal medication adherence (i.e., PDC >= 80%) was estimated from the intraclass correlation coefficient (ICC) derived

from a random intercept model controlled by numerous patient-level variables (e.g., sex, residence, income, etc.). We also measured the impact of unmeasured physician factors or latent effects based on the ICC of a random intercept model controlled by both patient variables and physician-level factors (e.g., country of medical training, remuneration type, statin patient count, etc.). Finally, we estimated the impact of specific physician-level factors [sex, country of medical training, years in practice, remuneration type, number of patients, and number of patients taking a statin (statin patient count)]. Unadjusted odds ratios (uOR) for each factor were generated from logistic regression models; adjusted odds ratios (aORs) were obtained from non-linear mixed-effects logistic regression models adjusted by patient-level variables.

Results: We identified 51,874 new statin users and 1,562 general practitioner (GP) prescribers. Overall, 6.4% of the observed variance in optimal adherence could be attributed to prescribers ($p<0.0001$, after adjusting for patient level variables only). Prescriber variables associated with higher odds of achieving optimal adherence were: medical training in Canada versus abroad [adjusted odds ratio (aOR) = 1.40, 95%CI 1.30 to 1.51], non-fee-for-service remuneration compared to fee-for-service (aOR = 1.18, 95%CI 1.08 to 1.29), higher statin patient count (aOR = 1.06, 95%CI 1.03 to 1.09 for every additional 100 statin patients), and more years prescribing statin (every additional ten years, aOR = 1.30, 95%CI 1.14 to 1.48). Physician variables associated with a lower odds of optimal adherence included years in practice (every ten additional years, aOR = 0.76, 95%CI 0.66 to 0.87), and a higher overall patient count (every 1,000 additional patients, aOR = 0.98, 95%CI 0.97 to 1.00). These physician-level characteristics explained very little of the overall variance. The majority of prescriber influence (5.2%) was attributed to the variance unexplained by patient and prescriber variables ($p<0.0001$).

Conclusions: The overall impact of prescribers on optimal statin adherence appears to be very limited. Even “high-performing” physicians face significant levels of sub-optimal adherence among their patients.

4.2 Introduction

Poor medication adherence is frequently observed among patients receiving chronic medications but specific causal factors remain poorly understood.[1] Evidence suggests that physicians strongly influence adherence through several pathways connected to their professional role.[2-13] Physicians are typically responsible for diagnosing the condition,[14] discussing the patient's needs and preferences,[14, 15] selecting the right medication,[16-18] and providing education and follow-up.[19-22] In each of these roles, physicians may have opportunity to influence the probability that their patient will achieve optimal adherence.[23, 24]

The most commonly investigated pathways of physician influence on medication adherence have focused on interpersonal skills such as communication and trust, [2, 3, 5, 10-12] as well as practice-related factors such as follow-up visits/organization of care.[6, 7, 9, 13] Given the evidence linking these physician-related factors with medication adherence,[2, 3, 5, 10-12] it is plausible that highly skilled prescribers would have relatively small numbers of patients who exhibit non-adherence.

The determinants of good communication and trust are not easily defined. Communication can be impacted by physician factors such as physician age, sex, years in practice, workload, and country of medical training.[25-29] Some of these physician characteristics will change over their career including age, experience, workload, and perhaps their ability to influence patient adherence. Also, physicians may influence adherence through unknown factors (e.g., physicians' personality, or attitude) that cannot be identified using typical research methods. Although these specific factors may not be identifiable, effects on adherence due to unmeasured variables can be detected and described as a latent effect.[30] To our knowledge, a comprehensive evaluation of the

impact of physicians on medication adherence has never been conducted at the population level. The aim of this study was to determine the extent to which 'prescriber effects' may help explain variance in patient adherence to statin medications. We further examined 'prescriber effects' in two components: a) a 'latent' effect (i.e., physician effect unexplained by patient and prescriber characteristics); and b) specific prescriber characteristics and their association with statin adherence.

4.3 Methods

Data sources

The study was conducted using administrative databases from Saskatchewan, Canada, which has a population of approximately 1.1 million,[31] and a universal health care system. These databases, linked by a common encrypted identification number for each patient, include the provincial health insurance registry file, the physician service claims file, the physician registry file, the hospital discharge abstract database, the emergency services file, and prescription drug dispensations files.[32] The variables and data definitions of these files have been described in other studies.[33, 34]

Study design and population

We performed a retrospective cohort study of new users of statin medications. Inclusion criteria were: at least one dispensation of statin medication and the first statin dispensation (based on a five-year washout) between January 1, 2012 and December 31, 2017; and, age >=18 years old on the date of the earliest dispensation of a statin medication (index date). Patients were followed for 365 days.

A previous study showed that general practitioner (GP) physicians prescribe over 85% of the statin mediations used in Saskatchewan.[34] A single GP physician was

assigned as the prescriber to each statin patient based on their statin prescription dispensations during the one-year follow-up period (i.e., the GP who prescribed the greatest number of statin dispensations, independent of any specialist-prescribed statin dispensations). Patients were excluded if: no GP prescribers were listed on their statin dispensations; there were missing values for specific variables (age or sex of patient or prescriber, country of medical training for prescriber), unable to determine the physician remuneration type;[34] insufficient follow-up (i.e., loss of beneficiary status, deceased, or admitted to a long term care facility in the 5 years before, or one year after, the index date; hospitalized in an out-of-province acute care facility during the follow-up period; pregnancy within one year before or after the index date [International classification of diseases codes (ICD) 9th version (ICD-9): 641-676, V27; 10th version (ICD-10) and 10th revision of Canada (ICD-10-CA): O1, O21-95, O98, O99, Z37].

Outcome measure

The study outcome was optimal adherence to statin medications during the first year of therapy, defined by the proportion of days covered (PDC) ≥80% using methods previously described [Supplementary Appendix A].[23, 24] Tablets dispensed during early refills were allowed to accumulate in the numerator and switching between different statin medications was allowed.

Explanatory variables

The variables of primary interest were focused characteristics of GP prescribers. Both time-invariant and time-varying variables were included [Table 1]. Time-invariant physician level variables included sex and country of medical training. Time-varying physician level variables included prescriber's age, years in practice, remuneration type

[i.e., fee-for-service (FFS) versus non-fee-for-service (NFFS)], overall patient count (i.e., to indicate a GP's workload),[35, 36] and statin patient count (i.e., to indicate a GP's experience with statin medications) [Table 1].

In addition, we included patient level variables that were previously used in medication adherence studies to addressing confounding [S-Table 1].[1] These variables were all time-invariant (i.e., did not vary over time), including: age, sex, area of residence (i.e., rural/urban[37]); calendar year on index date; neighborhood median household income quintiles (lowest=1, highest=5);[38, 39] number of distinct prescription medication classes;[40] number of out-patient visits to GPs and to specialists; percentage of prescription medication cost paid by government health insurance; number of hospitalizations for acute care; number of emergency department visits; Charlson comorbidity score;[41] and presence or absence of a set of clinical conditions using validated case definitions by the Canadian Chronic Disease Surveillance System dating back to January 1st, 1996 [S-Table 1]. We also included an indicator of continuity of care, which was strongly associated with medication adherence in a previous study.[33]

Statistical Analysis

We described patient and physician characteristics of the cohort. For each GP prescriber, we calculated the prevalence of optimal adherence within their statin patient group. To compare individual GP physicians, we ranked prescribers into quartiles of increasing prevalence of statin adherence and described patient and prescriber characteristics within these groups. Between-group differences for median values were assessed by the Wilcoxon rank-sum test, and percentages by the Chi-squared test.

Next, we quantified the influence of GP prescribers (independent of patient characteristics) with multivariable logistic regression analyses using two-level (patient and prescriber) non-linear mixed-effects models. We calculated the intraclass correlation coefficient (ICC) for prescribers from an empty model (i.e., a model with the random intercept only), a model that also included patient level variables, and a model that also both patient and physician level variables.[30] The intraclass correlation estimates the proportion of the total variance in patient adherence accounted for by the clustering of patients within physicians.

The effects of the prescriber level variables on optimal adherence were expressed as unadjusted (u) or adjusted (a) odds ratios (OR) and 95% confidence intervals (95% CIs). The unadjusted effect of each explanatory variable was examined in univariate logistic regression models (i.e., without a random intercept term). The adjusted effects of these variables were examined in multilevel multivariable logistic regression models with all patient and prescriber related variables.

Several models were constructed beginning with an empty model (i.e., without the random intercept term or explanatory variables), and adding the prescriber identification numbers (i.e., a random intercept term), then all patient-level variables sequentially [after excluding those exhibiting multicollinearity with any of the physician-level factors defined as variance inflation factor (VIF) > 2.5].[42] The likelihood ratio test (LRT) was applied in each step to determine whether the additional terms significantly improved model fit.[43]

Next, we added physician-level characteristics into the model containing the random intercept and patient variables. Each physician variable of interest was added individually and differences in goodness of fit statistics were assessed using the LRT.[43]

For time-varying, physician-level variables, we evaluated multiple possible components including a contextual effect (between prescribers), a compositional effect (between patients within a prescriber), a random slope (the compositional effect varying between prescribers), and between/within level interactions.[43] The mean centering method was used to decompose these effect components.[43 43-45]

Our initial modelling results indicated that prescriber age and prescriber years in practice were highly correlated. Prescriber age was excluded from all models after an analysis suggesting it did not interact with the effects of years in practice [Supplementary Appendix B]. Also, we found contradictory effects in the prescriber years in practice variable after decomposition. The between-prescriber analysis suggested that the odds of optimal adherence was lower for prescribers with longer years in practice while the within-prescriber estimate indicated the odds of optimal adherence improved during this time. This apparent contradiction was clarified by calculating a dispersion statistic to clarify the within-prescriber result (Supplementary Appendix C). To illustrate the impact of dispersion on the modelling results for optimal adherence, we contrasted the mean years in practice with the dispersion (or standard deviation of years in practice). SAS statistical software, version 9.4, (SAS Institute Inc., Cary, NC, USA) was used to conduct all analyses.[46]

Ethical considerations

Ethics approval was granted by the University of Saskatchewan Biomedical Research Ethics Board (14-143). Data was accessed at the Saskatchewan Health Quality Council under data sharing agreements with the Saskatchewan Ministry of Health and eHealth Saskatchewan.

4.4 Results

We identified 58,549 patients who initiated statin therapy between January 1, 2012, and December 31, 2017. Among them, 3,405 (5.8%) were excluded for residing in a long-term care setting, hospitalized in an out-of-province facility, pregnancy, or having no service claims by a GP within the follow-up period. Also, 3,270 (5.5%) patients were excluded because their statin prescriber was missing data on birth, sex, graduation, or remuneration type. Thus, 51,874 new users were included in the final cohort. These patients were paired to 1,562 statin prescribers [Figure 4.1]. The mean age of patients on the index date was 59.0 years (IQR 51.0/67.0) and 43.9% were female. Among the patients, 15,830 (30.5%) lived in a rural area, 16,988 (32.7%) had a Charlson score greater than 0, and 11,493 (22.2%) received acute care in hospital within 365 days prior to the index date. Of the prescriber-patient pairs, the mean age of the prescribers was 50.0 years (IQR 40.0/49.0), 26.1% (n=13,532) were paired to a female prescriber, and 29.8% (n=15,462) were with a prescriber receiving their medical training in Canada. Prescribers had a median overall patient count of 3,346 (IQR 2,203/5,453), and a median statin patient count of 276 (IQR 177/413). The median number of study patients (new statin users) per prescriber was 16 [IQR <6 (value suppressed due to small cell size)/43].

The median prevalence of optimal statin adherence within prescriber groups was 52.4% (IQR 35.7%/65.5%). After ranking prescribers into quartiles based on increasing prevalence of statin adherence, clear differences in patient characteristics were observed between physician groups [Table 4.2]. Prescribers in the highest quartile (i.e., with the highest prevalence of optimal adherence among their patients) had patients who were older (median age = 61.0 IQR 54.0/70.0 vs 55.0 IQR 47.0/64.0, $p<0.0001$), less likely to be female (39.9% vs 47.4%, $p<0.001$), more likely to have a previous hospitalization for

acute care (39.4% vs 16.4%, p<0.001) or emergency room visit (30.1% vs 19.9%, p<0.001), more visits to a specialist (median =4.0 IQR 1.0/10.0 vs median=2.0 IQR 0.0/5.0, p<0.0001), and more with a Charlson score greater than 0 compared to physicians in the lowest quartile (46.4% vs 26.9%, p<0.001). Prescriber characteristics also differed across these quartiles. Prescribers in the highest quartile were less likely to be females (21.9% vs 27.9%, p<0.0001), more likely to be trained in Canada (55.7% vs 12.2%, p<0.001), less likely to be a NFFS prescriber (14.0% vs 17.9%, p<0.001), and prescribed statins more often (median statin patient count=253 IQR 176/334 vs 210, IQR 116/350, p<0.0001) compared to prescribers in the lowest quartile [Table 4.2].

The random intercept model (without patient and prescriber variables) was significantly different from the empty model without random terms (p<0.0001). The ICC derived from the random intercept model was 8.1%. Based on the ICC from the model that included patient level variables, individual physicians accounted for 6.4% of the total variance in optimal adherence observed in the population (reduced by 21.0% from the random intercept model, p < 0.0001).

A GP prescriber's country of medical training was significantly associated with their patient's odds of optimal statin adherence (Canada vs foreign, uOR=1.53, 95%CI 1.47 to 1.59; aOR=1.40, 95%CI 1.30 to 1.51). However, on inspection of the patient characteristics between these prescribers (36,422 prescribed by foreign-trained GPs vs 15,452 by Canadian-trained GPs) several differences were observed. Patients prescribed statins by foreign trained GPs were more frequently living in rural areas (32.4% vs 26.1%, p<0.001), with a substantially lower incidence of prior hospitalizations (18.1% vs 31.8%, p<0.0001), fewer emergency department visits (17.5% vs 29.7%, p<0.0001), and fewer

with a Charlson score greater than 0 (i.e., score >1 = 29.0% vs 41.7%, p<0.001) [Table 4.3].

A similar finding was observed for prescribers classified as receiving a NFFS (versus FFS) remuneration type. In the adjusted analysis, NFFS was significantly associated with an increased odds of optimal adherence (aOR=1.18, 95%CI 1.08 to 1.29); however, the unadjusted estimate suggested the opposite effect (uOR = 0.94, 95%CI 0.90 to 0.99). Again, this variable appeared highly confounded when examining patient characteristics as well as the distribution of patients between these two types of prescribers (7,849 statin patients prescribed by NFFS GPs vs 44,025 by FFS GPs). Patients prescribed statins by NFFS GPs were more often living in a rural area (47.6% vs 27.5%, p<0.0001), less likely to have been hospitalized previously (17.5% vs 23.0%, p<0.0001) or having visited an emergency department (14.8% vs 22.2%, p<0.0001), and fewer having a Charlson score greater than 0 (26.4% vs 33.9%%, p<0.0001). Further, NFFS prescribers had fewer years in practice (median =15.0, IQR 9.0/27.0 vs 25.0, IQR 15.0/34.0%, p<0.0001), and lower overall patient counts (median =2,112, IQR 1,567/ 2,800 vs 3,720, IQR 2409.0/5,823.0%, p<0.0001) [Table 4.3].

The overall effect of the GP prescriber's years in practice was not significantly associated with optimal adherence (i.e., per ten additional years in practice: uOR= 0.98, 95%CI 0.96 to 0.99; aOR = 0.98, 95%CI 0.96 to 1.01). However, as described in the methods, decomposition of the overall effect into the between-prescriber effect (i.e., per ten additional years in practice: aOR=0.76, 95% CI 0.66 to 0.87) and the within-prescriber effect (per ten additional years in practice: aOR= 1.30, 95%CI 1.14 to 1.48) appeared to be contradictory. Additional analyses using dispersion to represent the

within-prescriber effect confirmed the existence of these two effects simultaneously [Supplementary Appendix C].

Finally, a small but positive association was observed with an increasing number of patients receiving statins from a GP prescriber (i.e., for every additional 100 statin patients uOR=1.01, 95%CI 1.00 to 1.02; aOR=1.06, 95%CI 1.03 to 1.09), while the total patient count of a prescriber (i.e., representing workload) showed a very slight negative association with the odds of achieving optimal adherence (i.e., for 1000 additional patients uOR = 0.98, 95%CI 0.98 to 0.99; aOR=0.98, 95%CI 0.97 to 1.00). Prescriber sex was not significantly associated with patients' adherence outcomes (uOR=0.93, 95%CI 0.90 to 0.97; aOR= 0.99, 95%CI 0.91 to 1.07) [Table 4.4]. After accounting for all patient and prescriber variables, the prescriber latent effect accounted for only 5.2% of the variance in optimal adherence among the study population (reduced by 18.8% from the overall prescriber variance, $p<0.0001$).

4.5 Discussion

In this population-based study, we examined the impact of GP prescribers on patient adherence to statin medications. When prescribers were ranked into quartiles based on the prevalence of optimal adherence among their patients, several notable observations were evident. First, the upper quartile boundary of optimal adherence was only 65.4%. In other words, it appeared that "performance" on medication adherence was not skewed and many of the highest 'performing' prescribers still failed to motivate optimal adherence in up to one-third of their patients. Furthermore, differences between the highest and lowest ranking prescribers included clear trends in the characteristics of their patients. Prescribers with the highest prevalence of optimal adherence cared for patients who were older, sicker, and more likely to include a specialist in their care.

Indeed, after controlling for differences in patient characteristics, individual GP prescribers only accounted for 6.4% of the variance in optimal adherence observed in the study population. In contrast to the extensive body of research linking optimal adherence to prescriber characteristics such as superior communication skills,[2, 3, 5, 10-12] our results indicate that physicians do not consistently impact statin medication adherence. Published associations between high adherence and physician skills such as communication may have been a result of reverse causality bias, where adherent patients were more likely to rate their physician highly (i.e., for communication or trustworthiness) while non-adherent patient may rate the same physician poorly on these same characteristics.

Among physician-level factors associated with optimal adherence, estimates for country of medical training and prescriber remuneration appeared to be influenced by bias. The effect estimate for country of medical training indicated a significantly higher odds of optimal adherence among prescribers trained in Canada. However, we found that the patient populations prescribed statins by foreign graduated GPs were more often living in rural areas with lower levels of comorbidity/illness (i.e., fewer hospitalizations or emergency department visits, and lower Charlson score). These differences in measured confounders suggest the possibility of unmeasured factors contributing to the observed association with medical training. Further study of these latent variables is warranted to understand the true causes underlying this association.

A similar result was discovered during the assessment of prescriber remuneration type. We found that GP prescribers in a NFFS practice increased their patients' odds of achieving optimal adherence Although this finding aligns with the theory that NFFS physicians spend more time with patients resulting in increased patient satisfaction and

quality of care,[47] we found evidence for bias in our effect estimate. Not only were the number of NFFS practitioners far lower than those with FFS remuneration, the types of patients receiving statins from these groups of prescribers were different also. Patients receiving care from NFFS prescribers were highly skewed towards living in rural areas with lower levels of comorbidity. As a result, it appears the distribution of NFFS prescribers in our province is not adequate to allow non-randomized evaluation without substantial uncertainty due to the role of bias. Further study is needed to quantify the benefits and weaknesses of NFFS remuneration models as a specific focus; quantitative evidence for the impact of remuneration models is lacking.[48-50]

The impact of a prescriber's years in practice was complex but decomposition revealed important findings. The absolute number of years in practice had a significant, albeit relatively small negative impact on a prescriber's ability to influence optimal adherence. In a systematic review of 62 studies between 1966 and 2004 by Choudhry and colleagues, 32 (52%) studies reported that clinical knowledge, adherence to diagnosis and treatment guidelines, and patient health outcome declined as years in practice increased.[25] However, our analysis of the within-prescriber effect suggested that the activity of prescribing statins throughout the years of practice was also an important factor. Specifically, GPs prescribing to new statin patients across multiple years tended to have more adherent patients than GPs who had initiated statin treatment for patients over fewer years. We also found that the absolute number of statin patients under a GP prescriber's care was associated with a higher odds of optimal adherence. These findings demonstrate the difference between the absolute impact of years in practice versus the influence of continued activity with statins during those years of practice. It is plausible that frequent

prescribing of statin medications throughout the course of a prescriber's career would improve the skills and experience in supporting patients receiving these medications.

Our study had limitations. First, we only captured dispensations but not consumption of statins. However, dispensation data have been widely used to estimate medication adherence with high validity.[51] Second, lack of randomization limited our control over unmeasured confounding. This limitation appeared to be especially problematic for assessments of remuneration type and country of medical training. Devlin and colleagues reported that physicians may self-select into a remuneration type due to uncaptured personal preference and characteristics.[52] The effect of remuneration type and graduate country on medication adherence should be examined in future studies in order to improve our understanding of these factors. Other unmeasured factors included perception of risk, communication style of provider, race/ethnicity concordance, patient-physician trust level, and conflicting medication information. These variables were not captured in administrative data and should be included in future studies when data is available. Finally, the impact of calendar year was a possible confounder in our analysis as adherence to many chronic medications has been increasing for years.[53] However, it is highly correlated to years in practice, and was excluded in this study.

4.6 Conclusion

Physicians have been identified as playing an important role in influencing medication adherence among their patients. Although our results confirm that physicians play a role, their overall impact on the odds of achieving optimal adherence is very limited. Even "high-performing" physicians face significant levels of sub-optimal adherence among their patients. Moreover, the ability to partition the physician effect to

examine important factors such as remuneration strategy is limited because of system-level differences between physician practices.

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Figure 4.1: Study flow chart.

[a]Index date = the first date receiving a statin medication between January 1, 2012 and December 31, 2017; [b]GP = general practitioner.

Table 4.1: Definitions of variables used to describe physician prescribers.

Variable	Levels	Description	Type of measurement
Prescriber's sex	Male/Female	Biologic sex listed in the patient registration file	Time-invariant
Prescriber's country of medical training	Canadian/ Foreign	Country of medical training listed in the physician registration file	Time-invariant
Prescriber's age	Years	Prescriber's age on the date of each patent's index date (date of earliest statin dispensation).	Time-varying
Prescriber's years in practice	Years	Number of years between a statin prescriber's year of medical graduation and a patent's index date.	Time-varying
Prescriber's remuneration type	Fee-for-service (FFS) / Non fee-for-service (NFFS)	Derived from all billing claims submitted by the prescriber (i.e., not only limiting to study patients) between 365 days before and 365 days after the index date of a patient. If at least 80% of these records were coded as FFS claims, the prescriber was deemed a FFS physician for that specific patient. Alternatively, if at least 80% were coded as NFFS claims, the prescriber was deemed a NFFS physician. Over 95% of GP prescribers could be categorized into one of the groups using this approach.	Time-varying
Prescriber's overall patient count	Number of patients	The number of patients receiving at least one billing claim based on all claims submitted by the prescriber (i.e., not only limiting to study patients) between 365 days before and 365 days after the index date of a patient.	Time-varying
Prescriber's statin patient count	Number of patients	The number of patients with at least one statin dispensation from the GP prescriber. (time-varying) between 365 days before and 365 days after the index date of a patient	Time-varying

Table 4.2: Patient and prescriber characteristics.

Characteristic	Total (all patients)	Prescriber Quartile 1 *(% of patients with optimal statin adherence <35.7%)*	Prescriber Quartile 2 *(% of patients with optimal statin adherence 35.7% to 52.2%)*	Prescriber Quartile 3 *(% of patients with optimal statin adherence 52.3% to 65.4%)*	Prescriber Quartile 4 *(% of patients with optimal statin adherence >65.4%)*
Prescribers (n)	n=1,562	n=393	n=387	n=391	n=391
Patients(n)	n=51,874	n=6,251	n=14,640	n=19,760	n=11,223
% of patients with optimal adherence[a]	53.6	25.5	45.3	57.8	72.5
Patient characteristics					
Age, median (IQR[b])	59.0 (51.0, 67.0)	55.0 (47.0, 64.0)	58.0 (50.0, 66.0)	59.0 (52.0, 68.0)	61.0 (54.0, 70.0)
Females, n(%)	22,781 (43.9)	2,966 (47.4)	6,669 (45.6)	8,669 (43.9)	4,477 (39.9)
1+ hospitalizations for acute care, n(%)	11,493 (22.2)	1,025 (16.4)	2,284 (15.6)	3,765 (19.1)	4,419 (39.4)
Visits to GPs[c], median(IQR)	6.0 (3.0, 9.0)	6.0 (3.0, 10.0)	5.0 (3.0, 9.0)	6.0 (3.0, 9.0)	5.0 (3.0, 9.0)
Visits to specialists, median (IQR)	2.0 (0.0, 6.0)	2.0 (0.0, 5.0)	2.0 (0.0, 5.0)	2.0 (0.0, 6.0)	4.0 (1.0, 10.0)
1+ visits to emergency department, n(%)	10,952 (21.1)	1,243 (19.9)	2,531 (17.3)	3,802 (19.2)	3,376 (30.1)
Income level, n(%)					
1	9,569 (18.4)	1,608 (25.7)	2,826 (19.3)	3,275 (16.6)	1,860 (16.6)
2	9,500 (18.3)	1,224 (19.6)	2,813 (19.2)	3,599 (18.2)	1,864 (16.6)
3	9,540 (18.4)	1,046 (16.7)	2,675 (18.3)	3,645 (18.4)	2,174 (19.4)
4	10,685 (20.6)	1,167 (18.7)	2,920 (19.9)	4,222 (21.4)	2,376 (21.2)
5	9,782 (18.9)	848 (13.6)	2,603 (17.8)	4,032 (20.4)	2,299 (20.5)
missing	2,798 (5.4)	358 (5.7)	803 (5.5)	987 (5.0)	650 (5.8)
Rural residence, n(%)	15,830 (30.5)	1,923 (30.8)	4,568 (31.2)	6,173 (31.2)	3,166 (28.2)
Charlson score > 0, n(%)	16,988 (32.7)	1,683 (26.9)	3,946 (27.0)	6,148 (31.1)	5,211 (46.4)
Prescriber characteristics[f]					
Caseload[d], median (IQR)	16 (<6[g], 43)	6 (<6, 14)	21 (7, 49)	33 (17, 67)	10 (<6, 35)
Age, median (IQR)	50.0 (40.0, 49.0)	55.0 (43.0, 67.0)	48.0 (40.0, 59.0)	49.0 (38.0, 58.0)	50.0 (41.0, 57.0)
Female, n(%)	13,532 (26.1)	1,746 (27.9)	4,205 (28.7)	5,125 (25.9)	2,456 (21.9)
Medical training in Canada, n(%)	15,462 (29.8)	765 (12.2)	2,405 (16.4)	6,038 (30.6)	6,254 (55.7)
NFFS[e] prescriber, n(%)	7,849 (15.1)	1,122 (17.9)	2,510 (17.1)	2,648 (13.4)	1,569 (14.0)
Years in practice, median (IQR)	24.0 (13.0, 33.0)	28.0 (16.0, 42.0)	22.0 (13.0, 32.0)	24.0 (12.0, 32.0)	25.0 (15.0, 32.0)
Overall patient count, median (IQR)	3,346 (2,203, 5,453)	3,535 (2,080, 5,745)	3,313 (2,217, 5,491.5)	3,273.5 (2,249.5, 5,362.5)	3,390 (2,120, 5,474)
Statin patient count, median (IQR)	276 (177, 413)	210 (116, 350)	289 (170, 418)	309 (206, 458)	253 (176, 334)

[a]Optimal adherence = proportion of days covered >=80% of statin medications; [b]IQR = interquartile range; [c]GP = general practitioners; [d]Caseload = number of study patient (new statin users) per prescriber; [e]NFFS = non-fee-for-service remuneration type; [f]index date = patient's first statin dispensation date; [g]<6: actual number of patients was suppressed as there were less than six patients in the group. Patient and physician characteristics measured within 365 days prior to the date of the first dispensation of a statin (index date), or on the index date, except that overall patient count, and statin patient count were measured within 365 days prior to and 365 days on and after the index date.

Table 4.3: Patient and prescriber characteristics stratified by prescriber's country of medical training and remuneration type.

Characteristics	Total	Prescriber country of medical training		Prescriber remuneration type	
		Canada	Foreign	NFFS	FFS[f]
Patients(n)	n=51,874	n=15,452	n=36,422	n=7,849	n=44,025
Prescribers (n)	n=1,562				
Caseload[a], median (IQR[b])	16 (<6, 43)				
% of patients with optimal adherence[c]	53.6	60.9	50.5	52.3	53.8
Patient characteristics					
Age, median (IQR)	59.0 (51.0, 67.0)	60.0 (52.0, 69.0)	58.0 (50.0, 67.0)	59.0 (52.0, 68.0)	59.0 (51.0, 67.0)
Females, n(%)	22,781 (43.9)	6,612 (42.8)	16,169 (44.4)	3,536 (45.1)	19,245 (43.7)
1+ hospitalizations for acute care, n(%)	11,493 (22.2)	4,911 (31.8)	6,582 (18.1)	1,370 (17.5)	10,123 (23.0)
Visits to GPs[d], median(IQR)	6.0 (3.0, 9.0)	6.0 (3.0, 9.0)	6.0 (3.0, 9.0)	5.0 (3.0, 9.0)	6.0 (3.0, 9.0)
Visits to specialists, median (IQR)	2.0 (0.0, 6.0)	3.0 (1.0, 9.0)	2.0 (0.0, 5.0)	1.0 (0.0, 5.0)	2.0 (1.0, 7.0)
1+ visits to emergency department, n(%)	10,952 (21.1)	4,591 (29.7)	6,361 (17.5)	1,159 (14.8)	9,793 (22.2)
Income level, n(%)					
1	9,569 (18.4)	2,763 (17.9)	6,806 (18.7)	1,766 (22.5)	7,803 (17.7)
2	9,500 (18.3)	2,678 (17.3)	6,822 (18.7)	1,649 (21.0)	7,851 (17.8)
3	9,540 (18.4)	2,949 (19.1)	6,591 (18.1)	1,262 (16.1)	8,278 (18.8)
4	10,685 (20.6)	3,181 (20.6)	7,504 (20.6)	1,672 (21.3)	9,013 (20.5)
5	9,782 (18.9)	3,098 (20.0)	6,684 (18.4)	1,133 (14.4)	8,649 (19.6)
missing	2,798 (5.4)	793 (5.1)	2,005 (5.5)	367 (4.7)	2,431 (5.5)
Rural residence, n(%)[f]	15,830 (30.5)	4,043 (26.1)	11,787 (32.4)	3,735 (47.6)	12,095 (27.5)
Charlson score > 0, n(%)	16,988 (32.7)	6,444 (41.7)	10,544 (29.0)	2,073 (26.4)	14,915 (33.9)
Prescribers characterstics[g]					
Age, median (IQR)	50.0 (40.0, 49.0)	49.0 (38.0, 59.0)	50.0 (41.0, 59.0)	41.0 (35.0, 53.0)	51.0 (41.0, 60.0)
Female, n(%)	13,532 (26.1)	5,006 (32.4)	8,526 (23.4)	3,012 (38.4)	10,520 (23.9)
Medical training in Canada, n(%)	15,462 (29.8)			1,868 (23.8)	13,594 (30.9)
NFFS[e] prescriber, n(%)	7,849 (15.1)	1,868 (12.1)	5,981 (16.4)		
Years in practice, median (IQR)	24.0 (13.0, 33.0)	21.0 (10.0, 33.0)	24.0 (14.0, 33.0)	15.0 (9.0, 27.0)	25.0 (15.0, 34.0)
Overall patient count, median (IQR)	3,346 (2,203, 5,453)	3,163 (2,022, 4,967)	3,448 (2,285, 5,619)	2,112 (1,567, 2,800)	3,720 (2,409, 5,823)
Statin patient count, median (IQR)	276 (177, 413)	237 (147, 329)	303 (188, 440)	176 (120, 250)	301 (200, 438)

[a]Caseload = number of study patients (new statin users) per prescriber; ; [b]IQR = interquartile range; [c]Optimal adherence = proportion of days covered >=80% of statin medications; [d]GP = general practitioners; [e]NFFS = non-fee-for-service remuneration type; [f]FFS= fee-for-service remuneration type; [f]Rural residence = living in areas of a population under 1,000;[g]index date = the date of the first dispensation of a statin medication.

Patient and physician characteristics measured within 365 days prior to the date of the first dispensation of a statin (index date), or on the index date, except that overall patient count, and statin patient count were measured within 365 days prior to and 365 days on and after the index date.

Table 4.4: Odds ratios (95% confidence interval) for the association of prescriber-related characteristics with optimal statin adherence (proportion of days covered by statin medications >=80%).

Prescriber characteristics[a]	Unadjusted odds ratio (95%CI[c])	Adjusted[d] odds ratio (95%CI)		
		Between prescribers	Within a prescriber	Random slope
Country of medical training (Canada vs foreign)	**1.53 (1.47, 1.59)[e]**	**1.40 (1.30, 1.51)**		
Sex (female vs male)	**0.93 (0.90, 0.97)**	0.99 (0.91, 1.07)		
Years in practice (per 10 years increase)	**0.98 (0.97, 0.99)**	**0.76 (0.66, 0.87)**	**1.30 (1.14, 1.48)**	**1.30 (1.26, 1.35)**
Remuneration type (NFFS vs FFS)[b]	**0.94 (0.90, 0.99)**	**1.18 (1.08, 1.29)**	1.23 (0.91, 1.66)	
Overall patient count (per 1,000 increase)	**0.98 (0.98, 0.99)**	**0.98 (0.97, 1.00)**	0.99 (0.96, 1.01)	
Statin patient count (per 100 increase)	1.01 (1.00, 1.02)	**1.06 (1.03, 1.09)**	1.02 (0.97, 1.06)	

[a]Country of medical training and sex were measured on the date of the first dispensation of a statin (index date), overall patient count and statin patient count measured on 365 days prior and 365 days on and after the index date;[b]NFFS = non-fee-for-service remuneration method, FFS = fee-for-service remuneration method;[c]95%CI = 95% confidence interval; [d]Adjusted for patient variables including age, sex, urban/rural living, household income level, number of medications by the anatomical therapeutic chemical (ATC) class, number of outpatient visits, percentage of medication cost paid by government health insurance, number of hospitalization for acute care, number of visits to emergency department, Charlson comorbidity score, clinical conditions (osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer); also adjusted for prescriber-related variables in the table; [e]Odds ratios in bold font are statistically significant ($p<0.05$).

4.8 Supplementary materials

Appendix A: Measure of medication adherence outcome.

The study outcome was optimal adherence to statin medications during the first year of therapy, defined by the proportion of days covered (PDC) ≥80%.[1, 2] The PDC was estimated using the sum of the number of tablets dispensed (assuming one tablet per day dosing) divided by the number of days in the follow up period (365 days minus the number of days spent in a hospital for acute care because hospital drug dispensations are not captured).[3] Tablets dispensed during early refills were allowed to accumulate in the numerator and switching between different statin medications was allowed.

S-Table 1: Patient level factors used to control confounding in the assessment of physicians' influence on statin medication adherence.

Variable	Levels	Description
Age	Years	Years since birth to the index date (i.e., the date of the earliest statin dispensation).
Sex	Male/female	-
Area of residence	Rural/urban	Rural area defined as a population under 1,000 based on linkage between residential postal code and national census data.
Household income	Quintiles	Calculated as the mean of the neighborhood mean based on linkage between residential dissemination area code and national census data.
Number of distinct prescription medications	Continuous	Defined by anatomical therapeutic chemical classification (ATC) level-5 classes, and measured within 365 days prior to the index date.
Number of out-patient visits to GPs	Number	Number of out-patient visits to physicians who were identified as general practitioners (GPs) within 365 days prior to the index date.
Number of out-patient visits to specialists	Number	Number of out-patient visits to physicians who were identified as specialists within 365 days prior to the index date.
Medication cost paid by government health insurance	Number	Proportion of spending on prescription medications paid by the government health insurance within 365 days prior to the index date.
Number of hospitalizations for acute care	Number	Number of hospitalizations for acute care within 365 days prior to the index date.
Emergency department visits	Number	Number of visits to emergency department within 365 days prior to the index date.
Charlson comorbidity score	0, 1-2, 3, >3	Charlson comorbidity index score[4] measured within 365 days prior to the index date.
Continuity of care	Yes/No	Having the same general practitioner (GP) as the most frequently visited GP, the most frequent prescriber of statin, and the complete medical examination provider within 365 days on and after the index date.
Calendar year of cohort entry	2012, 2013, 2014, 2015, 2016, 2017	Calendar year of the index date (excluded in statistical models as having multicollinearity to prescriber-related variable 'years in practice')
Chronic conditions	Yes/No	Including osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer. The diagnostic codes and algorithm of these clinical conditions are summarized in a table published by CCDSS.[5] The conditions were dated back to January 1, 1996.

Appendix B: Analysis of prescriber years in practice and prescriber age.

The components of prescriber years in practice were associated with optimal medication adherence as described in the main manuscript. However, we excluded prescriber age in this model because of a strong correlation with prescriber years in practice. As a result, we assessed the extent to which prescriber age may have confounded the association between years in practice and adherence to ensure our reported estimates were valid.

To examine the potential confounding by prescriber age, we repeated the analysis of prescriber years in practice within patient strata according to their prescribers' median age. A prescriber's media age was calculated according to the prescriber's age on index dates of paired patients (30-39, 40-49, 50-59, and 60-69).

The within-prescriber effects on years in practice among patient groups stratified by prescriber's age were consistent with the effect of the whole cohort [prescriber age 30 to 39: aOR = 1.18(0.88, 1.59), 40 to 49: 1.48(1.14, 1.91), 50 to 59: 1.28(1. 24, 1.60), and 60 to 69: 1.46(1.02, 2.09), Appendix table 2]. Similarly, the between-prescriber effects were also consistent with the overall analysis in that the estimated odds of achieving optimal adherence declined with additional years in practice. Of note, the odds ratio estimates were only significant for strata where prescribers' age was under 50 [prescriber age 30 to 39: aOR = 0.66(0.45, 0.98); 40-49: 0.73(0.55, 0.98), S-Table 2].

S-Table 2: Odds ratios (95% confidence interval) for the association of every 10 more years in practice with optimal statin adherence stratified by prescriber's age.

Strata by prescriber's age[a]	Number of patients/prescribers	Adjusted odds ratio (95%CI)[b]	
		Between prescribers	Within a prescriber
30 to 39	11,815/452	**0.66 (0.45 to 0.98)[c]**	1.18 (0.88, 1.59)
40 to 49	12,964/400	**0.73 (0.55, 0.98)**	**1.48 (1.14, 1.91)**
50 to 59	13,985/299	0.89 (0.67, 1.18)	**1.28 (1.24, 1.60)**
60 to 69	9,086/215	0.90 (0.59, 1.39)	**1.46 (1.02, 2.09)**

[a]Prescriber's age = prescriber median age of a prescriber's patients on the index date (date the first statin was dispensed); [b]Adjusted for patient variables including age, sex, urban/rural living, household income level, number of medications by the anatomical therapeutic chemical (ATC) class, number of outpatient visits, percentage of medication cost paid by government health insurance, number of hospitalization for acute care, number of visits to emergency department, Charlson comorbidity score, clinical conditions (osteoporosis, rheumatoid arthritis, hypertension, stroke, ischemic heart disease, acute myocardial infarction, heart failure, multiple sclerosis, Parkinson's disease, Alzheimer's disease and dementia, epilepsy, asthma, chronic obstructive pulmonary disease, diabetes, mood and anxiety diseases, schizophrenia, and cancer); also adjusted for prescriber-related variables including prescriber's sex, country of medical training, remuneration type, overall patient count, and statin patient count; [c]Odds ratios in bold font are statistically significant ($p<0.05$); optimal statin adherence = proportion of days covered by statin medications >=80%.

Appendix C: Analysis of prescriber years in practice (between prescriber effect versus within prescriber effect)

The between-prescriber analysis suggested that the odds of optimal adherence was lower for prescribers with longer years in practice while the within-prescriber estimate indicated the odds of optimal adherence improved during this time. This apparent contradiction was clarified by calculating a dispersion statistic to clarify the within-prescriber result. Dispersion was measured independently for each general practitioner (GP) prescriber as the standard deviation of years in practice (i.e., years in practice was a time-varying measure).[6] If the standard deviation (i.e., dispersion) was low, it suggested that the prescriber's new statin patients were clustered within a short period of time during the study period. In contrast, higher standard deviation values (i.e., higher dispersion) suggested that new statin patients were dispersed across the study period. To illustrate the impact of dispersion on the modelling results for optimal adherence, we contrasted optimal adherence with the mean years in practice and the dispersion (or standard deviation of years in practice) to illustrate how these trends co-existed [S-table 3].

S-Table 3: Percentage of patients exhibiting optimal adherence (proportion of days covered >=80% of statin medications) by quartiles of prescriber's years in practice, and standard deviation of years in practice.

			Length of years in practice (quartiles)				
			<10.0 years	10.0 to 19.3	19.4 to 31.4	>31.4	**Subtotal**
		Prescribers (n)	395	386	389	392	**1,562**
			Adherent patients[a]: % (adherent patients / total patients in the group)				
Dispersion[a] (standard deviation of years in practice when initiating statin for different patients)	< 0.5	390	52.8% (281/532)	44.9% (257/572)	49.0% (249/508)	46.4% (187/403)	**48.3% (974/2015)**
	0.5 to 1.1	391	53.0% (1528/2883)	49.7% (1086/2183)	46.8% (479/1023)	44.5% (509/1144)	**49.8% (3602/7233)**
	1.2 to 1.7	391	55.2% (1552/2811)	53.5% (2374/4437)	49.9% (2999/6005)	52.6% (2834/5389)	**52.3% (9759/18642)**
	> 1.7	390	57.6% (1505/2611)	58.0% (2656/4581)	56.6% (5222/9229)	53.8% (4069/7563)	**56.1% (13452/23984)**
	Subtotal	**1,562**	**55.1% (4866/8837)**	**54.1% (6373/11773)**	**53.4% (8949/16765)**	**52.4% (7599/14499)**	**53.6% (27787/51874)**

[a]Adherent patient = patients with a proportion of days covered >=80% of statin medications; [b]standard deviation of years in practice = the standard deviation of a prescriber's years in paired patients; [c]adherent patients = patients who presented optimal adherence.

4.9 References of supplementary materials:

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Chapter 5 Summary

5.1 Overview of key findings

This research consisted of three separate studies examining the impact of physicians on the occurrence of optimal medication adherence in a Canadian health care setting. Physicians are key participants in almost all aspects of prescription medication use in Canada and may influence adherence through several pathways connected to their professional role including diagnosing, counseling, prescribing, and follow-up.[1-8] The impact of physicians on medication adherence is an important research area for several reasons. Models attempting to predict (or explain) medication adherence have performed very poorly in published studies.[9-11] A study by Wong and colleagues tested a wide array of clinical factors and administrative data available for a cohort of 444,481 patients receiving oral blood-glucose-lowering medications but were only able to account for 2.9% of the variance in optimal adherence (i.e., adherence of at least 80%).[10] Studies such as these generally have not included the multiple possible contributions of individual physician prescribers, and a comprehensive assessment of the physician impact on medication adherence had not been conducted previously.

The first study (Chapter Two) examined the most commonly used measure representing continuity of care (COC) in population-based medication adherence studies.[12-15] We found evidence that physicians with relatively low visit frequency may still be providing diverse services to their patients. Moreover, integrating diverse services into the COC definition resulted in higher discrimination and also improved prediction performance of a population-based adherence model.

Our findings align with the concept of the 'medical home' where a single primary care team takes responsibility for "providing and arranging all the patient's health care needs".[16-18] Although it cannot be concluded that our integrated approach to COC is perfect, it was a clear improvement over the traditional one-dimensional measure based exclusively on the number of physician visits. Our study suggests that clinical service and prescribing dimensions should be integrated into COC measure in population-based adherence models.

The second study (Chapter Three) aimed to determine if age and sex concordance between physicians and patients influence optimal adherence to statin medications. We found no effect of age concordance but a possible association between sex-concordance and adherence could not be ruled out. Although it failed to reach statistical significance, a possible association could not be ruled out because of potential bias towards a null finding. Specifically, patients with a strong preference for a same-sex prescriber were likely over-represented in the sex-concordant group and under-represented in the discordant group. Future research should explore the relevance of sex concordance in underserved/rural areas where access is limited to a single physician. The role of sex concordance is supported by a strong theoretical rationale. [19-28]

The third study (Chapter Four) aimed to explore the extent to which 'prescriber effects' may help explain variance in patient adherence to statin medications. We further examined 'prescriber effects' as: a) a 'latent' effect (i.e., physician effect unexplained by patient and prescriber characteristics); and b) specific prescriber characteristics and their association with statin adherence. Overall, the physician impact on adherence was weak, only accounting for a small percentage of the overall variance between patients. Further, physician characteristics contributed very little as most of their effect could not be

explained by measured factors. The theoretical justification for investigating the overall impact of physicians on medication adherence was strong. Many papers reported significant associations between adherence and physician level skills such as communication and trust[22, 24, 29-32] as well as practice related factors such as workload[33-36] and COC.[12-15] Our findings suggest that the association between physician factors and adherence observed in previous studies may be similar to reverse causality bias where adherent patients may have been more likely to rate their physician highly on factors such as communication while a non-adherent patient may rate the same physician poorly on these characteristics. However, the findings of this study identified several important issues that need to be addressed in future studies, especially regarding physician remuneration types and their impact on medication adherence.

5.2 Strengths and limitations

Three population-based cohort studies were performed using validated administrative data. Thus the study population was highly generalizable to other Canadian health care settings. In these studies, we used robust statistical models (including GEE and multi-level models) along with a comprehensive array of patient- or physician- related variables to minimize confounding. For example, in study three, patients were nested within prescribers and form a two-level structure. Apart from the individual level confounders (e.g., age, sex, health conditions, etc.) that are commonly considered for optimal patient adherence, other potential confounding effects must be addressed. For example, ecological effects may be important such as cross-level effect modification as well as indirect/direct cross level effects.[37] We used multi-level models to address some of the possible ecological and cross-level confounding related to physicians; however, additional effects are possible.

Although the threshold to define optimal adherence (i.e., >=80%) is widely adopted,[38] evidence remains insufficient to confirm its clinical relevance. Recently, a study showed that optimal treatment effect (blood low-density lipoprotein <=1.8 mmol) can be achieve even though adherence to statin was as low as 50%.[39] The ideal adherence threshold may also vary for different medications or different lengths of follow-up.[40] A study showed that the cut-off for oral antidiabetic medications should be 90% to achieve target blood glucose level (Hemoglobin A1C <=7.0%).[41] As such, it is important to examine the distribution of the adherence level, and perform sensitivity tests by applying different adherence cut-offs ranging from 50% to 100%, as we did in our studies.

However, there were weaknesses to be considered. First, these studies were based on population of a public health care system in which patients can freely choose the care providers. Also, only statin medications were examined. Thus, generalizability of the findings to populations of other health care settings, or to other disease states such as mental health conditions cannot be assumed. Second, while it was reasonable to choose the most frequent prescribers, we did not measure the impact of other physicians such as other GP prescribers, primary care providers (i.e., the most frequently visited physicians), or specialists. Third, there was a lack of clinical data (e.g., laboratory test results and electronic medical records), and measures on social economic factors (e.g., ethnicity, education level, and employment). These could have confounded the findings. Fourth, there were limited physician variables that can be captured in the available data. Additional information about physicians such as knowledge, personality, working attitude, and communication skills may have confounded the results. Future studies should attempt to identify additional data about prescribing physicians and their relationship with patients. Finally, lack of randomization in these studies limited our control over

unmeasured confounding. This limitation appeared to be especially problematic for assessments of remuneration type and country of medical training. Devlin and colleagues reported that physicians may self-select into a remuneration type due to uncaptured personal preference and characteristics.[42] The effect of remuneration type and graduate country on medication adherence should be examined in future studies in order to improve our understanding of these factors.

5.3 Future research

The focus of this dissertation was the impact of physicians on the outcome of patient medication adherence. Traditional approaches in adherence research often focus solely on patient-related factors, almost as if non-adherence is a pathologic condition.[43] Raising awareness about the role of health care providers and the health care system is important as we continue to understand this complex phenomenon. The search for answers to the root causes of medication adherence remains elusive at the population level. However, continued research on this topic is crucial given the challenges facing health care sustainability in countries around the world. Medication adherence represents a prime target for improving care of chronic conditions and keeping people out of hospitals. The findings of this research can and should be extended.

First, it is not clear whether our candidate medication class, statins, influenced the findings of this research. Different findings may have been observed if other classes were used. For example, perhaps sex concordance is important for some drugs but not others. It would be logical to investigate sex-specific conditions such as menopausal or andropausal treatments in a similar analysis. It is also possible that the overall physician effect is small for statins but larger for patients with mental health conditions where relationships and counseling may be more prominent.

Second, some of our findings may not be generalizable to all health care settings. Future studies should re-examine the impact of sex-concordance in areas where provider access is limited or in health systems that limit choice of providers. In addition, further studies might explore the impact of physician-reimbursement strategies (i.e., NFFS or FFS) using methods that will address the high risk for bias due to non-randomization (e.g., methods to randomize patients into FFS and NFFS physician groups with consent from patients, or to adopt a quasi-experimental design which allows patients to switch between FFS and NFFS physicians).

Third, important potential confounders were not captured in administrative databases. These factors include perception of risk, communication style of provider, race/ethnicity concordance, patient-physician trust level, perceived medication complexity, and conflicting medication information. As such, efforts must continue to enable population-based researchers to access and link electronic medical records, behaviour-related data, and high-quality survey data in future studies.

Finally, specific follow-up studies should be conducted. For example, for the first study, the absolute number of visits to prescribers might further enhance the COC measure's performance so it should be tested in future studies. Also integrated COC measure may still be improved upon by investigating other services and customizing for local health care settings. In study two, the effect of age concordance on adherence may be more important among individuals treated for psychiatric conditions such as depression. Unlike statin users (who are usually at or above 40), patients suffering from mood disorders are of a wider age range, and are more likely to present age discordance.

Our findings suggest that physicians play a relatively minor role in medication adherence of their patients. However, many outstanding issues remain unexplored in this

area and medication adherence continues to be a critically important field of health research. It is hoped that his research will help move the field towards the next important breakthrough.

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